INTRODUCTION TO VOLUME 6: HETEROATOM MANIPULATION

This volume of 19 chapters focuses on developments over the past two decades in some of the most significant and useful topics in the general area of heteroatom manipulation. Each chapter has been prepared by an author (or team of authors) with established expertise in the title topic.

The presence of heteroatoms contributes decisively to the structural diversity, physical properties, and chemical reactivity of organic molecules. Heteroatom-containing functionalities serve as activating groups for a wide variety of bond-forming and bond-breaking reactions in organic synthesis, as surrogates for other functionality to which they ultimately can be transformed, and as linkers for connecting structural subunits. Organic synthesis, medicinal and agricultural chemistry, materials research, and chemical biology are among the fields dependent upon the enabling attributes of heteroatomic functional groups.

Although this volume, along with each of the others, provides ready access to specific, detailed treatments of mutually related topics in each of the chapters, a broader perspective is also beneficial. These chapters provide a fertile landscape for inspirational browsing, given that the state-of-the-art for each topic is illustrated, and residual areas for further development are apparent.

Because of the breadth and diversity of the topics covered in this volume, a brief overview of each chapter and the main topics covered therein is presented below:

Chapter 6.01 (Bohé and Crich) Synthesis of Glycosides. A mechanistic analysis of the factors influencing the various methods for selective formation of glycosidic bonds is advanced. The effects of protecting groups on the reactivities of glycosyl donors and glycosyl acceptors, the influence of promoters and leaving groups on glycosyl donor activation, and the role of reaction solvent are all evaluated from a mechanistic perspective. The specific contexts for comparing and contrasting glycosylation protocols are in the formation of difficult classes of *O*-glycosides, including uronic acid glycosides, α-sialosides, and β-arabinofuranosides.

Chapter 6.02 (Marvin) Synthesis of Amines and Ammonium Salts. Recent advances in the synthesis of amines and ammonium salts are summarized, including displacement reactions by nitrogen nucleophiles, amination by variants of the Mitsunobu reaction, epoxide opening, allylic activation, and transition metal-catalyzed (Pd, Rh, Ir) allylic amination. In particular, the Pd- and Ir-catalyzed allylic aminations are fully described, including issues of regio- and stereoselectivity. Among the examples involving Pd-catalyzed allylic aminations are instances of intramolecular reactions (cyclizations) and cascade reactions featuring successive metal-mediated steps. Dynamic kinetic asymmetric transformation and enantioselective allylic amination catalyzed by Pd and Ir are extensively discussed.

Chapter 6.03 (Nishiwaki) Synthesis of Nitroso, Nitro, and Related Compounds. Among the topics featured are new nitrating agents, organometallic methods, and production of nitro groups from other functionality. Substantial use of building blocks containing nitro groups is presented. Catalytic enantioselective Henry reactions are described, as are enantioselective conjugate additions to nitroalkenes. Cycloadditions of unsaturated nitro compounds and ring transformations of nitrated heterocycles to afford highly functionalized heterocycles are detailed.

Chapter 6.04 (Drabowicz, Długosz, Kiełbasiński, Zając, and Wach-Panfiłow) Synthesis of Sulfides, Sulfoxides, and Sulfones. Methods for synthesis of sulfides from alkyl-, aryl-, and vinyl halides are described, including transition metal cross-coupling reactions. Use of sulfur nucleophiles and sulfur electrophiles are exemplified, as are addition reactions of sulfenic acids to alkenes and alkynes. Ring-opening reactions of oxiranes and aziridines are also detailed. Among the methods described for the synthesis of sulfoxides are those resulting in *S*-chiral, nonracemic sulfoxides. Synthesis of unsymmetrical sulfones by reaction of sulfonyl halides with organometallic reagents is featured, in addition to methods focused on generating and trapping of sulfinic acid anions. Finally, [2,3] sigmatropic rearrangements of allylic and propargylic sulfinates yielding allylic and allenic sulfones, respectively, are illustrated.

Chapter 6.05 (Odinets and Aleksanyan) Synthesis of Phosphonium Ylides. Methods for the synthesis of highly functionalized phosphorus ylides are described. Environmentally friendly procedures, including ylide generation and reaction in water or under solvent-free conditions, are detailed. Descriptions of alternative methods for ylide generation, including nucleophilic addition of P(III) species to various electrophiles followed by proton transfer, and addition of nucleophiles to vinylphosphonium salts, are included. Discussion of the use of polymer-supported reagents, and preparations and uses of carbodiphosphoranes and phosphacumulenes bring this venerable topic up to date.

Chapter 6.06 (Liang and Ritter) Synthesis of Fluorides. This new stand-alone chapter reflects the intense current interest in the synthesis of organofluorine compounds. Traditional and recent approaches to C–F bond formation are described. Electrophilic and nucleophilic fluorination reactions are surveyed. Enantioselective methods, transition metal-mediated reactions, C–H insertion protocols, and fluorination α-to carbonyls are extensively discussed. Syntheses of alkenyl- and aryl fluorides are detailed, as are both nucleophilic and electrophilic methods for the incorporation of ^{18}F into organic molecules as radiotracers for positron emission tomography.

Chapter 6.07 (Bishop) Ritter-Type Reactions. This chapter describes recent developments in the Ritter reaction and similar transformations. Combination of a carbocation and a nitrile to generate a nitrilium ion is followed by addition of water to form an amide or by cyclization involving an internal nucleophile to generate a heterocycle. Recent examples of catalysis of the Ritter reaction, skeletal rearrangements observed during this process, the formation of bridged polycyclic products, and the development of multicomponent reactions based upon the Ritter reaction are described.

Chapter 6.08 (Zell and Schreiner) Acylation-Type Reactions: Synthesis of Esters via Acyl Transfer. Although this chapter topic has a history exceeding 230 years, the past two decades have resulted in many sophisticated advances, including the use of *N*-heterocyclic carbene-mediated organocatalytic acyl transfer, asymmetric acyl transfer, and enantioselective ring opening of *meso* anhydrides. Also described are methods involving metal complex-mediated enantioselective ester synthesis, and dynamic kinetic resolution methods for alcohols involving metal-mediated carbinol racemization in tandem with enzymatic acylation.

Chapter 6.09 (Siengalewicz, Mulzer, and Rinner) Synthesis of Esters and Lactones. This chapter features new protocols for ester and lactone synthesis, and examples from syntheses of natural products and industrially important molecules. Methods focused on carboxy group activation, hydroxy group activation, and double activation strategies are summarized. Transesterification and enzymatic esterification methods are briefly discussed, as are alkylative methods for ester formation. Miscellaneous methods for the formation of esters and lactones are presented, including the Baeyer–Villiger reaction, the Favorskii reaction, and metal-catalyzed alkoxycarbonylation.

Chapter 6.10 (Schaumann) Synthesis of Thioamides and Thiolactams. Incorporation of the nearly isosteric thioamide (or thiolactam) moiety in place of the natural amide (or lactam) unit in biologically relevant molecules has become increasingly popular, requiring developments in synthetic methodology for their production. Described here are methods for thioacylation of amines by thiocarboxylic acid derivatives, and synthesis of thioamides by thiolysis of imidocarboxylic acid derivatives, nitriles, or ynamines. Thiocarbamoylation protocols involving nucleophilic addition of arenes, electron-rich alkenes, enolates, carbanions, and carbon radicals to isothiocyanates are also surveyed as routes to thioamides.

Chapter 6.11 (Taylor and Bull) *N*-Acylation Reactions of Amines. The latest developments in *N*-acylation are featured, especially catalytic approaches to amide bond formation. Common additives for effecting amide bond formation are overviewed, as are stable, isolable *N*-acylating agents. Chemical ligation protocols for peptide subunit couplings are detailed, and the coupling methods involving carbodiimide mediation and those using onium- and pyridinium-based coupling agents are updated. Also described are the recently developed redox amidation methodologies, and strategies for kinetic resolution of racemic amines by *N*-acylation.

Chapter 6.12 (Hanson, Asad, Zang, Jayashinghe, and Markley) Inorganic Acid Derivatives. This chapter is focused on the phosphate functional group. Recent phosphorylation methods using P(III) and P(V) reagents are surveyed. Introduction of the phosphate moiety by Mitsunobu reaction with a phosphate nucleophile, and catalytic and asymmetric phosphorylation protocols are detailed. The recent development of peptide-catalyzed selective phosphorylation is illustrated. Preparation and use of enol phosphates for metal-catalyzed cross-coupling and advances in phosphate protecting groups are also featured. Throughout, this chapter provides excellent examples of the use of phosphorylation methods in the synthesis of biologically active natural products.

Chapter 6.13 (Schiltz) Use of Carbonyl Derivatives for Heterocyclic Synthesis. This chapter focuses on recent advances in the preparation of the most important medicinal chemistry-related heerocycles, including substituted thiazoles, imidazoles, pyrazoles, thiophenes, and oxazoles. For each of these heterocycles there is presented a summary of the most important methods currently in use for their synthesis that are based upon carbonyl manipulation. Included are examples of FDA-approved drugs containing the heterocyclic nucleus being discussed, and the methods illustrated are designed to provide multiple substituents of varying types on the heterocycle.

Chapter 6.14 (Uyanik and Ishihara) Functional Group Transformations via Carbonyl Derivatives. This chapter focuses on the use of oximes and hydrazones as versatile intermediates of high reactivity. For example, promotion of the Beckmann rearrangement by transition metals and organocatalysts are featured topics. Production of olefinic products via Bamford–Stevens and Shapiro reactions of arenesulfonylhydrazones are surveyed, including the formation of chiral alkenes via desymmetrization of ketones by Shapiro reactions involving chiral aziridinyl hydrazones. The synthesis of α-amino ketones via rearrangement of oxime sulfonates (the Neber reaction) is discussed, including the enantioselective production of indoles and chiral 2*H*-azirines.

Chapter 6.15 (Aube, Fehl, Liu, McLeod, and Motiwala) Hofmann, Curtius, Schmidt, Lossen, and Related Reactions. Synthetic methods based on the mechanistically related Hofmann, Curtius, and Lossen rearrangements and the Schmidt reaction are surveyed. All result in the production of amides and/or amines involving nitrogen insertion via concerted rearrangement of a nitrenoid intermediate. A featured segment of the chapter is the recently developed intramolecular Schmidt reaction, which enables the production of complex cyclic and polycyclic nitrogen heterocycles. For each of the title reactions, recent modifications and improvements in reagents and conditions for generating reactive intermediates are detailed.

Chapter 6.16 (Gu and Zacharian) Functional Group Transformation via Allyl Rearrangement. An extensive discourse on the mechanistic spectrum involved in allylic transposition is presented in this chapter. Main topics include nucleophilic and electrophilic substitution, metal-catalyzed allylic substitution and C–H functionalization, radical allylation, and various pericyclic reactions including the ene reaction and selected sigmatropic rearrangements ([2,3] and [3,3]). Transformations of halogen-to-oxygen (X-to-O), X-to-N, O-to-X, O-to-N, and O-to-O bonds via heteroatom transposition are surveyed, including numerous asymmetric variants. Throughout, illustrative examples of allyl rearrangement-based strategies applied to natural products synthesis are presented.

Chapter 6.17 (Bur) Polonovski- and Pummerer-type Reactions and the Nef Reaction. This chapter is focused on these reactions by which a formal transfer of oxidation level from a heteroatom to an adjacent carbon atom occurs. The oxidized functional groups in the Polonovsky (amine-*N*-oxide), Pummerer (sulfoxide), and Nef (nitro) reactions give rise to electrophilic iminium, thionium, and nitronate species, respectively. Subsequent reaction at carbon with nucleophiles completes the formal transfer of oxidation state. Numerous recent advances have been made that facilitate the formation and utilization of the reactive

intermediates involved in the title reactions. These are extensively surveyed, and skeletal modifications involving fragmentations, pericyclic reactions, and rearrangements during these name reactions are presented.

Chapter 6.18 (Biggs and Ogilvie) Eliminations to Form Alkenes, Allenes, and Alkynes and Related Reactions. Following an overview of mechanistic factors controlling elimination/substitution selectivity, and elimination regio- and stereoselectivity, recent advances in the stereoselective synthesis of alkenes are comprehensively surveyed. Widely varied protocols for the production of di-, tri-, and tetrasubstituted alkenes via eliminations and fragmentations are presented, as are methods for generating olefins from epoxides, episulfides, and aziridines. Stereocontrolled methods for the production of chiral allenes are highlighted, as are selected elimination routes to alkynes. Numerous eliminations employed in the context of complex natural products synthesis are also included.

Chapter 6.19 (Hoang, Dudley, and Williams) Fragmentation Reactions. This chapter features an historical and mechanistic perspective. This includes a framework for predicting and interpreting fragmentation reactions. Specific topics are focused on fragmentation reactions that yield alkenes, alkynes, allenes, macrocycles, and nitriles. Featured are regio- and stereoselective eliminations to form di-, tri-, and tetrasubstituted alkenes, and ring-opening and ring-expansion reactions via fragmentation. Fragmentations exploiting the ring strain of epoxide nucleofuges, which have recently played prominent roles in synthesis, are highlighted. The newly developed field of allenogenic fragmentions is discussed, and recent applications of the Beckmann fragmentation of oximes to afford nitriles are presented.

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6.01 Synthesis of Glycosides

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This article complements the previous edition article by Richard R. Schmidt, Vol. 6, pp 33–64, © 1991, Elsevier Ltd.

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Glossary

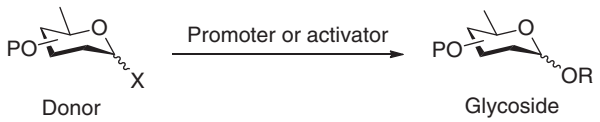
Contact ion pair (CIP) An ion pair in which the two ions are closely associated and which excludes solvent.
Glycosyl acceptor An alcohol that reacts with a glycosyl donor to form a glycosidic bond.
Glycosyl donor An electrophilic species capable of reacting with an alcohol (glycosyl acceptor) to form a glycosidic bond.
Glycosylation promoter or activator A substance, typically electrophilic, that reacts with a glycosyl donor to convert it into an activated donor suitable for reaction with a glycosyl acceptor.
Solvent-separated ion pair (SSIP) An ion pair in which the ions are separated by one or more layers of solvent molecules.

6.01.1 Introduction

This chapter surveys advances in the formation of the *O*-glycosides described since the publication of the first edition of Comprehensive Organic Synthesis (COS).[1] It takes a mechanistic approach to the problem of efficient and stereoselective glycosidic bond formation before focusing on the advances in the synthesis of the so-called 'difficult' classes of glycosidic bond that have been recorded in the past 20 years.

6.01.2 The Glycosylation Mechanism

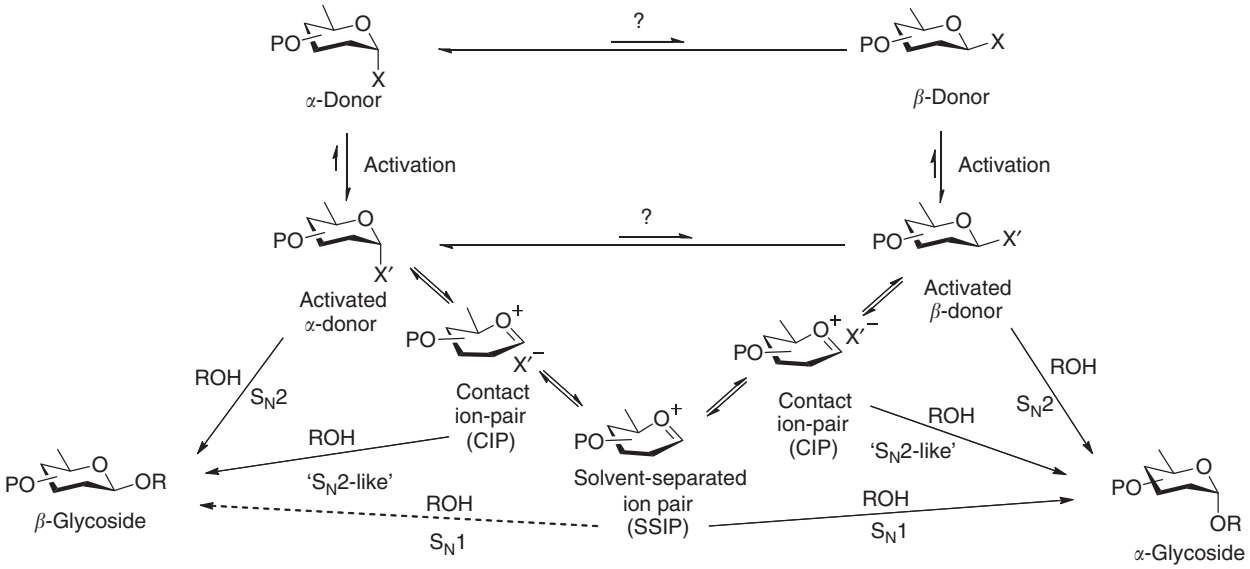
Glycosylation is a reaction that involves the displacement of a leaving group from a glycosyl donor by a glycosyl acceptor, typically in the presence of a promoter or activator, and falls in the category of nucleophilic substitution (equation 1).



Donor Glycoside (1)

As in all aliphatic nucleophilic substitution reactions, two extreme mechanisms exist for glycosylation, namely, the bimolecular stereoinvertive S_N2 process and the unimolecular stereorandomizing S_N1 process. These hypothetical extremes are bridged by a spectrum of mechanisms involving more or less tightly associated ion pairs and proceed with different degrees of association or dissociation in the rate-determining step. The application of Winstein's ion pair theory[2] to the glycosylation mechanism, first

advanced by Vernon[3] and subsequently expanded on by Schuerch[4] and Lemieux,[5] is complicated by a number of factors, first among which is the interaction between the leaving group and the promoter that converts the initial glycosyl donor into an activated donor, possibly containing an entirely different leaving group. Second is the ambiguous nature of the glycosyl oxocarbenium ion, a necessary component of any ion pair, which, although widely computed and drawn,[6,7] has yet to be observed experimentally.[8,9] A third important complication arises from the availability of possibly interconverting diastereomeric donors and of the associated ion pairs. Fourth, there is the influence of solvent on the position of any covalent donor–ion pair equilibrium and the possibility of the more direct involvement of the solvent in the form of adducts with the glycosyl oxocarbenium ion. Fifth is the possibility, as in any reaction bringing together two chiral partners, of double diastereoselectivity between the donor and the acceptor.[10] Last, but certainly not least, there is the influence of protecting groups on the reactivity of both the donor and the acceptor.[11] Taking all of these factors into consideration a generic glycosylation mechanism can be advanced as in **Scheme 1**.



Scheme 1

Given the number of factors involved it is not surprising that the field has evolved along largely empirical lines that have resulted in the description of a bewildering array of glycosylation methods and conditions, relatively few of which have seen broad application.[12,13] In spite of this, in recent years, greater emphasis has been put on a more mechanistic approach; spectroscopic evidence for activated glycosyl donors and intermediates has been presented in a number of cases, and kinetic studies have begun to distinguish between reactions operating at different ends of the S_N1–S_N2 mechanistic spectrum.

6.01.2.1 Influence of Protecting Groups on the Glycosyl Donor

It has long been known that protecting groups influence the reactivity of glycosyl donors, with electron-donating groups stabilizing the electron-deficient transition states of S_N2 reactions and the oxocarbenium ion intermediates of S_N1 reactions, and thereby accelerating glycosylation reactions, whereas electron-withdrawing groups have the opposite effect.[14] These fundamental effects were dubbed arming and disarming, respectively, by Fraser-Reid and coworkers, who showed that armed pentenyl glycosides could be activated in the presence of disarmed ones.[15,16] Quantification of the effect of a number of protecting groups, but especially that of the cyclic bisacetals, was subsequently undertaken by the Ley group and enabled the controlled one-pot syntheses of oligosaccharides.[17] The Wong group developed the concept further and published an extensive series of relative reactivity values for thioglycosides that made possible the programmable one-pot synthesis of a variety of important oligosaccharides by sequential addition and activation of mono-hydroxylated donors to a reaction flask containing the growing oligomeric chain.[18,19]

One no-doubt unintended consequence of the broad acceptance and application of the arming and disarming terminology to describe the influence of protecting groups on the reactivity of glycosyl donors has been the over-generalization of esters, particularly those at the 2-position, as disarming. In truth, while this is always the case for donors in which the leaving group and the ester have a *cis*-stereochemical relationship, it does not necessarily hold for donors in which the leaving group and the ester are on opposite faces of the system and capable of accessing an antiperiplanar conformation. Thus, it has been demonstrated that in weakly promoted systems a *trans* 2-*O*-ester is arming, and through anchimeric assistance accelerates departure of the leaving group.[20–23]

Other than in cases of anchimeric assistance, the influence of protecting groups on donor reactivity relates to their electron-donating/withdrawing effect on the oxygen atom to which they are affixed and consequently on its ability to stabilize or

destabilize incipient positive charge at the anomeric position. Such effects may be transmitted through space or through bonds, and thus the ability of a protecting group to influence the conformation of oxocarbenium-like intermediates is important.

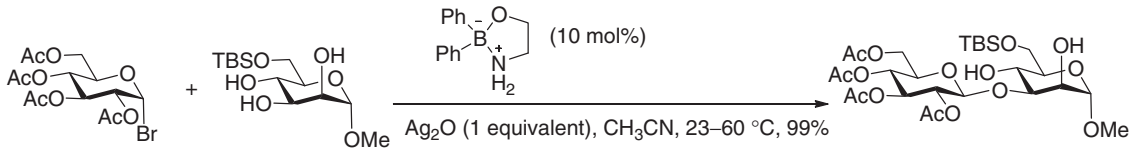
The situation regarding the stereodirecting influence of remote esters on glycosyl donors is in most cases unclear and requires further work. It is frequently suggested in the literature, often on the grounds of only small changes in selectivity, that an ester at a given position participates in a glycosylation reaction. The use of the Boc group as a probe for participation has been advocated and provided clear evidence for the formation of actual bridged intermediates in glycopyranosyl donors carrying axial esters at the 3-position.[24] No evidence was found for participation by axial esters at the 4-position using this approach, or by an isotopic labeling method,[24] but strong evidence for the participation by the 4-*O*-acetate in a peracetylated glucopyranosyl donor has been advanced.[25]

It has long been known that galactopyranosyl and mannopyranosyl systems are more reactive than their corresponding glucopyranosyl isomers,[26,27] a fact that is now convincingly attributed to the ability of a pseudo-axial C–O bond to stabilize the glycosyl oxocarbenium ion through space.[28–31] It follows that protecting groups, in addition to their ability to moderate the inductive effect of a C–O bond, can influence glycosyl donor reactivity by conformational effects. An elegant illustration of the concept is found in the multiple silylated donors studied by the Yamada[32,33] and Bols laboratories,[34] and dubbed super-armed donors by Bols, in which the presence of multiple silyl ethers results in the predominant population of ring conformations with several pseudo-axial C–O bonds and consequent high reactivity. 4,6-*O*-Benzylidene acetals, on the other hand, are disarming in the glucopyranose series because they enforce the *trans-gauche* conformation on the C5–C6 bond, which orientates the C6–O6 antiperiplanar to the C5-ring oxygen bond and thus maximizes the electron-withdrawing effect of O6.[35]

Woerpel has analyzed the stereoselectivity of C-glycosylation reactions in terms of the facial selectivity of glycosyl oxocarbenium ions as a function of their conformational equilibria.[9,31,36,37] For *O*-glycosylation, however, the close to diffusion-controlled rate of attack of simple alcohols on glycosyl oxocarbenium ions detracts from this model.[38] Although this approach to the analysis and prediction of glycosylation stereoselectivity is useful, particularly for the more armed systems, it has to be viewed with caution in the light of the recent demonstrations of associative mechanisms in certain cases.[39–41] Likewise, it must also be remembered that both anomers of a given saccharide are not necessarily formed by the same mechanism, as has been clearly demonstrated for the 4,6-*O*-benzylidene-protected mannopyranosides.[39,41] The work of Gilmour with a series of 2-deoxy-2-fluoro glycopyranosyl donors demonstrates the powerful *trans*-stereodirecting effect of a C–F bond at the 2-position, which is attributed to the stabilization of conformers of intermediate glycosyl oxocarbenium ions in which the C–F adopts a pseudoaxial orientation, perpendicular to the plane of the π-system (**Scheme 2**). The possibility that the C–F bond also directs glycosylation through stabilization of an Anh-Eisenstein transition state by overlap with the C-F$^{\pi}$ orbital also exists.[42,43] This model differs from the Woerpel analysis of the tetrabenzyl glucopyranosyl oxocarbenium ion, according to which, based on calculations by Woods,[44] the C2–O2 bond provides equal electrostatic stabilization to the oxocarbenium ion from either pseudo-axial or equatorial positions and thus prefers the pseudo-equatorial orientation for steric reasons (**Scheme 2**).[36]

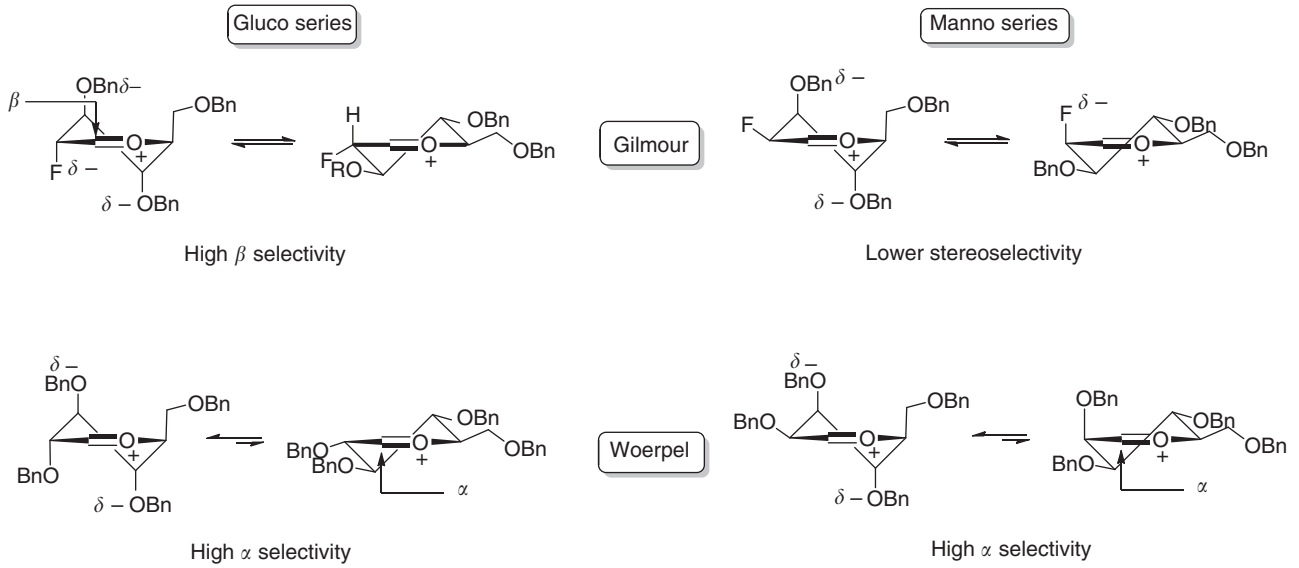
6.01.2.2 Influence of Protecting Groups on the Glycosyl Acceptor and Double Diastereoselectivity

The reactivity of the various hydroxyl groups around a pyranoside ring toward glycosylation is a function of their steric and electronic environment. Typically, it is considered that in the glucopyranose series the reactivity order is 6-OH >> 3-OH > 2-OH > 4-OH, and that alcohols flanked by benzyl ethers are more reactive than those with neighboring esters,[45,46] but quantitative reactivity studies are scarce. One of the more studied systems is the glucosamine 4-OH, which is considered to be one of the least reactive of alcohols in glycosylation. It has been demonstrated that glycosylation of such an alcohol is a function of the amine protecting group as well as of the bulk of the neighboring hydroxyl protecting systems. Thus, the *N*-acetyl-2*N*,3*O*-oxazolidinone-protected system has been shown to be one of the more reactive alcohols of its type, no doubt because of its tied-back nature, which reduces the steric hindrance around the 4-OH. The regioselective protection of carbohydrate polyols has long been possible through the use of dibutyltin oxide in conjunction with various electrophiles,[47] and through the regioselective reductive opening of acetals.[48,49] It is only recently, however, that regioselective glycosylation has become possible under certain conditions with the aid of a diarylborinic acid catalyst (equation 2).[40]



(2)

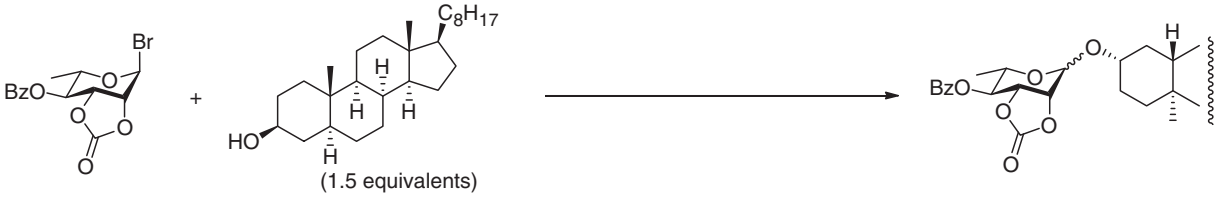
Enantiomeric alcohols are known to show differing reactivities and/or selectivities toward a given donor.[10,50] This manifestation of Horeau and Kagan's concept of double asymmetric induction[51,52] varies from system to system and can be considered to become more important with the more highly associative glycosylation reactions and their correspondingly more organized transition states.[10] It is not surprising therefore that more radical changes in the environment of a nucleophilic alcohol, such as those occasioned by the changing of protecting groups, influence reactivity. Likewise, the differing regioselectivity of polyhydric systems as a function of glycosyl donor, demonstrated and exploited in synthesis by the Fraser-Reid group,[53,54] is interesting and useful but unsurprising from a first principles standpoint.


Gluco series
Manno series
Gilmour
Woerpel
High β selectivity
Lower stereoselectivity
High α selectivity
High α selectivity

Scheme 2

6.01.2.3 Influence of the Promoter on Donor Activation and on Leaving Group Identity

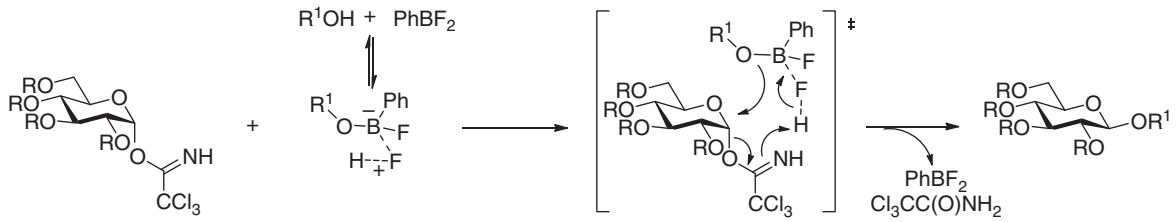
The promoter employed to activate a glycosyl donor cannot be considered to be an otherwise innocent bystander as it is capable of trapping any intermediate glycosyl oxocarbenium ion. Thus, it has been demonstrated that the triflate anion arising *inter alia* from the activation of glycosyl sulfoxides with triflic anhydride combines with the cation to form covalent glycosyl triflates.[55,56] Similarly, it has been shown by low-temperature NMR studies that the perchlorate anion[57] and the triflimide anion[58] are captured by and yield covalent adducts with glycosyl oxocarbenium ions, whereas the tetrafluoroborate anion provides a source of fluoride and results in the formation of glycosyl fluorides.[59] An attempted use of the stable anion tetrakis(pentafluorophenyl)borate to circumvent the trapping of the oxocarbenium ion simply resulted in the formation of an apparent glycosyl disulfonium resulting from reaction of the cation with a diaryl disulfide generated in the course of activation.[60] Many classical glycosylation reactions were promoted by insoluble heavy metal salts with the consequent incursion of surface effects and their influence on stereoselectivity, which sometimes lead to erroneous conclusions about reactivity. For example, the formation of β-manno- and rhamnopyranosides through the insoluble silver salt-promoted activation of 2,3-*O*-carbonate-protected manno- and rhamnosyl halides was attributed to the strongly electron-withdrawing nature of the carbonate group,[61,62] whereas it was subsequently shown that in homogeneous solution the *cis*-fused 2,3-*O*-carbonate is strongly α-directing with a range of donor/promoter combinations (equation 3).[63]



Heterogeneous conditions:	Ag_2O (2 equivalents), MS 4 Å, CH_2Cl_2, r.t., 12 h	76% β only
Homogeneous conditions:	AgOTf (2 equivalents), TTBP (2 equivalents), MS 4 Å, CH_2Cl_2, –60 to 25 °C, then 25 °C, 12 h	66% β:α = 1:5.6

(3)

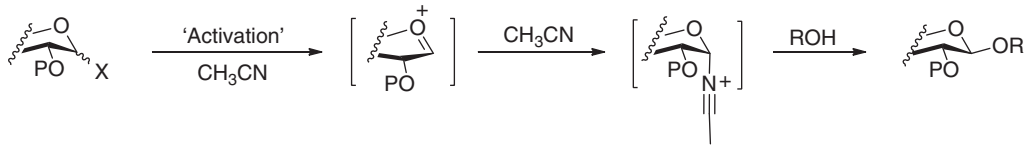
Promoters have also been designed to actively participate in the delivery of acceptor alcohols to the glycosyl donor through an eight-membered cyclic transition state, with phenylboron difluoride showing promise in this manner when used in conjunction with glycosyl trichloroacetimidates (Scheme 3).[64]



Scheme 3

6.01.2.4 Influence of the Solvent and of Additives

In view of the general mechanism it is evident that the choice of solvent will have a major impact on glycosylation reactions by influencing the position of the equilibrium between covalent donors and the various ion pairs. More polar solvents are expected to stabilize ion pairs and individual ions to a greater extent than less polar solvents and thus to promote dissociative mechanisms. The true picture, however, is more complex and includes the possibility of active participation by solvent. The most commonly invoked example of such participation is the so-called nitrile effect in which the use of acetonitrile as solvent leads in many cases to improved selectivity for the formation of equatorial glycosides.[65,66] The nitrile effect is considered to arise through trapping of intermediate glycosyl oxocarbenium ions in the form of axial nitrilium ions, which are subsequently displaced with inversion of stereochemistry by the incoming acceptor alcohol (equation 4). Although numerous examples exist of the Ritter-like trapping, inter- and intramolecular,[67–69] of such nitrilium ions, spectroscopic evidence has been difficult to obtain until recently.[70,71] The use of acetonitrile as solvent is not suitable for the formation of the 1,2-*cis*-equatorial glycosides owing to the predominant formation of Ritter-type products.[72]



(4)

The use of DMF as solvent has been shown to facilitate the formation of axial glycosides; NMR studies, however, reveal the formation of an observable axial imidate, leading to the speculation that the reaction proceeds via a minor but more reactive equatorial imidate.[73] The use of *N*-methyl acetimide as an additive has been reported to improve the reactivity of sialyl donors by disrupting the formation of aggregates in the course of the glycosylation reaction.[74] The use of ethers as solvents is also found to promote the formation of axial glycosides, and the intervention of an equatorial glycosyl oxonium ion is often invoked to explain this effect, albeit in the absence of any spectroscopic evidence.[75–77]

Somewhat akin to the glycosyl oxonium ions proposed as intermediates for reactions conducted in ethereal solvents are the glycosyl sulfonium ions, which are necessary intermediates in the activation of thioglycosides by alkylating agents such as methyl triflate, but which may also be generated by addition of sulfides to reactive glycosyl donors. Thus, following an initial report by West and Schuerch,[78] the spectroscopic characterization and application in glycosidic bond formation of β-configured glycosyl sulfonium salts has been revealed to be a promising area. For example, the Boons group characterized a number of β-configured sulfonium salts derived by activation of a glycosyl trichloroacetimidate in the presence of various sulfides and showed them to be useful intermediates in glycosylation,[79,80] while the Yoshida group reported similar studies based on the reaction of sulfides with electrochemically generated by glycosyl triflates. Specifically, it was found that glycosyl dialkylsulfonium ions are more thermally stable than their alkyl aryl counterparts and that solutions of these intermediates could be stored at low temperature for long periods before use as glycosyl donors.[81,82] The formation of bicyclic sulfonium salts by the intramolecular trapping of glycosyl oxocarbenium ion equivalents by suitably appended sulfides has been studied by several groups, and while these may be readily detected spectroscopically, the question of whether they undergo direct nucleophilic ring opening by an incoming glycosyl acceptor or merely serve as reservoirs for reactive glycosyl oxocarbenium ions is an open one.[80,83–86]

6.01.3 Classes of Glycosyl Donor

Glycosyl donors are classified according to the leaving group (X in equation 1 and Scheme 1) and many different types are known, each with its own advantages and peculiarities. The most widely employed glycosyl donors at the time of the last comprehensive survey in 1995[12] were the glycosyl halides, followed by the trichloroacetimidates, and the thioglycosides; these as well as the other various classes of glycosyl donor in common use have been systematically reviewed.[87,88] No attempt is made to systematically cover the different classes of glycosyl donor here, but many are illustrated in the examples that follow.

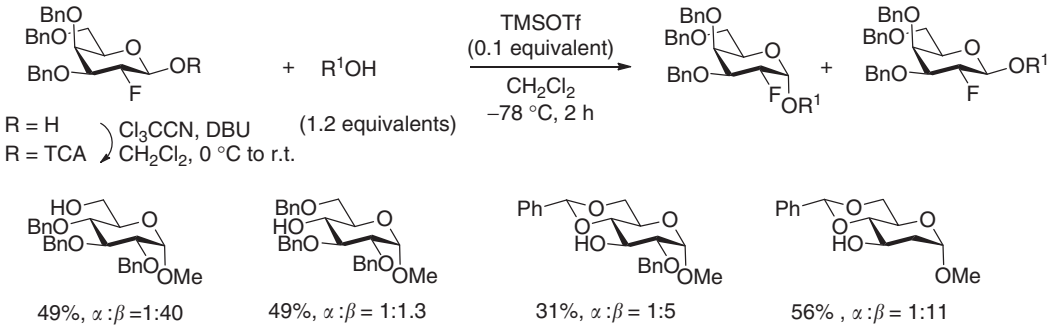
6.01.3.1 The Standard Classes of Glycosidic Bond

In the pyranose series, glycosidic bonds are typically described as 1,2-*trans*-equatorial, 1,2-*trans*-axial, 1,2-*cis*-axial, and 1,2-*cis*-equatorial, with the two *trans*-classes, corresponding to the β-glucosides and the α-mannosides, mostly considered as being relatively straightforward owing to the possibility of employing classical stereodirecting neighboring participation by 2-*O*-esters. The syntheses of the 1,2-*trans*-classes of glycosidic bonds were adequately covered in COS 1,[1] and, as subsequent advances have been limited to incremental steps and in the interest of space and brevity, they will not be covered further here. The two *cis* classes, represented by the β-mannosides and the α-glucosides, however, are considered to be far more difficult to achieve with high selectivity. The 2-deoxy-β-glycosides, the β-arabinofuranosides, the α-sialosides, and the β-glycosides of the uronic acids are also traditionally considered to be difficult classes of glycosidic bond to access in high yield and stereoselectivity. Fittingly, much work in recent years has been directed at these 'difficult' classes of glycosidic bond, to the extent that viable solutions are now available for most of them. These solutions, most of which were not available at the time of publication of COS I,[1] are outlined below.

6.01.3.2 The 2-Deoxy-β-Glycopyranosides

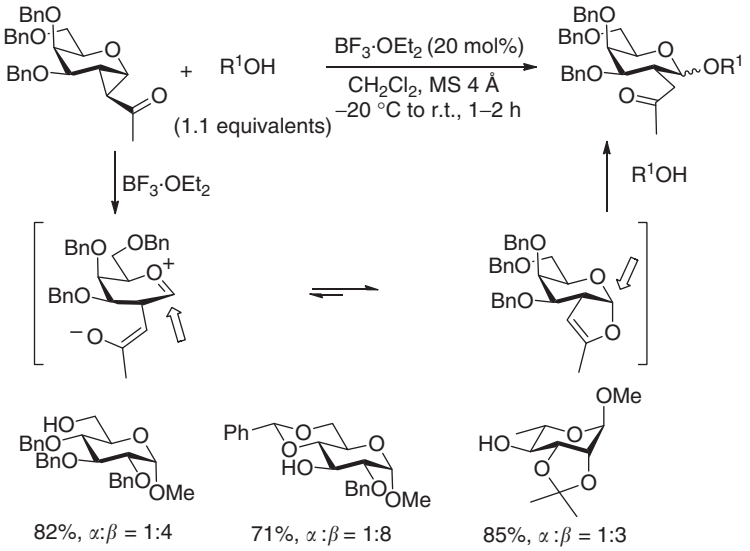
The stereocontrolled synthesis of both anomers of the 2-deoxy glycopyranosides, but more especially the β-series, is complicated by the absence of a C–O bond at the 2-position, as a consequence of which (1) direct advantage cannot be taken of neighboring group participation and (2) donors are strongly armed and prone to the more dissociative end of the mechanistic spectrum and the allied problems of elimination to the glycal. This area has been reviewed numerous times,[89–91] including in COS 1,[1] and most recently in 2009,[92] and as such only a brief overview of recent developments is given here. The most common approach by far, as is evident from the most recent review,[92] remains the use of a stereodirecting auxiliary at the 2-position that is removed reductively postglycosylation, and there has been considerable discussion in the literature as to the mechanisms, actual participation, or simple steric effects by which such auxiliaries, particularly thioethers, exert their influence.[83–85,93] One very interesting variation on this theme revolves around the use of the C–F bond as a powerful stereodirecting group (Scheme 2), resulting in the formation of the 2-deoxy-2-fluoro-β-glycopyranosides (equation 5).[43,94] This system has the clear advantages of high stereoselectivity, small size

of the auxiliary, which obviates the need for its removal, and stabilization of the newly formed glycosidic linkage by the disarming C–F bond. An interesting variation on the participation theme involves the use of *trans*-configured 2,3-oxido thioglycosides, which are activated by Lewis acids and function with migration of the thioether moiety. Either α- or β-2-deoxyglycosides are obtained after removal of the thioether dependent on the configuration of the initial epoxide.



(5)

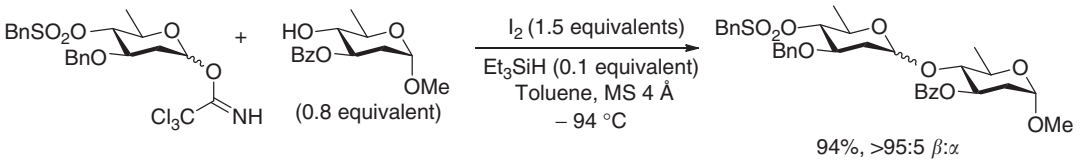
In a further variation on the theme, Shao and coworkers prepared a 1,2-cyclopropaneacetylated-1,2-deoxy-α-D-galactopyranose donor from methyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside and used this novel donor for the stereoselective synthesis of 2-*C*-acetonyl-2-deoxy-D-galactosides under Lewis acid catalysis.[95] Interestingly, the stereochemistry of the reaction may be controlled by the nature of the catalyst. The glycosylation was β-selective with $BF_3{\cdot}OEt_2$ (**Scheme 4**), whereas in the TMSOTf-catalyzed glycosylation the α-anomers are favored. The β-preference using $BF_3{\cdot}OEt_2$ as catalyst was rationalized by the formation of the cyclic enol ether from the zwitterionic intermediate initially formed by neighboring group participation from the C2-bonded acyclic enolate.



Scheme 4

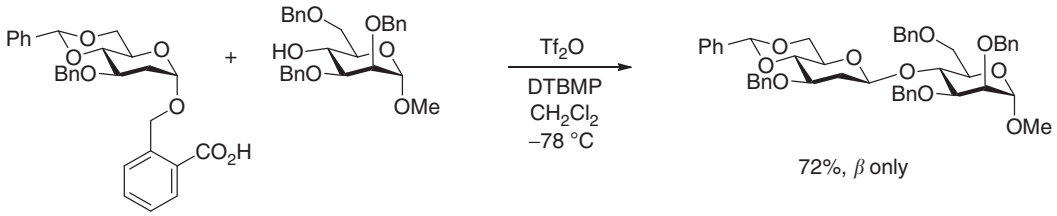
Trans-addition of alcohols across glycals continues to be a major entry into 2-deoxy-β-glycosides.[92] When the electrophile employed is heteroatom-based, the method is in reality a variation on the use of donors bearing temporary auxiliary groups at the 2-position and necessitates a further reductive step after glycosylation. Methods based on the use of protic electrophiles such as the $Ph_3P{\cdot}HBr$ complex[92,96] or a recently introduced thiourea-based organocatalyst are more direct but are typically α-selective,[97] as is true for various organometallic-catalyzed direct additions of alcohols.[98,99]

Direct approaches avoiding the use of temporary stereodirecting groups are of course preferable in terms of limitation of steps and overall efficiency, and good progress has been made in this area. For example, it has been demonstrated that the use of a powerfully disarming sulfonyl group at the 3-position of a 2,6-dideoxyglucopyranosyl donor is effective at directing glycosylation toward formation of the β-isomer (equation 6).[100] In this procedure activation of the trichloroacetimidate donor was achieved with HI generated *in situ* from iodine and triethylsilane.[100]



(6)

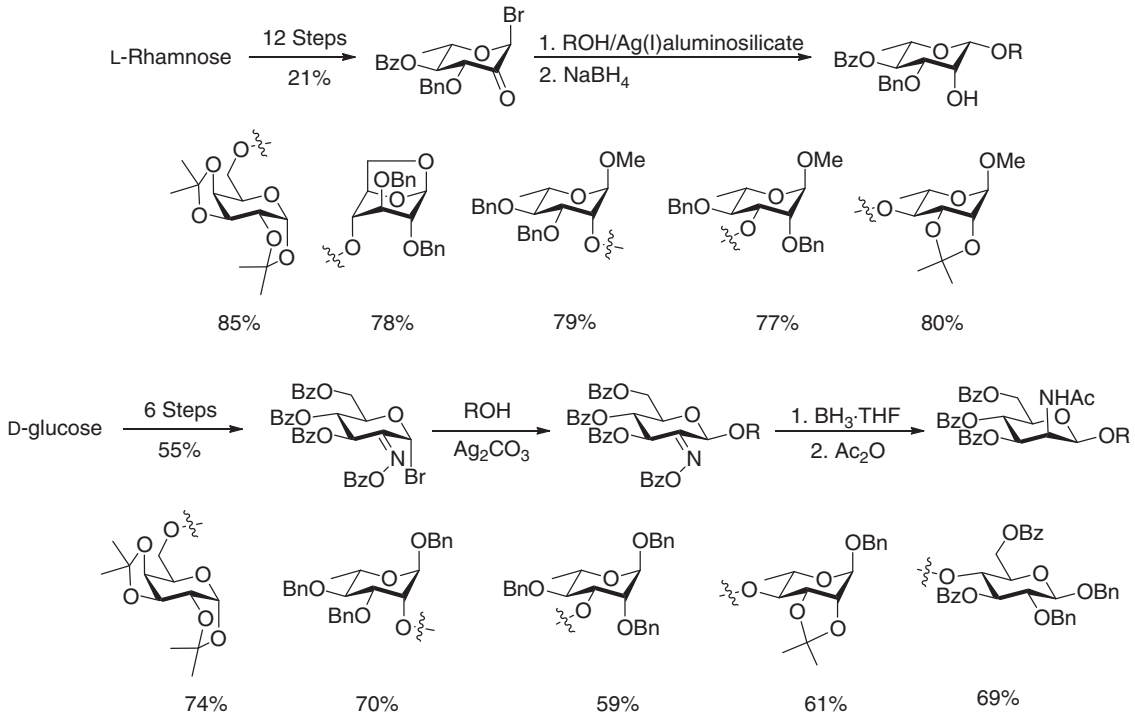
In conjunction with the use of a 4,6-*O*-benzylidene acetal protecting group, the 2-carboxybenzyl series of glycosyl donors have been found, on activation with triflic anhydride at −78 °C, to afford primarily *β*-glycosides (equation 7);[101] in the absence of the benzylidene acetal, stereoselectivities were notably lower. Related work on the generation of 2-deoxy-*β*-glucosides using 4,6-*O*-benzylidene acetal-protected donors has been reported by other groups using different donor classes,[102] most notably the glycosyl phosphites.[103]



(7)

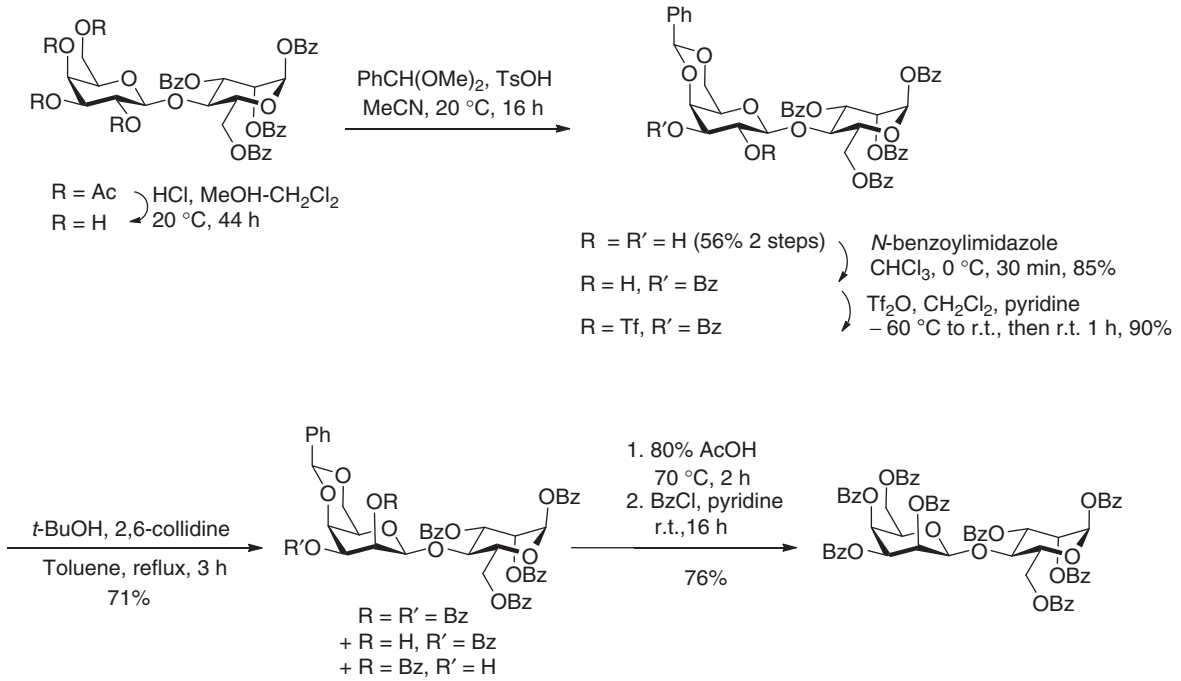
6.01.3.3 The 1,2-*cis*-Equatorial Glycopyranosides

The problem of the selective synthesis of the 1,2-*cis*-equatorial glycopyranosides arises from the need to overcome steric shielding of the *β*-face of the donor by the axial group at C2 and the need to avoid any active participation from groups at that position. Before the mid-1990s when viable practical solutions were introduced, the most reliable approaches to this class of glycosidic bond were indirect ones and depended on the synthesis of selectively protected 1,2-*trans*-equatorial glycosides followed by inversion at C2, either by oxidation/reduction or by S_N2 displacement. These methods, which continue to be used in some laboratories[104,105], and the use of insoluble silver salts in conjunction with glycosyl bromides, have been reviewed numerous times.[106–113] Lichtenthaler's ulosyl bromide approach was a considerable improvement on these classical methods as it reduced the number of steps postglycosylation to a single stereocontrolled reduction, and it remains a valuable route particularly for the synthesis of the *β*-rhamnopyranosides and in the mannosamine series (Scheme 5).[114]



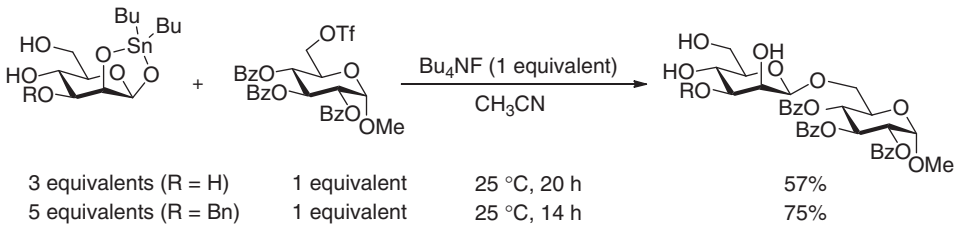
Scheme 5

The S_N2 approach to inversion at C2 remains viable when conducted concomitantly with inversion at C4 as this leads to the β-talopyranosides (Scheme 6), which are not accessible by the recent direct methods.[115–117]



Scheme 6

Kováč devised a clever adaptation of Schuerch's stannylene acetal approach to the β-mannosides that obviated the need for the use of protecting groups in the 'donor' but which, in view of the long reaction times required, can only be considered a solution for primary 'acceptors' (equation 8).[118]

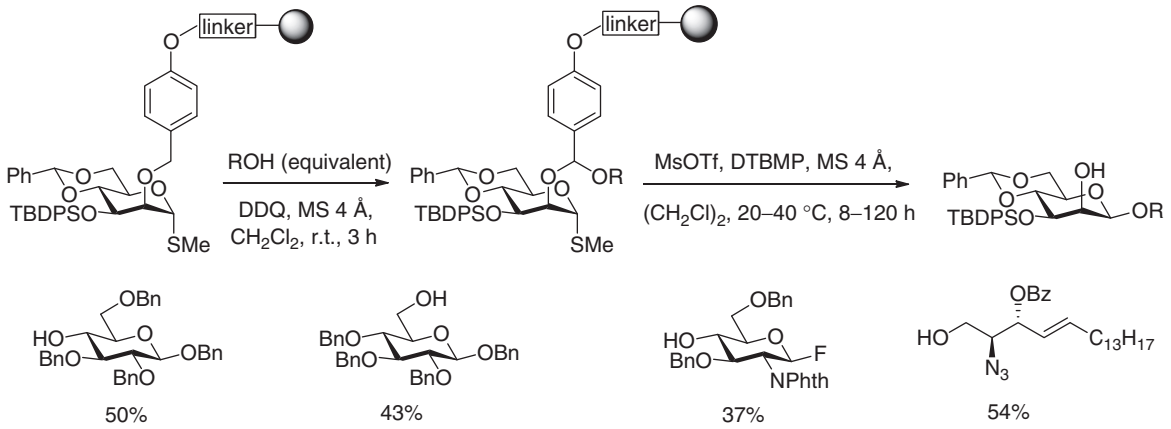


(8)

The intramolecular aglycone delivery (IAD) method, in which the acceptor is first tethered covalently to O2 by a suitable linker before cyclization onto the activated anomeric position, provided the first reliable method for the synthesis of the β-mannopyranosides with essentially complete control of stereoselectivity. The initial version of IAD, by Barresi and Hindsgaul[119–121] with improvements by the Fairbanks group,[122,123] employed mixed alkylidene acetals as the tether, whereas the Stork variation on the theme used the more accessible silylene acetals.[124–125] The most practical and widely applied IAD method, however, was introduced by Ito and Ogawa and relies on the oxidation of a 2-*O*-*p*-methoxybenzyl ether with dichlorodicyanoquinone (DDQ) in the presence of the acceptor alcohol for formation of the tether.[126] Although appendage of the acceptor to the donor in this manner results in the formation of a mixture of two stereoisomers, it was demonstrated that this is of no consequence as smooth, stereoselective formation of the β-glycoside occurs from both isomers.[127] When the tether additionally functions as a linker to a solid-support, the method enables polymer-supported oligosaccharide syntheses in which cleavage from the support is coupled with the highly stereoselective introduction of a β-mannoside linkage (Scheme 7).[128,129]

A subsequent variant on the theme, employing 2-*O*-naphthylmethyl ethers as oxidizable tether precursors,[130] has been employed for the synthesis of the β-L-rhamnopyranosides (Scheme 8).[131] A number of other tethers of varying lengths and bound to other positions around the donor and acceptor rings have been investigated for IAD, and are covered in several reviews on the topic,[132–134] but none have the generality and/or selectivity of the initial concept of transfer through a five-membered ring.

The use of donors protected with a 4,6-*O*-benzylidene acetal and ether groups at O2 and O3 provides a means for the direct formation of the β-mannopyranosides in high yield and selectivity in a single step. Initially developed using glycosyl sulfoxides as



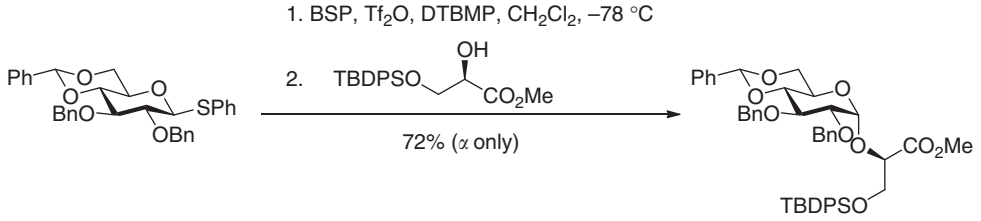
Scheme 7

donors,[135–137] the method was subsequently extended to the use of the corresponding thioglycosides with activation by the combination of trifluoromethanesulfonic anhydride with either 1-benzenesulfinyl piperidine[138] or diphenyl sulfoxide,[139] and related thiophilic systems.[140–144] Other types of donor, including trichloroacetimidates,[145] phosphates,[146] pentenoates,[147] carboxybenzyl glycosides,[148] and hemiacetals[149], and the like,[150–152] have also proven amenable to β-mannoside formation in conjunction with the use of suitable – usually but not exclusively triflate-based – electrophilic species provided the 4,6-*O*-benzylidene acetal or a surrogate is used to lock the conformation of the donor. The method, which has been reviewed,[56,153] relies on the *in situ* formation of a highly reactive but observable intermediate, typically an α-glycosyl triflate, that is displaced by the acceptor alcohol through a highly associated transition state that resembles an S_N2 reaction.[39] A number of oligosaccharides have been constructed by this method including various mannans,[113] such as the *Candida albicans* β-(1→2)-mannan (**Scheme 9**)[154] and the common-core of the *N*-linked glycoproteins (**Scheme 10**).[155,156]

Direct access to the 6-deoxy-β-mannopyranosides, or β-rhamnopyranosides, and their higher carbon sugar analogs by the benzylidene acetal-directed method is not possible owing to the absence of a hydroxyl group at the 6-position. Solutions to this problem include the use of mannosyl donors carrying modified acetals that enable regioselective reductive removal of the C6–O6 bond following glycosylation,[157,158] or acetal-protected 6-deoxy-6-thia mannosyl donors from which the sulfur atom is removed with Raney-nickel following glycosylation (**Scheme 11**).[159] Alternative but less selective approaches to the direct synthesis of the β-rhamnopyranosides employ donors carrying strongly electron-withdrawing but nonparticipating protecting groups on O2 such as sulfonate esters.[160,161]

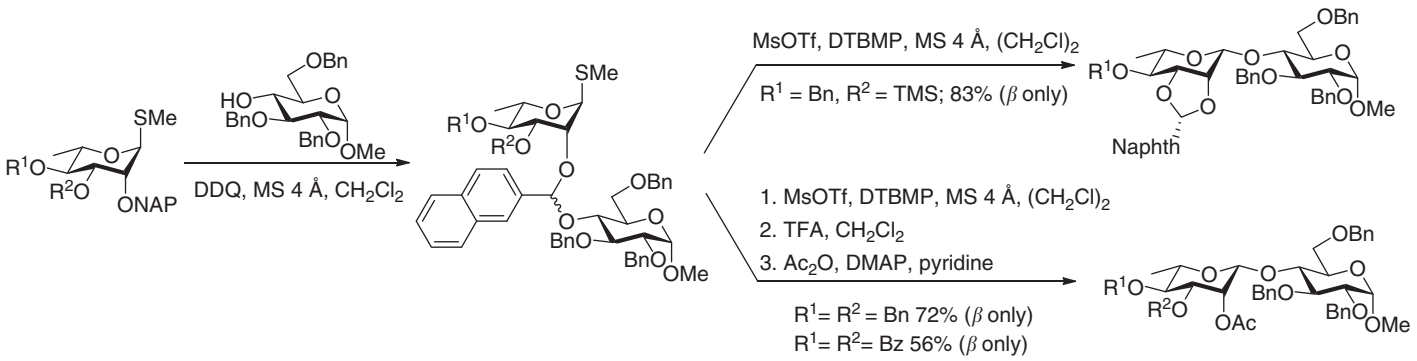
6.01.3.4 The 1,2-*cis*-Axial Glycopyranosides

The 1,2-*cis*-axial glycopyranosides, typified by the α-galacto- and α-glucopyranosides, are traditionally accessed by glycosylation in the absence of neighboring group participation from the 2-position. However, as straightforward as this approach may be, selectivities are rarely optimal, especially in the gluco-series. The use of a 4,6-*O*-benzylidene acetal in conjunction with benzyl ethers at positions 2 and 3 was found to give enhanced α-selectivity (equation 9)[162–164] through a process now recognized as involving the S_N2-like displacement of a transient β-glycosyl triflate.[39]

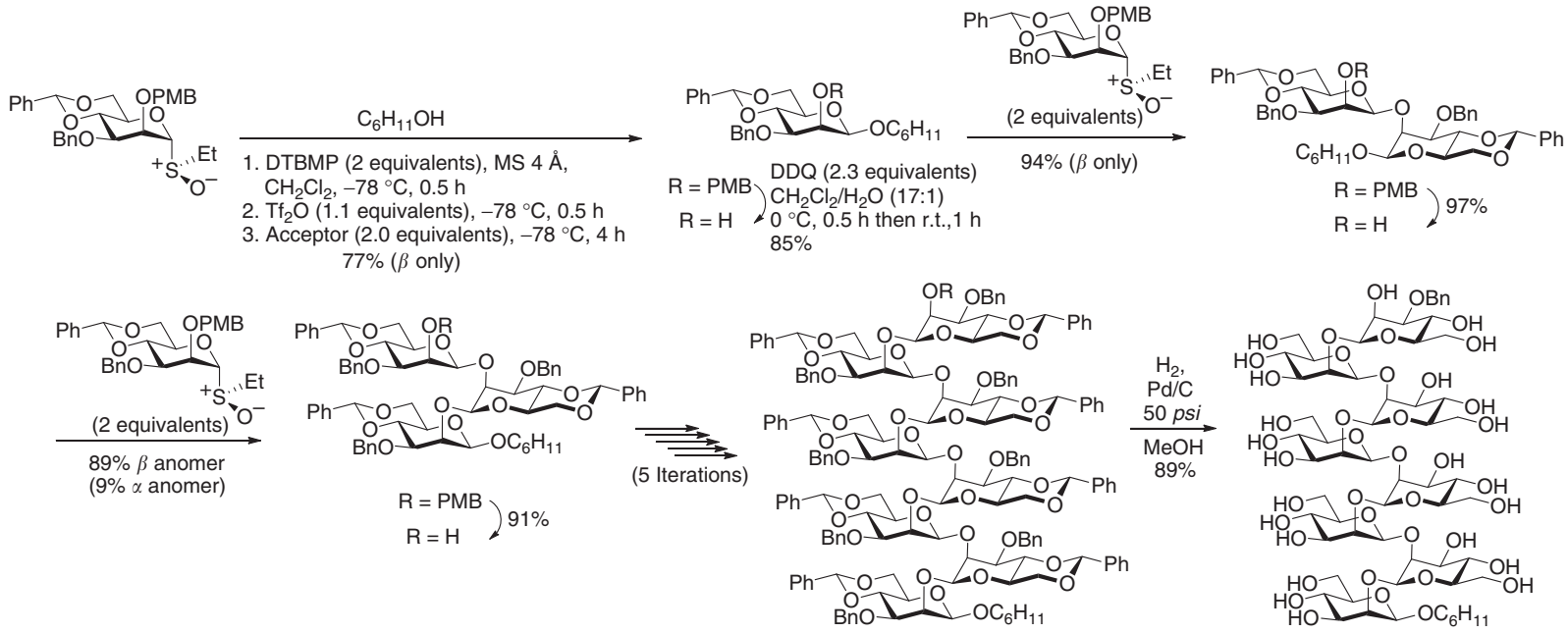


(9)

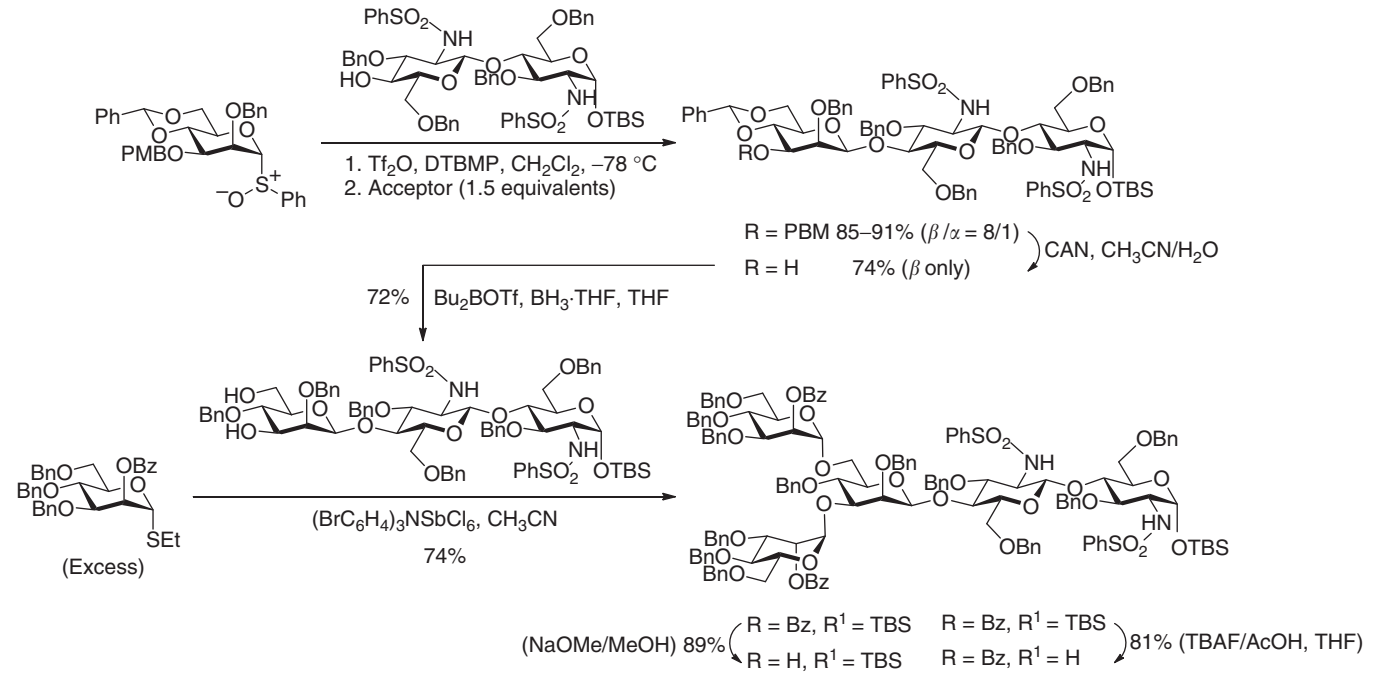
Both the 4,6-*O*-benzylidene acetals and the 4,6-*O*-silylene acetals have been found to be highly α-directing in the galactopyranose series, sometimes even to the extent of overcoming neighboring group participation from the 2-position (equation 10).[165–167]


SMe
R1O
R2O
ONAP
OBn
HO
BnO
BnO
OMe
DDQ, MS 4 Å, CH2Cl2
SMe
R1O
R2O
O
OBn
O
BnO
BnO
OMe
MsOTf, DTBMP, MS 4 Å, (CH2Cl)2
R1 = Bn, R2 = TMS; 83% (β only)
OBn
R1O
O
O
O
BnO
BnO
OMe
Naphth
1. MsOTf, DTBMP, MS 4 Å, (CH2Cl)2
2. TFA, CH2Cl2
3. Ac2O, DMAP, pyridine
R1= R2 = Bn 72% (β only)
R1= R2= Bz 56% (β only)
OBn
R1O
R2O
OAc
O
O
BnO
BnO
OMe

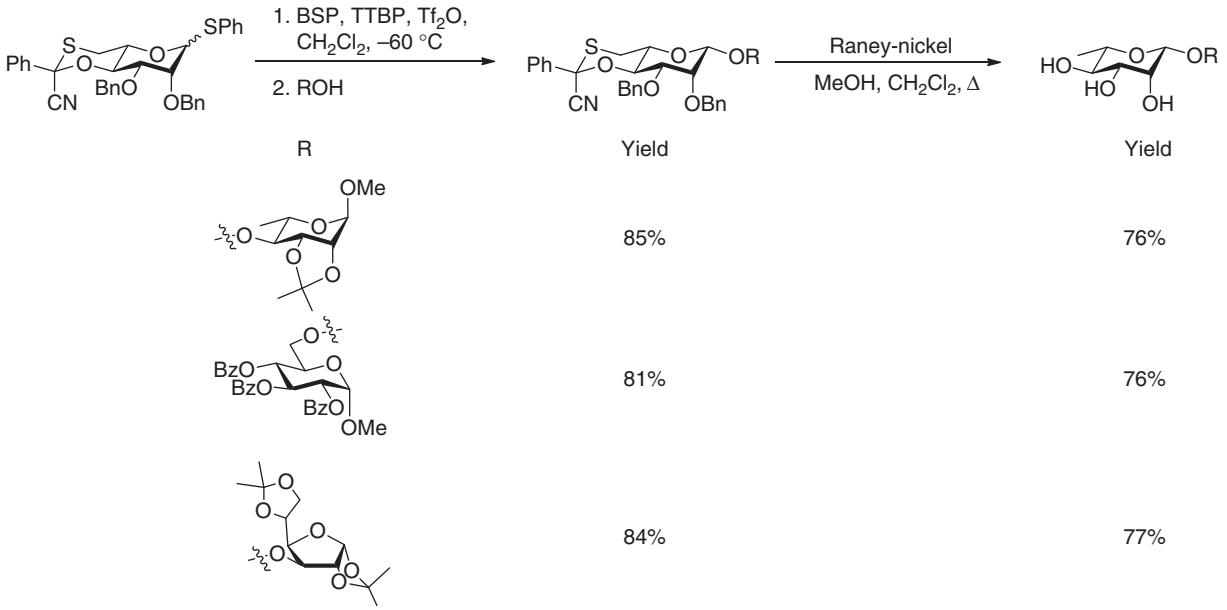
Scheme 8


C6H11OH
1. DTBMP (2 equivalents), MS 4 Å, CH2Cl2, –78 °C, 0.5 h
2. Tf2O (1.1 equivalents), –78 °C, 0.5 h
3. Acceptor (2.0 equivalents), –78 °C, 4 h
77% (β only)
R = PMB
R = H
DDQ (2.3 equivalents)
CH2Cl2/H2O (17:1)
0 °C, 0.5 h then r.t.,1 h
85%
(2 equivalents)
94% (β only)
R = PMB
R = H
97%
(2 equivalents)
89% β anomer
(9% α anomer)
R = PMB
R = H
91%
(5 Iterations)
H2,
Pd/C
50 psi
MeOH
89%

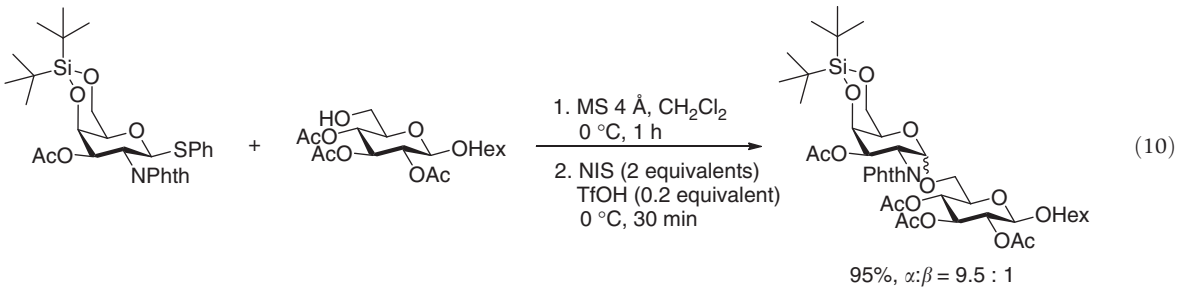
Scheme 9


1. Tf2O, DTBMP, CH2Cl2, –78 °C
2. Acceptor (1.5 equivalents)
R = PBM 85–91% (β/α = 8/1)
R = H 74% (β only)
CAN, CH3CN/H2O
72%
Bu2BOTf, BH3·THF, THF
(Excess)
(BrC6H4)3NSbCl6, CH3CN
74%
(NaOMe/MeOH) 89%
R = Bz, R1 = TBS
R = H, R1 = TBS
R = Bz, R1 = TBS
R = Bz, R1 = H
81% (TBAF/AcOH, THF)

Scheme 10



Scheme 11

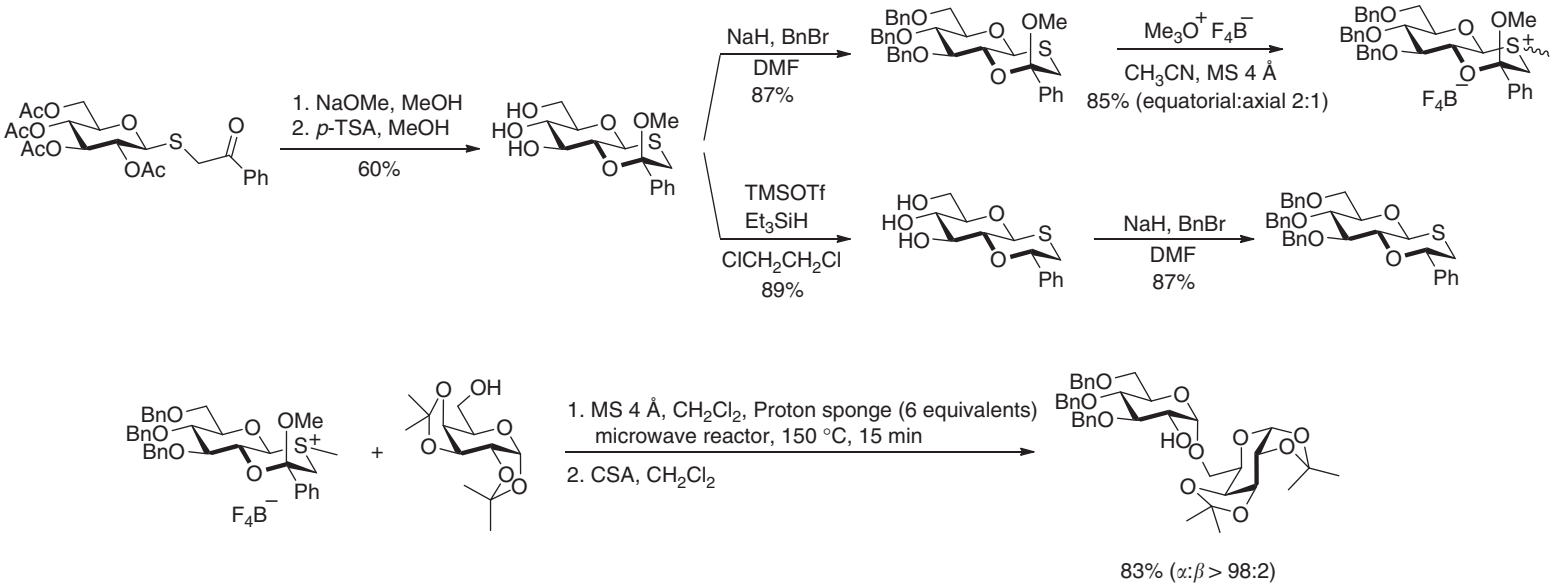


(10)

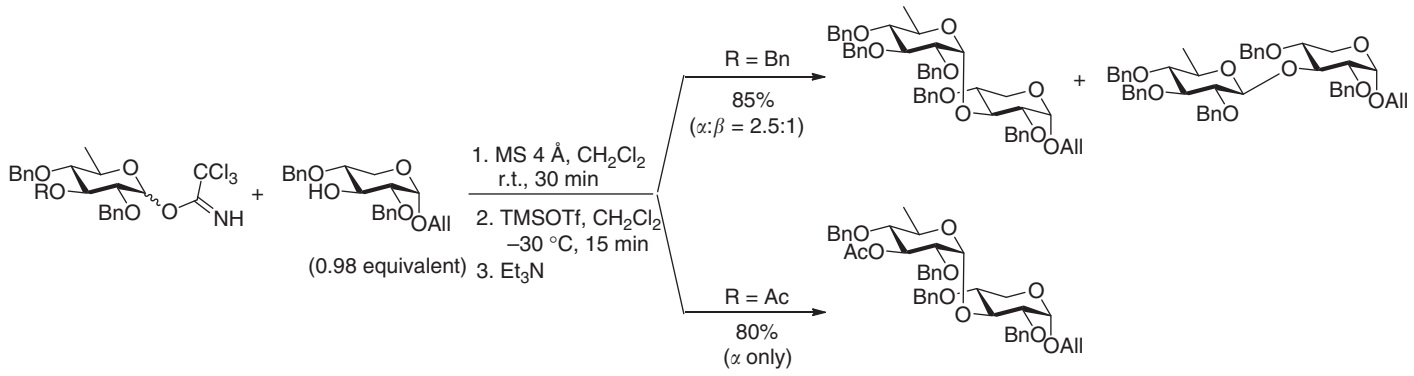
Boons and coworkers developed an ingenious entry into the α-galacto- and glucopyranosides based on participation by 2-*O*-(1*S*-phenyl-2-phenylthioethyl) auxiliary. Participation by the phenylthio group leads to the formation of a *trans*-decalin-like bicyclo[4.4.0]sulfonium ion in which the sulfonium group is equatorial to the original pyranoside ring and in which the phenyl group of the auxiliary occupies an equatorial site in the newly formed ring. Displacement of the sulfonium ion by the incoming acceptor is then considered to lead to the axial glycoside with excellent selectivity.[80,168] The method has been applied successfully in the polymer-supported synthesis of an α-glucan.[169] Turnbull and coworkers have introduced an elegant modification of the method that avoids the necessity for the use of a stoichiometric chiral auxiliary, relying instead on acetal formation between a free hydroxyl group at the 2-position and a β-configured *S*-phenacyl thioglycoside (**Scheme 12**).[86,170] The bicyclic sulfide may be activated either by conversion to the sulfoxide or by reaction with a benzyne.[170,171] A related concept employs 2-*O*-(2-pyridylmethyl) ethers as participating groups in glycosylation reactions, proceeding through the intermediacy of cyclic pyridinium ions. However, in such cases the *trans*-fused equatorial β-pyridinium ions are highly stable and not readily displaced, whereas the *cis*-fused α-pyridinium ions are somewhat more reactive and thus provide an entry into equatorial glycosides.[172]

An alternative approach to the 1,2-*cis*-axial glycosides, first noted for the 1,2-*trans*-axial glycosides and which appears not to involve active participation,[56] is the use of an ester group at the 3-position (**Scheme 13**).[173]

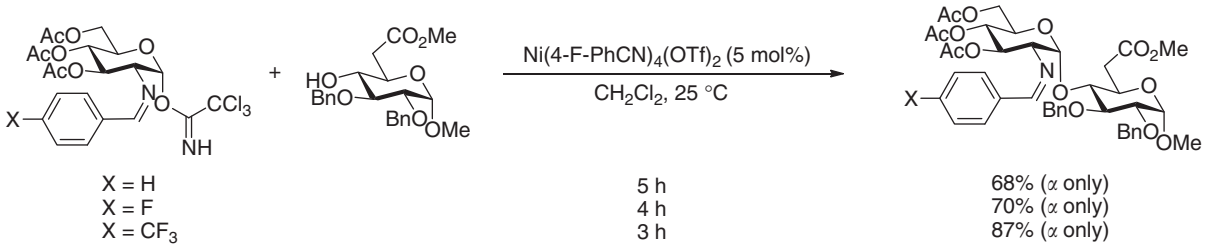
In the 2-amino-2-deoxy glucosamine series the azide function has traditionally been regarded as the optimal protecting group for the amine when the α-glycoside is required and was the group of choice in the landmark synthesis of the heparin pentasaccharide by Sinaÿ and coworkers,[174] and in modular approaches to related targets.[175] However, the use of benzylidene imines in conjunction with the nickel-catalyzed activation of α-glycosyl trichloroacetimidates has been introduced and is reported to be more α-selective (equation 11).[176] A promising IAD method using an aminal tether has also been developed but has yet to be widely applied.[177]


1. NaOMe, MeOH
2. p-TSA, MeOH
60%
NaH, BnBr
DMF
87%
Me3O+ F4B−
CH3CN, MS 4 Å
85% (equatorial:axial 2:1)
TMSOTf
Et3SiH
ClCH2CH2Cl
89%
NaH, BnBr
DMF
87%
1. MS 4 Å, CH2Cl2, Proton sponge (6 equivalents)
microwave reactor, 150 °C, 15 min
2. CSA, CH2Cl2
83% (α:β > 98:2)

Scheme 12


BnO
RO
BnO
O
CCl3
NH
+
BnO
HO
BnO
OAll
(0.98 equivalent)
1. MS 4 Å, CH2Cl2
r.t., 30 min
2. TMSOTf, CH2Cl2
–30 °C, 15 min
3. Et3N
R = Bn
85%
(α:β = 2.5:1)
R = Ac
80%
(α only)
AcO
OAll
+

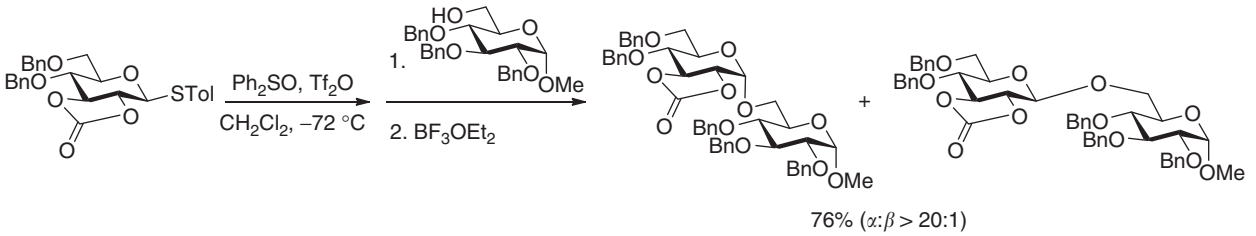
Scheme 13



(11)

The most noteworthy advance in the synthesis of the 2-amino-2-deoxy-α-glycopyranosides, however, has been the introduction of a cyclic carbamate group (oxazolidinone) spanning N2 and O3, which has evolved into a method for highly α-selective glycosidic bond synthesis (**Scheme 14**).[178–181]

Although the reasons for this selectivity remain unclear at the present time, it has been demonstrated that the 2-*N*,3-*O*-oxazolidinone group facilitates anomerization of β-to α-glycosides,[180,182] which it strongly favors thermodynamically, and does so via an endocyclic cleavage mechanism.[180,183–184] In a similar manner, cyclic carbonates spanning O2 and O3 in glucopyranosyl donors, reported to be moderately β-selective under kinetic conditions,[185] have been shown to be highly α-selective when the glycosylation is conducted in the presence of a Lewis acid (equation 12).[186] *cis*-Fused 2,3-*O*-carbonates in the manno- and rhamnopyranosides are also strongly α-directing but for different reasons.[56]



(12)

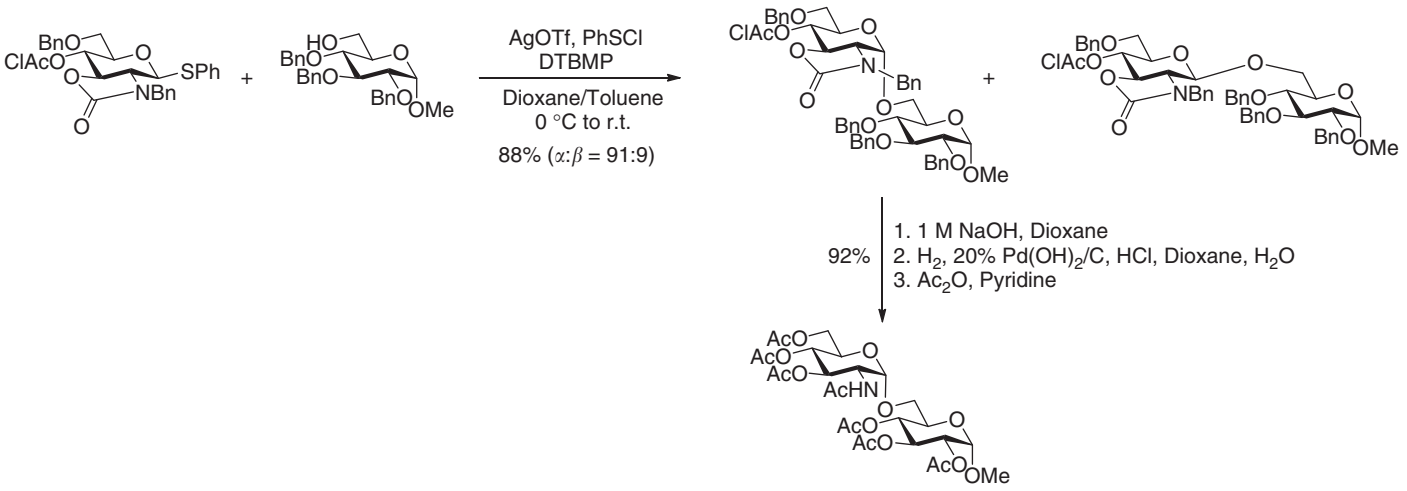
6.01.3.5 The Uronic Acid Glycosides

The uronic acid glycosides, whose chemistry has been reviewed,[187] are widespread in nature and present an interesting and challenging problem in synthesis because of the presence of the carboxylate moiety. The carboxylate functionality can be introduced before the glycosylation, which presents the need for a suitable protecting group and raises the problem of reduced donor reactivity owing to the presence of an electron-withdrawing ester group. Recent work, however, shows that at least in the mannuronic acid series the presence of the carboxylate ester is not disarming and provides a donor with comparable reactivity to that of a perbenzylated mannosyl system.[188] Alternatively, the carboxylate moiety can be introduced after the glycosylation, which side-steps the problem of altered donor reactivity but at the expense of the need for selective protection of the 6-OH and of postglycosylation oxidation.

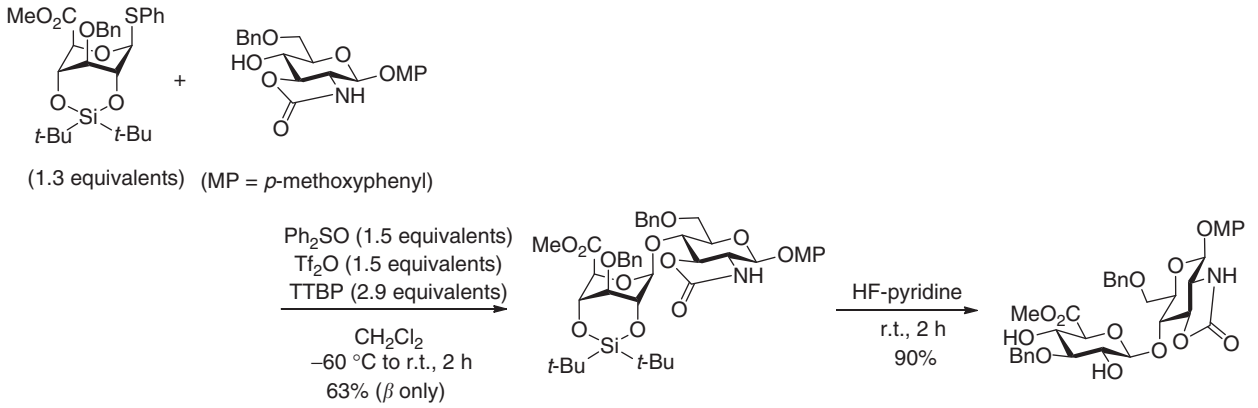
An elegant approach to the β-glucuronides, reported by Hinou and coworkers, takes advantage of a 2,4-*O*-silylene acetal to lock the pyranoside ring in an inverted $^1C_4$ conformation, which has the advantage of activating the donor because of the multiple axial C–O bonds and of providing extremely high levels of β-selectivity owing to the bicyclic nature of the system. The silylene acetal is removed postglycosylation by treatment with HF/pyridine (**Scheme 15**).[189]

A particularly interesting example of β-glucuronide synthesis was presented by the Gin group in the course of a synthesis of the immunoadjuvant QS-21A$_{api}$ in the course of which a first β-glucuronide was constructed by means of Gin's modification[190,191] of the Danishefsky glycal assembly method (**Scheme 16**).[192] The product of this coupling was converted to a trisaccharyl trichloroacetimidate by standard means and this latter was coupled to the pentacyclic triterpenoid core on activation with tris(pentafluorophenyl)boron giving the desired β-glucuronide in good yield with high β-selectivity (**Scheme 16**).[193] No explanation for the high selectivity of this process was advanced and model studies with simpler alcohols and other Lewis acids gave much less selective couplings.

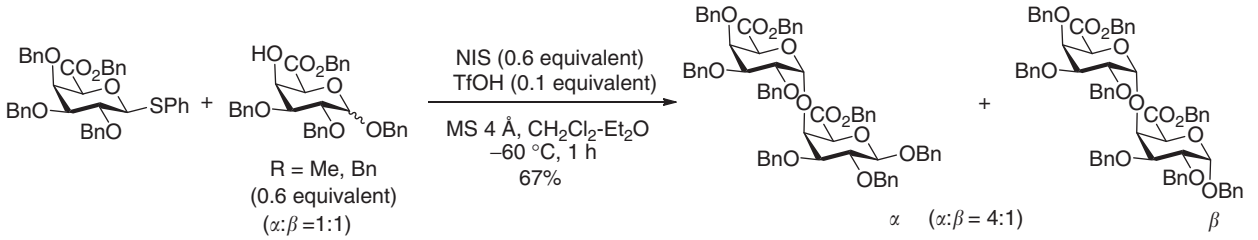
An example of the formation of an α-galacturonoside is taken from the work of Doutheau and coworkers on the synthesis of homogalacturonan fragments (equation 13).[194] This example is noteworthy because of the use of the urinate moiety in both the donor and acceptor and the demonstration, through competition experiments, of the differing reactivity of the two anomers of the acceptor alcohol.


AgOTf, PhSCl
DTBMP
Dioxane/Toluene
0 °C to r.t.
88% (α:β = 91:9)
92%
1. 1 M NaOH, Dioxane
2. H2, 20% Pd(OH)2/C, HCl, Dioxane, H2O
3. Ac2O, Pyridine

Scheme 14



Scheme 15



(13)

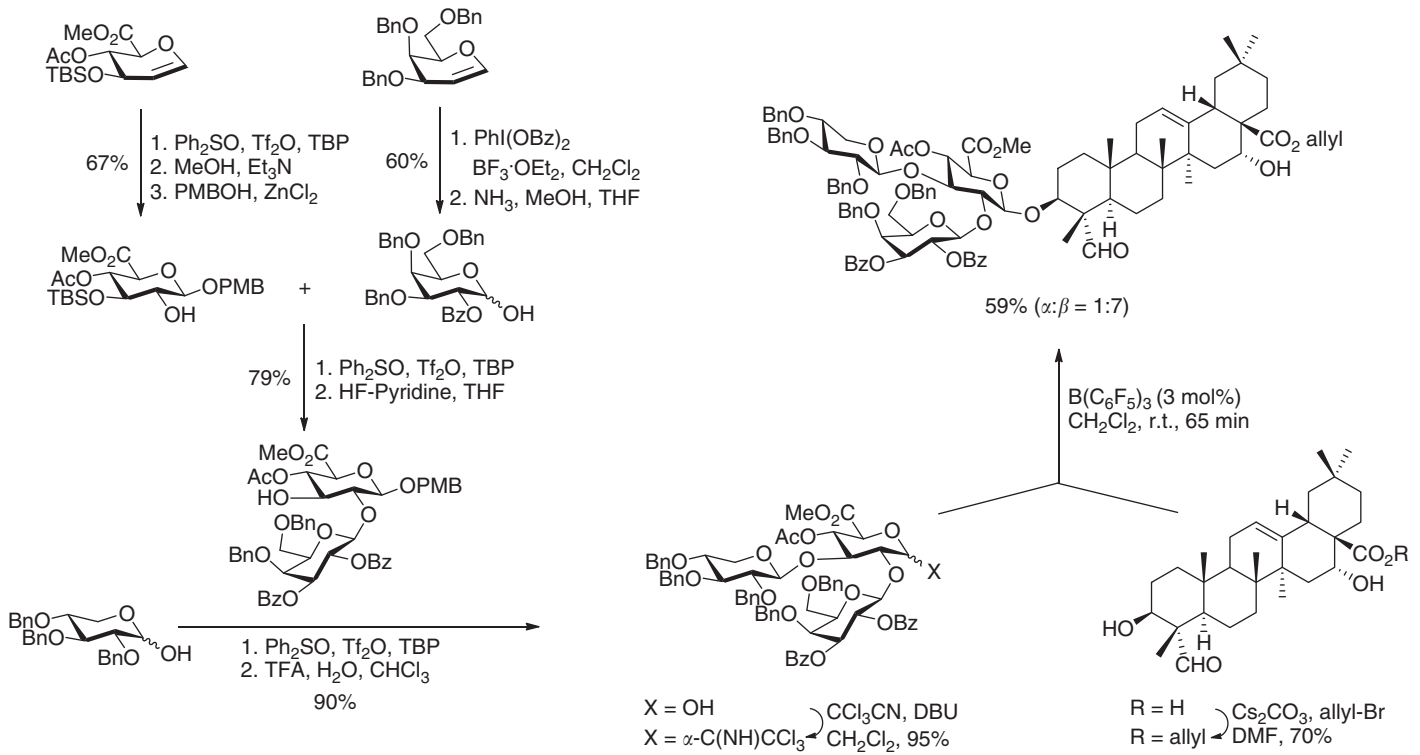
In the mannuronic acids, it has been demonstrated that preactivation of thioglycosides with the combination of diphenyl sulfoxide and triflic anhydride leads to the formation of an α-glycosyl triflate in the usual manner. Unusually, however, this glycosyl triflate exists as a mixture of two equilibrating chair conformers in which the inverted $^1C_4$ form predominates, thereby providing the first example of an observable equatorial glycosyl triflate. The authors hypothesize that the highly β-selective couplings observed on subsequent addition of an acceptor alcohol take place either through an S_N2 displacement of the covalent triflate or through β-selective attack on the preferred $^3H_4$ conformer of the closely related glycosyl oxocarbenium ion (Scheme 17).[195] A number of β-configured 2-amino-2-deoxy and 2,3-diamino-2,3-dideoxymannuronic acid glycosides were synthesized.[196,197] Additionally, the method has been shown to function with polymer-supported acceptors.[198]

6.01.3.6 The α-Sialosides

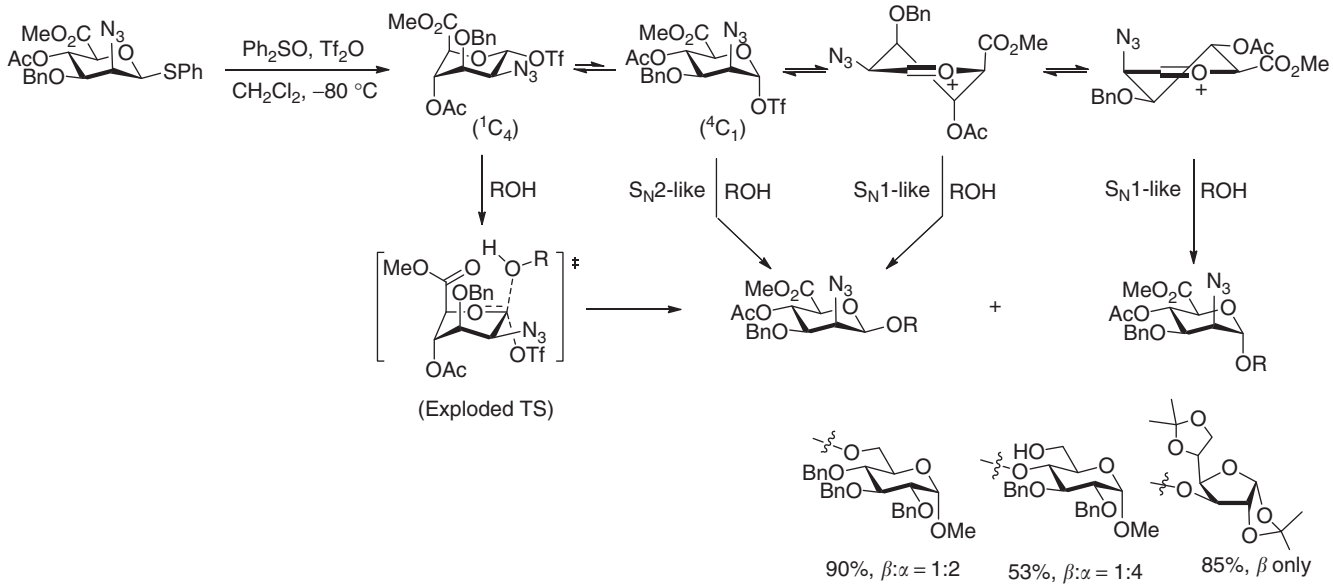
The α-sialosides are another class of equatorial glycosidic bond with the reputation of being extremely difficult to prepare selectively and in high yield, owing to their deoxyketose nature and their propensity toward glycal-forming elimination. Much of the early work in the area employed either auxiliaries at the 3-position with which to direct glycosylation, followed by their reductive removal, or glycosylation by means of electrophile-mediated addition across a 2,3-glycal with subsequent reductive removal of the electrophilic group. Stereodirecting participation by auxiliaries appended to the carboxylate moiety, either in the form of esters or as reduced derivatives, has also been investigated.[199,200] However, these methods, which are largely documented in a number of extensive reviews of the area,[201–204] have been displaced by direct approaches taking advantage of acetonitrile as a participating solvent or, more recently, the strong equatorial directing effect of an oxazolidinone group used to protect O4 and N5.

Most of the major classes of glycosyl donor have been employed in the sialic acid field, with the exception of the trichloroacetimidates and the sulfoxides, both of which are apparently too unstable to isolate. The description of the sialyl *N*-phenyltrifluoroacetimidates by the Yu group as stable entities, which can be activated with TMSOTf at low temperatures (Scheme 18), has provided a viable alternative to the trichloroacetimidates in the area.[205]

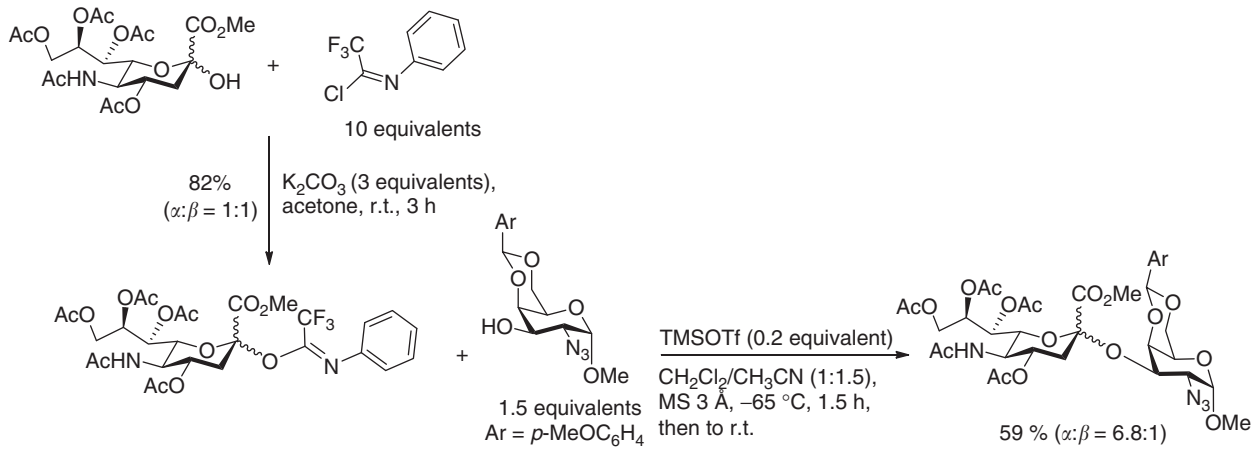
The example in Scheme 18 is typical of most work in the area in recent years in so far as, following the initial observations of Hasegawa,[65] it is conducted in a solvent mixture rich in acetonitrile. This solvent is considered to participate in the glycosylation reaction by the trapping of intermediate oxocarbenium ions with the formation of an axial glycosyl nitrilium ion that is subsequently displaced in an invertive manner by the incoming acceptor alcohol. Although this appears to be a reasonable explanation for the phenomenon, spectroscopic evidence in support of it remains thin,[71] and alternative explanations have been proposed.[206] The use of other participating solvents has been explored but has yet to find broad application.[207] Okamoto and Kajihara, extending the use of sialyl phosphites originally introduced by the Schmidt and Wong groups,[208,209] described the use of sialyl *N*-methyl amides as systems providing high α-selectivity in the absence of acetonitrile (Scheme 19).[210] The system was considered


MeO2C
AcO
TBSO
BnO
OBn
67%
1. Ph2SO, Tf2O, TBP
2. MeOH, Et3N
3. PMBOH, ZnCl2
60%
1. PhI(OBz)2
BF3·OEt2, CH2Cl2
2. NH3, MeOH, THF
OPMB
OH
BzO
+
79%
1. Ph2SO, Tf2O, TBP
2. HF-Pyridine, THF
HO
OBz
1. Ph2SO, Tf2O, TBP
2. TFA, H2O, CHCl3
90%
CO2Me
CO2 allyl
CHO
59% (α:β = 1:7)
B(C6F5)3 (3 mol%)
CH2Cl2, r.t., 65 min
X = OH
X = α-C(NH)CCl3
CCl3CN, DBU
CH2Cl2, 95%
R = H
R = allyl
Cs2CO3, allyl-Br
DMF, 70%

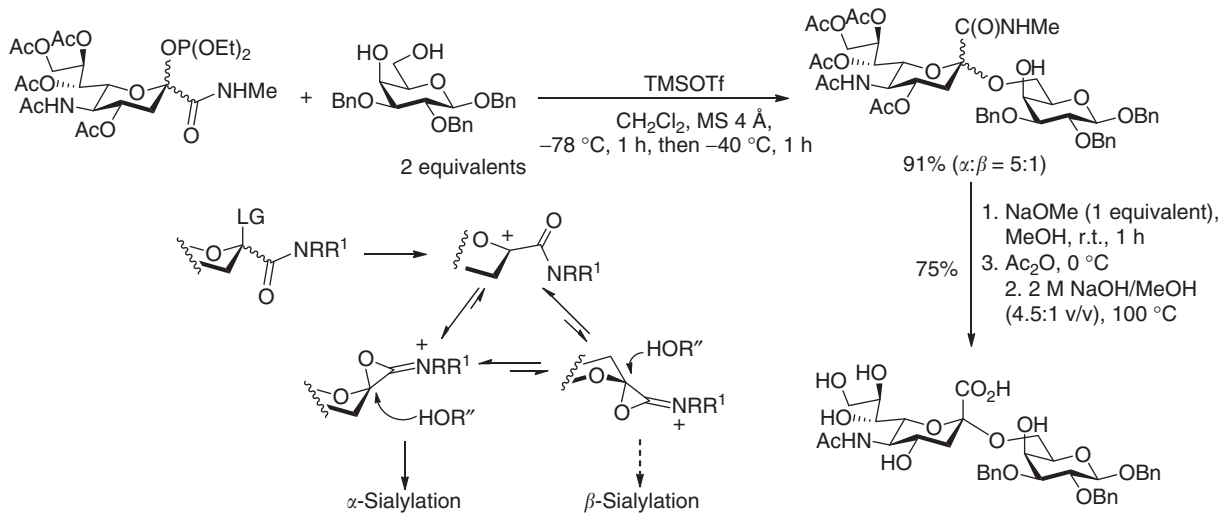
Scheme 16


Ph2SO, Tf2O
CH2Cl2, –80 °C
(1C4)
(4C1)
ROH
SN2-like
SN1-like
(Exploded TS)
90%, β:α = 1:2
53%, β:α = 1:4
85%, β only

Scheme 17



Scheme 18

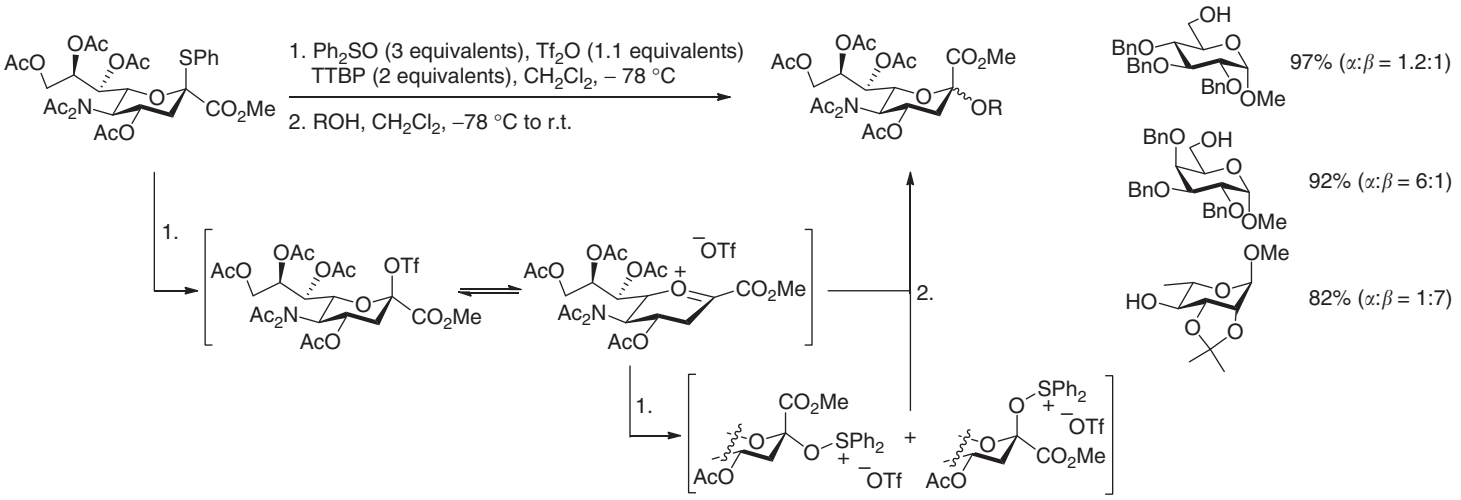


Scheme 19

to achieve selectivity by participation of the secondary amide group, which could be cleaved by treatment with methanolic sodium hydroxide following glycosylation.

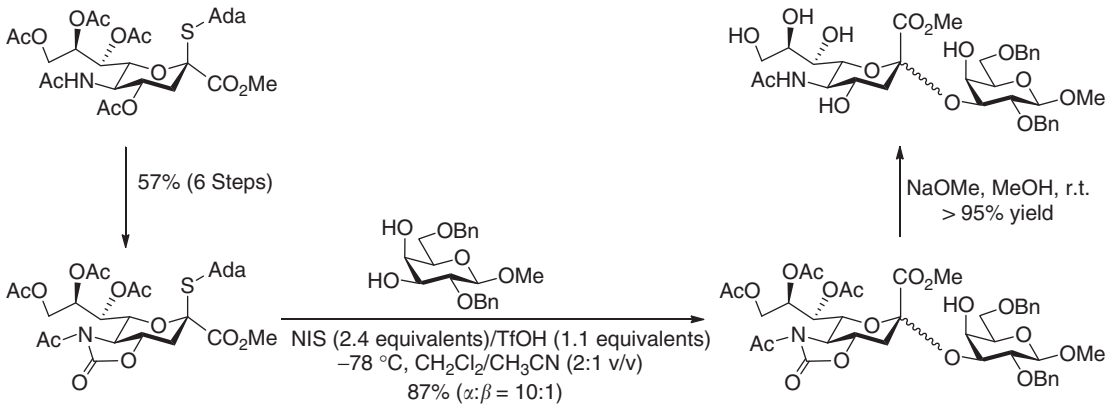
Crich and Li, employing a sialyl thioglycoside as donor and the diaryl sulfoxide/Tf_2O-activating system, were able to obtain moderate-to-good α-selectivities working in dichloromethane at low temperature in the absence of acetonitrile (**Scheme 20**).[211] Low-temperature NMR studies demonstrated for the first time in the sialic acid field the formation of observable intermediates, ascribed to two anomeric glycosyl oxysulfonium ions resulting from the trapping the glycosyl oxocarbenium ion by the excess of sulfoxide employed.

Beginning with the work of Demchenko and Boons on the *N*,*N*-diacetyl donors,[212,213] a number of workers reported the beneficial effect of use of sialosyl donors bearing strongly electron-withdrawing protecting groups on N5 for the formation of the equatorial glycosides. Thus, the *N*-trifluoroacetamides,[214–216] the 5-deamino-5-azido system,[217,218] the *N*-trichloroethylcarbamates,[219–221] and the *N*-phthalimido-based donors[222] were all shown to exhibit higher α-selectivity than the usual acetamide. The effect of the N5 protecting group on sialyl donor reactivity selectivity has been reviewed,[223] and attributed by various authors to various effects. Thus, for example, Fukase and coworkers attribute the beneficial stereodirecting effect of the phthalimido group to the stabilization of the intermediate glycosyl oxocarbenium ion by the dipole of the protecting group,[222] whereas Kononov and coworkers have advanced evidence in support of the disruption of intermolecular hydrogen bonding networks as the main reason underlying increased activity.[74,206,213,224] The most important advance in sialic acid glycosylation has been the introduction of the O4,N5-cyclic carbamate protecting group, which locks up these atoms in the form of an oxazolidinone ring. The system was introduced by the Takahashi and De Meo groups, both of whom showed high levels of α-selectivity using thioglycoside-based donors with a range of acceptor alcohols.[225,226] Crich and Li described the corresponding *N*-acetyl oxazolidinones, which also show excellent selectivity, and have the additional advantage of requiring milder conditions for


1. Ph_2SO (3 equivalents), Tf_2O (1.1 equivalents)
TTBP (2 equivalents), CH_2Cl_2, – 78 °C
2. ROH, CH_2Cl_2, –78 °C to r.t.
97% (α:β = 1.2:1)
92% (α:β = 6:1)
82% (α:β = 1:7)
(Intermediates observed by low temperature NMR)

Scheme 20

cleavage of the oxazolidinone while leaving in place the physiologically important acetamide.[227,228] The 1-adamantanyl thioglycosides are particularly useful as they can be reliably activated at −78 °C with the usual *N*-iodosuccinimide (NIS)/TfOH combination even in solvent mixtures containing acetonitrile (Scheme 21).[228] Indeed, the high reactivity of the adamantanylthioglycoside compared to that of the more typical arylthioglycosides enabled a sialylthioglycoside to be employed for the first time as the starting point in a Wong-type one-pot trisaccharide synthesis.[229,230]



Scheme 21

A further step forward was taken by Wong and coworkers, who demonstrated the conversion of the oxazolidinone-protected thioglycosides to the corresponding glycosyl phosphates by treatment with *N*-iodosuccinimide and dibutylphosphoric acid. The oxazolidinone-protected sialyl phosphates are stable entities that can be isolated by column chromatography and take part in highly α-selective glycosylation reactions on activation with TMSOTf in dichloromethane at −78 °C.[231] The use of these donors is illustrated through the iterative synthesis of oligomeric α-(2→9)-sialosides (Scheme 22).[232] Subsequently, it has been demonstrated that oxazolidinone-protected thioglycosides may be activated at low temperature with the diphenyl sulfoxide/triflic anhydride combination and that intermediated glycosyl oxosulfonium adducts can be observed under these conditions.[233]

It has also been demonstrated that oxazolidinone-protected sialyl *S*-benzoxazolyl derivatives can be activated toward glycosylation with silver and other metal triflates.[234] Most notably, however, the first examples of stable, isolable sulfoxides of sialic acid thioglycosides have been described in a system carrying the oxazolidinone protecting group; these derivatives can be activated with triflic anhydride in the usual manner and give excellent α-selectivity in dichloromethane at low temperature.[235] Cyclic protecting groups spanning N5 and O7, such as the oxazinones, show poor selectivity and are even β-selective in some cases,[236,237] but the combination of a 5-*N*,7-*O*-di(*tert*-butylsilyene)acetal and 4-*O*,5-*N*-oxazolidinone gives a highly α-selective tricyclic sialyl donor.[238] The influence of O4 protecting groups on the selectivity of the more classical 5-*N*-acetyl sialyl thioglycosides has been described.[239]

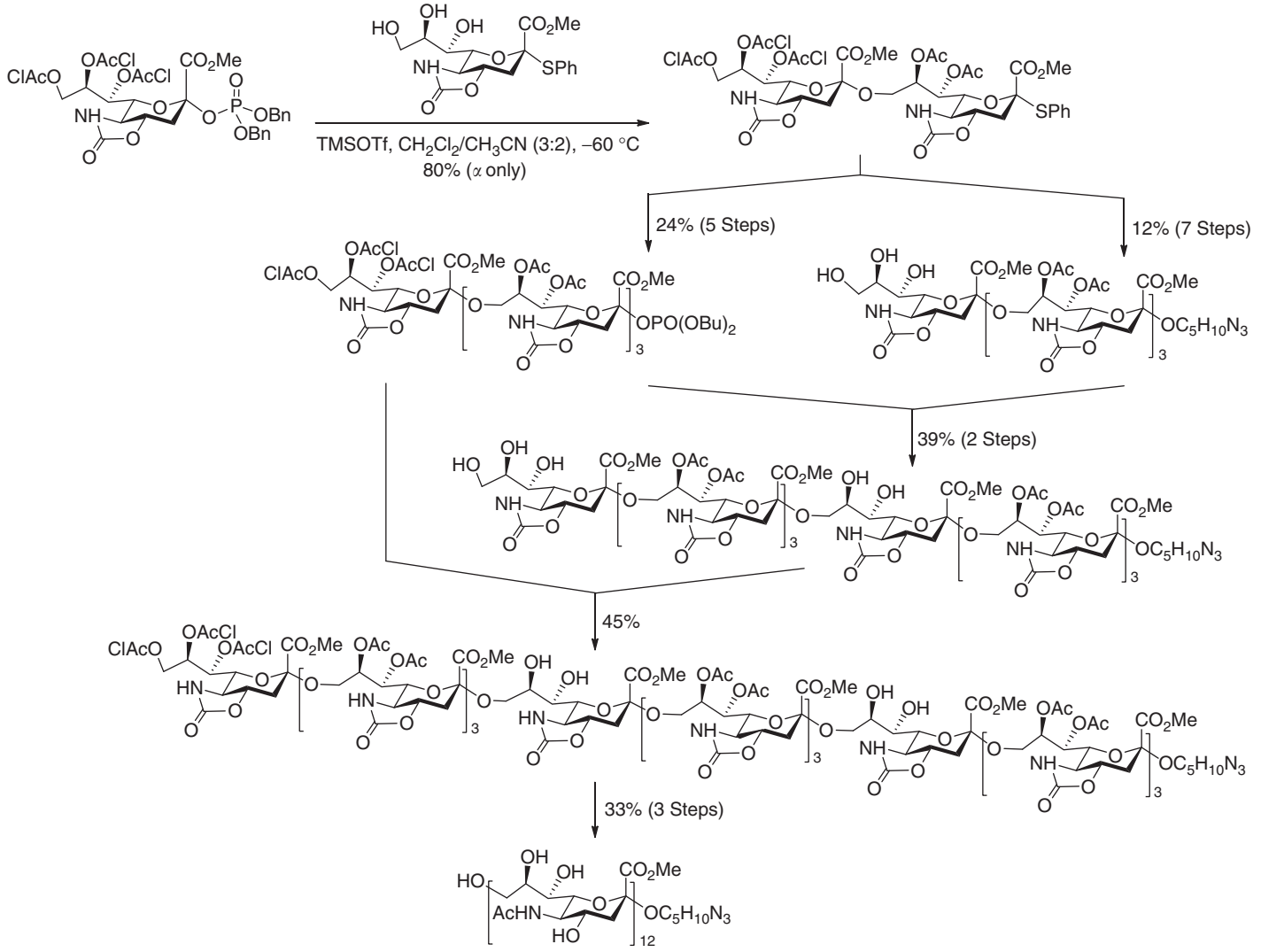
In the 2-keto-3-deoxy-D-glycero-D-galactononulosonic acid series it has been demonstrated that donors protected with a 4,5-*O*-carbonate group function as highly effective α-selective donors (Scheme 23).[240]

6.01.3.7 The β-Arabinofuranosides

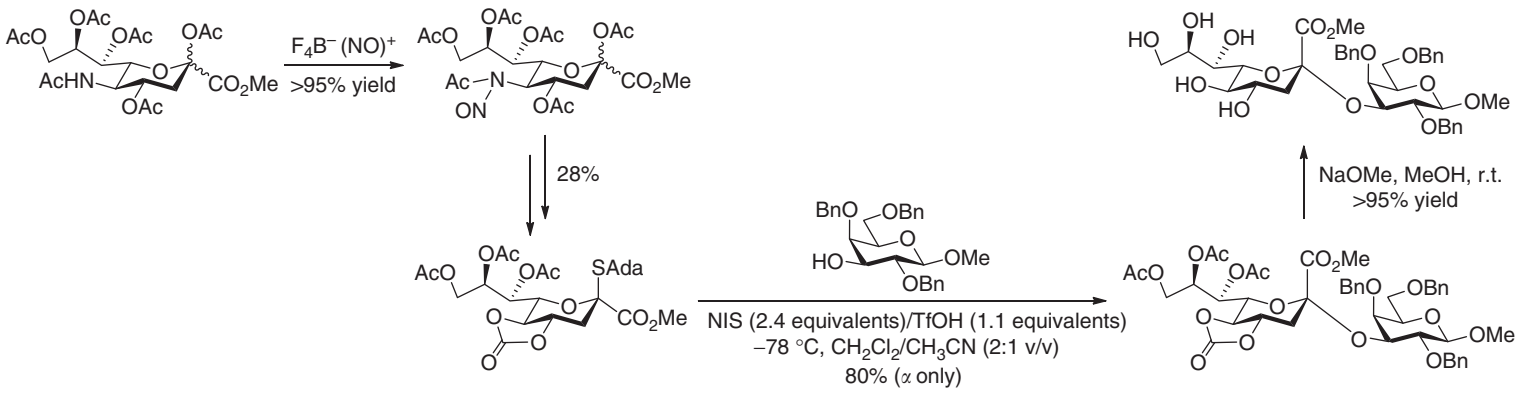
The β-arabinofuranosides are a cognate problem to the β-mannopyranosides and analogous solutions have been found for their synthesis, beginning with the use of cyclic protecting groups spanning the 3- and 5-positions. However, in view of the relative instability of 3,5-*O*-benzylidene-protected furanosides,[241] the more easily installed 3,5-*O*-di-*tert*-butylsilylene acetal is preferred. As first reported by Boons and coworkers, arabinofuranosyl thioglycosides protected in this manner are highly β-selective when activated by NIS and AgOTf at low temperature (Scheme 24).[242]

Ishiwata and Ito, in contrast, preferred the use of the 3,5-*O*-(tetraisopropyldisiloxane) group, with which they achieved excellent β-selectivity (Scheme 25).[243,244] Both systems are considered to proceed via stereoselective β-face attack on intermediate arabinofuranosyl oxocarbenium ions, whose conformation is such that approach to the α-face is hindered by eclipsing interactions with the C2–H2 bond that is perpendicular to the plane of the π-system.[242–244] Both systems have been employed in impressive convergent syntheses of docosasaccharides from mycobacterial cell walls.[244,245]

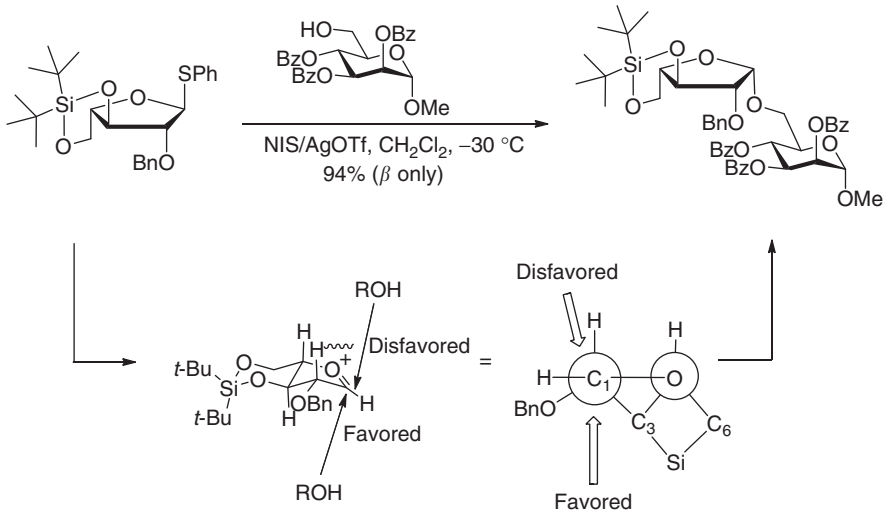
Work from the Lowary and Kim groups has demonstrated, however, that the use of cyclic protection for the 3- and 5-positions is not a *sine qua non* for β-selectivity in the arabinofuranoside series, as simple perbenzyl donors were also found to afford high β-selectivity under a variety of conditions (equation 14).[246,247] Interestingly, an arabinofuranosyl donor protected with a 2,3-*O*-xylylene group has also been reported to afford highly β-selective couplings.[248]


TMSOTf, CH2Cl2/CH3CN (3:2), –60 °C
80% (α only)
24% (5 Steps)
12% (7 Steps)
39% (2 Steps)
45%
33% (3 Steps)

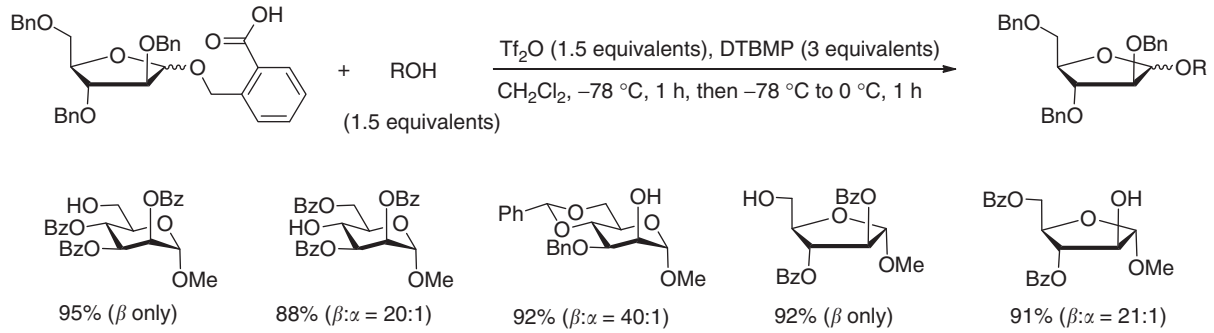
Scheme 22


AcO
OAc
OAc
OAc
AcHN
O
CO2Me
OAc
F4B− (NO)+
>95% yield
Ac
N
ON
28%
SAda
NIS (2.4 equivalents)/TfOH (1.1 equivalents)
–78 °C, CH2Cl2/CH3CN (2:1 v/v)
80% (α only)
BnO
OBn
HO
OMe
NaOMe, MeOH, r.t.
>95% yield
OH
BnO
OBn
OMe

Scheme 23

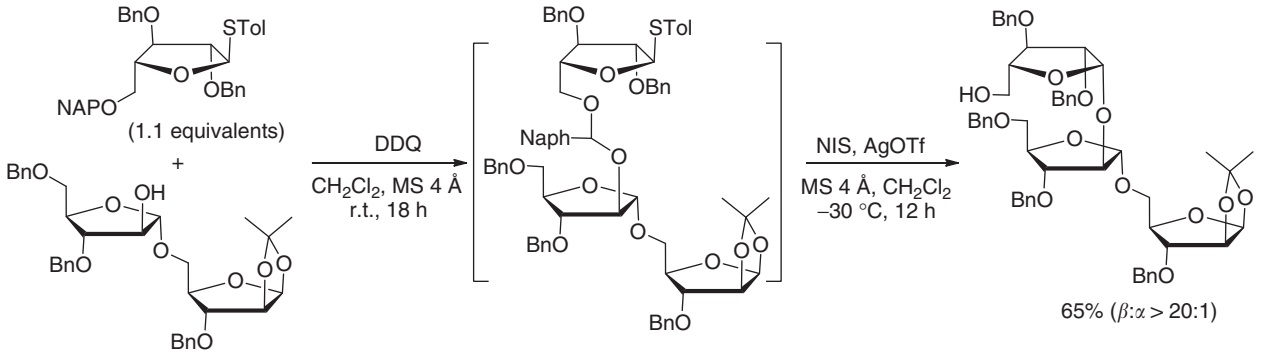


Scheme 24



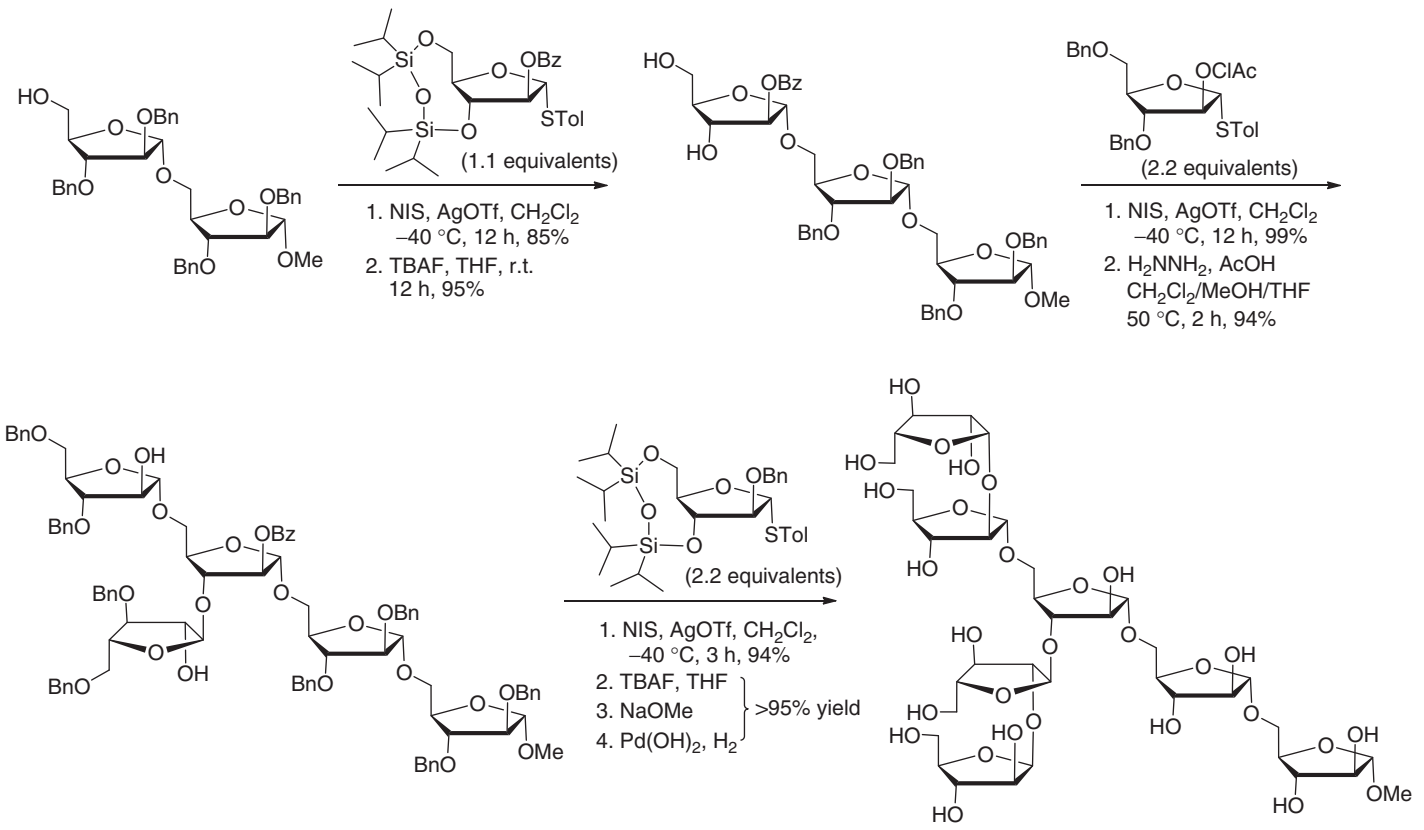
(14)

IAD approaches to the β-arabinofuranosides have also been successfully pursued by the Prandi and Ito groups, starting out from either the 2-*O*-*p*-methoxybenzyl ethers or the 2-*O*-naphthylmethyl ethers exactly as in the mannopyranosides.[249,250] In an interesting twist on the theme, Ishiwata and Ito demonstrated tethering of the aglycone to the 5-position was also effective for the synthesis of the β-arabinofuranosides (equation 15).[244]

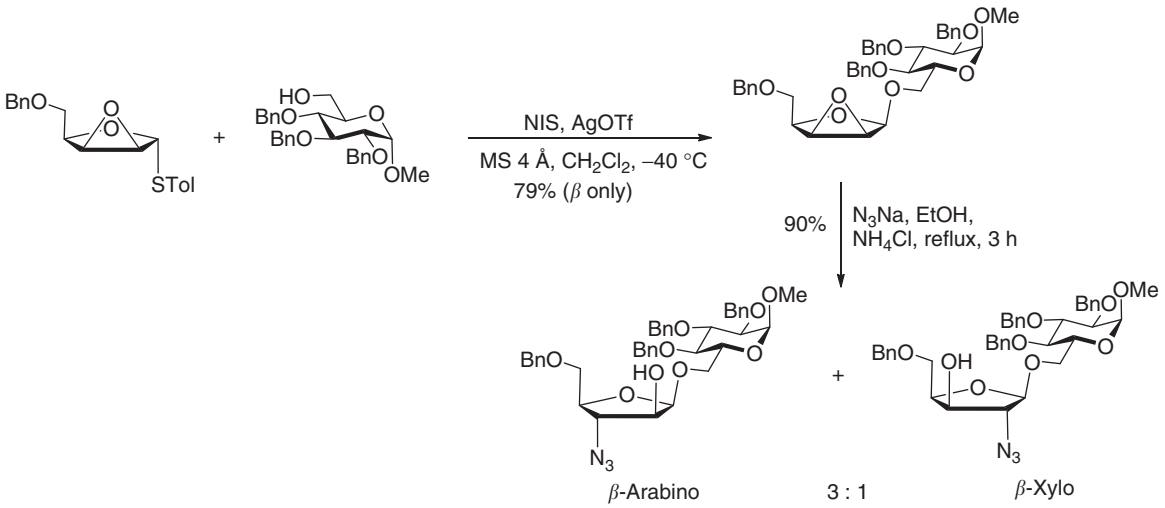


(15)

An alternative approach to the β-arabinofuranosides involves the use of 2,3-anhydro-lyxofuranosyl donors, which were found to be highly β-selective, followed by regioselective opening of the epoxide ring with sodium benzyloxide or other nucleophiles (Scheme 26).[251]


(1.1 equivalents)
1. NIS, AgOTf, CH2Cl2
–40 °C, 12 h, 85%
2. TBAF, THF, r.t.
12 h, 95%
(2.2 equivalents)
1. NIS, AgOTf, CH2Cl2
–40 °C, 12 h, 99%
2. H2NNH2, AcOH
CH2Cl2/MeOH/THF
50 °C, 2 h, 94%
(2.2 equivalents)
1. NIS, AgOTf, CH2Cl2,
–40 °C, 3 h, 94%
2. TBAF, THF
3. NaOMe
4. Pd(OH)2, H2
>95% yield

Scheme 25



Scheme 26

6.01.4 Polymer-Supported Oligosaccharide Synthesis

No discussion of modern oligosaccharide synthesis is complete without mention of polymer-supported methods and in particular automated polymer-supported oligosaccharide synthesis. After promising early work at the beginning of the 1970s[252] the field lay dormant until the early 1990s when, spurred by the explosive growth of glycobiology and the need for the preparation of large numbers of homogeneous glycoforms, it underwent a rapid and continuing expansion. As the field is extensive and as the fundamental glycosylation reactions employed are no different from those covered above, the reader is referred to the many reviews of the area for further information.[253–259]

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6.02 Synthesis of Amines and Ammonium Salts

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Glossary

Bimolecular nucleophilic substitution with allylic rearrangement (S_N2') This is a variant of the S_N2 reaction involving an allylic leaving group. Instead of the normal displacement, the nucleophile becomes attached to the γ-position relative to the leaving group, with migration of the double bond.

Conservation of enantiomeric excess (*cee*) A metric to describe the enantiospecificity of a reaction. Calculated as follows: *cee* = (product *ee*/ starting material *ee*) × 100.

Dynamic kinetic resolution The combination of a kinetic resolution with a racemization process. This is a Curtin–Hammett situation; the product distribution of enantiomers reflects the differences in the relative energies of the transition states leading to each enantiomer. Theoretically, a racemate can be converted exclusively into one enantiomer by this process.

Neighboring group participation An interaction between the reaction site and the electrons of a nearby functional group within the substrate. Such interactions can increase the rate of a reaction, or be used to account for unusual stereochemical outcomes. This is not an interaction involving conjugation. Neighboring group participation is also known as anchimeric assistance.

Substitution nucleophilic internal (S_Ni) Following ionization of a leaving group; part of the leaving group reacts with the substrate as a nucleophile, and detaches from the rest of the leaving group. The nucleophilic atom reacts from the same face as the leaving group and leads to retention of configuration.

6.02.1 Introduction

The introduction and functionalization of nitrogen is an important process in organic synthesis due to the frequency with which it appears in pharmaceuticals and the prevalence of alkaloid natural products. Many methods exist to introduce new

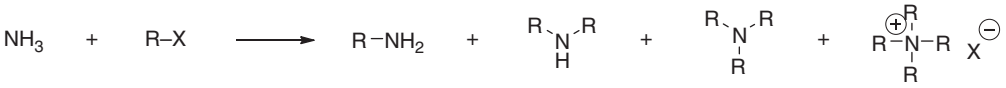
 doi:10.1016/B978-0-08-097742-3.00603-0

carbon–nitrogen bonds including displacement processes, reductive amination, and C–N cross couplings. This chapter, like its counterpart in the first edition of this work,[1] will focus on displacement reactions involving nitrogen nucleophiles. Due to the broad nature of this topic, discussion will be limited to reactions involving nitrogen nucleophiles. Section 6.02.2 will cover displacement reactions of reactive leaving groups and stoichiometric means to activate alcohols. Section 6.02.3 will emphasize transition metal-catalyzed allylic amination. Asymmetric ligand-controlled methods will be discussed, as will regiochemical issues regarding the substitution of unsymmetrically substituted allyl substrates. Amine rearrangements and the alpha alkylation of chiral amines will not be covered. Other chapters within this work discuss alternative methods for the preparation of amines. For example, amines can be prepared by nucleophilic addition to imines, their derivatives, and iminium ions. For detailed discussions, *see* Chapters 1.11, 2.16, and 2.17. Reductive amination is an important area and is covered in detail in several chapters within Volume 8: Reduction. For details *see* Chapters 8.02, 8.03, 8.05, 8.06, 8.08, 8.10, 8.13, and 8.14.

6.02.2 Alkylation of Amines and Amine Equivalents

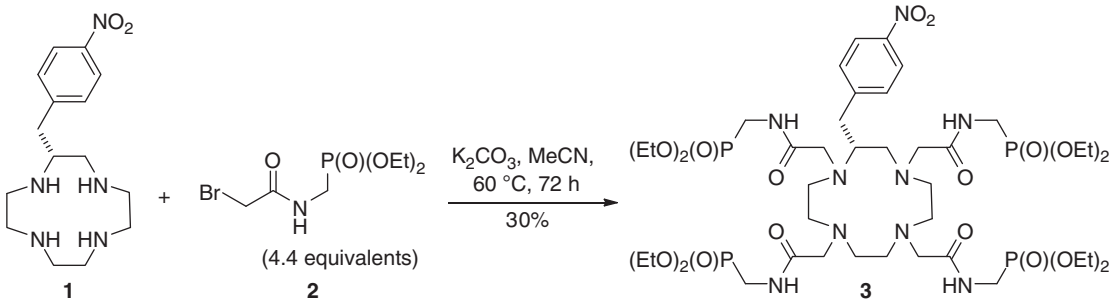
6.02.2.1 Displacement of Halide and Sulfonate Leaving Groups

The preparation of amines and ammonium salts via nucleophilic displacement remains a vital process for organic synthesis. These reactions are conceptually straightforward: A nucleophilic nitrogen source reacts with an electrophile containing an appropriate leaving group. However, this simple paradigm is often complicated by competitive elimination of the leaving group and polyalkylation of simple amine nucleophiles (equation 1). Therefore, many amine equivalents have been developed that utilize diverse protecting schemes so that polyalkylation can be avoided. Phthalimide is the classic ammonia equivalent that is used in the Gabriel synthesis of primary amines; its use was covered in detail by Mitsunobu in Chapter 1.3 Synthesis of Amines and Ammonium Salts, within the previous edition of this work.[1] This section will survey illustrative examples involving the nucleophilic aminations of substrates with halide and sulfonate leaving groups as a preface to more recent developments including microwave chemistry, novel amine equivalents, and nontraditional leaving groups.



(1)

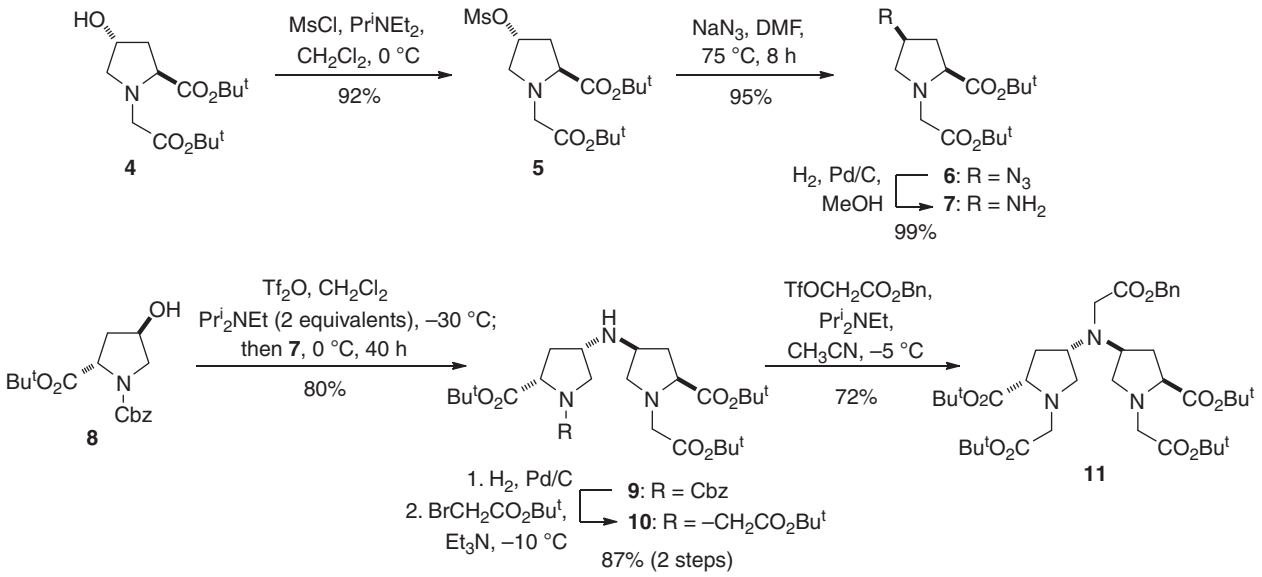
Several excellent examples come from research involving the development of novel polyamines envisioned as ligands for MRI contrast agents (equation 2). The reaction of chiral cyclen derivative **1** with bromoacetamide **2** demonstrates the difficulties that arise with the preparation of such compounds via S_N2 chemistry.[2] The desired alkylated product **3** was obtained in 30% yield after reacting for 72 h at elevated temperature. Although the balance of the product mixture was not described, the low yield is presumably due to competitive formation of various ammonium salts.



(2)

Rapoport has prepared numerous ligand analogs for use as MRI agents. This work provides excellent examples of the preparation of primary, secondary, and tertiary amines via alkylations. Iterative displacement reactions using amines and amine equivalents were used to form the carbon–nitrogen bonds that link the pyrrolidine rings in ligand **11** (Scheme 1).[3] This compound is ultimately derived from the *tert*-butyl ester of 4-hydroxyproline (**4**). In each case, the hydroxyl group was activated for displacement as a sulfonate ester. The first of the two new carbon–nitrogen bonds was introduced by reacting mesylate **5** with NaN_3 followed by reduction of the resulting azide to a primary amine.

Azide is often used as ammonia equivalent due to its low molecular weight and the ease with which it is reduced to a primary amine. On a laboratory scale, reduction of azides is often accomplished via the Staudinger reduction with Ph_3P. A by-product of this reaction is stoichiometric triphenylphosphine oxide, a waste material that can be difficult to remove on a larger scale. Additionally, basic and nucleophilic intermediates are formed during the Staudinger reduction, which can be problematic in cases where sensitive functional groups are present. To prepare **7**, azide **6** was hydrogenated. This helped streamline purification, as **7**



Scheme 1

was filtered through Celite to remove the catalyst and used in the subsequent reaction after evaporating the solvent. A more recent alternative to Ph_3P involves azide reduction by $CeCl_3{\cdot}7H_2O$ and an excess of NaI in refluxing acetonitrile.[4]

Primary amine **7** was then reacted with the triflate of **8**, which was generated *in situ* using Tf_2O. It was essential to conduct this reaction at low temperature to minimize elimination of the triflate and obtain a high yield of **9** (80%, 95:5 diastereoselectivity). This is an impressive example of the direct coupling of a primary amine with a secondary leaving group. Polyalkylation was not a problem due to the sterically hindered nature of secondary amine **9**. Surprisingly, the minor diastereomer is not due to epimerization of either of the C-2 esters, but is produced due to the retention of configuration at the triflate. Retention of stereochemistry could be due to formation of a carbocation, or to neighboring group participation of the Cbz group.

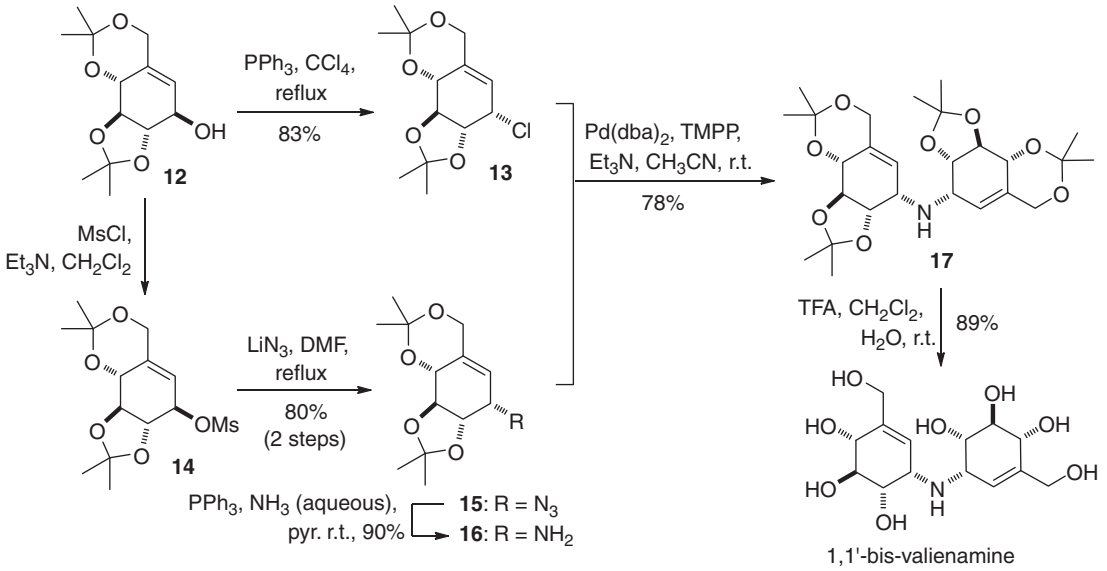
Two more alkylations were involved in the preparation of **11**. Following the removal of the Cbz group from **9**, alkylation with *tert*-butyl bromoacetate gave **10**. Even at low temperature, **10** was accompanied by alkylation at the central secondary amine linking the pyrrolidine rings (3–4%). The product **11** was obtained by alkylating the remaining hindered secondary with the more reactive triflate.

A similar strategy was employed for the preparation of 1,1-bis-valienamine, a strong trehalase inhibitor (Scheme 2).[5] This inhibitor is a dimer of the valienamine where the pseudosaccharides are linked by a common nitrogen atom. Cyclitol **12** was a key intermediate for the preparation of 1,1-bis-valienamine that was synthesized in several steps from (–)-quinic acid. The reaction of **12** with Ph_3P and CCl_4 gave chloride **13**, which would serve as an electrophilic coupling partner for an amine also prepared from **12**. Conversion of the alcohol in **12** to this primary amine required three synthetic operations, the first step of which was the formation of mesylate **14**. Displacement with LiN_3 and Staudinger reduction reduced then gave primary amine **16**. As shown in Scheme 1, displacement of this hindered, secondary, mesylate with azide required elevated reaction temperature in a polar solvent. The reactivity of this secondary mesylate contrasts with secondary triflate **8** (Scheme 1, above), which reacted with sterically demanding amines even at low temperature.

Amine **15** and chloride **13** were coupled with Pd-catalysis rather than a traditional displacement approach. The Pd°-coupling of **13** was possible due to the presence of an allylic leaving group. Allyl chloride **13** and amine **15** have the same relative configuration and their coupling to provide **17** occurs with retention of stereochemistry. The stereochemical outcome for this Pd-catalyzed coupling contrasts with the S_N2 displacements, which are well known to proceed with an inversion. Retention of stereochemistry is typical for Pd°-catalyzed allylic amination and is the result of a double inversion process (see Section 6.02.3.1 for more detail). The authors did not discuss whether a traditional displacement reaction between **15** and **14** (or the corresponding triflate) was examined.

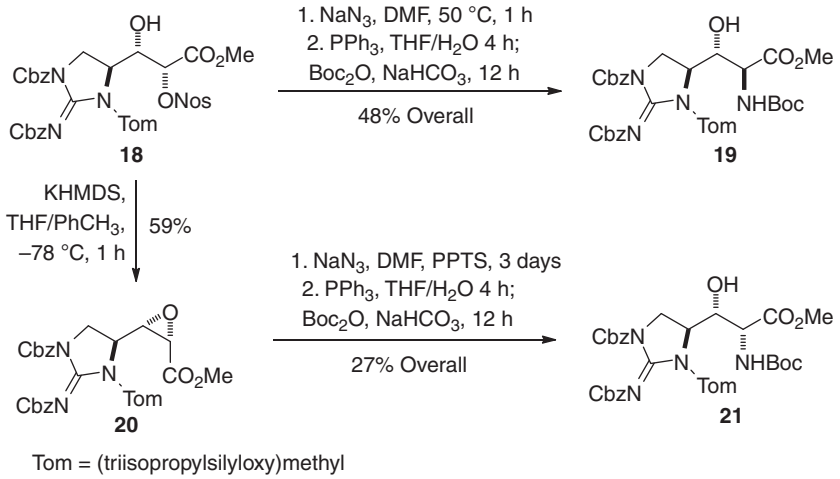
Various halides and sulfonates have been used to prepare amines by displacement reactions. Although mesylate, tosylate, and triflate are the most commonly used sulfonate leaving groups, the nosylate group (4-nitrophenylsulfonate) has intermediate reactivity. Nosylate is 10-fold more reactive than mesylate and tosylate, whereas a triflate is 10^4 times more reactive versus the mesylate and tosylate.[6] This confers a reactivity advantage for the nosylate, which is generally stable enough to be isolated and stored, in contrast to the triflate.

Nieuwenhze took advantage of this reactivity while preparing **19** and **21**, which are protected derivatives of nonproteinogenic amino acids required for the synthesis of mannopeptimycin antibiotics (Scheme 3).[7] Secondary nosylate **18** was transformed to Boc-protected amine **19** using a standard azide displacement (78% yield) and Staudinger reduction. In this case, Boc_2O was added



Scheme 2

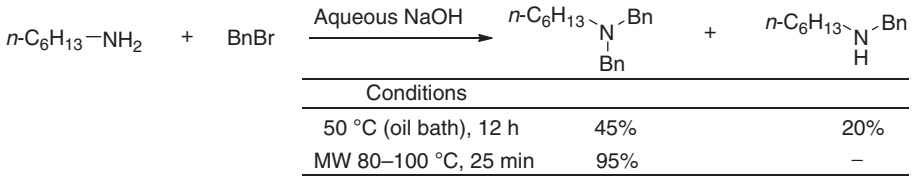
to the crude reduction mixture, so that Staudinger reduction and protection were completed in one pot (62% yield). The reactivity of the nosylate was advantageous for this substrate, which is relatively hindered due to the presence of the nearby *N*-Tom group [(triisopropylsiloxy)methy].



Scheme 3

The impact of sterics on the reactivity of **18** can be appreciated by examining the reaction of epoxide **20** with azide. Nucleophilic addition of NaN_3 to epoxide **20** was much slower compared to the corresponding nosylate displacement. Although reactions of azides with epoxides can be relatively slow, requiring several days to complete, the reaction of **20** appears to be particularly challenging. Even with the addition of an acid catalyst (PPTS) to facilitate epoxide opening, this reaction required 3 days and gave a relatively moderate yield of the azide (44% yield).

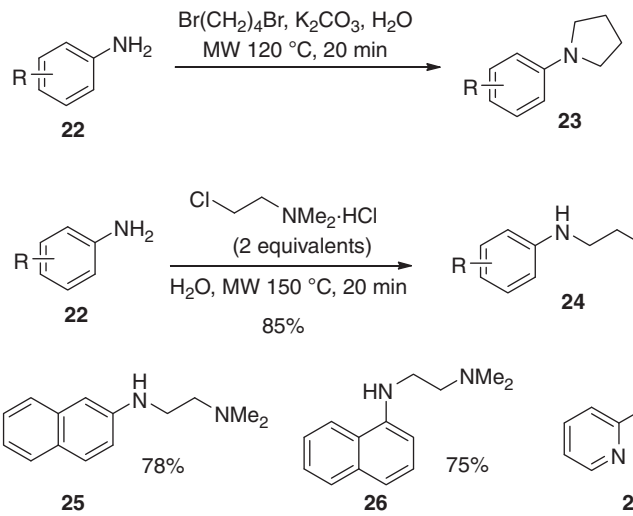
Even simple intermolecular *N*-alkylation reactions between amines and primary halides can be relatively slow, requiring several hours to complete at elevated temperature. Varma has found that microwave heating is an attractive method for *N*-alkylations, as it promotes the rapid formation of tertiary amines in water (equation 3).[8] In a direct comparison, benzyl bromide and hexylamine were stirred in aqueous hydroxide without the addition of any phase transfer agents. Conventional heating in an oil bath gave a mixture of mono (20%) and dibenzyl products (45%) after 12 h. Microwave irradiation substantially improved the rate of this reaction. With microwave heating, the reaction was complete within 25 min and produced the dibenzyl product in 95% yield.



Conditions		
50 °C (oil bath), 12 h	45%	20%
MW 80–100 °C, 25 min	95%	–

(3)

Anilines are less reactive toward *N*-alkylation than amines. This reactivity difference makes it relatively easy to selectively obtain monoalkylation products, as the addition of a second *N*-alkyl group requires more forcing conditions. Microwave irradiation greatly accelerates aniline alkylation and is particularly useful for preparing *N*-aryl heterocycles. The reaction of anilines with dihalides and ditosylates gives *N*-aryl pyrrolidines **23**, as well as piperidines in only 20 min under microwave irradiation (Scheme 4).[9,10] Electron-withdrawing groups were well tolerated. High yields were obtained with bromides, ketones, and esters at the *para* position. Ethyl 3-aminobenzoate also gave a 93% yield.



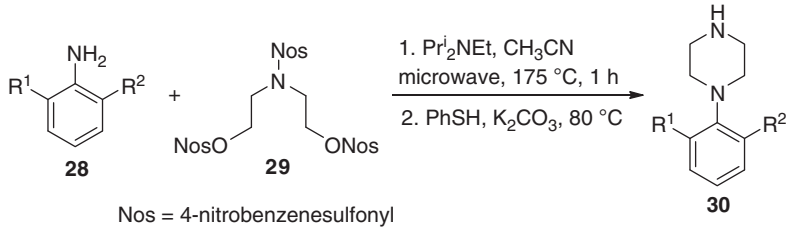
Substrate	Yield
R = H	85%
R = 4-Ac	90%
R = 4-Br	65%
R = 4-CO_2Et	91%
R = 3-CO_2Et	93%

Substrate	Yield
R = H	89%
R = 4-Me	90%
R = 3-Me	82%
R = 2-MeO	72%
R = 4-NO_2	10%
R = 4-CO_2H	35%
R = Cl	67%

Scheme 4

The monoalkylation of anilines was also reported to occur under microwave conditions (e.g., **22**–**24**, Scheme 4).[11] Here it was found that excellent results were obtained even under neutral conditions. Other halides were examined under these conditions, including ethylbromide, 2-bromobutane, *t*-butylbromide, and 1,4-dibromobutane. With the exception of 1,4-dibromobutane, which underwent dialkylation to the *N*-arylpyrrolidine, all gave mono alkylated products with *p*-toluidine (68–85% yields). It is interesting to note that the yield of **24** decreased when an electron-withdrawing group was present on the aniline. This contrasts with the high yields reported for the dialkylation of 4-aminobenzoates in the presence of K_2CO_3. Naphthylamines are also viable substrates for microwave-promoted alkylation (**25** and **26**), although 2-aminopyridine was unreactive (**27**).

N-Aryl heterocycles with sterically demanding groups at the 2-position of the aromatic ring are difficult to prepare. Microwave irradiation is helpful in these cases, and was used to prepare *N*-arylpiperazines represented by **30** in good-to-excellent yields (equation 4).[12] The optimal electrophile was bis-nosylate **29** under microwave irradiation, which gave excellent yields for anilines with R^1 = *t*-butyl, phenyl, and morpholine (**28a–c**). An even more impressive result was obtained with 2,6-diisopropylaniline (**28d**), where the hindered product (**30d**) was formed in 61% yield. The nosylate group (4-nitrophenylsulfonate) plays an important role in the success of this reaction. It is more reactive than the tosylate derivative of **29**, which gave only a 40% yield of the 2-*tert*-butylaniline **30** (R^1 = Bu^t). Furthermore, *N*-nosyl groups are removed under mild conditions with thiophenolate.

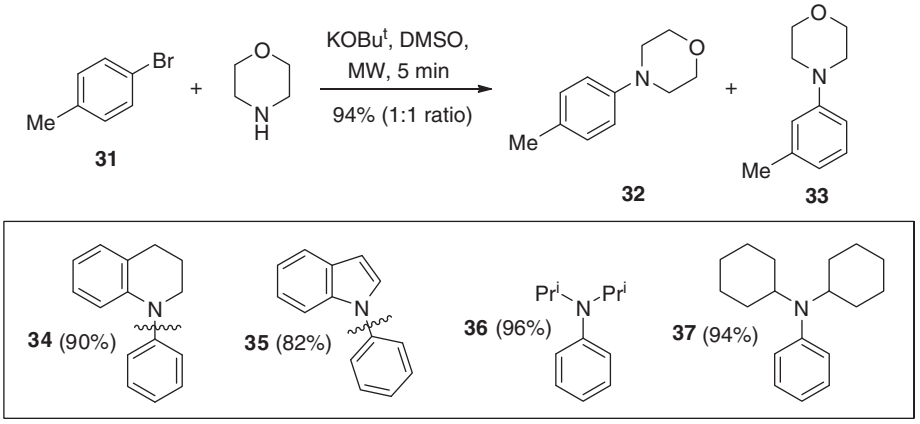


Nos = 4-nitrobenzenesulfonyl

Substituents	Yield
a: R^1 = Bu^t, R^2 = H	71%
b: R^1 = Ph, R^2 = H	86%
c: R^1 = morpholine, R^2 = H	81%
d: R^1 = R^2 = Pr^i	61%

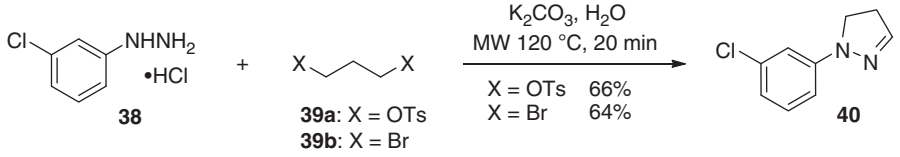
(4)

Microwave conditions also promote the direct amination of aryl halides and secondary amines (equation 5).[13] *p*-Bromotoluene and morpholine gave a 1:1 mixture of **32**:**33** under these conditions, which suggests that this reaction involves the formation of a benzyne. The implication of a benzyne intermediate was corroborated by its capture with furan in a [4+2] reaction. A variety of nitrogen nucleophiles provided *N*-phenyl products in excellent yield. Although this reaction is not a displacement reaction, it is complementary to routes involving the dialkylation of aniline and transition metal couplings.



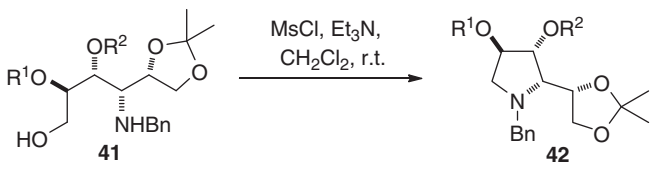
(5)

The microwave-promoted reaction of hydrazines with dihalides was also examined (equation 6).[10] These reactions unexpectedly occurred with dehydrogenation. For example, dihydropyrazole **40** was isolated as the product of the dialkylation of **38** with **39**. Oxygen likely plays a role in the dehydrogenation process, but the mechanism of this reaction was not studied in detail. For additional reading on microwave-accellerated organic reactions, *see* Chapter 9.10.



(6)

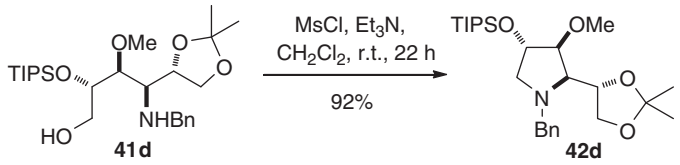
A common route to prepare nitrogen heterocycles involves the cyclization of acyclic amino alcohols by activating the alcohol toward displacement. Ease of cyclization is influenced by substitution patterns and relative stereochemistry and their impact on the conformations of the cyclization precursor. For polyol amines, the protecting group scheme can affect cyclizations in subtle ways (equation 7).[14] For example, yields and reaction rates varied according to the protecting group scheme for derivatives of polyol amine **41**. Selective activation of diol **41a** was not possible, and the yield of pyrrolidine **42a** was low even when two equivalents of MsCl were used. Better yields of the corresponding pyrrolidines were obtained from amino alcohols **42b** and **42c**, wherein the secondary alcohol at the 2-position was protected as ether. There was also a marked difference for the reaction of **42d** compared to **42b**, which demonstrates the influence of relative stereochemistry.



Product	Time	Yield
a: R^1 = H, R^2 = TMSE	4 h	43%
b: R^1 = TIPS, R^2 = Me	3 days	74%
c: R^1 = Bn, R^2 = Me	15 h	82%

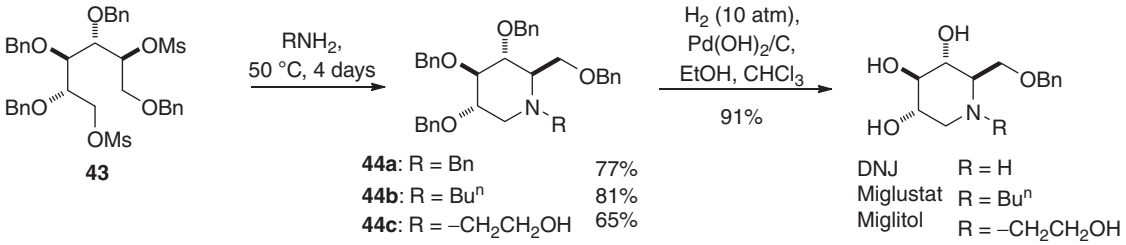
TMSE = 2-Trimethylsilylethoxy

(7)



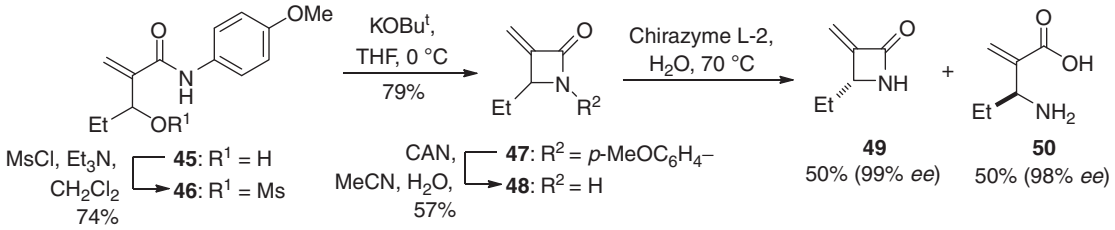
(8)

N-Heterocycles can be formed by the dialkylation of primary amines. Piperidines were prepared in this manner using dimesylate **43** (Scheme 5).[15] The dimesylate used in this clever double displacement route is available after a short series of synthetic steps from glucose. Hydrogenolysis of piperidines **44a-c** removed the benzyl protecting groups to produce DNJ (1-deoxynojirimycin), miglustat, and miglitol.



Scheme 5

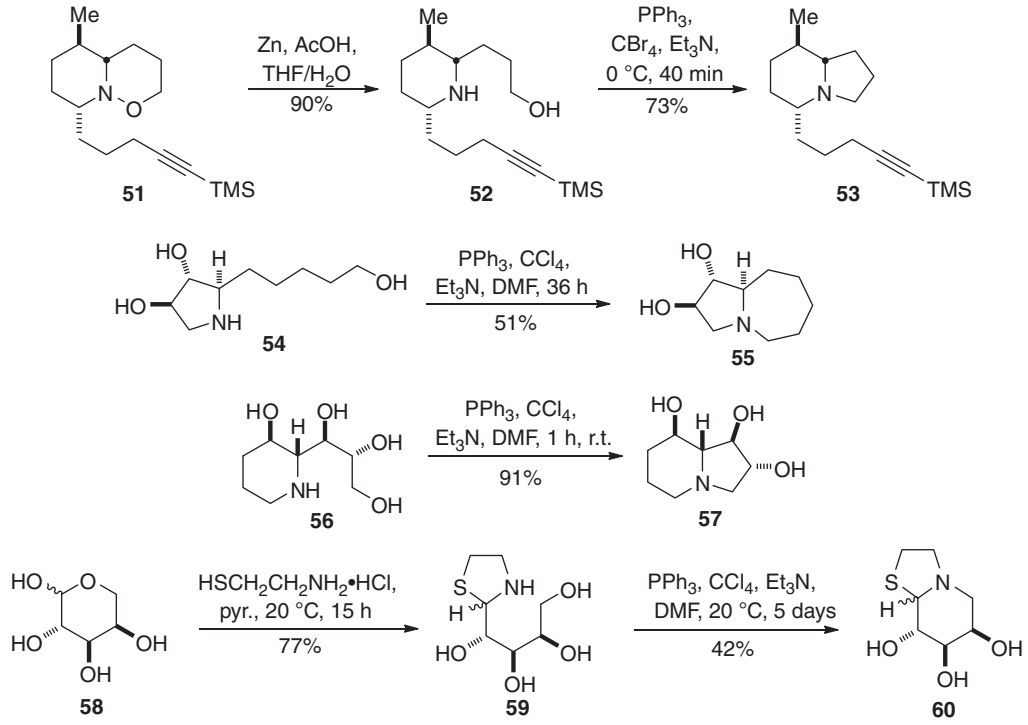
Nucleophilicity and ring strain have a significant effect on the spontaneity of cyclization. Mesylate **46**, prepared from alcohol **45**, is an isolable compound (Scheme 6).[16] Unlike cyclizations to 5- and 6-membered heterocycles, *β*-lactam **47** is not formed spontaneously due to the ring strain of the product and the low nucleophilicity of the *p*-anisidine amide. To induce cyclization, amide **46** had to be deprotonated by $KOBu^t$, a condition that gives **47** in 79% yield. Enantiopure lactams could be prepared by enzymatic hydrolysis after deprotection of **47** to **48**.



Scheme 6

The Appel reaction is often used to prepare heterocycles from amino alcohols. This method involves activation of an alcohol on treatment with Ph_3P and a carbon tetrahalide. Isolated alcohols are converted into halides under Appel conditions. In contrast, amino alcohols cyclize immediately with the intermediate alkoxyphosphonium salt (ROP^+Ph_3), which is displaced by the amine to produce the azacycle and an equivalent of triphenylphosphine oxide.

This method has found particularly wide use for the synthesis of indolizidine alkaloid natural products (Scheme 7). Kibayashi prepared amino alcohol **52** following the reductive cleavage of the N–O bond in **51**.[17] Appel cyclization of **52** with Ph_3P and CBr_4

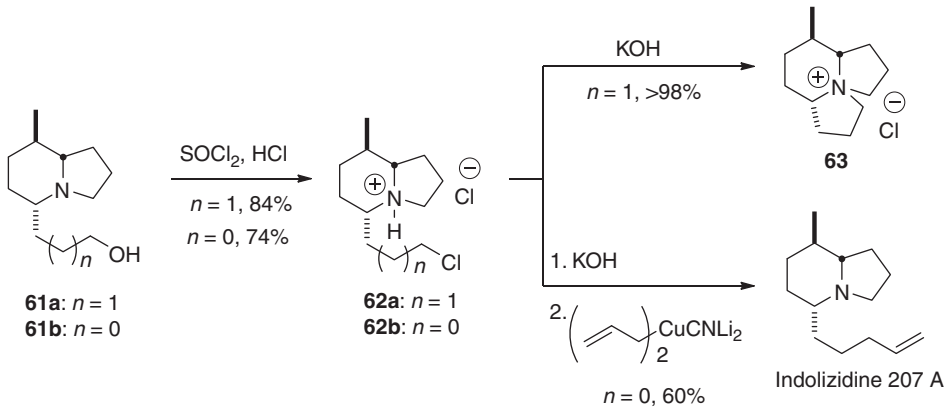


Scheme 7

then gave **53** in 73% yield. These conditions work well to form 5–7-membered rings, although the cyclization of 6- and 7-membered rings is slower. Compared to the rapid closure of 5-membered rings, the Appel cyclization to the form azepane **55** required 36 h to complete.[18] Although this was a relatively slow reaction with a moderate yield, it was a successful route to this 7-membered ring after a ring-closing metathesis had failed.

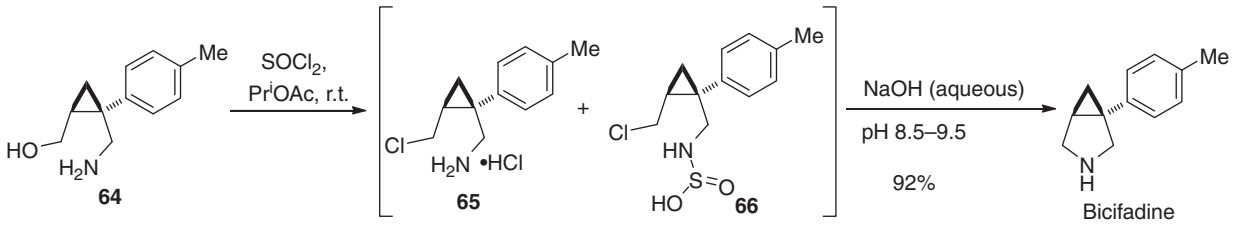
These conditions will selectively activate primary alcohols in the presence of free secondary hydroxyl groups. An excellent example of this is Casiraghi's synthesis of 1-*epi*-swainsonine.[19] Amino tetraol **56** produced indolizidine **57** in 91% yield on reaction with Ph_3P, CCl_4 and Et_3N. In this case, the Appel reaction was successful, whereas the attempted cyclization with Ph_3P and DEAD was not (Mitsunobu conditions, see Section 6.02.2.5). In another example, the Appel conditions were used in the second step of a very short two-step route to indolizidine analogs from arabinose (**58**).[20] Although the chemical yield was modest in this final case, selective activation of the primary alcohol occurred to provide the six-membered ring as the major product.

Chlorides derived from amino alcohols are isolable intermediates when the alcohol is converted under acidic conditions. Protonation of the amine prevents it from serving as a nucleophile. Such amino chlorides can cyclize on neutralization, but do so at a rate dependent on the size of the ring that formed. For example, indolizidine **61a** was converted to chloride **62a** on treatment with $SOCl_2$ in the presence of HCl (Scheme 8).[21] When this salt was free based with KOH, an undesired cyclization occurred rapidly to form ammonium salt **63**. To avoid cyclization, derivative **61b** was prepared where the linker between amine and alcohol was shortened by one carbon. Following chlorination, the shorter chain homologue (**62b**, $n=0$) gave the indolizidine 207 A after neutralization and coupling with a higher-order cuprate.



Scheme 8

Xu Feng et al. at Merck developed a preparation of (–)-bicifadine that involved cyclization of an amino alcohol after its activation as a chloride using $SOCl_2$ (Scheme 9).[22] Direct chlorination of the amino alcohol with $SOCl_2$ was investigated out of the desire to activate and cyclize an amino alcohol in one step. While other one-step protocols exist, such as the Appel and Mitsunobu conditions (see Section 6.02.2.5), those conditions have poor atom economy due to the requirement for stoichiometric activators with relatively high molecular weights. Although $SOCl_2$ is attractive from an atom economy standpoint, such reactions often suffer poor yields due to the formation of side products. Careful work demonstrated that the order of addition is critical for the chlorination of amino alcohols; slow inverse addition of the amino alcohol to a solution of $SOCl_2$ is essential for high yields.



Scheme 9

Monitoring the reaction with nuclear magnetic resonance (NMR) provided insight regarding the importance of an inverse addition protocol for this reaction.[23] It was found that *O*-sulfinylation occurs faster than *N*-sulfinylation. Thus, a chlorosulfinate ester is formed rapidly and is accompanied by protonation of the amine to form an ammonium salt. Although it was expected that

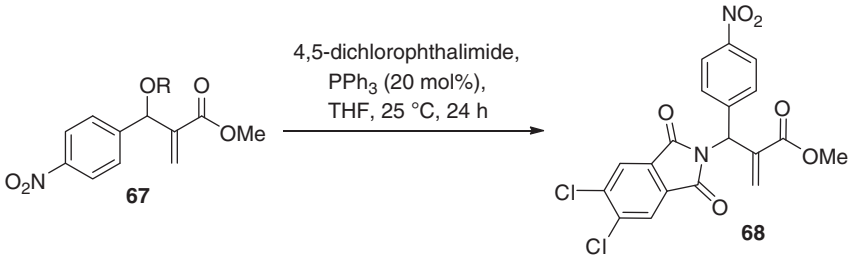
the ammonium salt would not be nucleophilic, it unexpectedly reacts slowly to form *N*-sulfinylated products. Slow inverse addition of amino alcohol to a solution of $SOCl_2$ facilitates complete conversion of alcohol to chloride before significant quantities of insoluble salts form. In this way, **64** is rapidly converted into intermediates **65** and **66**; these intermediates then converge to the pyrrolidine product after the addition of aqueous base. This method was shown to be a general process for preparing pyrrolidines and piperidines with additional examples presented. Notably, 1,3- and 1,4-amino alcohols do not cyclize to aziridines or azetidines; instead they produce amino chlorides that do not spontaneously cyclize.

6.02.2.2 Conjugate Displacements of Ester and Carbonate Leaving Groups

Although substitution routes to amines traditionally involve the displacement of halides or sulfonates, other leaving groups are viable in special cases. Allylic esters and carbonates derived from Morita–Baylis–Hillman (MBH) reactions between an activated alkene and an aldehyde are excellent examples.[24,25] Allylic nucleofuges are also general substrates for transition metal-catalyzed substitutions (see Section 6.02.3). In the case of MBH adducts, the presence of a vinylic electron-withdrawing group activates less reactive leaving groups toward displacement. The mechanism for displacements involving these substrates is dictated by the reactivity of the leaving groups and varies from an S_N2 displacement (Scheme 6, above) to a conjugate addition/elimination (E1cb).

Soft amine nucleophiles, such as sulfonamides and phthalimides, react with MBH derivatives in the presence of tertiary amine and trialkylphosphine catalysts. The heteroatom catalyst generates a reactive quaternary ammonium or phosphonium salt on its addition to the unsaturated system and is accompanied by elimination of the initial leaving group. This conjugate addition/elimination process is then repeated with the soft nucleophile displacing the more reactive ammonium or phosphonium leaving group.

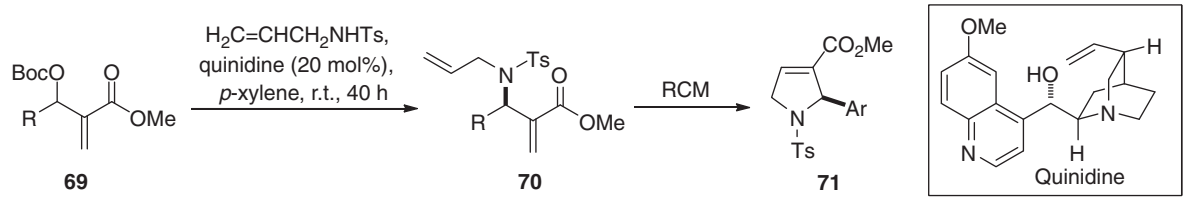
Krische found that Ph_3P catalyzes the amination of MBH acetates with 4,5-dichlorophthalimides in high yields (equation 9).[26] Phthalimide itself gives considerably lower yields than 4,5-dichlorophthalimide under otherwise identical conditions (8% for **67a**). Acetate was the optimal leaving group in these reactions, with *t*-butylcarbonate and benzoate also giving good yields (77% and 79%, respectively). By comparison, only 32% of the amination product was formed when the leaving group was 4-NO_2Bz using 4,5-dichlorophthalimide as a nucleophile. These results suggest that the reactivity of the leaving group and nucleophile must be carefully balanced in this reaction. To rationalize these results, it was hypothesized that the leaving group must be sufficiently basic to deprotonate the pronucleophile.



MBH Derivative	Yield
67a: R = Ac	90%
67b: R = Boc	77%
67c: R = Bz	79%
67d: R = *p*-NO_2Bz	32%

(9)

Tertiary amines also catalyze substitution reactions between sulfonamides and MBH acetates. DABCO and alkaloid catalysts render $TsNH_2$ a viable nucleophile for substitution reactions with MBH adducts.[27,28] Quinidine catalyzes an enantioselective allylic substitution between *N*-tosyl allylamine and carbonate **69** (Scheme 10, Table 1).[29] Several other cinchona alkaloids were examined, yet quinidine gave the best results in terms of yield and enantioselectivity. The resulting allylamine product **70** was converted into dihydropyrrole **71** by ring-closing metathesis. Enantioselectivities were best for MBH adducts with aromatic groups (entries 1–5). Aliphatic substrates represent a limitation of this chemistry, giving lower yields and poor enantioselectivity under these conditions (entry 6).



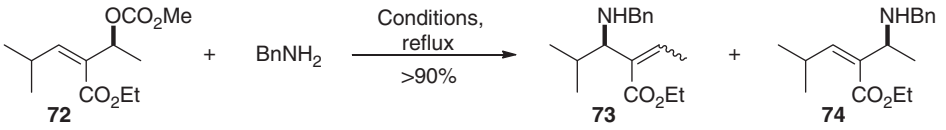
Scheme 10

More nucleophilic primary and secondary amines obviate the need for catalysts, although elevated temperatures then become necessary (equation 10). For example, $BnNH_2$ reacts with allylic carbonate **72** without the need for catalyst (Table 2,

Table 1 Enantioselective substitutions of MBH carbonates with *N*-tosyl allylamine

Entry	*R*	*Yield* ***70*** *(%)*	ee *(%)*	*Yield* ***71*** *(%)*	ee *(%)*
1	C_6H_5	93	87	90	86
2	2-ClC_6H_4	91	83	87	83
3	3-MeC_6H_4	88	90	84	87
4	4-BrC_6H_4	90	86	86	86
5	4-MeC_6H_4	96	90	92	87
6	$PhCH_2CH_2$	60	35	–	–

entries 1 and 2).[30] Use of enantioenriched (*S*)-**72** indicated that this was a stereospecific process involving the *syn*-approach of the neutral nucleophile to produce the *R*-configured product. An interesting solvent effect was observed when the reaction was conducted under Pd-catalysis. When run in tetrahydrofuran (THF), the Pd-catalyzed process gave the same product (**73**) as the uncatalyzed reaction, albeit with increased amounts of minor product **74** (90:10 ratio, entry 3). This regioselectivity was reversed when the reaction was run in acetonitrile (entries 4 and 5).

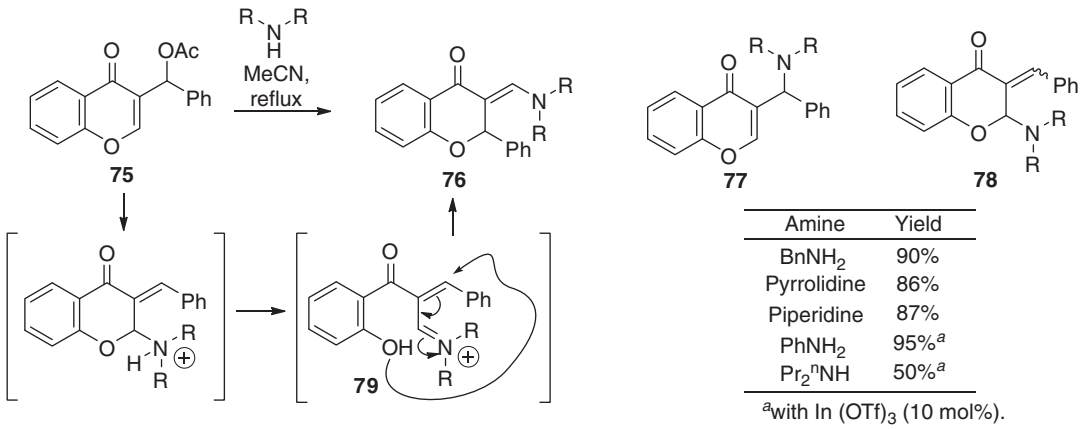


(10)

Table 2 Uncatalyzed substitution of allylic carbonate **72** with benzylamine

Entry	*Catalyst*	*Solvent*	*Ratio of* ***73*** *to* ***74***
1	None	THF	>99:1
2	None	MeCN	>99:1
3	$Pd_2(dba)_3{\cdot}CHCl_3$	THF	90:10
4	$Pd_2(dba)_3{\cdot}CHCl_3$	MeCN	20:80
5	$Pd_2(dba)_3{\cdot}CHCl_3$, PPh_3	MeCN	1:99

Chromone-derived Baylis–Hillman adducts (e.g., **75**, Scheme 11) were examined as substrates for an uncatalyzed allylic amination.[31] Instead of the expected substitution products **77** and **78**, vinylogous amide **76** was formed. This unexpected result can be explained considering a mechanism where conjugate displacement of acetate is followed by ring opening to **79**. The vinylogous amide is subsequently produced by the cyclization of this compound. Primary and cyclic secondary amines give high yields in this reaction. Less reactive nucleophiles, such as aniline and Pr^n_2NH, participate in this reaction, but require the addition of catalytic $In(OTf)_3$.

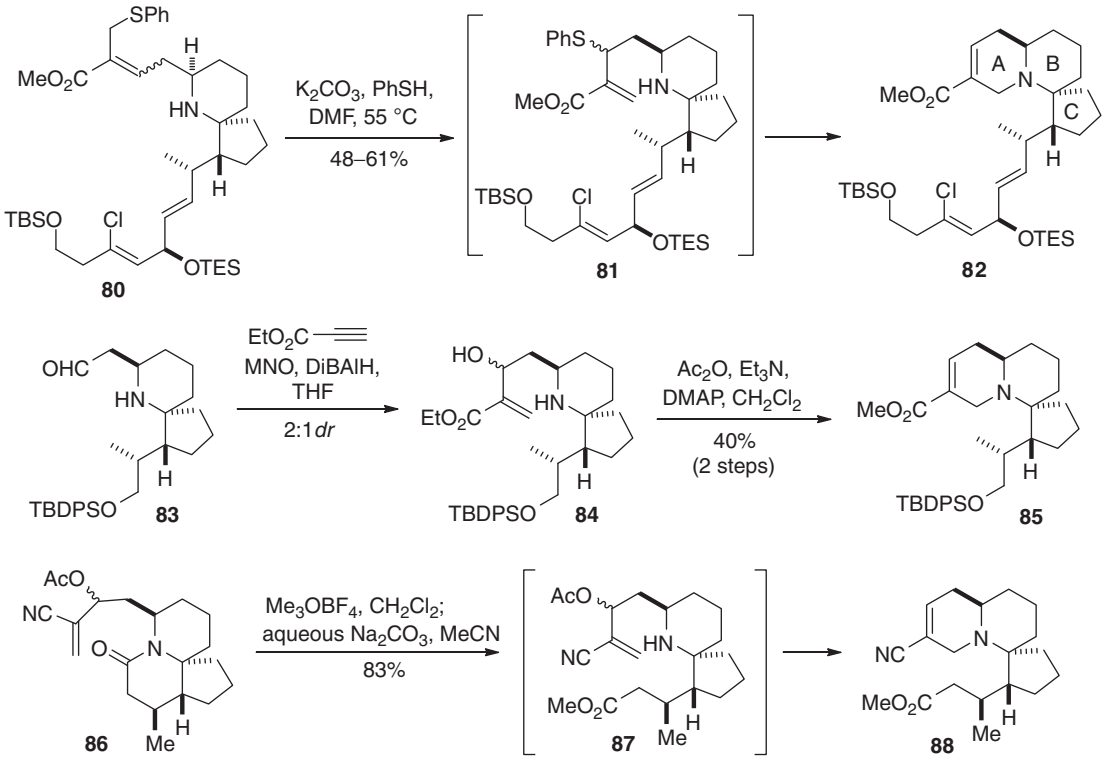


Amine	Yield
$BnNH_2$	90%
Pyrrolidine	86%
Piperidine	87%
$PhNH_2$	95%[a]
Pr^n_2NH	50%[a]

[a]with In $(OTf)_3$ (10 mol%).

Scheme 11

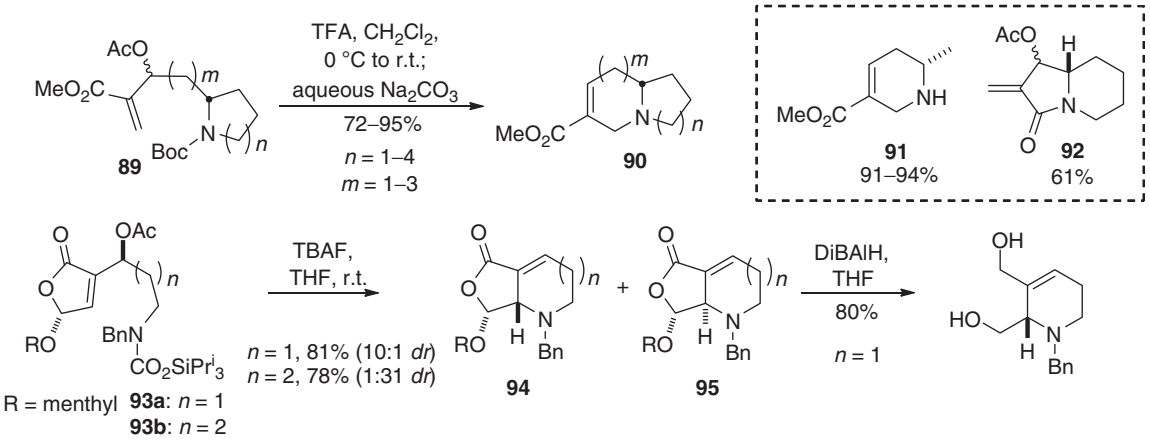
The intramolecular variant of this allylic substitution reaction has been applied in the synthesis of the natural product halichlorine (Scheme 12). Heathcock prepared **80** where the thiophenol serves as a leaving group.[32] Treating **80** with K_2CO_3 and PhSH promoted its isomerization to **81**, which then cyclized to **82**.



Scheme 12

Related approaches to prepare halichlorine were realized by Martin and by Clive.[33,34] These approaches both involved displacement of an acetate, but used different strategies to affect cyclization (Scheme 12). In Martin's formal synthesis, **84** could not be prepared by a Baylis–Hillman reaction, but was prepared by the addition of a vinylaluminum reagent to **83**. Acetylation of allylic alcohol **84** led to immediate cyclization to **85**. Clive employed a similar approach to close the A ring, proceeding through key intermediate **86**. This compound was prepared via the Baylis–Hillman reaction of the corresponding aldehyde and acrylonitrile. *O*-Alkylation of lactam **86** with Meerwein's salt (Me_3OBF_3) led to the formation of an imidate salt that gave amino ester **87** after hydrolysis. Amino alcohol **87** immediately underwent cyclization to **88** (83% yield).

The general scope of this intramolecular conjugate displacement reaction has been studied in greater detail (Scheme 13). Good-to-excellent yields of bicyclic amines (**90**) were obtained for a series of MBH adducts generalized by **89**.[35,36] Treatment of **89** with trifluoroacetic acid (TFA) cleaves the *N*-Boc group to produce a salt, which then cyclizes on treatment with aqueous base. The size of the nitrogen heterocycle in the starting material has no impact on the reaction. Acyclic MBH adducts also participate, as demonstrated by the excellent yield by which **91** was obtained. Furthermore, tether lengths where $m = 1–3$ are well tolerated. A shorter tether ($m = 0$), however, leads to the formation of lactam products, such as **91**. This is a manifestation of Baldwin's rules, where conjugate displacement is disfavored due to its 5-endo-trig geometry.

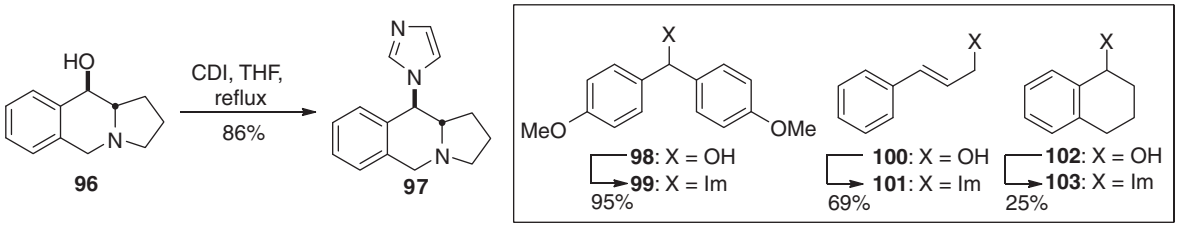


Scheme 13

An asymmetric route to 2,3-substituted piperidines and azepanes was developed based on this strategy with menthol serving as a chiral auxiliary (**93**).[37] Cyclization of **93a** and **93b** was induced by the deprotection of triisopropylsilyl carbamates with tetrabutylammonium fluoride (TBAF). Curiously, the size of the newly formed ring affects the relative stereochemistry of the product. In the case of **93a**, piperidine diastereomer **94** was the major product. A longer tether (**93b**) favors azepane rings, with *trans*-diastereomer **95** being formed as major product from **93b**. The differences in diastereoselectivity for the six- versus the seven-membered rings are due to an interplay of steric and stereoelectronic influences. The cyclization of **93a**–**94** reflects the steric influences of a chair-like transition state that disfavors a *syn* approach of the amine relative to the leaving group. In contrast, azepane **95** is formed by the *syn* approach that is consistent with the intermolecular reactions covered earlier, reflecting the greater conformational flexibility of the seven-membered transition state.

6.02.2.3 Carbonyldiimidazole (CDI) Activation of Alcohols

N-Alkylimidazoles can be prepared in one step from alcohols by reaction with CDI, which simultaneously serves as an activating agent and imidazole source. This reaction is relatively limited and works best when the alcohol is benzylic with additional stabilization provided by a neighboring heteroatom or conjugation. Scheme 14 highlights several alcohols that react with CDI in refluxing THF to provide *N*-alkylimidazoles.[38] Neighboring group participation by the amine in **96**, and additional conjugation in **98** and **100**, leads to good yields in these reactions. In comparison, the absence of additional stabilizing features in α-tetralol (**102**) contributes to the low yield of **103** under these conditions. Although neighboring heteroatoms are not present in **98** or **100**, reasonable yields were obtained due to additional conjugation of the carbocation.



Scheme 14

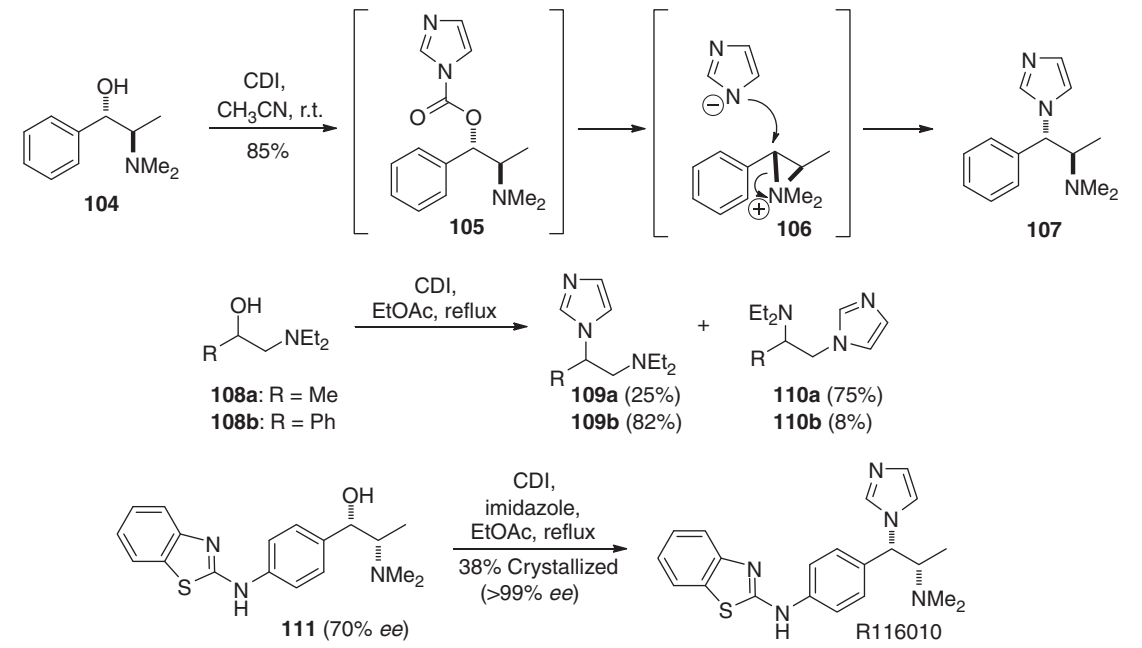
Imidazole carbamates are clearly formed as stable intermediates, which then decompose to form the *N*-alkylimidazole at higher temperatures. Contradictory evidence has been reported, leading to some debate about whether the final alkylation step occurs via an S_N1, S_Ni, S_N2, or double inversion pathway.[38–41] It is clear that the structure of the substrate has a significant influence on the mechanism and ease with which it occurs. Simple benzylic alcohols, such as *p*-methoxybenzyl alcohol, also give *N*-alkylimidazole products; however, they require much higher reaction temperatures (170 °C in NMP (*N*-methylpyrrolidone)).[40]

The presence of a neighboring heteroatom is necessary for the reaction of benzylic alcohols to occur at relatively low temperatures. Examining the results of several amino alcohols provides some insight into why such compounds are more reactive in the CDI reaction (Scheme 15). *anti*-Amino alcohol **104** produces *anti*-aminoimidazole **107** at room temperature.[41] The stereospecific outcome of this reaction suggests neighboring group participation to form aziridinium salt **106**. Further support for an aziridinium ion intermediate comes from the reactions of **108a** and **108b**.[40] Both **108a** and **108b** give mixtures of *N*-alkylimidazoles **109** and **110**. The ratio of **109** to **110** reflects the influence of substrate structure on competitive S_N2 and S_N1-like pathways for the ring opening of the aziridinium ion. Additional evidence for a double inversion pathway is offered by *syn*-amino alcohol **111**.[42] The reaction of **111** is consistent with a double inversion pathway, involving an intermediate aziridinium ion. Interestingly, the reaction of *syn*-**111** requires a higher temperature than *anti*-**104**, which could be indicative of the higher energy required to form a *cis*- versus a *trans*-aziridinium ion.

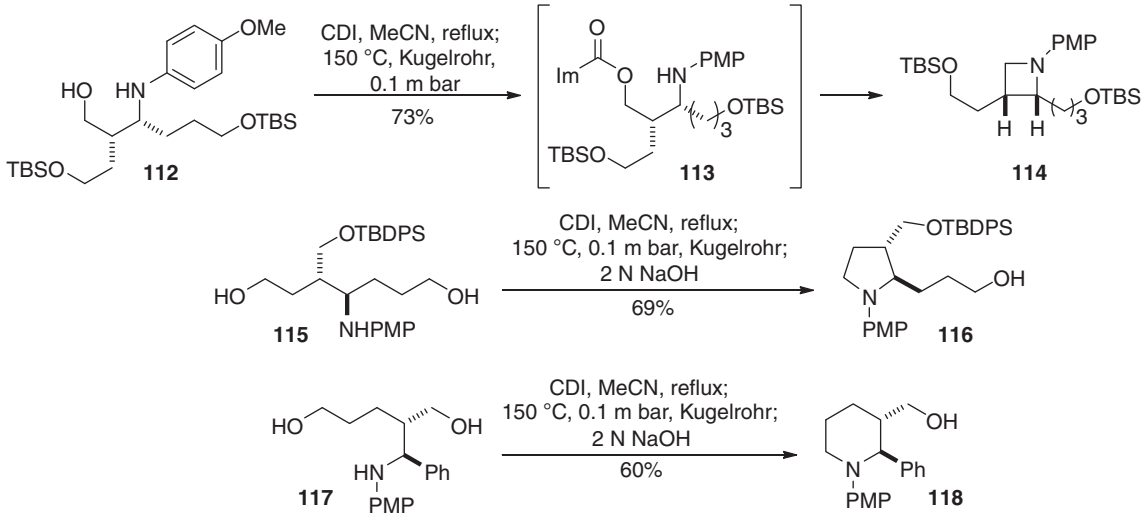
Christmann discovered that CDI activates primary alcohols toward cyclization (Scheme 16).[43,44] This serendipitous discovery was made while attempting to prepare a cyclic carbamate from **112** in order to determine its relative stereochemistry. The desired carbamate did not form; refluxing amino aniline **112** with CDI in acetonitrile only produced carbamate **113**. In order to force a reaction from **113**, this material was heated in a Kugelrohr oven at 150 °C under vacuum. However, azetidine **114** was produced in 73% yield rather than the expected cyclic carbamate. This method can also be used to prepare five- and six-membered rings. The reaction of **117** under these conditions is particularly interesting, as piperidine **118** is formed in preference to the alternative azetidine product.

6.02.2.4 Chlorosulfonyl Isocyanate (CSI) Activation of Allylic Ethers

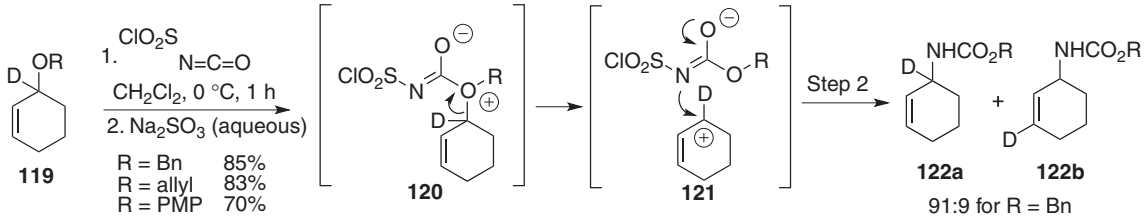
Ethers are typically poor leaving groups for substitution reactions. However, carbamates can be prepared from allylic ethers in a unique amination reaction with CSI as an activating agent. Young Hoon Jung has extensively studied this reaction and has used it to synthesize several alkaloid natural products.[18,45–51] CSI serves as an electrophile to activate allylic ethers by forming an oxonium ion (**120**, Scheme 17).[45] The oxonium ion is then converted into a carbamate (**122**) by competing S_Ni and S_N1



Scheme 15



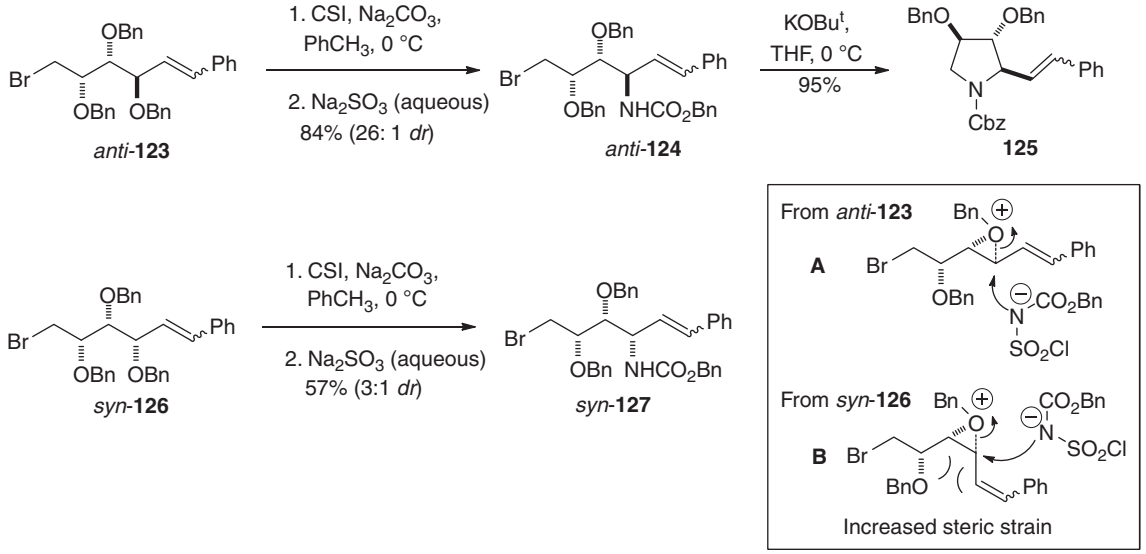
Scheme 16



Scheme 17

pathways. A deuterium labeling experiment found that **122a** was the main product from **119**. The regiochemical outcome of this experiment suggests that the major product is formed via an S_Ni pathway involving a tight ion pair.

The CSI reaction is chemoselective for allylic ethers and is compatible with polyether substrates. Polybenzyl ether *anti*-**123** cleanly yields Cbz-carbamate *anti*-**124** on treatment with CSI (Scheme 18).[46] Deprotonation of the carbamate with $KOBu^t$ coaxed this material to cyclize via a bromide displacement to pyrrolidine **125**, a key intermediate for preparing several alkaloid natural products. The CSI reaction of *anti*-**123** is high yielding (84%) and demonstrates impressive chemo-, regio-, and diastereoselectivity (26:1). It is interesting to note that *syn*-diastereomer **126** predominantly reacts with retention of stereochemistry to provide **127**, albeit with lower diastereoselectivity (3:1) and yield (57%).



Scheme 18

The varying levels of diastereoselectivity for these epimeric polyethers are due to a more S_N1-like mechanistic pathway, which is characteristic of CSI reactions with cinnamyl ethers.[48,49] Cinnamyl ethers exhibit a more pronounced solvent effect compared to simple allylic ethers, suggesting the formation of free allylic cation rather than a tight ion pair. Thus, the differences in diastereoselectivity for *anti*-**123** and *syn*-**127** can be rationalized by neighboring group participation to form oxonium ions **A** and **B** (Scheme 18, inset). The lower diastereoselectivity in the *syn*-series is due to steric interactions in **B** that are absent in the *anti*-series.

6.02.2.5 Mitsunobu Amination

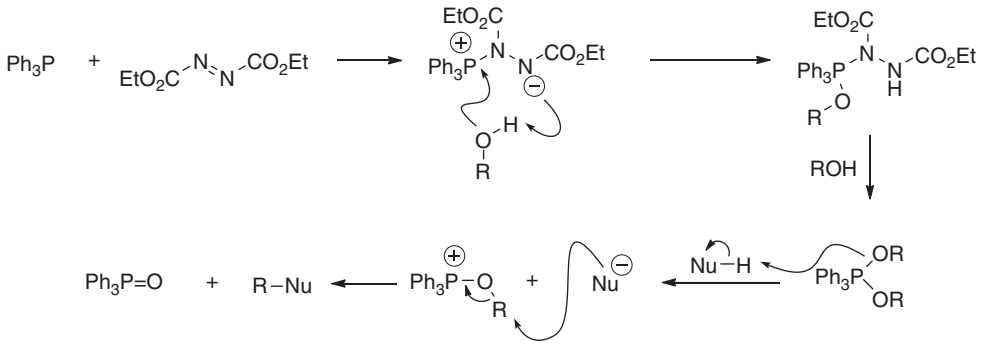
6.02.2.5.1 Mitsunobu reactions of imide and sulfonamide nucleophiles

The Mitsunobu reaction is the most common method by which primary and secondary alcohols are directly aminated without prior activation. Because this reaction has been reviewed in detail,[52–54] this section will present an overview of the Mitsunobu amination, providing a discussion of participating nitrogen nucleophiles and modifications to the classic conditions.

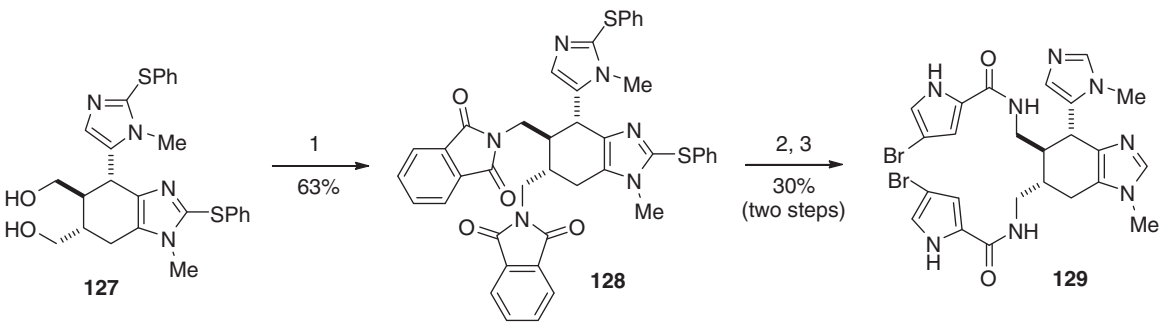
Standard Mitsunobu conditions involve the reaction of an alcohol with a pronucleophile in the presence of a phosphine and an azodicarboxylate, such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DEAD). Displacement of the hydroxyl group occurs with inversion and is driven forward by the oxidation of a phosphine to a phosphine oxide and reduction of the azodicarboxylate (Scheme 19). For a high-yielding reaction, the pronucleophile must be sufficiently acidic so that it is deprotonated by azodicarboxylate, typically a $pK_a < 11$ under standard conditions. Therefore, phthalimide and related imide Gabriel reagents work particularly well for Mitsunobu aminations.[55] Indeed, the pK_a of imide (imidodicarbonate) nucleophiles strongly correlates to the yields obtained in the Mitsunobu reaction with ethyl lactate in dimethylsulfoxide (DMSO).[56]

Phthalimide is generally a good nucleophile for amination under Mitsunobu conditions. For example, Ohta took advantage of phthalimide as an aminating nucleophile to prepare a **129** via the simultaneous displacement of two primary alcohols in **127** (Scheme 20).[57] Deprotection of **128** to the corresponding primary diamine was accomplished in the normal way by hydrazinolysis, followed by acylation to diamide **129**.

Phthalimide is effective for the displacement of both primary and secondary alcohols in the presence of DEAD and Ph_3P.[1] The deprotection of this group to a primary amine by Ing-Manske hydrazinolysis is not always straightforward, and these conditions are not always compatible with other functional groups present within a complex compound.[58,59] As a result, the development of modified Gabriel reagents is an important area of research.



Scheme 19

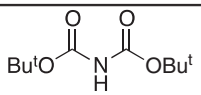
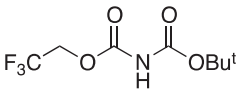
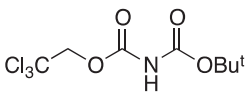
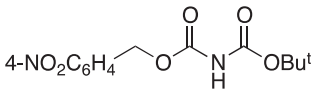


1. HNPhth, DEAD, PPh_3, THF, 0 °C to r.t., 63%; 2. $NiCl_2•6H_2O$, $NaBH_4$, THF, MeOH, 0 °C to r.t., 62%; 3. NH_2NH_2, 70 °C, then K_2CO_3, 4-bromo-2-(trichloroacetyl)pyrrole, DMA, r.t., 49%.

Scheme 20

Acyclic imides are simple alternatives to phthalimide that participate in Gabriel and Mitsunobu reactions. Di-*tert*-butyl iminodicarboxylate (**130**) is representative of these nucleophiles (Table 3). Initially introduced in 1964,[60] the use of **130** has become more prevalent with improved methods for its preparation (entry 1).[61,62] Although **130** is useful for the Gabriel amination, the

Table 3 Mitsunobu reactions of iminodicarbonates with 2-octanol

Entry	*Iminodicarbonate*	*Mitsunobu yield (%)*[a]	*Deprotection conditions*[b]	*Monodeprotection yield (%)*
1	 **130**	40	TFA, CH_2Cl_2, r.t.[c]	See Reference 64
2	 **131**	88	1 M NaOH, THF, H_2O, r.t.	96
3	 **132**	71	Zn, NH_4OAc	96
4	 **133**	76	H_2, $Pd(OH)_2$	92

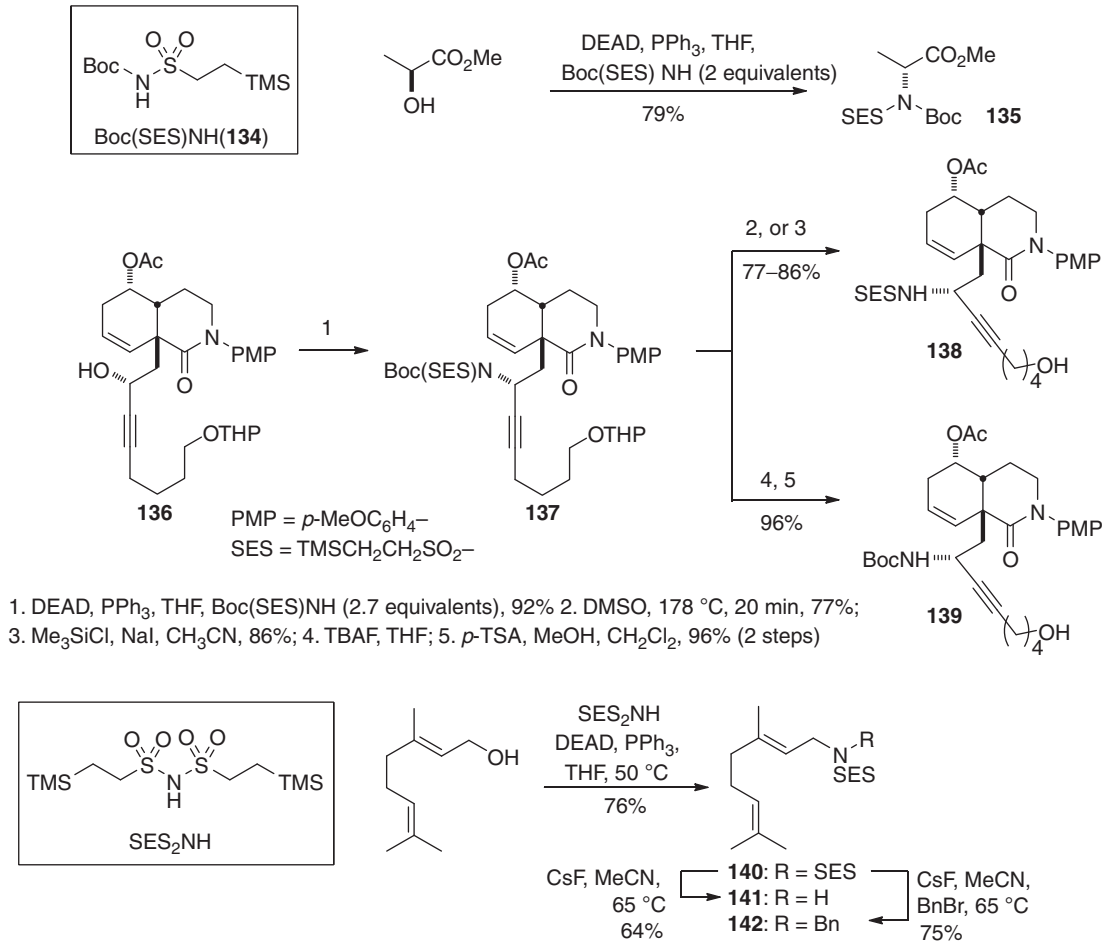
[a]Reaction with 2-octanol, DEAD, PPh_3, THF, r.t., overnight.

[b]Monodeprotection of the dicarbonate to an *N*-Boc carbamate.

[c]TFA selectively removes one of the Boc groups to give an *N*-Boc carbamate.[64]

yield for its reaction with 2-octanol under Mitsunobu conditions is moderate due to the relatively low acidity of its N–H bond.[63] Mitsunobu reactivity improves for mixed *tert*-butyl iminodicarbonates that contain an electron-withdrawing group (entries 2–4). The resulting products from these mixed iminocarbonates (**131–133**) can be deprotected to *N*-Boc carbamates via a variety of conditions, thereby increasing the utility of these nucleophiles. Furthermore, they are readily available in three synthetic steps from acid chlorides without the need for chromatography (≥80% overall yield).

Weinreb introduced *N*-acyl and *N*-alkyl *p*-toluenesulfonamides as pronucleophiles for the Mitsunobu reaction.[65] The *p*-toluenesulfonamide group is alkylated in good yield, but requires harsh reducing conditions for its deprotection to an amine. In contrast, the (trimethylsilyl)ethylsulfonyl (SES) group is a sulfonamide that can be cleaved under mild conditions by the addition of fluoride ion.[66] Hart noted the advantages of the SES group and incorporated it into sulfonamide **134**, a novel amine surrogate, which is compatible with the Mitsunobu alkylation of primary and secondary alcohols (**Scheme 21**).[67]



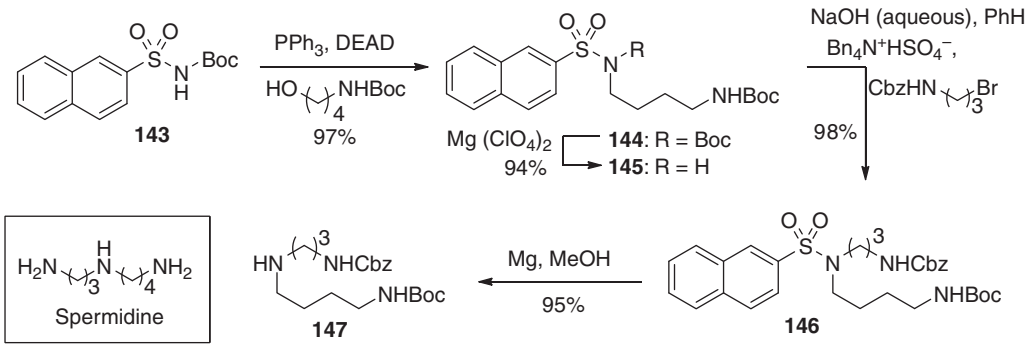
Scheme 21

It is interesting to note that although amination of (*S*)-lactate occurs with inversion, retention was observed with a more highly functionalized substrate, **136**. Retention of configuration in **137** was rationalized considering the proximity of the reaction site to the lactam and the likelihood of neighboring group participation with this group. A distinct advantage of using **134** as a nucleophile comes from the fact that either the SES or the Boc group can be deprotected under orthogonal conditions. Selective removal of the Boc group can be accomplished on heating **137** in DMSO, or by the *in situ* generation of trimethylsilyl iodide from trimethylsilyl chloride and NaI. In the case of **137**, the tetrahydropyran (THP) group is removed under both sets of conditions. Alternatively, the SES group can be cleaved from **137** using TBAF. The THP group is not removed under these conditions, but can be deprotected with *para*-toluenesulfonic acid (*p*-TSA) to give **139**.

Weinreb introduced SES_2NH as a pronucleophile for the Mitsunobu reaction.[68] This nucleophile requires elevated temperatures even for reactions with primary alcohols. Bissulfonimides are robust amine protecting groups; *N*-alkylated products derived from SES_2NH are stable overnight at room temperature to 1 N HCl, 5% NaOH, and benzyl Grignard reagents. Like di-*tert*-butyl iminodicarbonate (**130**), products derived from SES_2NH can be selectively monodeprotected. Treatment of **140** (the Mitsunobu product of SES_2NH and geraniol) with CsF in acetonitrile at 65 °C gives **141**. Both SES groups cannot be removed in one-pot;

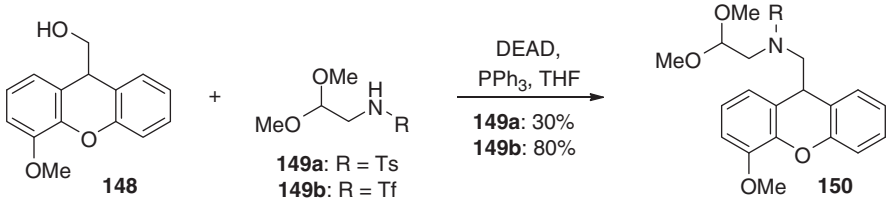
however, it is possible to affect a one-pot SES deprotection/*N*-alkylation process by adding an alkyl halide during deprotection with CsF.

Naphthylsulfonamide **143** is another *N*-acyl sulfonamide nucleophile that was developed as an alternative to benzenesulfonamide (Scheme 22).[69] This nucleophile was used in a short synthesis of spermidine derivative **147**. Following the high-yielding alkylation of **143** using DEAD and Ph_3P, the sulfonamide Boc group was selectively removed from **144** to provide **145**. Alkylation of **145** was completed using phase-transfer conditions, which gave a higher yield of **146** (98%) than the corresponding Mitsunobu reaction (60% yield, not shown). The 2-naphthalenesulfonamide could then be reductively removed by magnesium in methanol. These conditions are more convenient and milder in comparison to the standard conditions used for the reductive cleavage of benzenesulfonamide [Na, NH_3 (l)].



Scheme 22

The acidity of the sulfonamide N–H bond affects the yields of Mitsunobu reactions using these ammonia surrogates. An excellent example involves the amination of xanthene **148** with *N*-alkyl sulfonamides **149a** and **149b** (equation 11).[70] Although a low yield (30%) was obtained with the *N*-tosyl nucleophile **149a**, *N*-trifluorosulfonamide **149b** significantly improved the yield of this reaction.



(11)

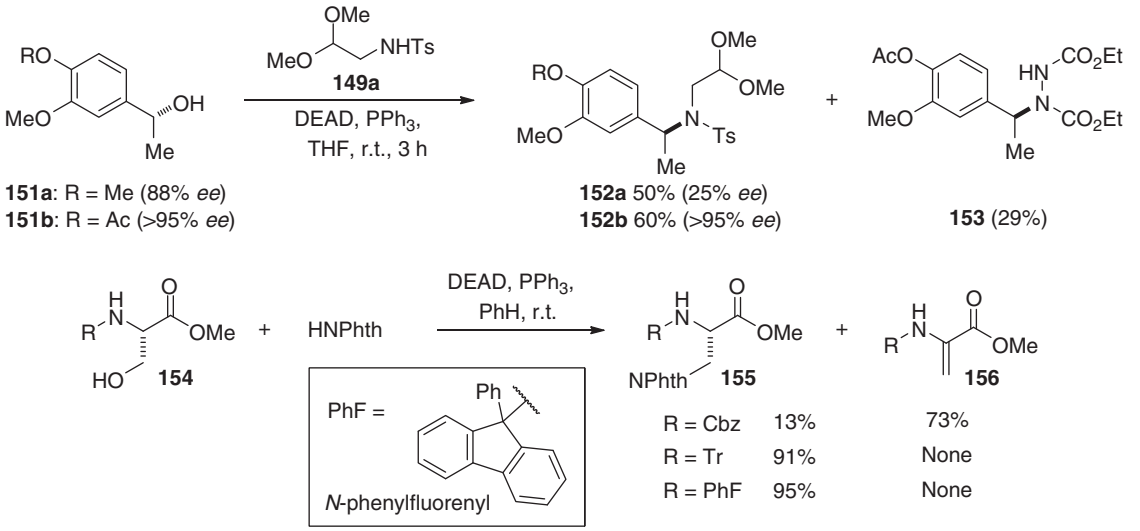
Undesirable reaction processes can occur in certain cases where alcohols generate stabilized carbocations, or with substrates particularly susceptible to elimination. The Mitsunobu reaction of benzylic alcohol **151a** and *N*-tosyl amine **149a** unexpectedly occurred with significant erosion of stereochemistry due to a competitive S_N1 process (Scheme 23).[71] Replacing the *p*-methoxy group with an acetate group (**151b**) sufficiently attenuated the reactivity of this system so that **152b** was formed with clean inversion (60% yield). The balance of this reaction was identified as alkylated hydrazine **153**. Hydrazines such as **153** are frequently formed as by-products when *N*-alkyl sulfonamides are used as nucleophiles, due to the low acidity of sulfonamide.[65]

Serine esters generally undergo elimination rather than substitution under Mitsunobu conditions. Elimination to **156** was the predominate pathway for the Cbz derivative of **154** when amination was attempted with phthalimide using DEAD and Ph_3P.[72] Judicial choice of the *N*-protecting can avoid the elimination pathway. *N*-Trityl (Tr) and *N*-phenylfluorenyl (PhF) are known to prevent epimerization in amino acids. By using these sterically demanding protecting groups, serine esters give amination products **155** in excellent yield (91–95%).

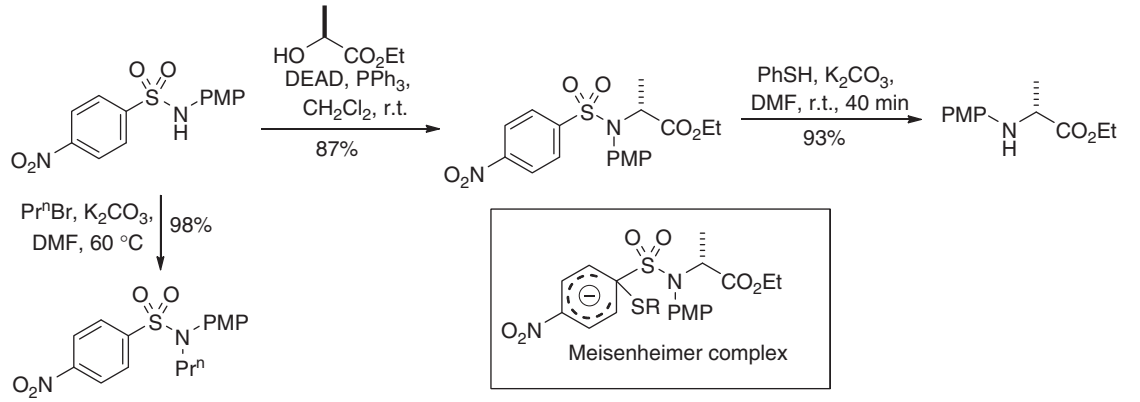
6.02.2.5.2 Fukuyama-Mitsunobu conditions: nitrobenzenesulfonamide nucleophiles

Nitrobenzenesulfonamides are the most commonly employed sulfonamide nucleophiles in the Mitsunobu reaction.[73] Fukuyama introduced *N*-alkyl nitrobenzenesulfonamides (nosyl group, Ns) as nucleophiles for the Mitsunobu amination in 1995 (Scheme 24).[74] The electron-withdrawing nature of the nitro group serves to activate nosyl-protected amines in the Mitsunobu reaction. Thus, alkylations of this amine equivalent occur in high yield at ambient temperature with primary and secondary alcohols. The nosyl group is stable to strong acids and hydroxide but is removed by thiolate nucleophiles.

Cleavage of the sulfonamide is thought to occur via nucleophilic aromatic substitution. Addition of thiolate generates a Meisenheimer complex, which then decomposes to a thioether, SO_2, and the secondary amine. The most common deprotection conditions use either thiophenol or thioglycolic acid ($HSCH_2CO_2H$) in the presence of base. An advantage of thioglycolic acid is the fact that the cleavage side product, nitrophenylthioacetic acid, can be washed away from the product with aqueous $NaHCO_3$.



Scheme 23



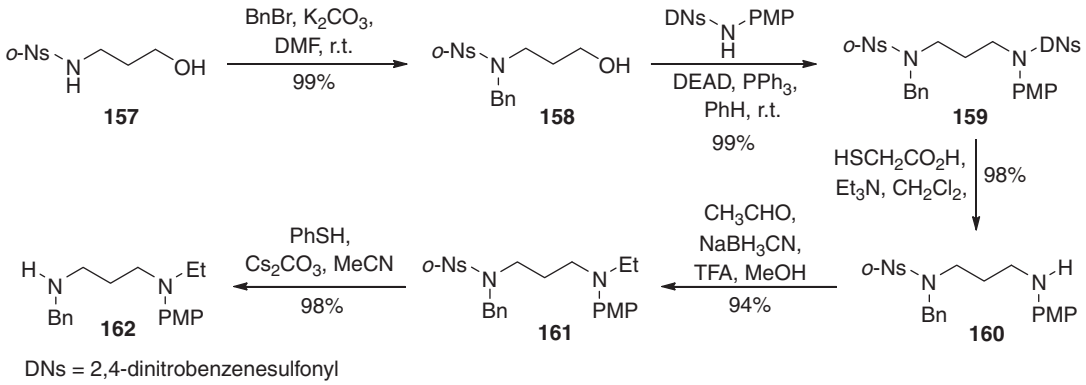
Scheme 24

The *ortho*- and *para*- isomers of nitrobenzenesulfonamide have comparable reactivity in the alkylation step, but have slightly different reactivity in the deprotection step. Nucleophilic aromatic substitution is less regioselective in the case of *para*-nosylates, with minor products arising due to attack at the nitro group.[75] In contrast, the *ortho*-isomer does not suffer from these regioselectivity issues.

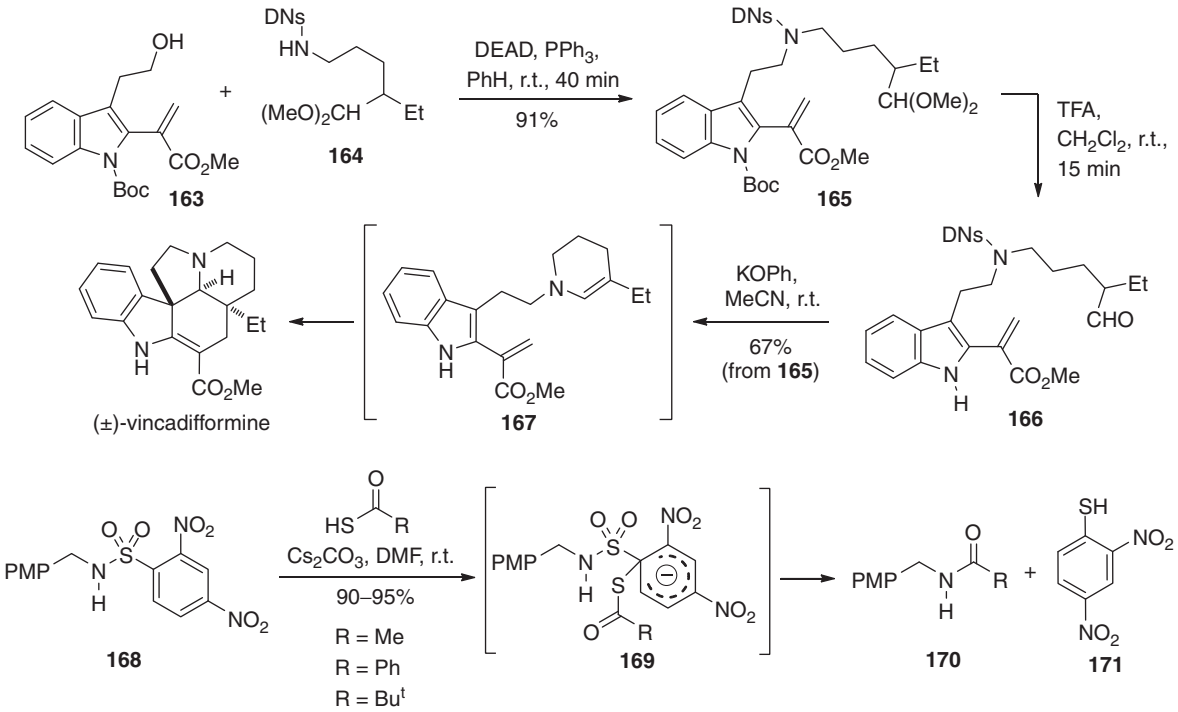
The use of *N*-alkylated 2,4-dinitrobenzenesulfonamides (DNs) was also studied by Fukuyama (Scheme 25).[76] The DNs group can be alkylated to the corresponding *N*,*N*-dialkylsulfonamide in high yield using Mitsunobu conditions or by a traditional displacement under basic conditions. It is more reactive toward S_NAr than the related mononitrobenzenesulfonamides. This presents an advantage for preparing differentially protected polyamines, as the DNs group can be selectively deprotected in the presence of *o*-Ns. The value of this new activating group and its selective deprotection was demonstrated in the preparation of diamine **162**.

2,4-Dinitrobenzenesulfonamides are susceptible to cleavage using other nucleophiles aside from thiolates. This can be useful in the context of complex substrates containing other reactive functional groups.[77] This advantage is apparent in the synthesis of the aspidosperma alkaloid vincadifformine (Scheme 26). A Fukuyama–Mitsunobu reaction united indole fragment **163** with DNs-protected amine **164**. Following the hydrolysis of the acetal to aldehyde **166**, an elegant cascade of reactions (enamine formation and then an inverse demand Diels–Alder reaction) was initiated by cleavage of the dinitrobenzenesulfonamide group with potassium phenoxide. Deprotection with potassium phenoxide was necessary to avoid an unusually rapid Michael addition between thiolate nucleophiles and the acrylate group within **166**.

The enhanced reactivity of the 2,4-dinitrobenzenesulfonamide was essential for a clever deprotection/acylation sequence of **168** (Scheme 26). Deprotection method was developed using thioacids under basic conditions. The resulting Meisenheimer complex (**169**) decomposes to form an amide and a thiophenol product. This reactivity is unique to the matched nucleophilicity



Scheme 25

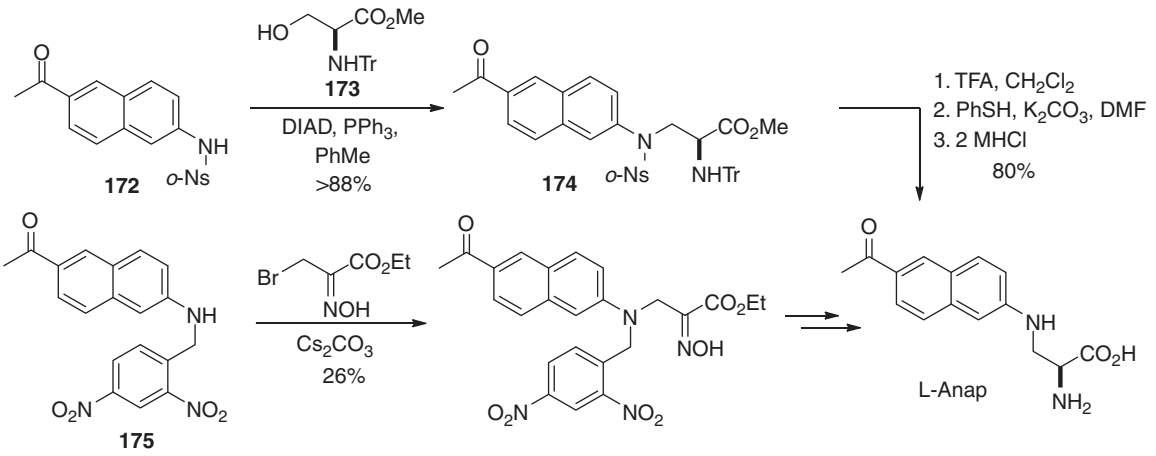


Scheme 26

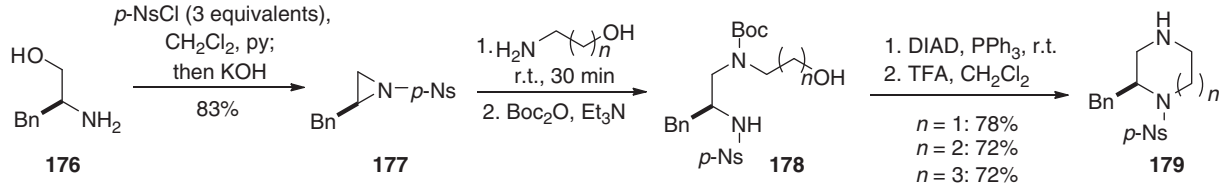
of a thioacid and the electron-deficient DNs group. Mononitro derivatives of **168** were unreactive under these conditions and no reaction was observed when the thioacid was replaced with a carboxylic acid.

The Fukuyama–Mitsunobu reaction is a reliable and robust amination method that can be successful when other traditional alkylation methods fail. These conditions become especially useful for poor nucleophiles such as arylamines. A synthetic approach to prepare the fluorescent amino acid L-Anap was developed involving a Fukuyama–Mitsunobu reaction between nosyl-protected 2-naphthylamine **172** and *N*-tritylserine methyl ester **173** (Scheme 27).[78] As addressed previously (Scheme 23, above), the trityl protecting group on serine is necessary to suppress an elimination reaction that commonly occurs under Mitsunobu conditions. Three deprotection steps were then necessary to provide L-Anap in an otherwise short route. Despite the somewhat lengthy deprotection protocol, this route was an improvement over the original synthesis, which required eight steps and suffered from a low-yielding alkylation of **175**.[79]

Heterocycles of various sizes are prepared by the intramolecular alkylation of nosylamides. Franzyk has developed a short, modular route to prepare chiral 1,4-diazaheterocycles that form C–N bonds in an iterative manner (Scheme 28).[80] This route begins by treating amino alcohol **176** with an excess of *p*-nosyl chloride to prepare aziridine **177**. Ring opening of the aziridine with an amino alcohol and Boc protection of the secondary amine gave **178**, which was then cyclized on exposure to diisopropyl azodicarboxylate (DIAD) and Ph_3P. Treatment with TFA removed the Boc group to provide the 1,4-azacycles **179**. Notably, the four-step sequence from **177** was high yielding and only required chromatography after the final step. Heterocycles ranging in size



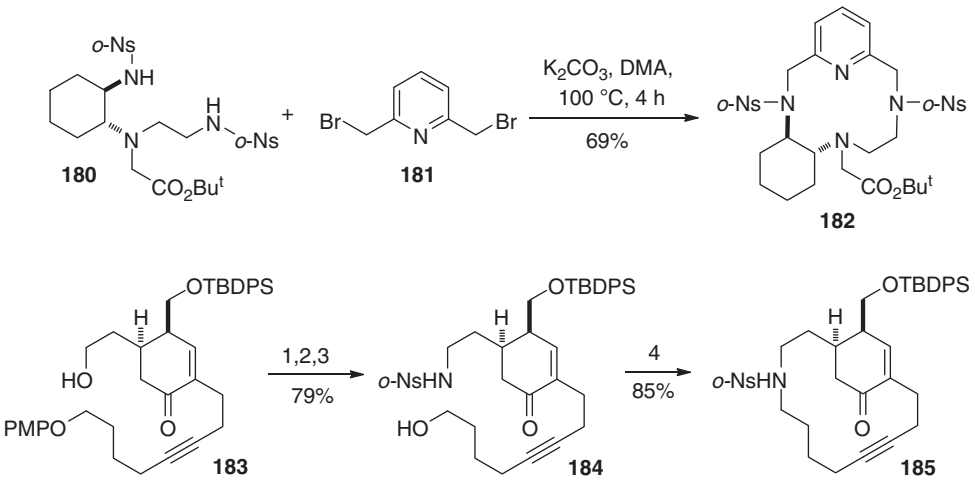
Scheme 27



Scheme 28

from piperazine to 1,4-diazocane were prepared using this method. However, the Fukuyama–Mitsunobu reaction failed for the preparation of medium-sized rings (9–10 membered rings, **178** $n=4$ and 5).

Although the formation of medium-sized rings is generally challenging due to ring strain, larger macrocyclic azocycles can be prepared in good yield from nosyl-amines (Scheme 29). Triamine **180**, which has two activated nitrogens, was alkylated with bisbromo pyridine **181** in 69% yield to form 12-membered metacyclophane **182**.[81] An approach using iterative Fukuyama–Mitsunobu reactions was used to synthesize **185**, an intermediate in the synthesis of manzamine A.[82] Strained macrocycles typically require high dilution conditions; however, this 15-membered ring was formed at a relatively high concentration (0.01 mol l^{-1}).

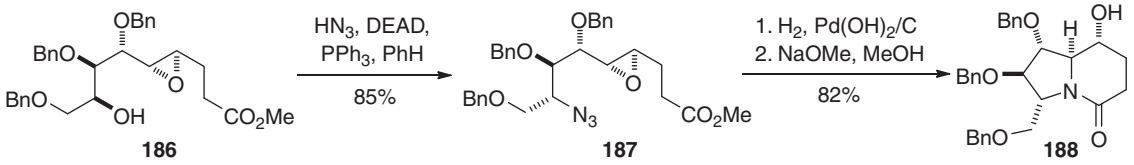


1. *o*-NsNHBoc, DEAD, Ph_3P, PhH, r.t.; 2. TFA, r.t.; 3. CAN, $MeCN/H_2O$, 0 °C; 4. DEAD, PPh_3, $PhCH_3$ (0.01 mol l^{-1}), r.t.

Scheme 29

6.02.2.5.3 Mitsunobu reactions with azide and other nitrogen nucleophiles

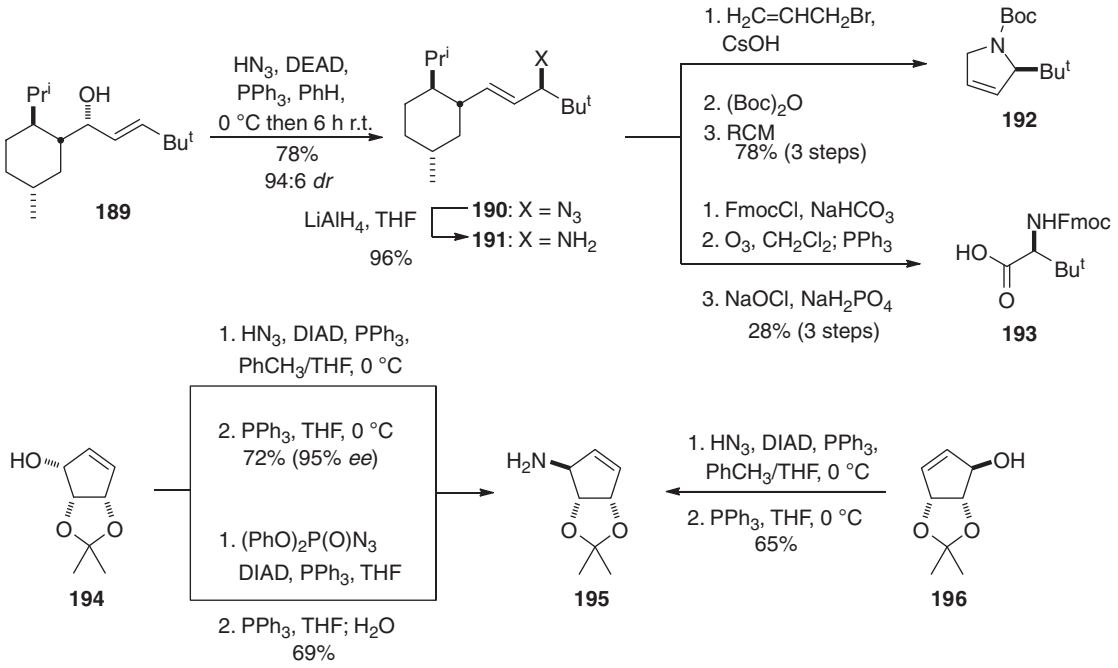
Hydrazoic acid is used to introduce azides under Mitsunobu conditions.[83] It shares many of the known hazards of its conjugate base, azide, but is also volatile. Despite these hazards, this compact nucleophile is a useful surrogate for primary amines. Azide **187** was prepared by the reaction of **186** with hydrazoic acid under standard Mitsunobu conditions (Scheme 30).[84] After hydrogenation of azide **187** to a primary amine, treatment with sodium methoxide promoted intramolecular epoxide opening and acylation to bicyclic lactam **188**.



Scheme 30

Allylic alcohols are interesting substrates for the Mitsunobu reaction due to the complication of regioselectivity. Inversion by an S_N2 process is expected, but reaction can also occur via an S_N2' pathway when favored by sterics and/or electronic factors.[85] The Mitsunobu reaction of allylic alcohols with hydrazoic acid is further complicated by the fact that the allylic azide products can undergo thermodynamic 3,3-sigmatropic rearrangements. It is not always trivial to identify the mechanistic pathway for these reactions, as a S_N2 reaction/3,3-rearrangement and S_N2' processes would provide identical products.

The Mitsunobu reaction of allylic alcohol **189** and hydrazoic acid leads to a mixture of epimeric allyl azides **190**, favoring the *β*-anomer shown in Scheme 31.[86] The ratio of diastereomers and regioisomers was studied for a series of compounds where the *tert*-butyl group was replaced with other alkyl groups, including a phenyl ring. This led to the conclusion that azide **190** was formed by an inversion/rearrangement process. The value of allylic amine **191** as a synthetic intermediate was then demonstrated by its divergent conversion to pyrrolidine **192** and amino acid **193** via brief sequences.



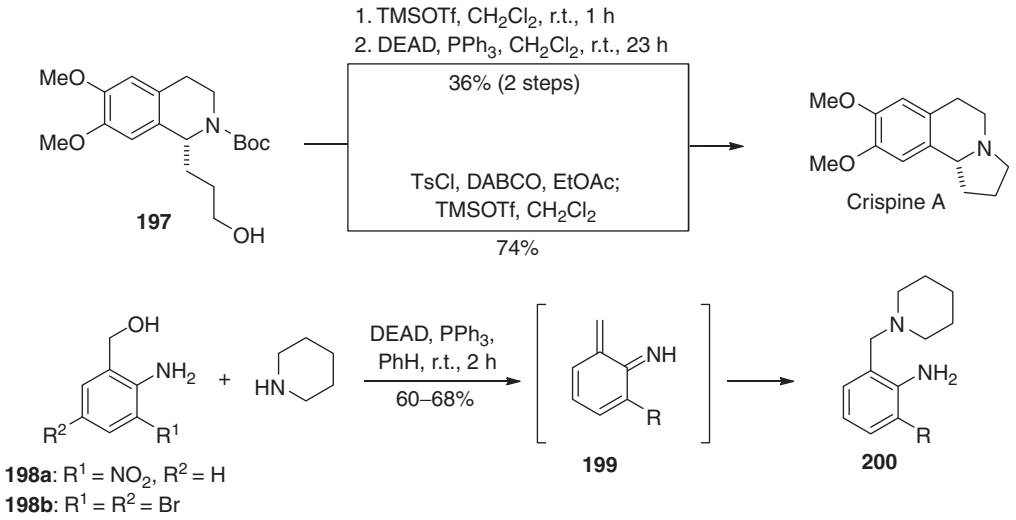
Scheme 31

The 3,3-sigmatropic rearrangements of allylic azides can be particularly problematic for pseudosymmetric substrates, such as allylic alcohol **194** (Scheme 31). Enantiopure **194** can be prepared in a short, four-step sequence from D-ribose and thus represents a useful precursor for allylic amine **195**.[87] To prevent scrambling of stereochemistry, Mitsunobu amination of **194** must occur with clean inversion without competing S_N2' reaction or rearrangement. Carell discovered that reaction temperature was critical for preparing **195**. Amine **195** is isolated in $<80\%$ *ee* if the Mitsunobu reaction is conducted at room temperature. Conducting the reaction at higher temperature leads to increased erosion of stereochemistry, with complete racemization within hours at 60 °C due to sigmatropic rearrangement. Lowering the reaction temperature to 0 °C for the Mitsunobu and Staudinger reactions was

critical to suppress rearrangement and provided **195** in 95% *ee*. Interestingly, diastereomeric allyl alcohol **196** also provides **195**. In this case, *syn*-S_N2' attack of azide occurs due to an unfavorable steric and/or electronic interactions with the acetonide on the α-face of the molecule.

The hazards of volatile hydrazoic acid can be avoided by using diphenylphosphoryl azide [DPPA, $(PhO)_2P(O)N_3$] in its place. A direct comparison between DPPA and hydrazoic acid can be made for the preparation of **195** from **194**, where essentially identical results were obtained.[88] As above, the DPPA reaction required careful monitoring of temperature and gave one enantiomer according to NMR analysis of the Mosher amide derivative.[89]

Amines are not typically used in the Mitsunobu reaction because most are not sufficiently acidic to react in good yield. The cyclization of secondary amines by intramolecular Mitsunobu reaction is possible, but yields are generally inferior to standard alkylation conditions (Scheme 32). Crispine A was prepared by two deprotection/alkylation sequences from **197**.[90] The Mitsunobu sequence gave only a moderate 50% yield for cyclization (36% yield overall). In comparison, a one-pot alcohol activation/*N*-Boc deprotection sequence provided crispine A in 74% yield.



Scheme 32

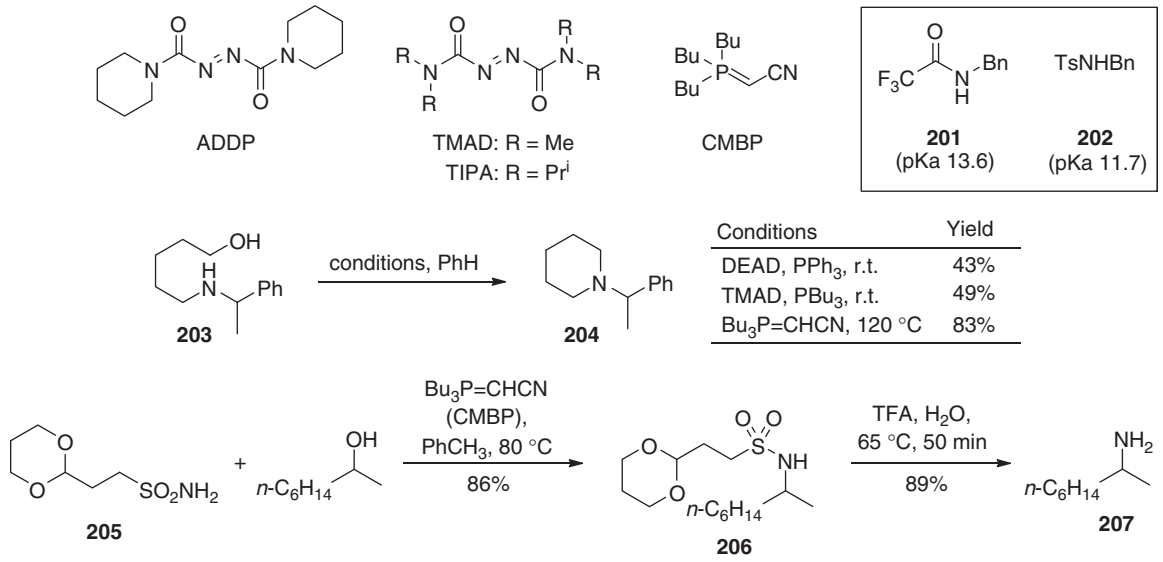
Intermolecular amination by a secondary amine under Mitsunobu conditions is even more rare than the intramolecular reaction. An example involving benzyl alcohol **198** and piperidine is shown in Scheme 32.[91] This intermolecular amination is thought to occur via the formation of quinone methide intermediate **199**. The intermediacy of this reactive intermediate dictates that the benzylic alcohol has a specific substitution pattern, including an electron-withdrawing group *ortho* to the amino group.

6.02.2.5.4 Modified Mitsunobu reagents

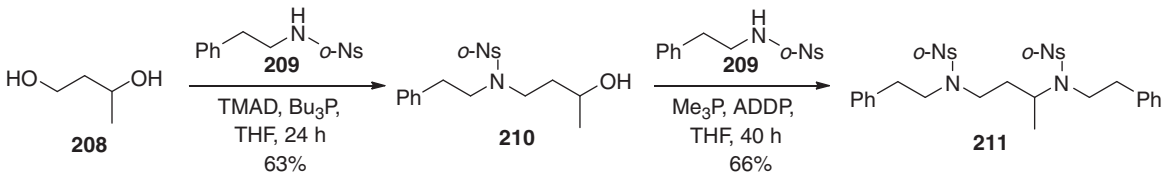
Tsunoda has developed several modified Mitsunobu reagents to improve the reaction scope with regard to less acidic nucleophiles (Scheme 33).[92–94] Three of these reagents, ADDP, TMAD, and TIPA, are amide analogs of azodicarboxylate. The zwitterion generated by conjugate addition of phosphine to these amide-containing azo derivatives is less stabilized in comparison to zwitterion generated from DEAD and DIAD. In these reagents, the amide carbonyls are more electron-rich than their ester counterparts in DEAD/DIAD. As a result, conjugate addition of phosphine generates a more strongly basic zwitterion due to the fact the amides are not as capable of stabilizing the alpha anion. As a consequence of this electronic effect, Ph_3P must be replaced by more nucleophilic trialkylphosphines in order to form the zwitterion intermediate. The three amide-containing reagents (ADDP, TMAD, and TIPA) all give better yields for the alkylation of **201** and **202** with primary alcohols at room temperature as compared to DEAD and Ph_3P.[93]

An additional reagent, cyanomethylenetributylphosphorane (CMBP), was developed based on the similarity between an ylide and the zwitterionic intermediate formed in the Mitsunobu reaction.[95] CMPB is a unique, single-component, Mitsunobu reagent. At room temperature, it generally alkylates **201** and **202** in yields comparable to TMAD/Bu_3P and gives better results than DEAD/Ph_3P for these nucleophiles. A unique advantage of CMBP is its ability to promote high-yielding cyclizations of amino alcohol **203** to piperidine **204** at elevated temperatures.[94] However, this amino alcohol cyclization does require sealed tube conditions. A more recent development involves CMBP-mediated amination of alcohols using amines activated by the 2-(1,3-dioxane-2-yl)ethylsulfonyl (Dios) group (e.g., **205**).[96] Excellent yields for the alkylation of **205** with 2-octanol were obtained, and the Dios group can be removed from the product **206** under acidic conditions.

Tsunoda's reagents are useful for the selective amination of primary versus secondary alcohols. Higher yields had been noted for the alkylation of **201** primary alcohols using TMAD/Bu_3P.[93] Franzyk found a similar selectivity for the alkylation of *o*-nosyl-activated amine **209** with diol **208** using TMAD/Bu_3P (Scheme 34).[97] Amination of the remaining secondary alcohol was



Scheme 33



Scheme 34

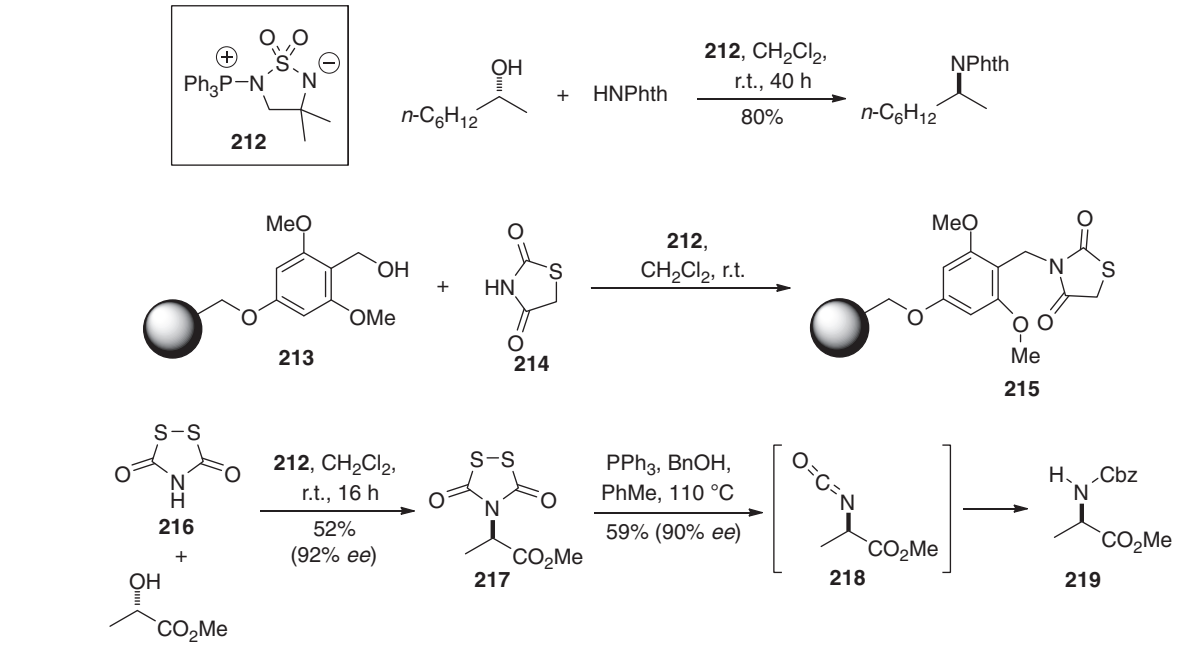
completed using the more reactive ADDP/Me_3P reagent combination, providing **210** after 40 h at room temperature. The identity of the phosphine reagent has an important impact on selectivity, as the pairing of TMAD/Me_3P (instead of Bu_3P) promotes the alkylation of *o*-nosylamides with *sec*-butanol in 51% yield.

Castro et al. at Merck serendipitously discovered zwitterionic reagent **212** during an attempted Mitsunobu reaction (Scheme 35).[98] Like CMPB, **212** is a single-component Mitsunobu reagent. Although **212** is capable of promoting the amination of secondary alcohols with phthalimide, it is most valuable for alkylating phosphine-sensitive nucleophiles. This reagent was superior to DEAD/Ph_3P for coupling thiazolidinone **214** to a resin-bound benzyl alcohol **213**.[99] Standard Mitsunobu conditions of DEAD/Ph_3P were also ineffective for the alkylation of dithiazolidine **216** due to phosphine-promoted degradation of **216**.[100,101] Betaine **212** successfully promotes the formation of **217** since this single-component reagent does not contain any free phosphine that would reduce the sensitive disulfide bond in **216**. Treating product **217** with phosphine generates an isocyanate (**218**), which can be trapped with benzyl alcohol to form a carbamate.

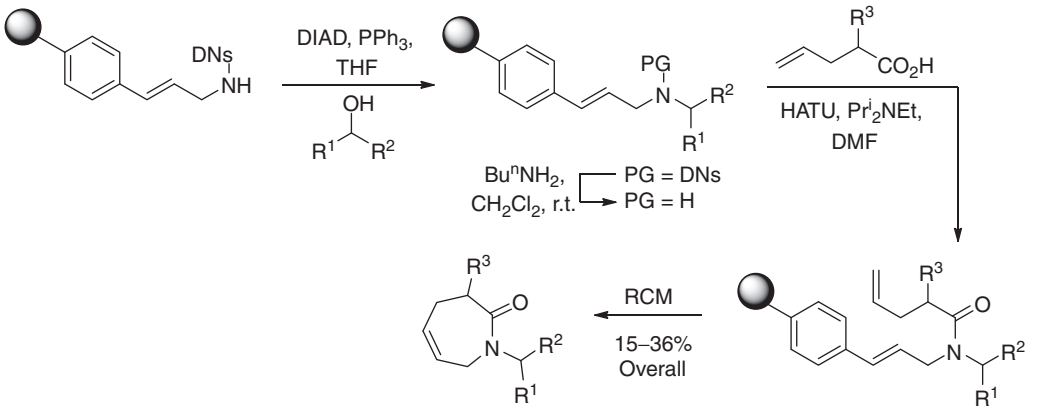
Despite the mild and robust nature of the Mitsunobu reaction, a major disadvantage of this method is the fact that purification can be challenging due to the formation of several stoichiometric byproducts, including triphenylphosphine oxide. Solid-phase synthesis is one means to address this problem. There are several approaches to this, with the most common being to tether either the alcohol or the nucleophile to a resin. Many examples appear in the literature featuring this strategy, with a representative case illustrated in Scheme 36.[102] By tethering the substrate to the solid phase, excess reagent can be used to force the reactions to completion. Purification is accomplished simply by washing the resin-bound product with solvent. Other approaches using polymer-bound reagents have also been reported.[103] However, these solid-phase approaches are only appropriate for a discovery-scale synthesis as they are expensive to scale up.

A more general approach involves substituting di-*tert*-butylazodicarboxylate (DTBAD) and diphenyl-2-pyridylphosphine for DEAD/Ph_3P (Figure 1).[104,105] Acidic work-up is the only purification needed with this reagent combination. DTBAD decomposes to isobutene and carbon dioxide and hydrazine under acidic conditions, and the presence of the pyridyl group can be protonated to render the phosphine and phosphine oxide water-soluble.

Barrett has reported a substitution process involving the *in situ* formation of a Vilsmeier-type reagent from oxalyl chloride and dimethylformamide (Scheme 37).[106,107] The resulting imidate salt activates alcohols toward displacement with phthalimide in acetonitrile. Although this reaction is not a true Mitsunobu-type process, it is complementary to that chemistry and affects the amination of unactivated alcohols and occurs with inversion. This process provides an alternative to the Mitsunobu reaction that is



Scheme 35



Scheme 36

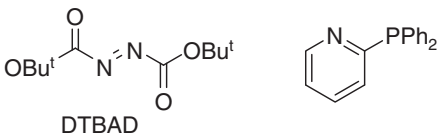
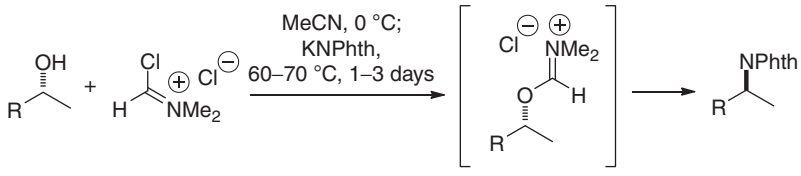


Figure 1 Modified Mitsunobu reagents.



Alcohol	Yield (%)	% *ee*
R = *n*-C_6H_{13}	95	96
R = Pr^n	92	92
R = Ph	73	72

Scheme 37

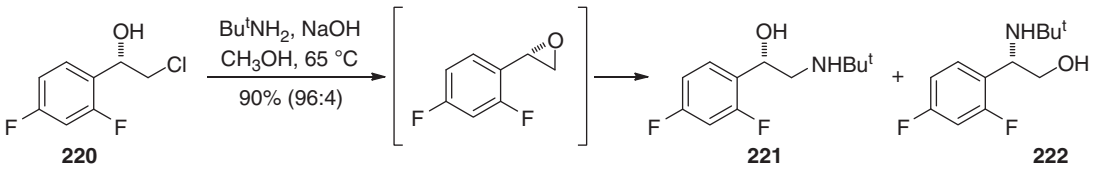
attractive for large-scale reactions, since the only by-products are DMF and potassium chloride. A clear disadvantage of this reaction is the need for long reaction times at elevated temperatures.

6.02.2.6 Nucleophilic Ring Opening of Epoxides

The ring-opening reaction of epoxides with amines and amine equivalents leads to 1,2-aminoalcohols. The release of ring strain is the primary driving force, with regioselectivity governed by a combination of steric and electronic factors. As covered in the previous edition of this work,[1] the ring opening of methyloxirane in water at 20 °C is a reference point for comparing the amine reactivities, which follows the order: piperazine > dimethylamine > pyrrolidine > piperidine > morpholine > diethylamine.[108] Secondary amines and amine equivalents are more common than primary amine nucleophiles, due to competitive polyalkylation of the latter.

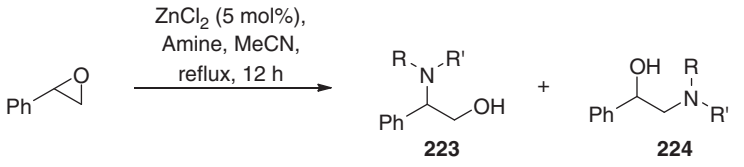
Nucleophilic addition to the C1 or C2 position of an epoxide is strongly influenced by the reaction conditions. Sterics are the dominant factor under basic and neutral conditions, with addition occurring at the sterically most accessible carbon. Regiochemistry is altered in the presence of Lewis acids, which increase the importance of electronic effects and can shift the mechanism toward an S_N1 pathway. Styrene oxide derivatives are simple substrates that are illustrative of these regiochemical considerations.

Under basic conditions chlorohydrin **220** forms an epoxide that reacts with Bu^tNH_2 to produce a mixture of 1,2-aminoalcohols favoring **221** (equation 12).[109] Since direct displacement of the chloride would lead exclusively to **221**, the formation of **222** supports the involvement of an epoxide intermediate. This reaction was conducted on a multikilogram scale, and hence it was important to optimize this reaction to minimize the formation of **222** and any polyalkylation side products. In this case, the ratio of MeOH/Bu^tNH_2 affected selectivity for reaction at C1. Bu^tNH_2 was used as a cosolvent, and increasing the ratio of MeOH/*t*-$BuNH_2$ from 1:1 to 1:5 improves selectivity for **221** from 4:1 to 96:4. The large excess primary amine and its hindered nature mitigate the formation of polyalkylation products.



(12)

Typical regioselectivity for a reaction under Lewis acidic conditions is observed for the aminolysis of styrene oxide with catalytic $ZnCl_2$ (equation 13).[110] Aminolysis was consistently selective for ring opening at the benzylic position for several nitrogen nucleophiles including aniline, 4-hydroxyaniline, and Pr^n_2NH. The reaction with benzylamine also favored **223** as the product, but was less selective and lower yielding. The capability of $ZnCl_2$ to catalyze the reaction of aniline and styrene oxide is noteworthy; aniline is weakly nucleophilic and no reaction is observed in the absence of $ZnCl_2$. Furthermore, this method is practical, as $ZnCl_2$ is inexpensive and easily handled.



Amine	Ratio **223**:**224**	Yield
$PhNH_2$	93:7	100%
p-$HOC_6H_4NH_2$	89:11	100%
Pr^n_2NH	80:20	100%
$BnNH_2$	59:41	40%

(13)

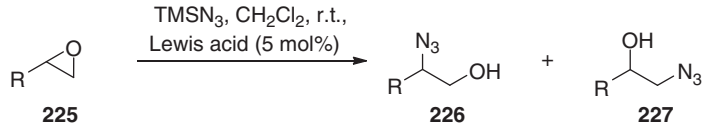
$TMSN_3$ has been employed as an ammonia surrogate to prepare amino alcohols from monosubstituted epoxides. The regioselectivity of this reaction can be adjusted by tuning the steric and electronic environment of the Lewis acid catalyst (equation 14, Table 4).[111] Imido complexes of chromium give relatively poor regioselectivity. Chromium catalyst **228** favors addition of azide to the benzylic position by only a 2:1 ratio (entry 1). The selectivity is even more modest for aliphatic epoxide substrate **225b** (entry 2). Regioselectivity was improved by rendering the Lewis acid less electrophilic by adjusting the metal and its ligands, albeit at the expense of decreasing the reaction rate (entries 3 and 4).

Lanthanide-based Lewis acids also accelerate the azidolysis of epoxides. $SmI_2(THF)_2$ catalyzes the addition of $TMSN_3$ in the typical manner, favoring **226** by a 10:1 ratio (Table 4, entry 5).[112] Curiously, use of the modified samarium complex **230** alters the regioselectivity to favor attack at the less hindered carbon to provide **227** as the major regioisomer (entry 6). The selectivity for this catalyst was attributed to the increased steric crowding due to the *t*-butyl group, which directs nucleophilic attack to the more accessible terminal carbon. Interestingly, $SmI_2(THF)_2$ promotes azide addition to the terminal carbon for aliphatic-substituted epoxides (entry 7).

Table 4 Tunable addition of $TMSN_3$ to monosubstituted epoxides

Entry	*Substrate*	*Lewis acid*	*Yield of **226** (%)*	*Yield of **227** (%)*
1[a]	Ph (**225a**)	$Cr(NBu^t)Cl_3(dme)$ (**228**)	64	31
2	Bu^n (**225b**)	$Cr(NBu^t)Cl_3(dme)$ (**228**)	39	26
3[b]	Ph (**225a**)	$W(NBu^t)_2(NHBu^t)_2$ (**229**)	95	–
4	Bu^n (**225b**)	$W(NBu^t)_2(NHBu^t)_2$ (**229**)	80	–
5	Ph (**225a**)	$SmI_2(THF)_2$	50	5
6	Ph (**225a**)	$SmI_2OBu^t(THF)_n$ (**230**)	21	73
7	n-C_6H_{13} (**225c**)	$SmI_2(THF)_2$	12	65

[a]Reaction complete in 3 h.
[b]Reaction complete in 12 h.



(14)

Glycidate esters (α,β-epoxy esters) are a synthetically valuable class of epoxide-containing compounds. Glycidic esters can be prepared in high enantiopurity by a variety of methods including the Darzens condensation,[113] Jacobsen epoxidation,[114] and the ring-closure of Sharpless dihydroxylation products.[115,116] Therefore, regioselective ring opening of these epoxides represents a useful route to prepare chiral derivatives of α-amino and β-amino acids. The β-amino-acid phenylisoserine is an important synthetic target that corresponds to the C13 side chain of Taxol (Figure 2). Derivatives of phenylisoserine became even more valuable targets following the discovery that 10-deacetylbaccatin III (10-DAB) could be isolated in a renewable manner from the needles of the English yew. Thus, the efficient preparation of phenylisoserine or its derivatives became an important synthetic goal for the semisynthesis of Taxol from 10-DAB.

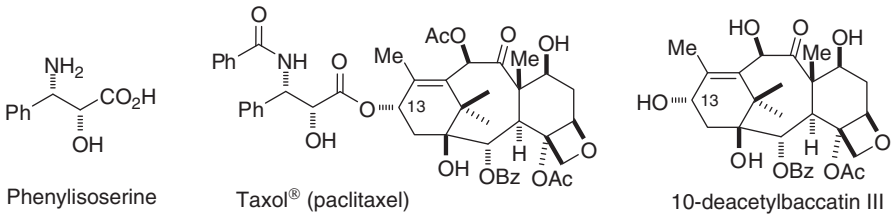
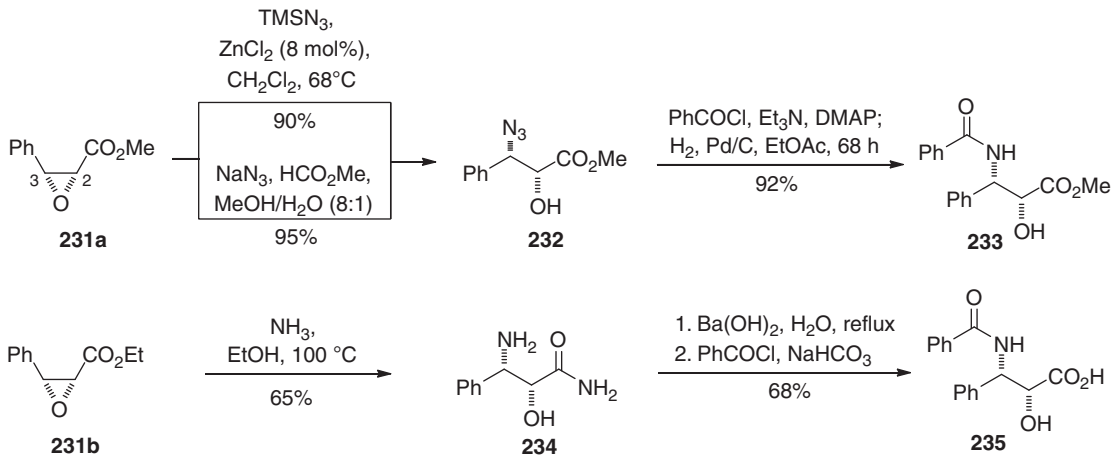


Figure 2 Phenylisoserine, Taxol, and 10-DAB.

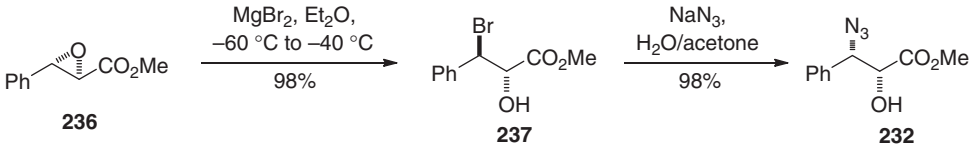
Several routes to prepare phenylisoserine derivatives are shown in Scheme 38. Azide nucleophiles react with *cis*-epoxide **231a** at C3 to produce the *threo*-amido alcohol **232** as the exclusive product.[117,118] Essentially identical results were obtained regardless of whether this reaction was promoted by catalytic Lewis acid ($TMSN_3$ and $ZnCl_2$) or conducted under basic conditions (NaN_3). In



Scheme 38

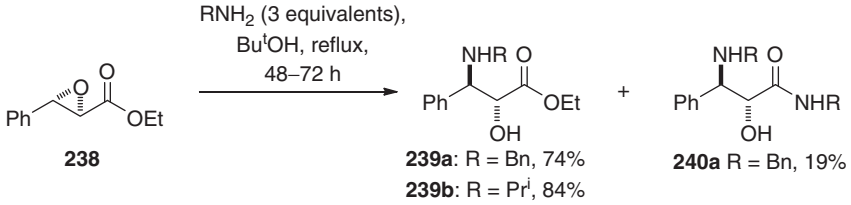
this case, it appears that both steric and electronic effects are operative to favor reaction at C3. The regioselectivity for the reaction of *cis*-epoxide **231b** with ammonia is consistent with the results for azide nucleophiles, but yields amide **234** due to competitive aminolysis of the ethyl ester.[114]

A clever double inversion strategy has been used to prepare *threo*-amino alcohol derivatives from *trans*-epoxide **236** (Scheme 39).[119] The reaction of *trans*-glycidate esters with magnesium halides salts promotes the formation of halohydrin **237** with excellent regioselectivity and is also general for substrates possessing an aliphatic group.[120] Subsequent displacement with azide provides **232** in quantitative yield. Compared to the route from the *cis*-epoxide (**231a**), this route from **236** requires one more step to obtain the *threo*-product.



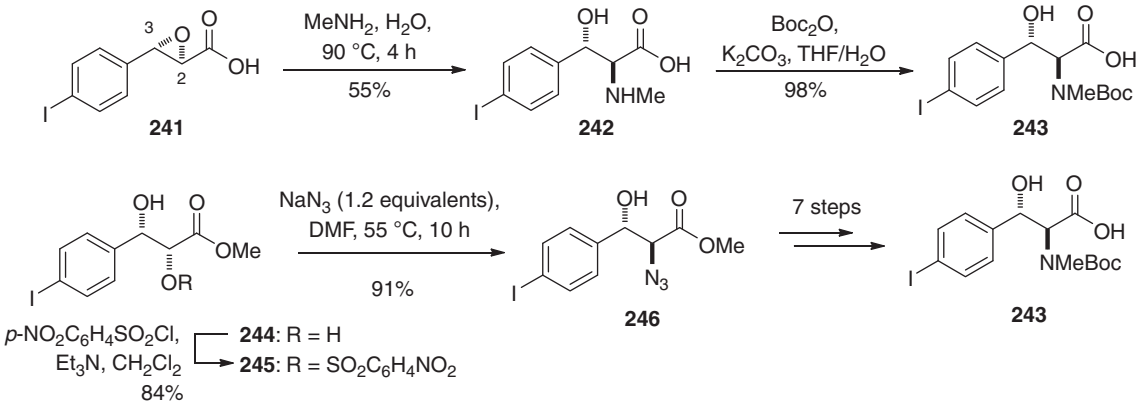
Scheme 39

Amine nucleophiles react relatively slowly with 3-phenylglycidic esters in the presence of protic solvents.[121] Amines preferentially react at C3, but regioselectivity is influenced by the identity of the amine and the solvent. Regioselectivity was approximately 4:1 for the reaction of **238** with benzylamine in Bu^{t}OH (equation 15). By comparison, the addition of isopropylamine to **238** cleanly produced ester **239b** in 84% yield after 72 h. Switching the solvent from Bu^{t}OH to EtOH (less hindered, more acidic) decreased the selectivity for **239b** to only 2:1.



(15)

In contrast to the regiochemistry for glycidate esters, nucleophilic ring opening of glycidic acid **241** occurs exclusively at C2 (Scheme 40).[122] Methylamine reacts with **241** at C2 to give **242** in 55% yield as the only product. The amine was then protected as a carbamate to obtain **243**, which was a key synthetic intermediate for preparing the natural product bouvardin. An alternative approach to **243** involving diol **244** was examined due to the moderate yield of **242**. This second route involved the selective activation of the C2 alcohol as *p*-nosylate **245** from diol **244**. Although the displacement of this sulfate with sodium azide gave **246** in excellent yield, multiple steps were ultimately required to adjust the protecting groups of this substrate to intersect **243**.

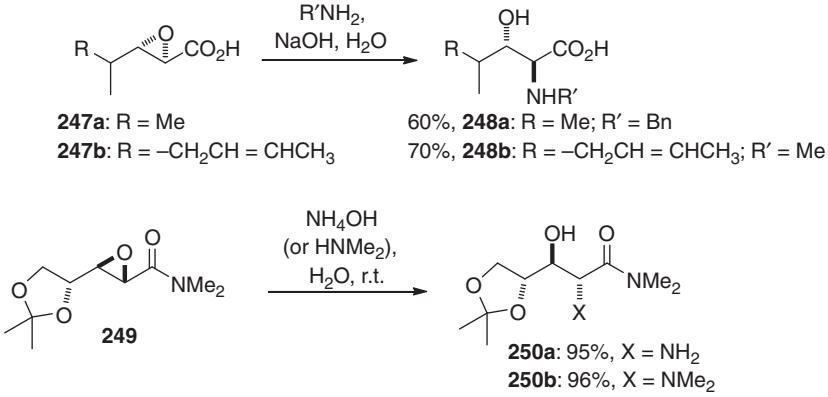


Scheme 40

The preference of *αβ*-epoxy acids to react at the C2 position appears to be general, as evidenced by the regioselectivity for aliphatic glycidic acids **247a** and **247b** (Scheme 41).[123,124] Curiously, the corresponding *t*-butyl ester of **247a** (R=Me) does not give the ring-opened product with BnNH$_2$, nor does it react with NaN$_3$.[123]

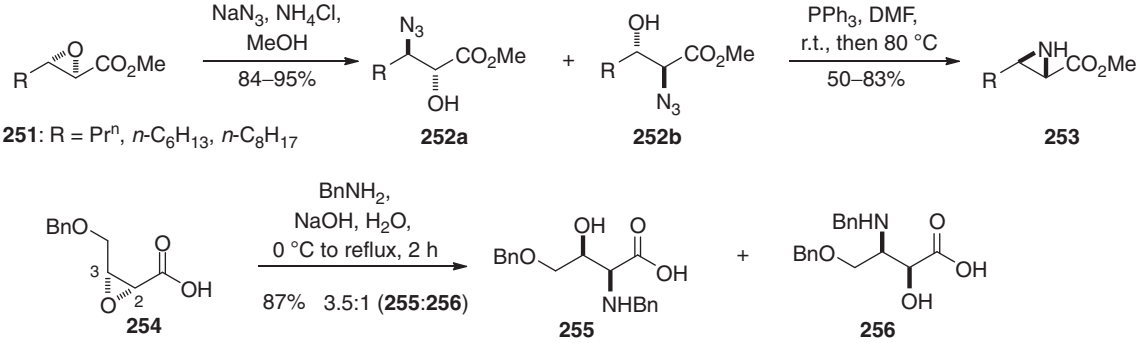
Similarly high selectivity for reaction at C2 is observed in amination of epoxide **249**, derived from the 2,3-*O*-isopropylidine of glyceraldehyde.[125] Direct displacement using aqueous ammonia or dimethylamine provides amination products **250a** and **250b**

in high yield. As is often the case when ammonia is the nucleophile, excess ammonia was necessary to avoid dialkylation. When only 2 equivalents of ammonium hydroxide were used the major product was a dimeric secondary amine that was isolated in 85% yield.



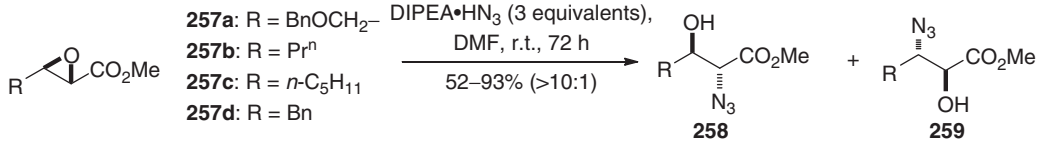
Scheme 41

Reactions of unbranched aliphatic glycidic esters with amine nucleophiles are generally less regioselective. The reaction of *trans*-glycidate ester **251** with azide gave a mixture of azidohydrin products (Scheme 42).[126] In this case, the product mixture was inconsequential, as a Staudinger reaction converted both regioisomers to aziridine **253**. Nucleophilic additions of benzylamine to *cis*-glycidic acid **254** faired much better in terms of selectivity. Under basic conditions, the reaction of **253** with benzylamine favors ring opening at C2 to give **255** by a 3.5:1 ratio.[127]



Scheme 42

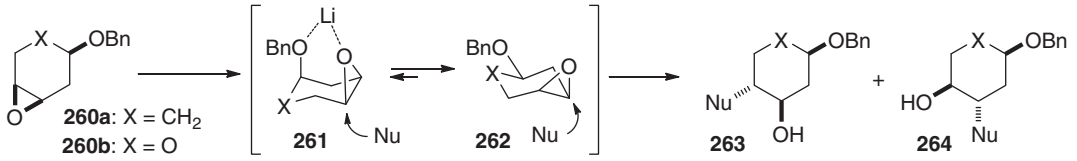
The regioselectivity for the addition of azide to α,β-epoxy esters can be affected by the counter cation for the azide nucleophile. Epoxide **257a** was unreactive to traditional conditions, such as $TMSN_3$, NaN_3/DIPEA (Pr^i_2NEt), or NaN_3 in DMF, and produced an intractable mixture of regioisomers with NaN_3/NH_4Cl. In contrast, **257a** reacted slowly with a complex formed by DIPEA and HN_3 to give azido product **258** with dramatic $>10{:}1$ selectivity (equation 16).[128,129] These conditions were general for other *trans*-epoxides, giving uniformly excellent selectivity for α-azido product **258**. Much lower selectivity for the α-azido product was observed for the corresponding *cis*-epoxides (1.3–5.8:1 ratio of C2 to C3 products). It was hypothesized that the improved reactivity of the HN_3·DIPEA complex versus NaN_3/DIPEA was due to a 5-membered transition state involving hydrogen bonding with the carbonyl group. This interaction is thought to help direct the nucleophilic addition to C2 in these substrates.



(16)

Chelation of a Lewis acid between the epoxide and another heteroatom can alter the regioselectivity for the aminolysis of an epoxide. Epoxides derived from six-membered rings typically undergo ring opening according to the Fürst-Plattner rule, that is, they undergo a stereospecific ring opening where the nucleophile and resultant hydroxyl group have a *trans*-diaxial relationship in the transition state.[130]

In the case of cyclohexene oxide **260a** (equation 17, Table 5), reaction with NaN_3 or Et_2NH occurs primarily through **262** to favor the formation of **264**.[131] This product ratio is fairly consistent, and holds even for pyran-derived epoxides (entries 1–4). The product distribution can be reversed by the addition of a coordinating Lewis acid. When $LiClO_4$ is present, **263** emerges as the major product due to a six-membered lithium chelate that enforces **261** as the reactive conformation (entries 5–8).[132]

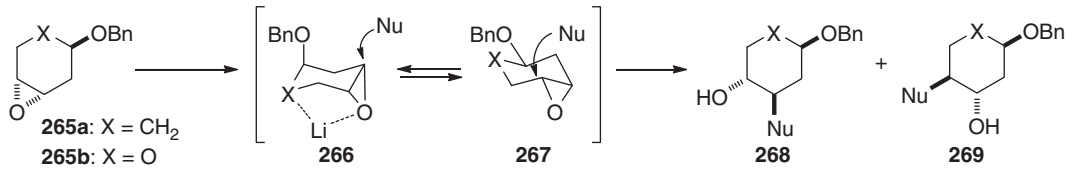


(17)

Table 5 Regioselective addition of nitrogen nucleophiles to epoxides **260a** and **260b**

Entry	*Substrate (X =)*	*Conditions*	*Solvent*	*Yield (%)*	*Ratio (**263**:**264**)*
1	**260a** (–CH_2–)	NaN_3, NH_4Cl, 80 °C	MeOH:H_2O	97	4:96
2	**260b** (–O–)	NaN_3, NH_4Cl, 80 °C	MeOH:H_2O	92	6:94
3	**260a** (–CH_2–)	Et_2NH, 55 °C	EtOH	50	5:95
4	**260b** (–O–)	Et_2NH, 80 °C	EtOH	50	24:76
5	**260a** (–CH_2–)	NaN_3, $LiClO_4$, 80 °C	MeCN	95	97:3
6	**260b** (–O–)	NaN_3, $LiClO_4$, 80 °C	MeCN	93	86:14
7	**260a** (–CH_2–)	Et_2NH, $LiClO_4$, 55 °C	MeCN	95	92:8
8	**260b** (–O–)	Et_2NH, $LiClO_4$, r.t.	MeCN	95	82:18

trans-Epoxide **265a** (equation 18) cannot form a chelate and gives the same product regardless of whether $LiClO_4$ is present (Table 6, entries 1–4). However, a chelation effect was evident for the related series of pyran-derived *trans*-epoxide **265b** (entries 6 and 8). In this substrate, a 5-membered chelate is thought to occur between the pyran oxygen and the epoxide. As a result, conformer **266** should govern reactivity rather than **267**.



(18)

Table 6 Regioselective addition of nitrogen nucleophiles to epoxides **265a** and **265b**

Entry	*Substrate (X=)*	*Conditions*	*Solvent*	*Yield (%)*	*Ratio (**268**:**269**)*
1	**265a** (–CH_2–)	NaN_3, NH_4Cl, 80 °C	MeOH:H_2O	95	5:95
2	**265a** (–CH_2–)	NaN_3, $LiClO_4$, 80 °C	MeCN	93	7:93
3	**265a** (–CH_2–)	Et_2NH, 55 °C	EtOH	52	27:73
4	**265a** (–CH_2–)	Et_2NH, $LiClO_4$, 55 °C	MeCN	95	40:60
5	**265b** (–O–)	NaN_3, NH_4Cl, 80 °C	MeOH:H_2O	92	20:80
6	**265b** (–O–)	NaN_3, $LiClO_4$, 80 °C	MeCN	92	83:17
7	**265b** (–O–)	Et_2NH, 80 °C	EtOH	97	67:37
8	**265b** (–O–)	Et_2NH, $LiClO_4$, r.t.	MeCN	96	89:11

It is noteworthy that the regioselectivity for the nucleophilic addition to pyran **265b** is somewhat lower than what is observed for **265a**. Diminished selectivity for the pyran substrate can be rationalized by considering unfavorable electrostatic interactions between the anionic nucleophile and oxygen atoms in the pyran substrate. Neutral Et_2NH does not suffer this interaction, yet exhibits an interesting preference for the product **268** with both nonchelating and chelating conditions (entries 7 and 8). Addition of Et_2NH could be directed by a hydrogen bond with the benzyloxy group, thereby increasing the role of **266** for this nucleophile. The synergy of a directing hydrogen bond and chelating lithium atom could explain the high selectivity for product **268** observed in entry 8. The reaction of **265b** with Et_2NH and $LiClO_4$ also occurs at a lower temperature than the other reactions (room temperature vs. 80 °C), providing evidence to support a dual activation mechanism (chelation/hydrogen bonding).

6.02.3 Transition Metal-Catalyzed Allylic Amination

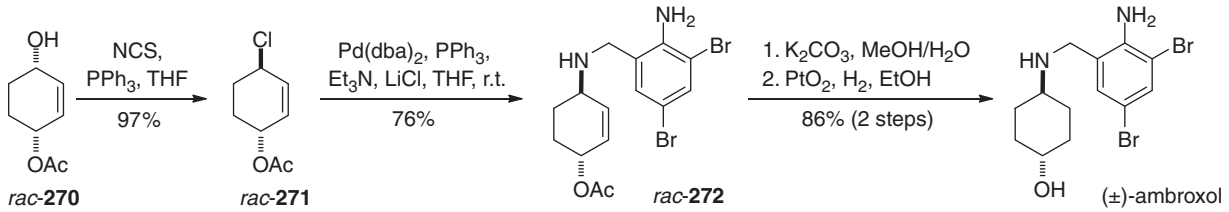
Catalysis is an important area of methods development due to intrinsic advantages with regard to atom economy over stoichiometric methods. Transition metal catalysis in particular is attractive due to the ability to fine-tune reactivity by introducing ligands. This provides opportunities to modulate regiochemical outcomes, and to develop asymmetric reactions with chiral ligands.

Many powerful transition metal-catalyzed reactions are known for forming new carbon–nitrogen bonds. The Tsuji–Trost reaction is a palladium-catalyzed substitution process wherein an allylic leaving group is displaced by a nucleophile.[133–135] Carbon nucleophiles are typically associated with this reaction, but nitrogen nucleophiles are compatible with these conditions, thus providing a valuable means for allylic amination. Other important transition metal-catalyzed C–N forming reactions include the Buchwald–Hartwig coupling and 'borrowing hydrogen' methods. The Buchwald–Hartwig coupling is widely used for the formation of *N*-aryl bonds.[136] 'Borrowing hydrogen' reactions are redox processes involving a single catalyst that oxidizes an alcohol to a carbonyl and then returns the hydrogen in a reductive amination step.[137,138] Due to this chapter's focus on displacement reactions, this section will be restricted to allylic aminations involving palladium, rhodium, and iridium catalysis. For a discussion of borrowing hydrogen methods within this work (*see* Chapter 8.05).

6.02.3.1 Palladium-Catalyzed Allylic Amination

Palladium is the most broadly studied transition metal for allylic amination, although rhodium and iridium have recently emerged as general catalysts for this chemistry. A distinct advantage of these catalysts is the fact that a broad range of leaving groups participates in allylic substitution. For the palladium-catalyzed process, the reactivity of allylic leaving groups roughly follows the trend: chloride > phosphate > carbonate > acetate > ether.

Orthogonal reactivity is possible when more than one allylic leaving group is present. Differential reactivities for chloride versus acetate led to a short synthesis of (±)-ambroxol (Scheme 43).[139,140] In contrast to the inversion of stereochemistry observed with an S_N2 process, allylic amination occurs with net retention due to the intermediacy of a π-allyl Pd complex.

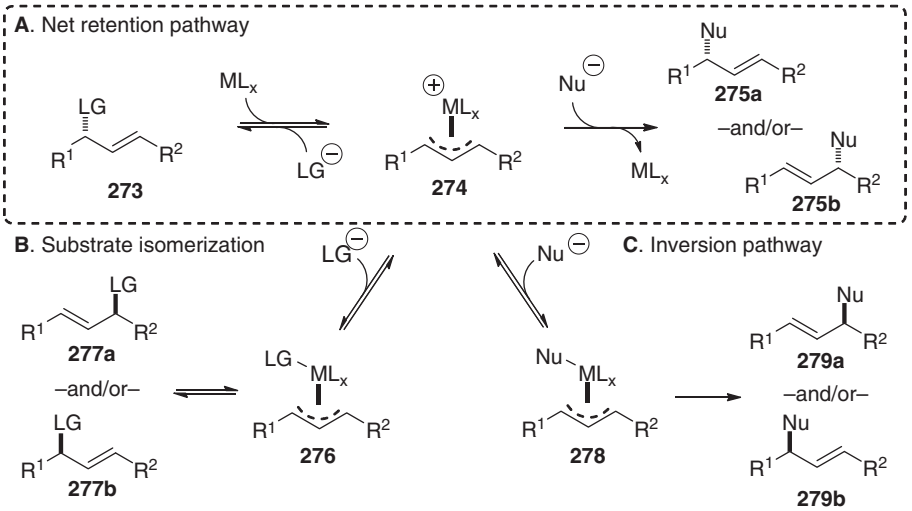


Scheme 43

Allylic aminations typically occur via a stereospecific mechanism involving the oxidative addition of the metal catalyst to displace the allylic leaving group with inversion to give cationic π-allyl metal complex **274** (Scheme 44a). Subsequent addition of a nucleophile to this metal complex occurs with a second inversion, thus providing the product with the net retention of stereochemistry. The nucleophile, leaving group,[141] and metal/ligand combination each can affect the outcome of these reactions. Erosion of stereoselectivity can occur via coordination of the leaving group to the cationic metal complex to give **276**, which scrambles the stereochemistry by reductive elimination to give **277a** and/or **277b** (Scheme 44b). Stereoselectivity can also be altered due to coordination of the nucleophile to the cationic metal complex (**278**). Intramolecular delivery of the nucleophile then occurs with retention and leads to a net inversion of stereochemistry (Scheme 44c, **279a** and **279b**). Bidentate ligands attenuate both of these detrimental pathways by disfavoring the coordination of additional groups to the transition metal. The trade-off is a slowing of the overall reaction rate. Another strategy to improve stereoselectivity involves the additive LiCl.[142] Chloride is thought to coordinate to the metal complex, thus precluding coordination of the nucleophile and leaving group. Furthermore, chloride additives have little effect on the rate of these reactions.

Two other competing pathways involving palladium can impact the stereochemical outcome of these reactions. π-Allyl metal complexes where R^1 or $R^2 = H$ can isomerize via a π–σ–π mechanism. This process also can account for the isomerization of the double bond geometry. This π–σ–π process is important for stereoconvergent reactions by which racemic substrates can be equilibrated before a ligand-controlled asymmetric amination (see Section 6.02.3.1.5).

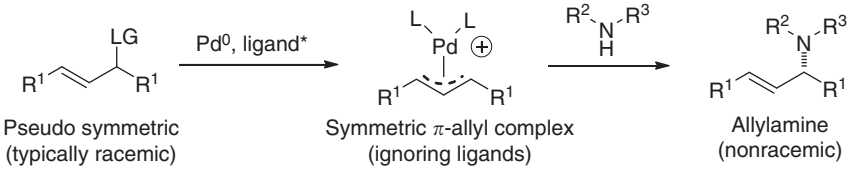
Cyclic substrates cannot isomerize by the π–σ–π process, but they can be isomerized via an intermolecular S_N2 pathway when sufficiently high concentrations of Pd^0 are present.[143] Additional detail about this process and other considerations influencing the stereochemistry has been given elsewhere in the context of the Tsuji–Trost allylation with carbon nucleophiles.[135,134]



Scheme 44

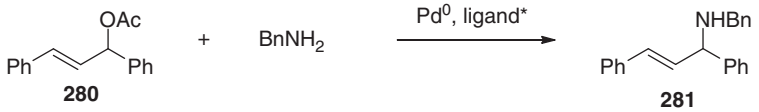
6.02.3.1.1 Enantioselective Pd-catalyzed allylic aminations

Since regiochemical control in allylic amination is not trivial, most enantioselective conditions are developed with 1,3-disubstituted allyl substrates that contain identical groups at each terminus of the allyl fragment (Scheme 45). Such substrates are pseudo symmetric and yield symmetrical π-allyl complexes; thus, the complication of regiochemistry is avoided. Chiral ligands will often catalyze both allylic alkylation and amination reactions with comparable efficiency and selectivity. However, neither reaction is always reported with novel chiral ligands and therefore direct comparison is not always possible.



Scheme 45

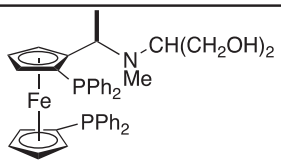
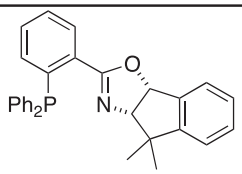
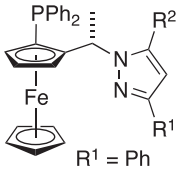
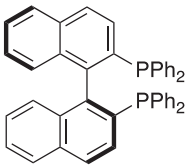
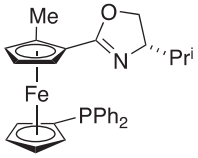
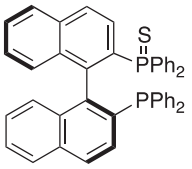
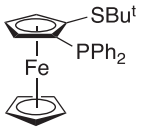
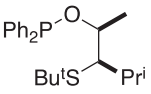
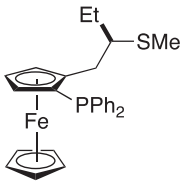
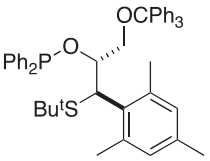
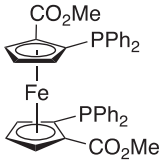
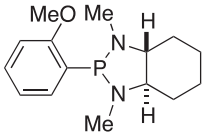
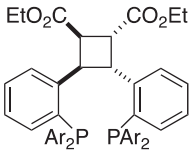
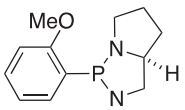
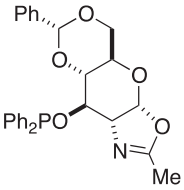
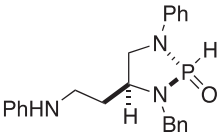
The reaction of 1,3-diphenylprop-2-enyl acetate (**280**) and benzylamine is a popular system for validating new chiral ligands (equation 19). In these reactions, an excess of benzylamine (≥3 equivalents) typically must be used to avoid polyalkylation. A wide variety of ligands catalyze this reaction in high yield and enantioselectivity (Table 7). Although C_2-symmetric bidentate ligands function well (entries 6, 7, and 10), ligands do not need to be symmetric for excellent *ee*s. Other effective ligand motifs include mixed bidentate ligands that pair a strong phosphorus donor with a weaker nitrogen or sulfur donor (entries 1–5), and monodentate ligands (entry 11). Table 7 presents only a small sampling of chiral ligands. A recent review is available with a more comprehensive discussion of chiral ligands for asymmetric allylic alkylation and amination reactions.[133]

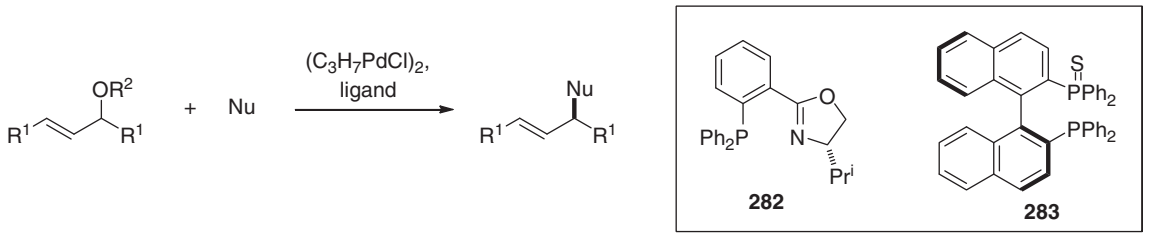


(19)

Since **280** is often the only substrate reported to demonstrate proof-of-concept, it can be difficult to gauge the substrate scope for individual ligand systems. In the few examples where direct comparison is available, it appears that aliphatic substrates are more challenging than their diphenyl counterparts (equation 20, Table 8).[164,149] For example, the phosphino-oxazoline ligand **282** provides good levels of enantioselectivity with **280** but is less effective for the asymmetric amination of **285** (compare entries 1–2 and 4–5). Much better results have been obtained with the palladium complex derived from BINAP(S) (**283**), which gives 87% *ee* for the amination of **286** (entry 6).

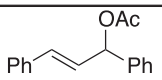
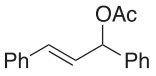
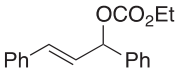
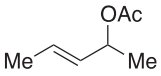
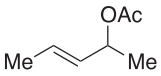
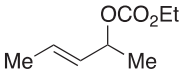
Table 7 Selected chiral ligands for the asymmetric allylic amination of **280** with $BnNH_2$

Entry	Ligand	Yield (%) (ee %)	References	Entry	Ligand	Yield (%) (ee %)	References
1		81 (96.6)	144	9		89 (97)	145
2	 R^1 = Ph R^2 = Me	>90 (96)	146	10		99 (94)	147
3		99 (96.5)	148	11		99 (95)	149,150
4		80 (97)	151,152	12		96 (99)	153,154
5		50 (94)	155,156	13		97 (94)	157
6		94 (99)	158	14		68 (78)	159
7	 Ar = 4-MeC_6H_4	91 (97.5)	160	15		85 (83)	161
8		78 (94)	162	16		91 (98)	163



(20)

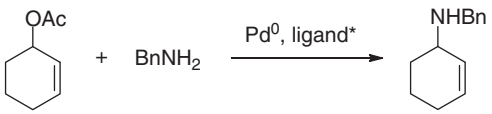
Table 8 Enantioselective amination of pseudosymmetric allylic substrates

Entry	*Substrate*	*Ligand*	*Nucleophile*	*Yield (%) (ee %)*	*References*
1[a]	 **280**	**282**	KNPhth	34 (84)[b]	164
2[a]	 **280**	**282**	$NaNHSO_2Tol$	84 (90)	164
3[c]	 **284**	**283**	$BnNH_2$	99 (95)	149
4[a]	 **285**	**282**	KNPhth	93 (56)	164
5[a]	 **285**	**282**	$NaNHSO_2Tol$	92 (49)	164
6[c]	 **286**	**283**	$BnNH_2$	99 (87)	149

[a]Conditions: $(C_3H_5PdCl)_2$ (2 mol%), **282** (4 mol%), THF/DMSO (80:20), 50 °C, 24 h.
[b]A yield of 70% (96–98% *ee*) was obtained in THF.
[c]Conditions: [(η^3-allyl)Pd(*S*-BINAP(S))]SbF_6] (5 mol%), EtOAc, r.t.

π-Allyl-Pd complexes of cyclic substrates have a very different geometry compared to those derived from acyclic allylic leaving groups. It is known that acyclic π-allyl complexes adopt a 'W' instead of a 'U' conformation to minimize 1,3-allylic strain. Cyclic substrates (e.g., **287**) do not have rotational freedom and must form a π-allyl complex with 'U'-geometry. These two geometries lead to dissimilar steric environments, and thus it is unusual for one set of chiral ligands to be effective for both acyclic and cyclic substrates.

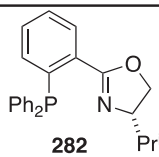
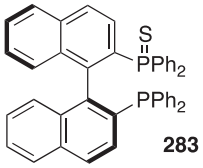
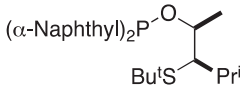
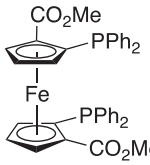
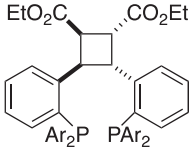
Table 9 illustrates several ligands that have been examined for the asymmetric amination of cyclohexenyl acetate **287** (equation 21). Phosphino-oxazoline **282** and BINAP(S) (**283**) ligands give rather poor enantioselectivity for this substrate (entries 1 and 2), in contrast to their results with acyclic allylic acetates (Table 8, above). Excellent results have been obtained for **287** with a mixed bidentate phosphorus/sulfur ligand developed by Evans (entry 3).[154,153] Also of interest are C_2-symmetric ligands based on ferrocene (entry 4) and cyclobutane (entry 5). The last two ligands are unique, as they provide ≥77% *ee* for both cyclic and acyclic allylic acetates.[158,160]



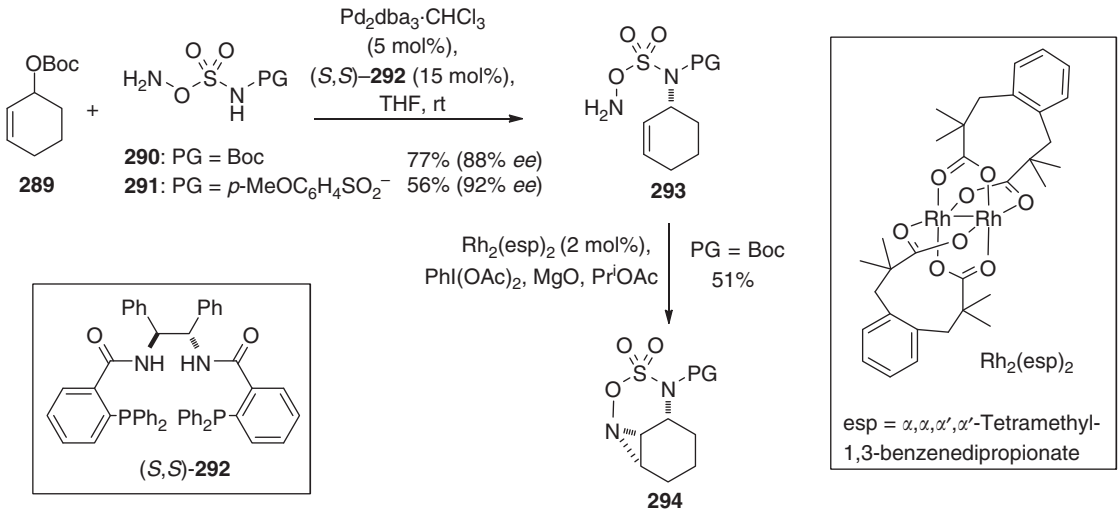
(21)

Trost's C_2-symmetric diamine-based ligands are effective for the asymmetric amination of cyclic substrates with sulfamate nucleophiles **290** and **291** (Scheme 46).[165–167] The unusual sulfamate nucleophiles [$BocNHOSO_2NH_2$ and $MbsNHOSO_2NH_2$] are prepared in two steps from hydroxylamine and were designed so that additional C–N bonds could subsequently be formed by

Table 9 Enantioselective allylic amination of cyclic substrates

Entry	*Ligand*	*Yield (%) (*ee *%)*	*References*
1	 **282**	89 (12)[a] 47 (18)[b]	164
2	 **283**	99 (13)	149
3		97 (91)	153,154
4		88 (77)	158
5	 Ar = 4-MeC_6H_4	74 (78)	160

[a]The nucleophile was KNPhth.
[b]The nucleophile was $NaNHSO_2Tol$.

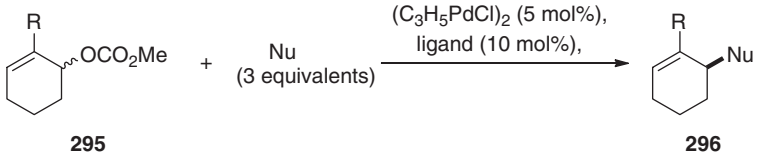


Scheme 46

an intramolecular Rh-catalyzed aziridination. The resulting aziridine **294** can be ring-opened with a variety of nucleophiles, including azide and phthalimide. This asymmetric allylic amination/aziridination method represents a novel two-step method to prepare protected polyamino cyclohexanes.

The amination of cyclic substrates such as **295** (equation 22) is a reaction of some importance due to its relevance to the synthesis of several alkaloids (Figure 3). As with the cyclohex-2-enyl alcohol derivatives above, developing a highly

enantioselective reaction has been challenging. Enantioselectivities vary according to a delicate balance of factors (**Table 10**), including the identities of the vinyl substituent, nucleophile, catalyst, and leaving group (carbonate vs. phosphate). For example, (*S*)-BINAPO gives useful *ee*s for 2-aryl cyclohexene derivatives, but distant groups can have a significant effect on enantioselectivity (entries 1 and 2).[168–171]



295 **296** (22)

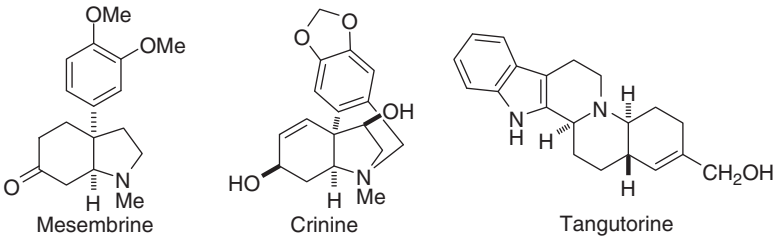
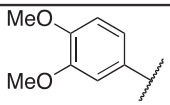
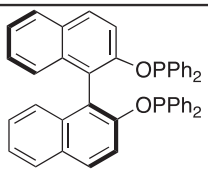
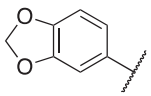
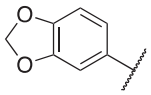
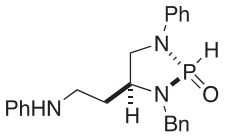
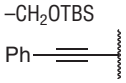
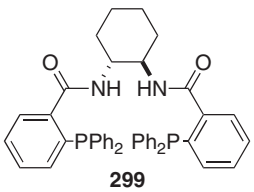


Figure 3 Alkaloids prepared via allylic amination.

An aspartic acid-derived ligand, (S,R_P)-Ph-DIAPHOX (**298**), catalyzes the asymmetric amination with a wide tolerance for groups at the 2-position of **295** and for primary and secondary amine nucleophiles (**Table 10**, entries 3–7).[163,172] Notably, the reaction outlined in entry 7 was used as a key step early in the total synthesis of the alkaloid tangutorine.[173] This demonstrates that asymmetric allylic aminations with DIAPHOX ligand **298** are robust and can be reliably scaled up to a multi-gram scale. Trost's cyclohexadiamine-based ligand **299** also promotes the Pd-catalyzed allylic amination of **295** in excellent enantioselectivity.[174] However, although **299** works well for protected ammonia-equivalents, such as phthalimide and *p*-toluenesulfonamide (entries 9 and 10), it is ineffective for primary amine nucleophiles (entry 8).[173]

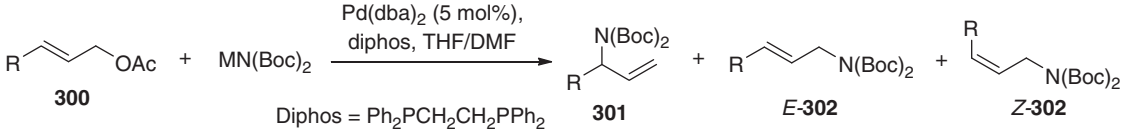
Table 10 Pd-catalyzed asymmetric amination of substituted cyclic allyl carbonates

Entry	*R*	*Nucleophile*	*Ligand*	*Yield (%)*	ee *(%)*	*References*
1		$TsNHCH_2CH(OEt)_2$	 (*S*)-BINAPO (**297**)	87	84	171
2		$TsNHCH_2CH(OEt)_2$		68[a]	60[a]	169,171
3		$TsNHCH_2CH(OEt)_2$	 (S,R_P)-Ph-DIAPHOX (**298**)	98	97	163
4	Ph	Morpholine		90	97	163
5	$-CH_2OTBS$	$BnNH_2$		95	72	163
6		$BnNH_2$		75	80	163
7	$-CO_2Me$	N^{in}-Boc-tryptamine		99	95	172,173
8	$-CO_2Me$	N^{in}-Boc-tryptamine	 **299**	12	77	173
9	$-CO_2Me$	HNPhth		93	97	174
10	$-CO_2Me$	H_2NTos		93	97	174

[a]Higher yield and enantioselectivity (84% yield; 88% *ee*) were obtained when $-OPO(OEt)_2$ was the leaving group instead of methyl carbonate.

6.02.3.1.2 Regioselectivity with unsymmetrical allyl substrates

In unsymmetrical substrates, such as **300**, regioselectivity is described in terms of branched versus linear products (equation 23). Pd-catalysis generally favors the linear amination product, but the linear to branched ratio varies according to the reaction conditions.[175] For aminations with metalated di-*tert*-butyl iminodicarbonates, the nucleophile's counterion has a minor effect on the product ratio (Table 11).[64] The *N*-allylated products can be monodeprotected in high yield using trifluoroacetic acid to obtain the corresponding *N*-Boc carbamates.

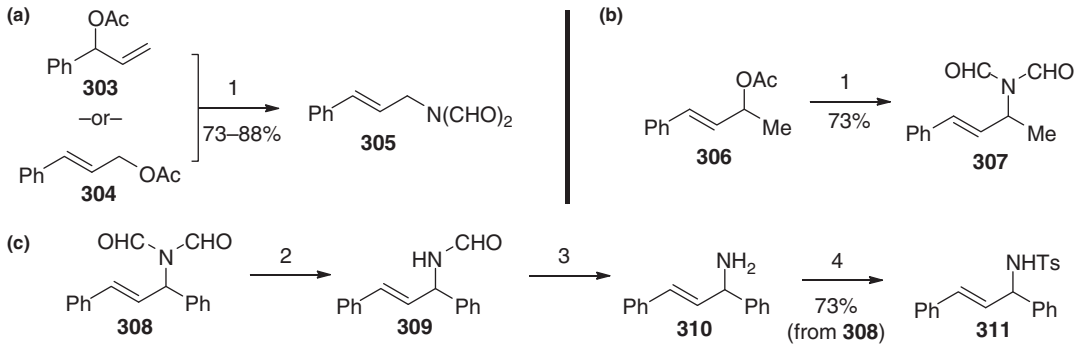


(23)

Table 11 Palladium-catalyzed allylic amination of **300**

Entry	*Substrate*	*Nucleophile*	*Temperature (°C)*	*Yield (%)*	*Ratio (**301**:E-**302**:Z-**302**)*
1	R=Me	$LiN(Boc)_2$	25	94	42:50:8
2	$R=Pr^n$	$NaN(Boc)_2$	45	81	8:78:14
3	R=*E*-MeCH=CH	$LiN(Boc)_2$	25	84	0:85:15
4	R=Ph	$LiN(Boc)_2$	25	100	6:87:7
5	R=Ph	$NaN(Boc)_2$	25	85	0:100:0

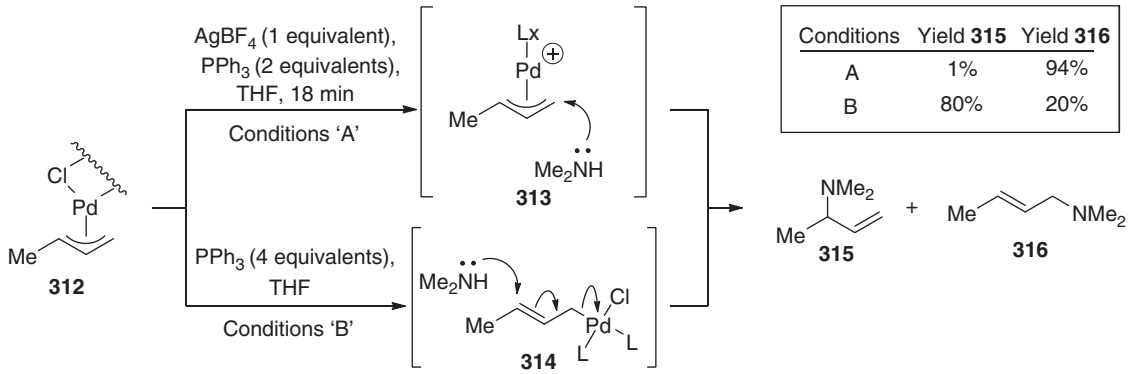
A preference for the linear amination product was observed for the reaction of **303** with sodium *N*,*N*-diformylamide (Scheme 47(a)).[147] It is interesting to note that isomers **303** and **304** both converge to the same linear product (**305**). The regiochemistry of unsymmetrical allyl acetates where R^1 and $R^2 \neq H$ is typically difficult to control. However, when $NaN(CHO)_2$ and Pd-dppf were used for the amination of **306**, a single product was obtained in 73% yield (Scheme 47(b)). The high selectivity for **307** is likely governed by greater stability of this product wherein the alkene is conjugated with the phenyl ring. As with the di-*tert*-butyl iminodicarbonates discussed previously, diformylamide **308** can be deprotected in a step-wise manner under acidic conditions (Scheme 47(c)).



1. $NaN(CHO)_2$, $(C_3H_5PdCl)_2$ (2.5 mol%), dppf (5 mol%), MeCN, 60 °C; 2. 5% HCl/EtOH, reflux;
3. 1 N NaOH (aqueous), r.t.; 4. TsCl, Et_3N, CH_2Cl_2, r.t.

Scheme 47

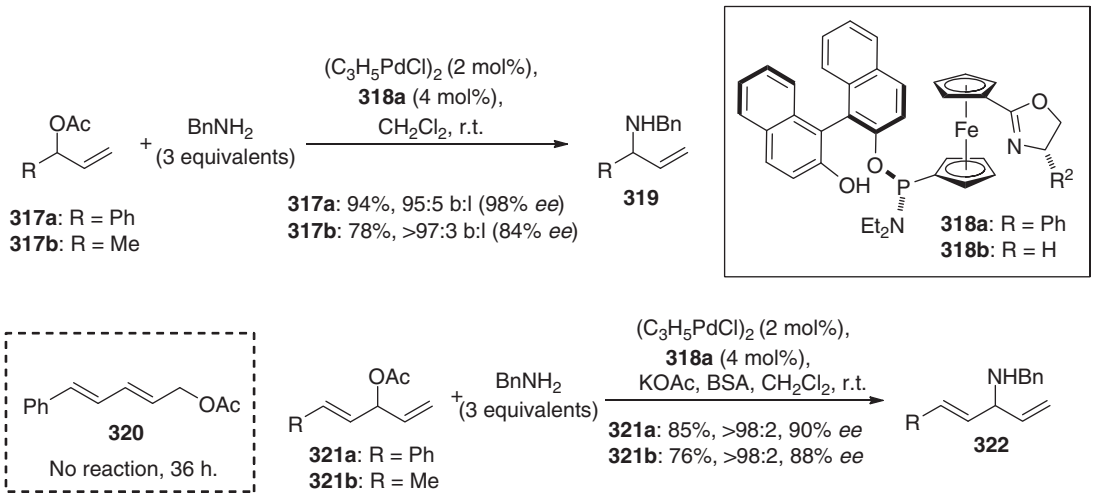
The nature of the reacting π-allylpalladium complex affects the regioselectivity for allylic amination (Scheme 48).[176] Evidence has been obtained suggesting that selectivity for the linear or branched product is influenced by the nature of the reactive organopalladium intermediate, which can vary between a cationic π-allylpalladium complex (**313**) and a neutral σ-complex (**314**). To assess the reactivity of a cationic π-complex, π-crotyl palladium chloride (**312**) was treated with $AgBF_4$ and Ph_3P to stoichiometrically form **313** (AgCl was filtered before amine addition). Conductivity measurements verified that a cationic complex was formed, and reaction with excess dimethylamine then led to the linear product.



Scheme 48

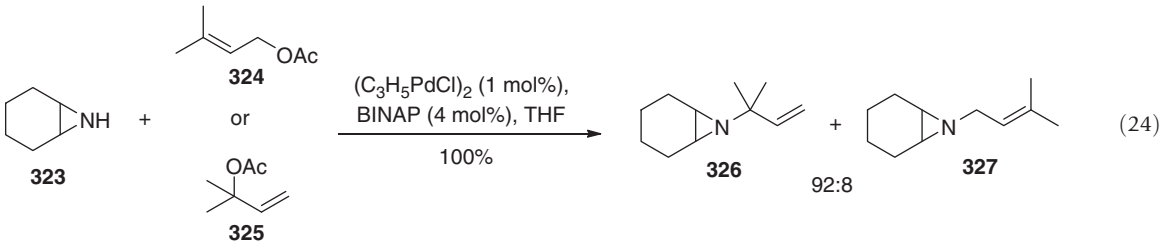
In contrast, a branched product is favored when four equivalents of Ph_3P are added to π-crotylpalladium chloride in THF (conditions 'B'). Conductivity measurements suggested that a neutral complex is present under these conditions with NMR providing additional evidence for formation of σ-complex **314**. The selectivity for branched products from the σ-complex can be rationalized by considering an S_N2' mechanism for nucleophilic attack. The influence of conditions on the nature of the reactive intermediate thus plays an important role in determining the regioselectivity of Pd-catalyzed allylic aminations. This implied that conditions favoring **314** and the π–σ–π interconversion of organopalladium complexes could be used to form branched products if the σ-allyl complex can be intercepted as the reactive species.

Branched products can be favored by sterically demanding monodentate ligands. The ferrocene-based ligand **318a** gives excellent regio- and stereoselectivity for the Pd-catalyzed amination of allyl acetates with benzylamine (Scheme 49).[177] For the amination of branched allyl acetates, aromatic groups are well tolerated, with the ratio of branched to linear products consistently high (>90:10 b/l) with excellent enantioselectivity (>94% *ee*). High selectivity for the branched product was also obtained with butenyl acetate (**317b**, R=Me), although the enantioselectivity was diminished (84%). Ligand **318a** also leads to branched amination products with polyene substrates, such as **321**.[178] With polyene substrates, it was noted that branched isomer **321** gave better results than linear substrate **320**, which was unreactive after 36 h. More recently, a related ferrocene ligand **318b** has been used to obtain branched amination products applying BocNHOMe as an amine equivalent.[179]



Scheme 49

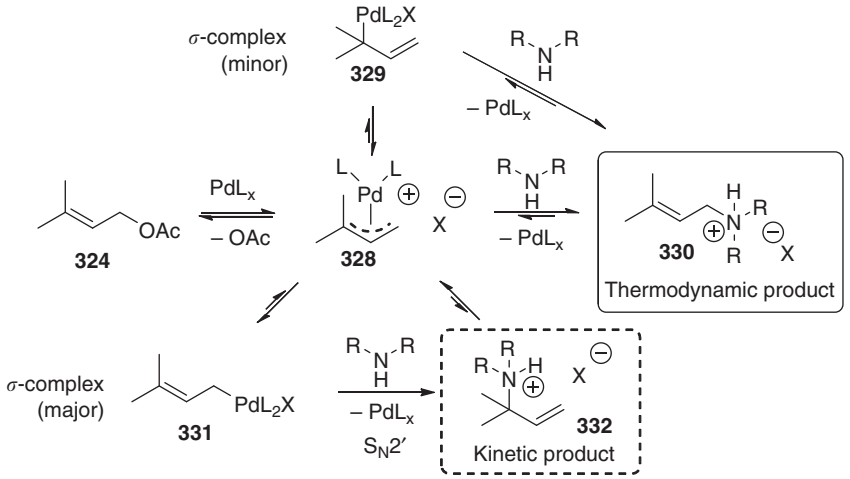
An interesting result was obtained in the course of a project involving the Pd-catalyzed allylic amination using aziridine nucleophiles. Surprisingly, the initial reaction of aziridine **323** with prenyl acetate **324** gave the branched isomer as the only product using Pd and Ph_3P, a condition that typically favors linear products (equation 24).[180] This reaction was slow with PPh_3, but can be accelerated using BINAP. The Pd-BINAP catalyzed reaction is complete within 6 h, and favors branched product **326** over expected linear isomer **327**.



(24)

A systematic examination of the reaction parameters provided additional insight into this process.[181] The ratio of branched to linear prenylation products varied between 85:15 (b/l) and 96:4 (b/l) for a series of 10 unique phosphine ligands for the reaction of aziridine **323** and **324**. This suggests that although ligand structure had some influence on regiochemistry, it was not the most important factor. A significant solvent effect was observed, with the following trend: THF (92:8, b/l) > PhMe~MeCN (1:1) > CH_2Cl_2 (4:6, b/l). This solvent effect was rationalized by considering the effect of solvent on the coordination of allylpalladium complexes. For example, it is known that the neutral σ-allyl complex forms to a greater extent in THF than in more polar solvents.[182,183]

Another surprise came on applying these optimized allylic amination conditions to other secondary amines. Instead of forming the branched amination product, piperidine, morpholine, methyl aniline, and tetrahydroisoquinoline all favored the linear product after 6 h. Careful gas chromatography monitoring of the reaction demonstrated that, like aziridine **323**, piperidine initially reacts with prenyl acetate to give the branched amination product. However, the branched allyl piperidine isomerizes over time to the linear isomer. Additional crossover experiments demonstrated that branched allylamines equilibrate to linear allylamines under the reaction conditions. Thus, it appears that the branched isomer is likely formed as a kinetic product under Pd-catalyzed allylic aminations, but it then isomerizes to a thermodynamic linear product over time. The resulting mechanistic hypothesis is depicted in Scheme 50.

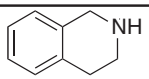
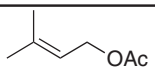
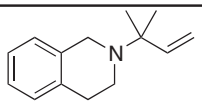
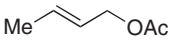
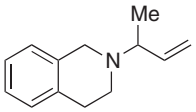
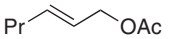
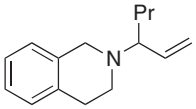
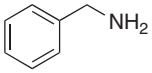
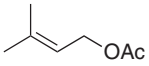
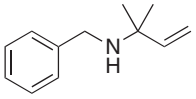
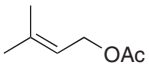
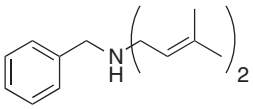
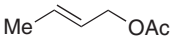
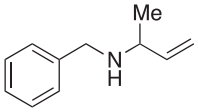
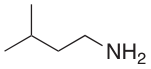
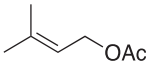
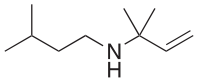
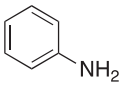
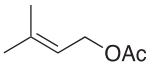
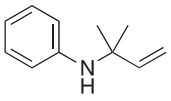


Scheme 50

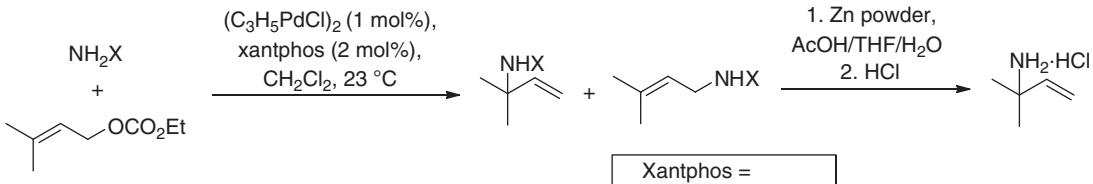
This analysis implicates protonated amine **332** as a kinetic product that is in equilibrium with **328**. The rate of isomerization from branched to linear products also correlates with the pK_a of the amine;[181] thus, it was hypothesized that addition of a base to the reaction would arrest the equilibrium and facilitate isolation of the kinetic branched product. Deprotonation of ammonium intermediate **332** should slow its conversion into cationic π-allyl complex **328** via Pd^0 displacement and essentially render amination of σ-complex **331** irreversible. This hypothesis was successfully validated by the addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[184] Table 12 summarizes the application of these conditions to prepare a variety of branched allylic amines. Several results from this table are noteworthy. 1. Branched products are isolated with a variety of allyl acetates, including prenyl acetate, but-2enyl acetate, and hex-2-enyl acetate (entries 2, 3, and 6). 2. Monoallylation of primary amines only occurs when DBU is present (entries 4, 6, and 7). 3. Finally, aniline is prenylated in good yield (entry 8).

Hydrazine and hydroxylamine nucleophiles also give rise to branched products under Pd^0 catalysis (Scheme 51).[185] These products can then be converted into amines by reductive cleavage of the N–N (or N–O) bond with zinc. This process preferentially gives the branched product with a variety of bidentate phosphine ligands, including xantphos, dppf, and BINAP, among others. Under these conditions, the nature of the nucleophile and the identity of the leaving group are important for selectively obtaining the branched products. Interestingly, amine nucleophiles favor the linear product under these conditions.

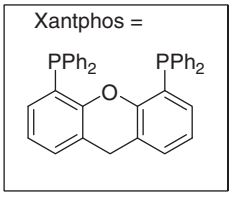
Table 12 Pd-catalyzed preparation of branched allylic amines[a]

Entry	Amine	Acetate	Ligand	Base	Product	B/L	Yield (%)
1			$P(OEt)_3$	DBU		19:1	92
2[b]			Cy_2P(*o*-biphenyl)	DBU		13:1	82
3[b]			Cy_2P(*o*-biphenyl)	DBU		2:1	80
4			$P(OEt)_3$	DBU		9:1	90
5[c]			$P(OEt)_3$	None		0:100	100
6[b]			Cy_2P(*o*-biphenyl)	DBU		99:1	84
7			$P(OEt)_3$	DBU		9:1	80
8			$P(OEt)_3$	DBU		4:1	71

[a]Conditions: 1 mol% $(C_3H_7PdCl)_2$, 4 mol% $P(OEt)_3$, DBU (1 equivalent), THF.
[b]Cy_2P(*o*-biphenyl) ligand was used.
[c]No DBU was used.
Source: Adapted from Table 2 in Dubovyk, I.; Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 14172–14173, with permission from American Chemical Society.



Nucleophile (NH_2X)	b/l	Yield
NH_2NPh_2	98:2	98%
NH_2OCPH_3	90:10	75%
NH_2OBn	95:5	90%



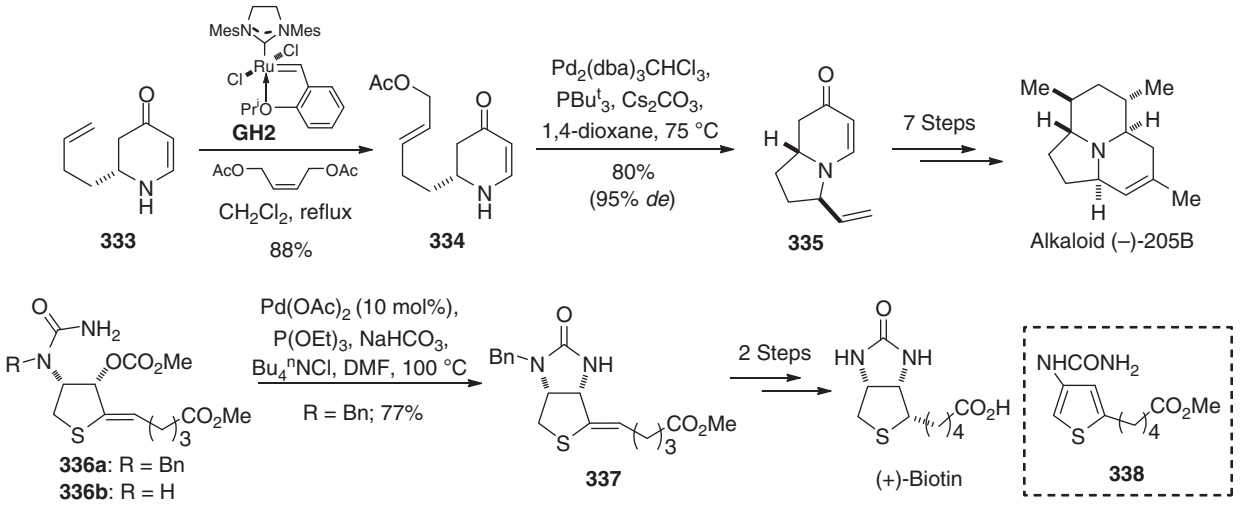
Scheme 51

6.02.3.1.3 Intramolecular allylic amination

Intramolecular Pd-catalyzed allylic amination is an important synthetic process for the preparation of heterocycles. As with its intermolecular counterpart, the value of this C–N bond-forming process is enhanced by the fact that it can be accomplished asymmetrically.

Diastereoselective reactions provide a reasonably straightforward means to form a new C–N bond asymmetrically. Such reactions occur under substrate control and therefore require the presence of a preexisting chirality center. An efficient total synthesis of the frog alkaloid (−)-205B provides a recent example of a diastereoselective intramolecular allylic amination (Scheme 52).[186] Dihydropyridone **333** was prepared in two steps from 4-methoxy-3-triisopropylsilylpyridine. This material was subjected to a cross metathesis to provide acetate **334**. A highly diastereoselective (95% *de*) cyclization of **334** was then achieved

with $Pd_2(dba)_3{\cdot}CHCl_3$ when Bu^t_3P was used as a ligand. The use of a sterically demanding ligand was essential for high diastereoselectivity, as Bu^n_3P gave only a 1:1.5 ratio of diastereomers. It is also noteworthy that this is a rare case wherein a vinylogous amide functions as a nucleophile in a Pd-catalyzed allylic amination.



Scheme 52

A Pd-catalyzed amination has also been used as a key step in the preparation of biotin (Scheme 52).[187,188] The key step in this synthesis involved the cyclization of **336a** to **337** and provides an example where the nucleophilic group is a urea. The substitution pattern on the urea had a significant effect on the yield for amination. The *N*-benzyl group in **336a** was necessary for a high yield, as it played a critical role in increasing the rate of the cyclization. Without it, a low yield (30%) was obtained for **336b** despite increased catalyst loadings. The high yield of **337** from **336a** is impressive, especially considering the potential for aromatization of the π-allyl complex by loss of H_2. The use of $NaHCO_3$ as a base was important for avoiding this competing reaction. In the absence of base, thiophene **338** was formed in 78% yield from **336b**.

Enantioselective intramolecular reactions can require extensive optimization, or even the development of new ligands, in order to achieve satisfactory *ee*. Ojima used an enantioselective allylic amination to prepare a chiral tetrahydroisoquinoline intermediate for a total synthesis of schulzeine B (Scheme 53).[189] Although phosphoramidite **340** was an effective ligand for the asymmetric amination of **339**,[190] it surprisingly gave low enantioselectivity with the closely related substrate **342**. Better results were achieved with the bidentate BOP ligand **343**, but this ligand had to be significantly modified to **344** in order to obtain >80% *ee*. The disparate results obtained for related substrates **339** and **340** underscore the fact that minor structural changes to either the substrate or ligand can have a significant impact on the enantioselectivity for a reaction system.

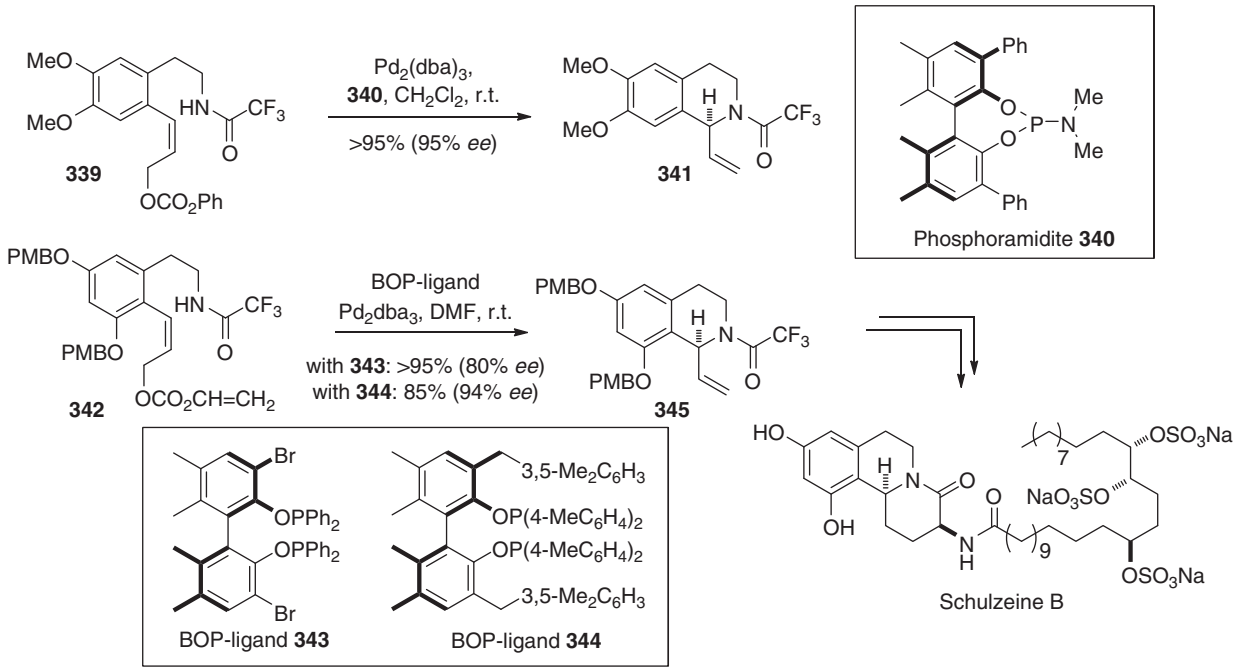
A similar challenge was encountered in Trost's synthesis of anatoxin-a (Scheme 54).[174] This synthesis involved a clever approach wherein cyclic allyl carbonate **346a** was prepared as a racemate. Although one could imagine cyclization of the related racemic alcohol **346b** under Mitsunobu conditions, this would lead to racemic product. In the Pd^0-catalyzed reaction, the asymmetric center at the carbonate in **346a** is obliterated to generate a meso π-allyl complex. This means that an enantioselective ligand-controlled reaction would convert this meso intermediate into a single enantiomer of the azabicyclo product **348**.

Initial attempts using the standard DPPBA [*N*,*N*′-bis(2′-diphenylphosphinobenzoyl)-1,2-diaminocyclohexane] ligand (**299**) gave no reaction at room temperature and were poorly enantioselective at higher temperatures (88% yield, 11% *ee* at 100 °C). It was hypothesized that the ligand formed a chiral pocket that was inadequate for the steric demands of **346a**, and therefore the ligand structure was modified to **347**. This novel ligand catalyzed the cyclization of **346a** to bicyclic amine **348** in 90% yield and 88% *ee* at 0 °C. This product was then elaborated to (–)-anatoxin-a after four additional steps. Ligand **347** has proven useful for reactions that give poor *ee* with **299**. For example, the asymmetric allylic alkylation of malonate with **349** gives poor results with ligand **299**, but proceeds in 86% *ee* when pyridyl ligand **347**.

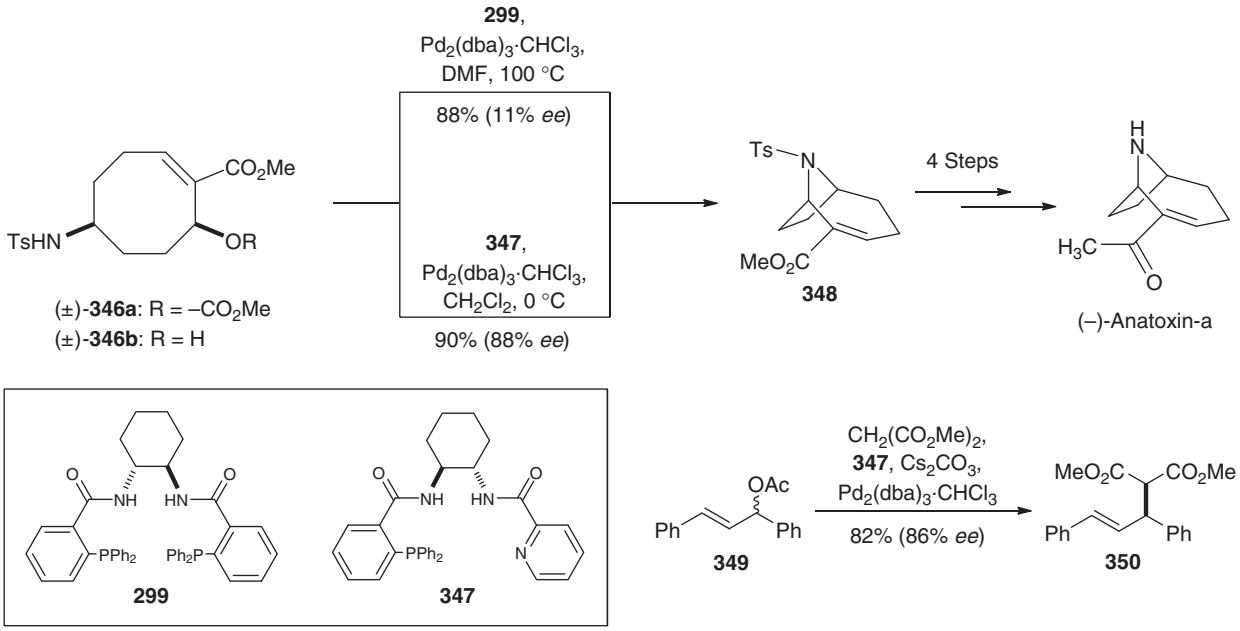
6.02.3.1.4 Domino reactions involving Pd-catalyzed allylic amination

The rich diversity of chemistry catalyzed by Pd is attractive from a synthetic viewpoint, as it presents opportunities for designing domino reaction processes. Domino (or cascade) reaction sequences are powerful due to the potential to create molecular complexity from relatively simple starting materials.

A short synthesis of the natural product lycorane has been completed via a Pd^0-catalyzed domino sequence (Scheme 55).[191] This alkaloid was prepared using a series of Pd-catalyzed reactions, two of which were in tandem. The first step in this sequence involved the desymmetrization of meso dibenzoate **351** via an asymmetric allylic alkylation. The enantioselectivity for this first alkylation step is moderate, but is typical for Pd/BINAPO systems. With **353** in hand, the stage was set for a tandem intramolecular



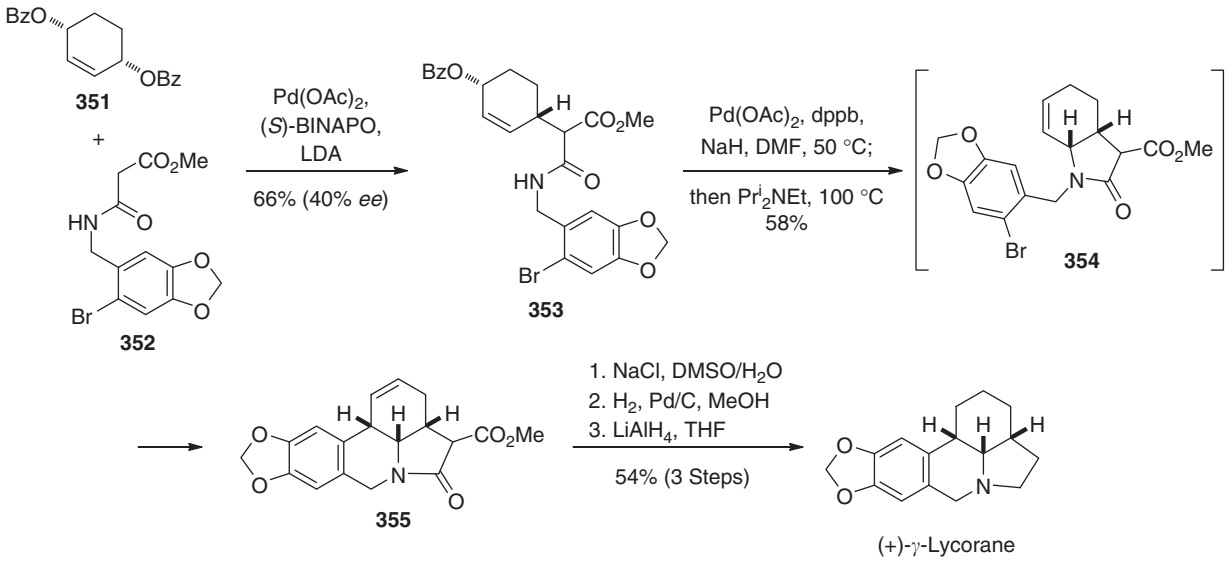
Scheme 53



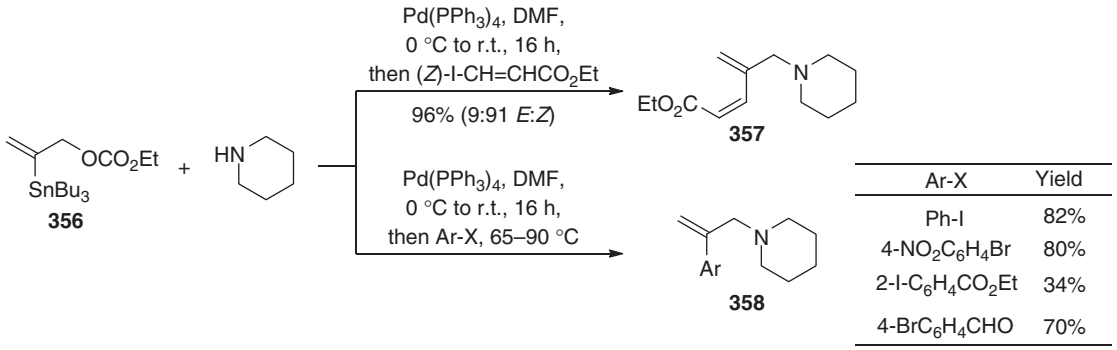
Scheme 54

allylic amination/Heck annulation sequence that gave **355** in 58% yield. The natural product lycorane was completed in three more steps involving decarboxylation, hydrogenation, and amide reduction. The brevity of this synthesis illustrates the advantages of a short tandem reaction sequence.

As part of project to develop libraries of compounds, a one-pot allylic amination/Stille coupling was developed (Scheme 56).[192] Thus, carbonate **356** was combined with piperidine in the presence of palladium tetrakis at room temperature. Following the completion of the amination step, a vinyl or aryl halide was added and the reaction heated to promote Stille coupling. The key to this one-pot process was the recognition that allylic aminations frequently occur at or below room temperature, whereas Stille couplings generally require elevated temperatures.



Scheme 55



Ar-X	Yield
Ph-I	82%
4-$NO_2C_6H_4Br$	80%
2-I-$C_6H_4CO_2Et$	34%
4-BrC_6H_4CHO	70%

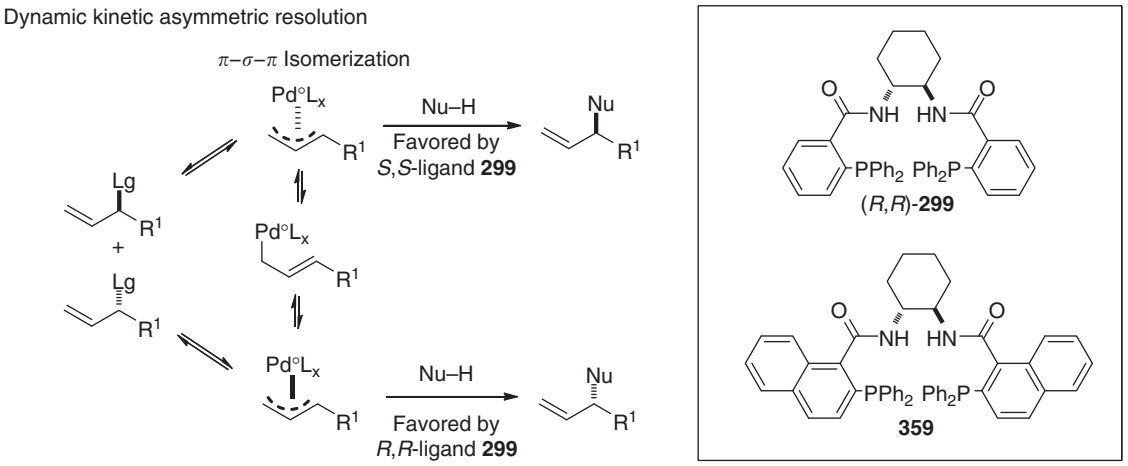
Scheme 56

6.02.3.1.5 Dynamic kinetic asymmetric transformations (DYKAT)

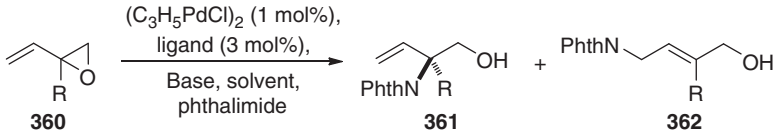
Trost has developed a method based on the dynamic kinetic asymmetric transformation (DYKAT) of racemic substrates (Scheme 57). In this method, Pd displacement of an allylic leaving group to form a π-allyl complex obliterates the chirality center in a racemic substrate. Each enantiomer of the allylic substrate gives rise to a diastereomeric π-allyl complex when a chiral ligand is used. This amination reaction becomes stereoconvergent if the π–σ–π process by which the diastereomeric π-allyl complexes interconvert is rapid relative to a rate-determining nucleophilic attack.

Racemic butadiene monoxides **359** have been aminated with phthalimide under DYKAT conditions (Table 13).[193] Amination of **360a** with phthalimide occurs regioselectively to give a 4:1 ratio of branched to linear products with a Pd/Ph_3P catalyst system (entry 1). The regioselectivity for this substrate contrasts with allyl acetates, which typically favor the linear product. Selectivity for the branched amination product is further improved with Trost's ligand **299** (entry 2). More significantly, this chiral ligand promotes an asymmetric amination of **360a** that is not a kinetic resolution. It was subsequently discovered that naphtho ligand **359** provides optimal selectivity for this reaction (entry 4). The improved performance of this ligand was ascribed to the naphtho linker, which further restricts conformational freedom with regard to the ligand's amide bond and thus creates a more defined chiral pocket.

Isoprene monoxide (**360b**) would provide access to chiral *tert*-alkylamines, but represents a greater challenge with regard to regiochemistry. A control reaction with dppf as a ligand indicated that **360b** preferentially reacts at its terminus to favor the linear amination product by a 7:1 ratio (entry 5). Trost's ligands reverse this regiochemical bias, giving only branched product **361** (entries 6 and 7). Changing the base from Na_2CO_3 to Cs_2CO_3 is significant, as the cesium salts react more slowly and thus permit equilibration of the diastereomeric π-allyl intermediates.



Scheme 57



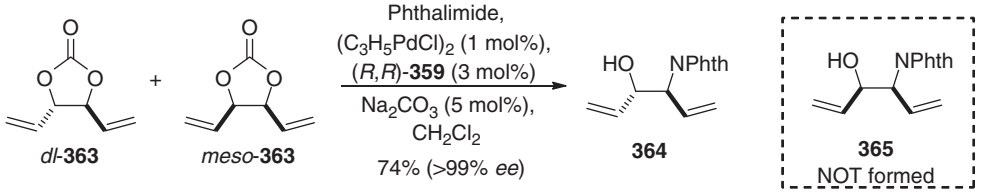
(25)

Table 13 Dynamic kinetic asymmetric transformations (DYKAT) amination of diene monoxides **360**

Entry	*Substrate*	*Ligand*	*Base*	*Solvent*	*Yield (%)*	*b/l*	ee *(%)*
1	R = H (**360a**)	PPh_3	Na_2CO_3	THF	71	4:1	–
2	R = H (**360a**)	**299**	Na_2CO_3	THF	87	16:1	77
3[a]	R = H (**360a**)	**299**	Na_2CO_3	CH_2Cl_2	83	–	68
4[a]	R = H (**360a**)	**359**	Na_2CO_3	CH_2Cl_2	99	75:1	98
5	R = Me (**360b**)	dppp	Cs_2CO_3	CH_2Cl_2	85	1:7	–
6[a,b]	R = Me (**360b**)	**299**	Cs_2CO_3	THF	58	>75:1	83
7[b,c]	R = Me (**360b**)	**359**	Cs_2CO_3	CH_3CN	62	>75:1	>90

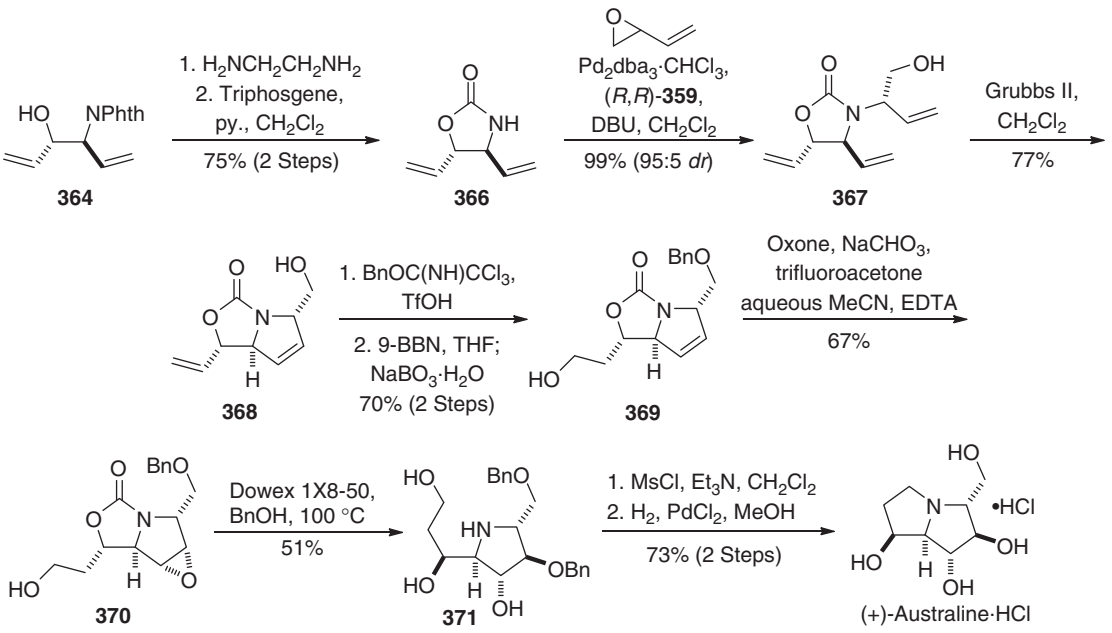
[a]Conducted at room temperature.
[b]This reaction required 2 days to complete.
[c]Conducted at 55 °C.
Abbreviation: dppp, 1,3-bis(diphenylphosphino)propane.

Enantiomerically pure amino alcohol **364** can be prepared from *dl*-**363** and *meso*-**363** (equation 26).[194] Racemic carbonate **363** is kinetically resolved to produce **364** as expected (43% yield, >99% *ee*). The meso diastereomer surprisingly gave **364** instead of the expected diastereomer **365**. This result was rationalized by suggesting that the Curtin–Hammett scenario whereby the matched mode of ionization for *meso*-**363** with the chiral catalyst is followed by a kinetically favored intramolecular cyclization back to the starting carbonate. A productive intermolecular reaction only occurs in the mismatched ligand/substrate case, which involves equilibration of the Pd-allyl complexes by *π–σ–π* isomerization. Since both diastereomers of **363** produce the same amination product, a 1:1 mixture of meso and dl carbonates was reacted under optimized conditions to give **364** in 74% yield and 99% *ee*. The maximum yield for this process is expected to be 75% (50% due to reaction of the meso diastereomer, plus 25% from kinetic resolution of the dl).



(26)

A total synthesis of australine was completed to showcase the Pd-catalyzed asymmetric allylic amination method involving Trost's ligands (Scheme 58).[195] This synthesis forms each of the three C–N bonds in australine by means of a displacement

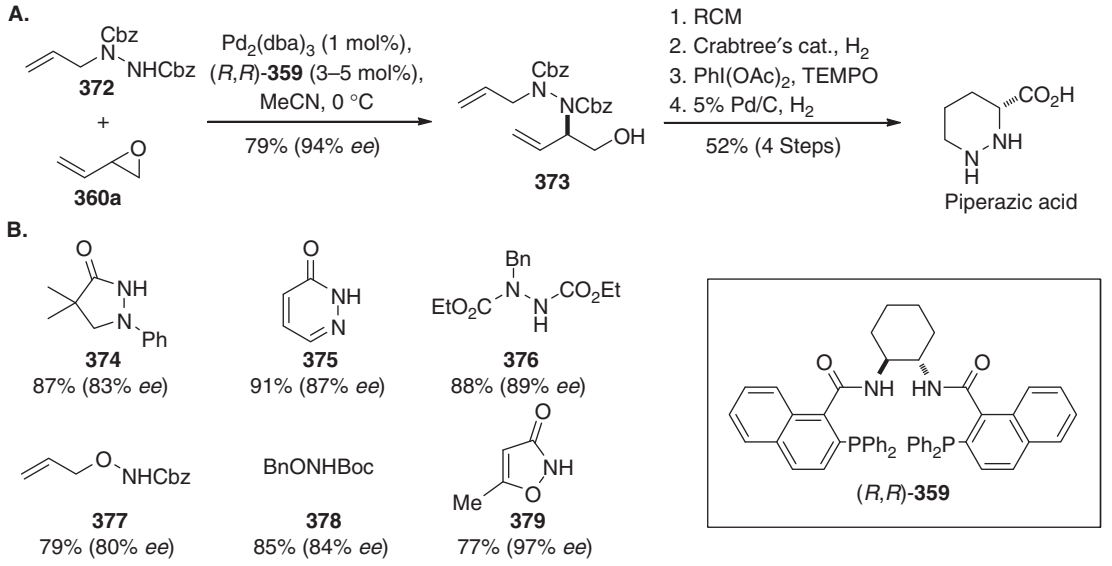


Scheme 58

reaction, two of which are Pd-catalyzed allylic aminations. A standard two-step sequence converted **364** (prepared from a 1:1 mixture of meso/dl-363, equation 26) into oxazolidinone **366**. This then served as a nucleophile for the DYKAT amination of racemic butene oxide. This allylation of oxazolidinone **366** occurs with complete catalyst control, where the (*R*,*R*)-ligand **359** favors the required diastereomer **367** by 95:5 mixture and the antipodal ligand favors the epimeric product by an identical ratio.

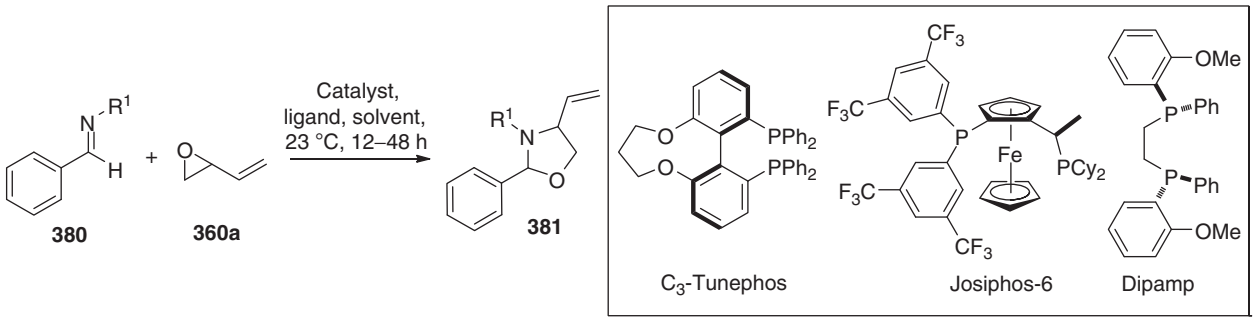
Following the ring-closing metathesis of triene **367**, a series of oxidations provided epoxide **370**, which was opened via solvolysis to give triol **371**. The remaining N–C bond was formed by treating triol **371** with Et_3N and MsCl at –30 °C to form a primary mesylate, which cyclizes on warming to room temperature. Hydrogenolysis of the benzyl ether protecting groups then provided the natural product (+)-australine.

Hydrazines and hydroxylamines are competent nucleophiles for the DYKAT amination of butadiene monoxide (Scheme 59).[196] The naphtho ligand **359** tolerates a diverse set of these nucleophiles, providing the high levels of enantioselectivity (80–97% *ee*). The reaction of allyl hydrazine **372** is notable, as the resulting product **373** was elaborated in four steps to piperazic acid.



Scheme 59

Jarvo has examined a variation of the DYKAT amination of butadiene monoxide with imines as the nucleophile (equation 27, Table 14).[197] The initial adduct between an imine and the π-allyl transition metal complex yields an unstable iminium ion that subsequently cyclizes to form an oxazolidine. Several transition metal/ligand systems catalyze this transformation.



(27)

Table 14 Transition metal-catalyzed oxazolidine synthesis

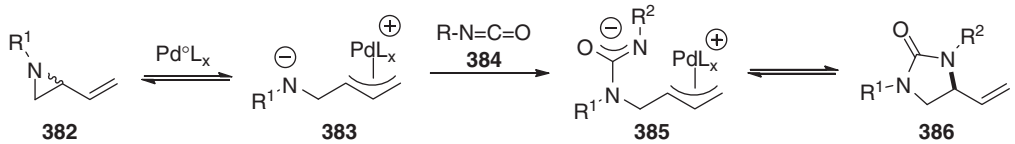
Entry	*R^1*	*Catalyst (mol %)*	*Ligand*	*Solvent*	*Yield (%)*	dr *(cis.trans)*	ee *(%)*[a]
1	SO_2Me	$Pd_2dba_3{\cdot}CHCl_3$ (5)	C_3-Tunephos	THF	92	1:3	82
2	SO_2Me	$Pd_2dba_3{\cdot}CHCl_3$ (5)	Josiphos-6	Diglyme	96	2:1	91
3[b]	SO_2Me	$Ni(cod)_2$ (10)	(*S*,*S*)-Dipamp	THF	96	≥20:1	58 (*R*,*R*)
4[b]	SO_2Me	$Ni(cod)_2$ (10)	(*R*,*R*)-Dipamp	THF	78	≥20:1	56 (*S*,*S*)
5[c]	PMP	$Rh(cod)_2(OTf)$ (5)	None	CH_2Cl_2	86	6:1	99
6	SO_2Tol	$Rh(cod)_2(OTf)$ (5)	None	CH_2Cl_2	≤5	n.d.	NA

[a]% *ee* is provided for the major diastereomer.
[b]Additional additives: 30 mol% $Ti(O\text{-}Pr^i)_4$, 1.0 equivalent tetrabutylammonium difluorotriphenylsilicate.
[c]Using enantiopure (99% *ee*) butadiene monoxide.

The Pd-catalyzed reaction with Tunephos and Josiphos-6 ligands is stereoconvergent, consistent with rapid equilibration of the π-allyl complexes, and provides >82% *ee*. Although diastereoselectivity for the oxazolidine is modest for these Pd-catalysts, it is influenced by the ligand (entries 1 and 2). Nickel and rhodium complexes also catalyzed the formation of **381**. Optimized conditions with Ni and dipamp gave improved diastereoselectivity relative to the Pd-ligand systems, albeit at the expense of enantioselectivity (entries 3 and 4).

With Rh the reaction is stereospecific, wherein enantiopure **360a** provides the oxazolidine in 99% *ee* (entry 5). This indicates that the π–σ–π is slow under Rh-catalyzed conditions relative to the addition of imine and cyclization. The nucleophilicity of the imine nitrogen is an important factor. Best results under Rh-catalysis were obtained with imine containing an *N*-PMP group, whereas sulfonyl-protected imines were essentially unreactive (entry 6).

Racemic *N*-alkyl vinylaziridines (**382**) react under DYKAT conditions with isocyanates to form imidazolidinones (Scheme 60, Table 15).[198] This is a challenging enantioselective process and presents an excellent case study on reaction optimization. Initial reactions between **382** and phenyl isocyanate (**38**) under standard DYKAT conditions with Pd and the naphtho ligand **359** gave a disappointing 29% yield and 59% *ee*. It was hypothesized that the formation of **385** or its cyclization to **386** was rapid relative to the interconversion of enantiomers via π-allylpalladium complexes. For DYKAT to be successful, Curtin–Hammett conditions must be met. In this case, the enantio-discriminating cyclization must be the rate-limiting step to achieve a stereoconvergent reaction.



Scheme 60

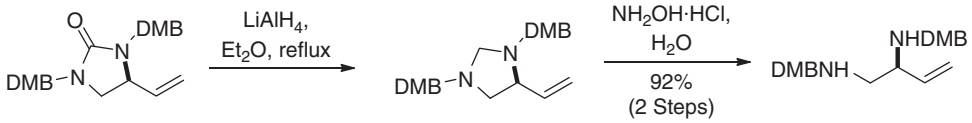
A logical strategy to improve the enantioselectivity would involve either increasing the rate of the interconversion for the π-allyl complex or slowing the rate of cyclization. Although it is known that halide additives increase the rate of π-allyl interconversion, it was not successful in this case. Acidic additives, however, had a substantial impact on the enantioselectivity. The addition of acetic acid (10 mol%) was optimal. Presumably, this establishes Curtin–Hammett conditions by protonating intermediates **383** or **385**.

Table 15 DYKAT of aziridines to imidazolidinones[a]

Entry	R^1	R^2	*Yield (%)*	ee *(%)*	*References*
1	Bn	Ph	99	82	198
2	Bn	COC_6H_5	94	13	198
3	Bn	Bn	98	95	198
4	*o*-$NO_2C_6H_4CH_2$–	Ph	99	83	198
5	*p*-$MeOC_6H_4CH_2$–	Ph	52	74	198
6	DMB[b]	DMB	88	94	199
7	Ts	Ph	61	65	198

[a]Conditions: $(C_3H_5PdCl)_2$ (2 mol%), (*R,R*)-**359** (6 mol%), AcOH (10 mol%), isocyanate (1 equivalent), CH_2Cl_2 (0.12 M), 2 h.
[b]DMB = 2,4-Dimethoxybenzyl.
Source: Adapted from Table 2 in Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 11836–11837, with permission from American Chemical Society.

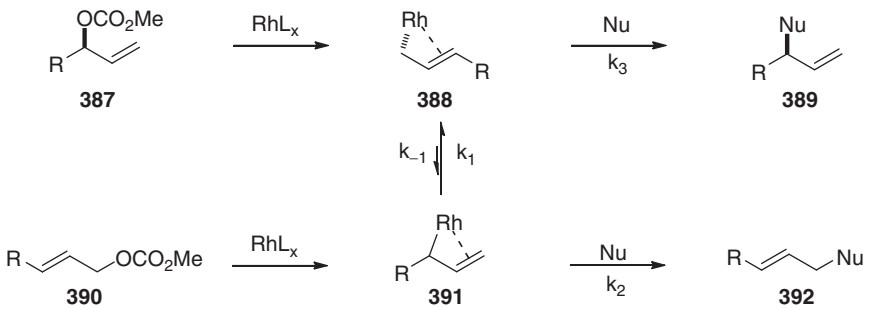
It was noted that enantioselectivity was diminished for *N*-tosyl aziridine (entry 7) and when benzoyl isocyanate was used (entry 2). This may hint at the importance of the acid additive and the equilibrium between intermediate **383** and its protonated form. The imidazolidinone can be converted into diamines in a two-step process (Scheme 61).



Scheme 61

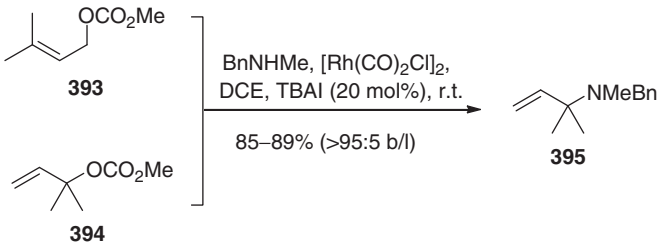
6.02.3.2 Rhodium-Catalyzed Allylic Amination

Rhodium-catalyzed allylic amination is mechanistically distinct from the Pd^0 process and has proven to be a general process. The regiochemical outcome for amination under these conditions reflects the formation of an enyl ($\sigma+\pi$) rhodium complex followed by S_N2' displacement (Scheme 62).[200] Equilibration of rhodium enyl intermediates **388** and **391** is typically slow relative to nucleophilic attack. As a result, there is a significant memory effect whereby the product structure maps onto the structure of the starting material. This regiochemistry contrasts with what is observed for Pd^0-catalyzed allylic substitutions, which typically favor linear products and have rapid π–σ–π equilibration of allyl metal complexes.



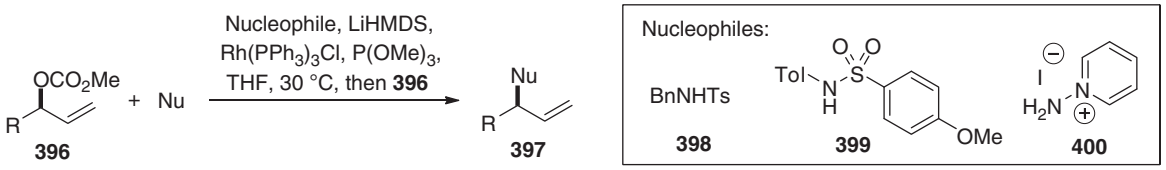
Scheme 62

Several exceptions to the memory effect have been documented where the substitution does not occur at carbon to which the leaving group was attached. These results can be rationalized by considering steric and electronic factors that increase the rate of enyl intermediate equilibration, or decrease the rate of the final nucleophilic substitution. For example, the amination of both **393** and **394** occurred to provide the branched product **395** (>95:5 b/l) with catalytic $[Rh(CO)_2Cl]_2$ (equation 28).[201] Evans has also documented an example where branched and linear isomers of an allyl carbonate substrate converge to a branched substitution product.[200] These results implicate isomerization of enyl intermediates to favor **388** as the reactive intermediate.



(28)

A convenient catalytic system is prepared by treating Wilkinson's catalyst [$Rh(PPh_3)_3Cl$] with $P(OMe)_3$.[202] The resulting complex is effective for the amination of allyl carbonates with metalated nitrogen nucleophiles (equation 29, **Table 16**). Best results are obtained with lithium amides that are stabilized by sulfonyl groups (**398** and **399**),[202,203] and with a lithiated aza-ylide nucleophile (**400**).[204] Sodium and potassium salts are also compatible, but give diminished yields due to competitive elimination pathways and their tendency to react at a slower rate.[202]



(29)

Table 16 Rhodium-catalyzed synthesis of branched allylic amines

Entry	*Substrate (R =)*	*BnN(Li)Ts (**398**) Reference 202*		*TolN(Li)Mbs (**399**) Reference 203*		*$PyrNH_2$, LiHMDS (**400**) Reference 204*	
		Ratio b/l	*Yield (%)*	*Ratio b/l*	*Yield (%)*	*Ratio b/l*	*Yield (%)*
1	Me	≥99:1	86	≥99:1	96	≥19:1	76
2	$CH_2=CH(CH_2)_3$–	19:1	87	46:1	91	≥19:1	73
3	Bu^i	–	–	12:1	94	≥19:1	86
4	Hex^c	9:1	92	–	–	≥19:1	75
5	Bn	10:1	94	20:1	86	≥19:1	78
6	$TBSOCH_2$–	9:1	91	23:1	83	≥19:1	84
7	$BnOCH_2$–	≥99:1	84	8:1	85	≥19:1	88
8	Ph	19:1	87	47:1	94	≥19:1	81

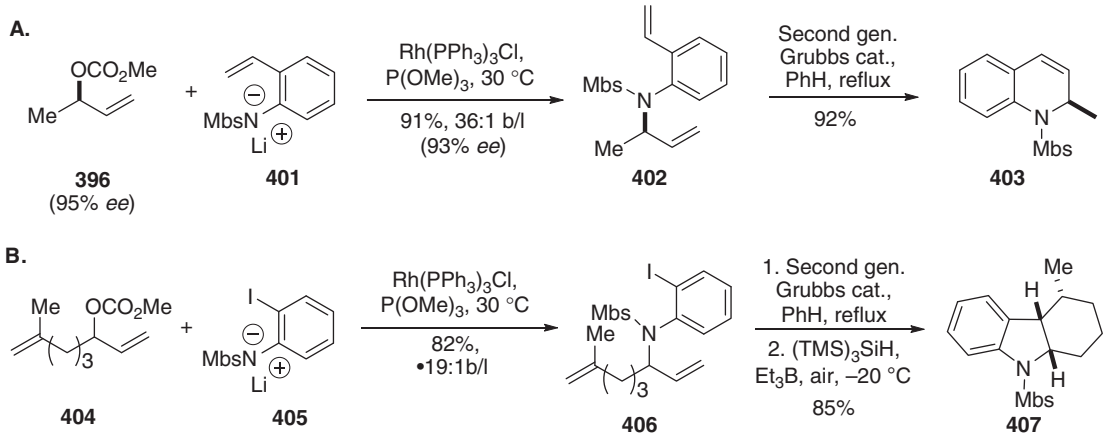
Mbs = 4-methoxybenzenesulfonyl.

In all cases, the Rh-catalyzed amination selectively forms the branched product from allyl carbonate **396** with net retention of stereochemistry. The conservation of enantiomeric excess for these reactions is outstanding (*cee* ≥98%). (Conservation of enantiomeric excess (*cee*) is a metric to describe enantiospecificity. *cee* = (product *ee*/starting material *ee*) × 100.) Although the branched product is uniformly favored, selectivity for the branched product is affected by the structure of the substrate. Branching near the reaction site decreases selectivity for the branched product (entries 3 and 4), as does the presence of ethers that can coordinate to rhodium (entries 6 and 7).

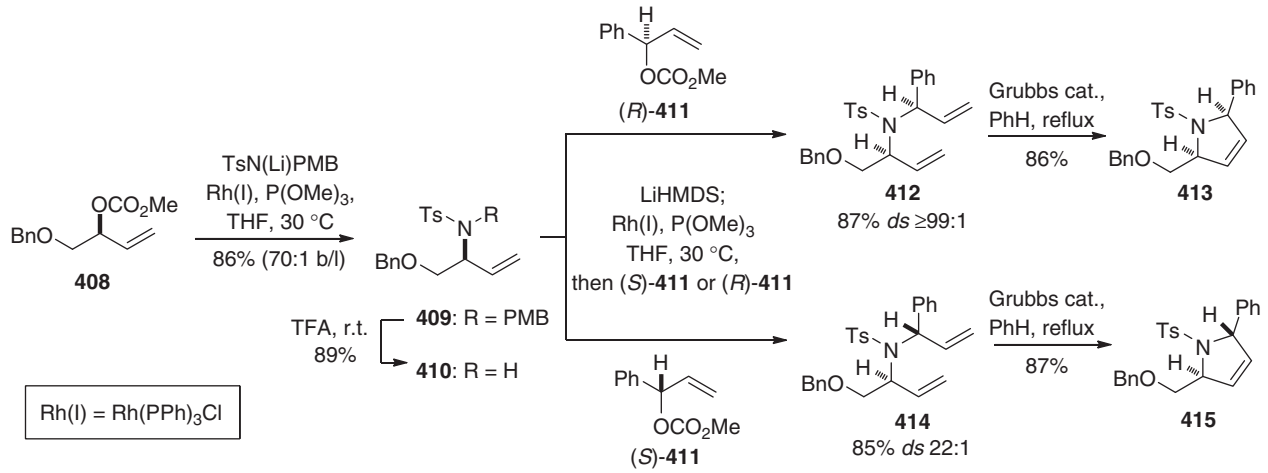
The three nitrogen nucleophiles summarized in **Table 16** can be deprotected to provide access to secondary and primary amine products. This chemistry is not limited to tosyl-protected amines. Other sulfonyl groups work equally well, including the nitrobenzenesulfonyl group (Ns), which can be removed under mild deprotection conditions using thiophenolate.[201] In the case of **398**, or its Ns-derivative, an iterative deprotection sequence is needed to obtain a branched primary amine. Alternatively, if aza-ylide **400** is used as the nucleophile, **397** can be deprotected in one step to a primary amine via the reductive cleavage of the N–N bond with SmI_2 or Zn/NH_4Cl.[203]

Anilines are poor nucleophiles, and thus it is significant that excellent results are obtained with **401**. In addition to the scope demonstrated for allyl carbonate **396** in **Table 16**, *ortho*-substituted aniline nucleophiles are well tolerated (**Scheme 63**).[202] Aryl nucleophiles with this substitution pattern are valuable as their amination products can be elaborated into heterocycles. Dihydroquinoline **403** was synthesized by a two-step route involving allylic amination of carbonate **396** with **401**, and ring-closing metathesis. A similar sequence was used to prepare dihydroindole **407**. In the case of **407**, ring-closing metathesis was followed by a radical cyclization promoted by triethylborane in the presence of air.

Rh-catalyzed allylic amination can be conducted iteratively to form multiple carbon–nitrogen bonds within a compound (**Scheme 64**).[205] The first iteration with TsNLiPMB as the nucleophile yielded **409**. The PMB group can be removed in high yield



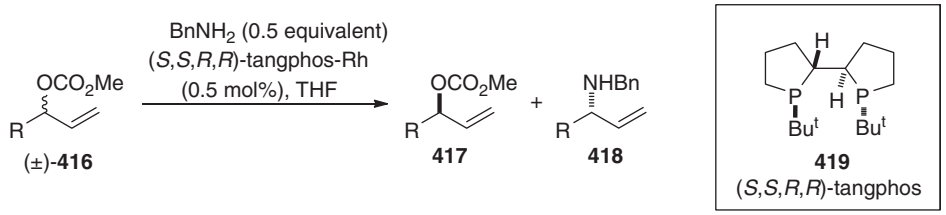
Scheme 63



Scheme 64

(89%) with TFA to tosyl-protected amine **410**. This product then becomes the nucleophile for a second allylic amination after deprotonation by LiHMDS. This second amination involving chiral nucleophile **410** and chiral allylic carbonate **411** is diastereoselective and remains highly selective for the branched products **412** and **414** (>31:1 b/l). There is a clear matched and mismatched case for this diastereoselective amination, and yet the mismatched case to **414** still proceeds with a synthetically useful level of diastereoselectivity (*ds* 22:1). This further demonstrates the robust nature of the Rh-catalyzed reaction and the relatively slow isomerization of Rh-enyl intermediates under these amination conditions.

Asymmetric allylic amination by rhodium catalysis is not as developed as its palladium counterpart. In part, this may be a consequence of slower isomerization for enyl-Rh intermediates in comparison to Pd π-allyl complexes. The isomerization of enyl Rh intermediates is sufficiently slow to permit the kinetically resolution of racemic secondary carbonates (equation 30, Table 17).[206] Excellent selectivities are achieved using tangphos (**419**) as the chiral ligand for substrates containing aliphatic substituents (entries 1–4). In these cases, excellent enantioselectivities are obtained and the maximum theoretical yield of 50% is approached for both the amination product and the recovered carbonate.



(30)

Table 17 Resolution of racemic carbonates using Rh-catalyzed allylic amination

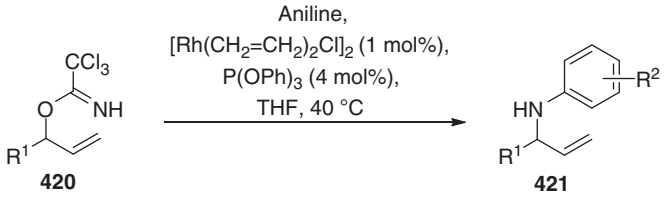
Entry	*Substrate (R =)*	*Percent Yield Carbonate (ee, %)*	*Percent Yield Benzylamine (ee, %)*
1	Me (**416a**)	42 (>99.9)	46 (>99.9)
2	Et (**416b**)	47 (>99.9)	49 (91.5)
3	Bu^{i} (**416c**)	44 (>99.9)	34 (97.5)
4	Bn (**416d**)	36 (>99.9)	50 (>99.9)
5[a]	Ph (**416e**)	–	88 (89.1)

[a]One equivalent of $BnNH_2$ was used.

Source: Adapted from Table 2 in Vrieze, D. C.; Hoge, G. S.; Hoerter, P. Z.; Van Haitsma, J. T.; Samas, B. M. *Org. Lett.* **2009**, *11*, 3140–3142, with permission from American Chemical Society.

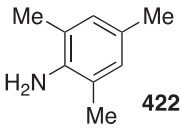
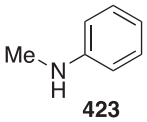
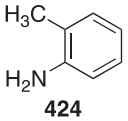
Surprisingly, a dynamic asymmetric amination occurs when the substituent is an aromatic group (entry 5, R=Ph). In this case it is possible to use a stoichiometric equivalent of benzylamine and obtain a yield of 88%. The presence of the aromatic group may facilitate ionization to produce a carbocation in this case due to benzylic stabilization. This ionization process could facilitate a background reaction where the unreacted enantiomer of carbonate **416e** is racemized, and could enable a dynamic kinetic resolution. In any event, this example underscores the influence of substrate on the mechanism of this reaction.

Nguyen has developed a variant of the Rh-catalyzed allylic amination conditions where trichloroacetimidate serves as leaving group (equation 31).[207] The complex derived from Wilkinson's catalyst and $P(OMe)_3$ works poorly for these systems, providing low yield and modest branched to linear selectivity (14%, 5:1 b/l). Screening several sources of Rh and trialkyl phosphites led to the identification of $[Rh(ethylene)_2Cl]_2$ and $P(OPh)_3$ as the optimal catalyst system. The reaction scope is impressive for this method (Table 18). Mesitylamine (**422**, entries 1–3), *N*-methylaniline (**423**, entries 4–6), and *o*-toluidine (**424**, entries 7 and 8) all participate in allylic amination in high yields with good regioselectivity. It is also noteworthy that neutral anilines are reactive nucleophiles under these conditions. In contrast, Evans's conditions require lithiated nucleophiles.



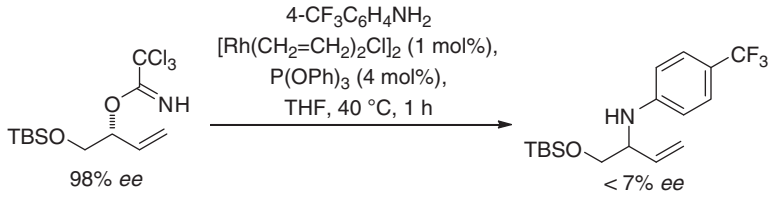
(31)

Table 18 Rh-catalyzed allylic amination of secondary trichloroacetimidates

Entry	*R =*	*Aniline*	*Yield (%)*	*Ratio b/l*
1	$TBSOCH_2$–	 **422**	94	>99:1
2	$BnOCH_2$–		87	>99:1
3	Bn		93	80:1
4	$TBSOCH_2$–	 **423**	94	>99:1
5	$BnOCH_2$–		99	32:1
6	Bn		98	30:1
7	Hex[c]	 **424**	70	12:1
8	Pr^{i}		73	14:1

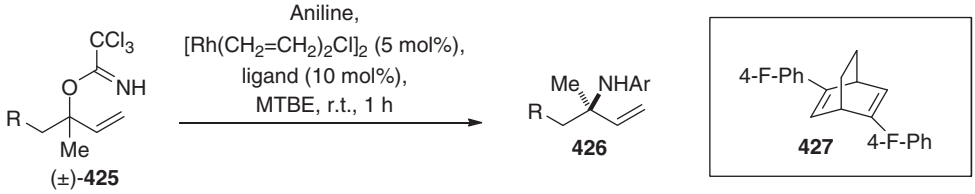
Source: Adapted from Tables 3 and 4 in Arnold, J. S.; Stone, R. F.; Nguyen, H. M. *Org. Lett.* **2010**, *12*, 4580–4583, with permission from American Chemical Society.

The Rh-catalyzed amination of allyl trichloroacetimidates is mechanistically distinct from the reaction of allyl carbonates with lithiated anilines. The most striking difference is the fact that the amination of trichloroacetimidates is not stereospecific; racemization occurs when enantiomerically enriched substrates are used (equation 32). Control reactions also indicated that neither allyl acetates nor allyl carbonates react with aniline in the presence of the catalyst derived from $[Rh(ethylene)_2Cl]_2$ and $P(OPh)_3$. Although the full mechanistic studies have not been reported at the time of this writing, the racemization of these substrates presented an opportunity to develop a dynamic asymmetric reaction with chiral ligands.



(32)

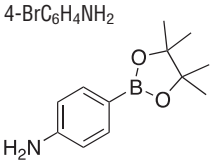
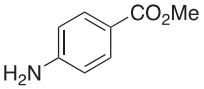
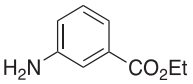
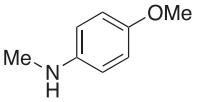
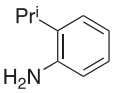
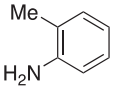
There is a delicate balance between substrate structure and catalyst activity. The $RhCl[P(OPh)_3]_3$ catalyst that was optimized for secondary allylic trichloroacetimidates gives more moderate yields when applied to tertiary substrates (45%, 14:1 ratio b/l). Continued optimization identified commercially available $[Rh(cod)_2Cl]_2$ as a competent catalyst for reactions involving **425** (equation 33).[208]



(33)

Subsequently, an asymmetric version of this amination was developed based on chiral diene ligands.[209] Fluorinated diene ligand **427** was most effective in terms of both enantioselectivity and yield. Selected examples shown in Table 19 highlight the scope of this asymmetric reaction.[210] This method presents a unique route to chiral *tert*-alkyl aryl amines **426** that tolerates electron-deficient anilines (entries 1–5) and sterically demanding anilines bearing ortho-substituents (entries 7–9). The regioselectivity for the branched products shows some substrate dependence, with a chelating group required for highest levels of selectivity (entries 9 and 11). In any event, this method represents an interesting application of chiral diene ligands to asymmetric amination.

Table 19 Enantioselective preparation of *tert*-alkyl *N*-arylamines

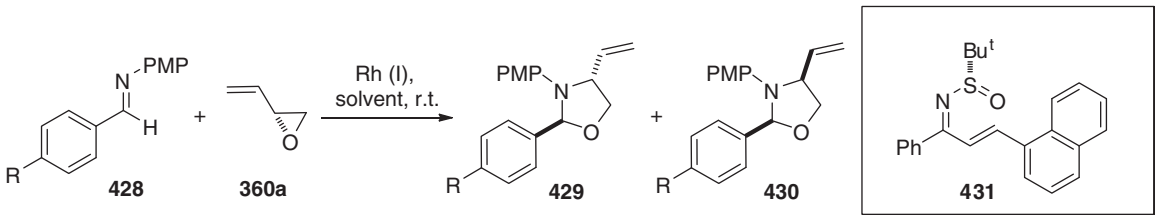
Entry	*Aniline*	*R* =	*Yield (%)*	*Ratio b/l*	ee *(%)*
1	$4\text{-}FC_6H_4NH_2$	BnO– (**425a**)	82	>99:1	96
2	$4\text{-}BrC_6H_4NH_2$	BnO– (**425a**)	86	>99:1	91
3		BnO– (**425a**)	54	>99:1	91
4		BnO– (**425a**)	51	>99:1	85
5		BnO– (**425a**)	79	>99:1	94
6		BnO– (**425a**)	70	30:1	93
7		BnO– (**425a**)	74	48:1	94
8		BnO– (**425a**)	69	51:1	89
9		$BnOCH_2$– (**425b**)	70	5:1	56
10	$4\text{-}MeOC_6H_4NH_2$	BnO– (**425a**)	77	33:1	90
11		$PhCH_2$– (**425c**)	68	7:1	52

Source: Adapted from Tables 2 and 3 in Arnold, J. S.; Nguyen, H. M. *J. Am. Chem. Soc.* **2012**, *134*, 8380–8383, with permission from American Chemical Society.

Strained oxygen heterocycles are useful substrates for Rh-catalyzed allylic amination. Butadiene monoxide (**360a**) participates in a formal cycloaddition with imines to produce 1,3-oxazolidines that are catalyzed by several transition metals including Rh, Pd,

and Ni (equation 34). These heterocycles are formed in a stepwise manner. The transition metals catalyze *N*-allylation of the imine to generate an electrophilic iminium ion that subsequently cyclizes to produce the 1,3-oxazolidine.

As discussed previously (Section 6.02.3.1), the Pd-catalyzed reaction is stereoselective, occurring under ligand control. The Rh-catalyzed reaction can be stereospecific or stereoselective according to the Rh-ligand combination (Table 20). $Rh(cod)_2OTf$ promotes a stereospecific process with enantiopure butadiene monoxide, which favors the thermodynamically favored *cis* oxazolidine **430**.[196] This cycloaddition occurs stereoselectively with racemic **360a** using a catalyst derived from $[Rh(C_2H_4)_2Cl]_2$, AgOTf, and chiral sulfoxide **431**.[211] Interestingly, the asymmetric reaction with sulfoxide ligand **431** favors the trans diastereomer by a modest ratio for several substrates (entries 1 and 2).



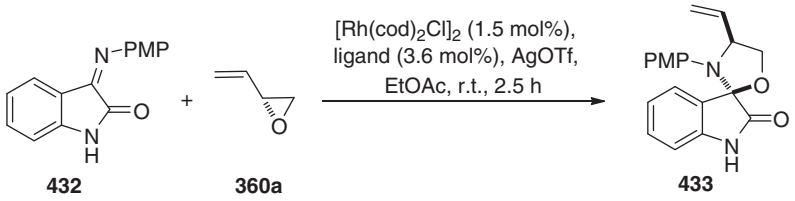
(34)

Table 20 Rh-catalyzed preparation of 1,3-oxazolidines

Entry	*Substrate (R =)*	*$Rh(cod)_2OTf$ (5 mol%)[197] CH_2Cl_2*	*$[Rh(C_2H_4)_2Cl]_2$ (2.5 mol%),[211] **431** (6 mol%), AgOTF (6 mol%), EtOAc*	
		*Yield (%); (*trans:cis*)*[a]	*Yield (%); (*trans:cis*)*[a]	ee *(%)*[b]
1	H	86 (1:6)	90 (3.5:1)	97
2	4-Cl	88 (1:5)[c]	70 (3.5:1)	93
3	4-Me	81 (1:6)[c]	–	–
4	4-MeO	60 (1:6)	65 (1:1.5)	96

[a]By crude ^1H NMR.
[b]All *trans:cis* ratios are by ^1H NMR. The *dr* was improved for some products after chromatography. Enantiomeric excess is given for the major diastereomer.
[c]When the reaction was conducted with enantiopure **360a** (99% *ee*), the product was obtained in 99% *ee*.

This formal [3+2] cycloaddition between butadiene monoxide and imines has been used to prepare spirooxindole **433** from isatin-derived imine **432** (equation 35, Table 21).[211] Chiral sulfoxide ligand **431** controls the stereochemistry of the product (entry 1). In the absence of ligand **431**, conversion to spirooxindole **433** is low, and occurs with racemization of chiral butadiene monoxide (entry 2). This suggests that the asymmetric reaction is the result of a dynamic kinetic resolution. Curiously, there are clear matched/mismatched pairings between nonracemic butadiene monoxide and each enantiomer of the sulfinamide ligand (entry 3 vs. 4). As a result, there remains some mechanistic ambiguity to this process, as both kinetic resolution and dynamic kinetic resolution pathways appear to be operative.



(35)

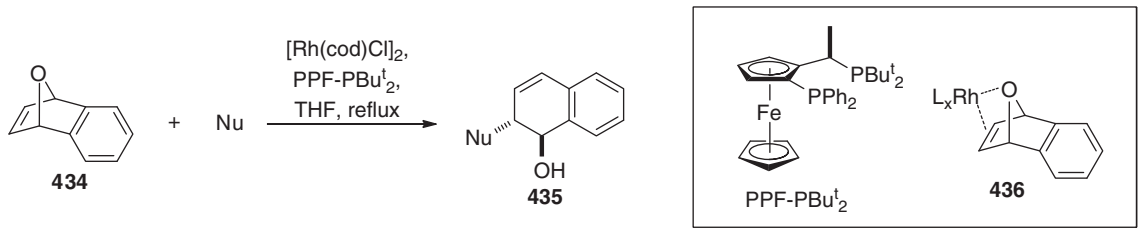
Table 21 Rhodium-catalyzed synthesis of spirooxindoles via formal [3+2] cycloaddition

Entry	*Butadiene monoxide*	*Ligand*	*Conversion (%)*	dr	ee *(%)*
1[a]	(±)-**360a** (3 equivalents)	**431**	90[b]	12:1	94
2	(*R*)-**360a** (1.2 equivalents)	none	10	10:1	16
3	(*R*)-**360a** (1.2 equivalents)	**431**	>99	12:1	93
4	(*R*)-**360a** (1.2 equivalents)	ent-**431**	41	10:1	54

[a]The metal source for this reaction was $[Rh(C_2H_4)_2Cl]_2$.
[b]Isolated yield.

Oxabicyclic alkenes (e.g., **434**) have sufficient ring strain that they can be ring-opened by Rh-catalysis (equation 36). Neutral nucleophiles asymmetrically add to these substrates in the presence of chiral catalysts to produce amino alcohols **435**.[212] This reaction is unique, as a *trans*-product is formed instead of the *cis*-product that would be expected to arise via a double inversion process. A mechanistic hypothesis involves the rapid and reversible coordination of Rh to the more accessible, *exo*, face of oxabicycle, as in **436**.[213,214] Insertion of Rh into the bridgehead C–O bond produces an enyl-Rh complex that undergoes S_N2' displacement of rhodium from the *endo* face to yield the *trans* product.

Neutral amines add to **434** in yields of 83–96% (**Table 22**) and with moderate-to-good enantioselectivities in the presence of a chiral ligand, PPF-PBu^t_2. Lautens discovered that there was a significant halide effect on enantioselectivity in these reactions.[215,216] Best results are obtained if a halogen exchange to replace chloride with iodide is completed before the addition of substrate. This process involves treatment of $[Rh(cod)_2Cl]_2$ with AgOTf and then addition of Bu_4NI to replace chloride with iodide. Nitrogen nucleophiles that are basic can be problematic due to their coordination to, and poisoning, of transition metal catalysts. With this catalyst system, this problem can be mitigated by the addition of a proton source, such as CSA (entries 6 and 7).



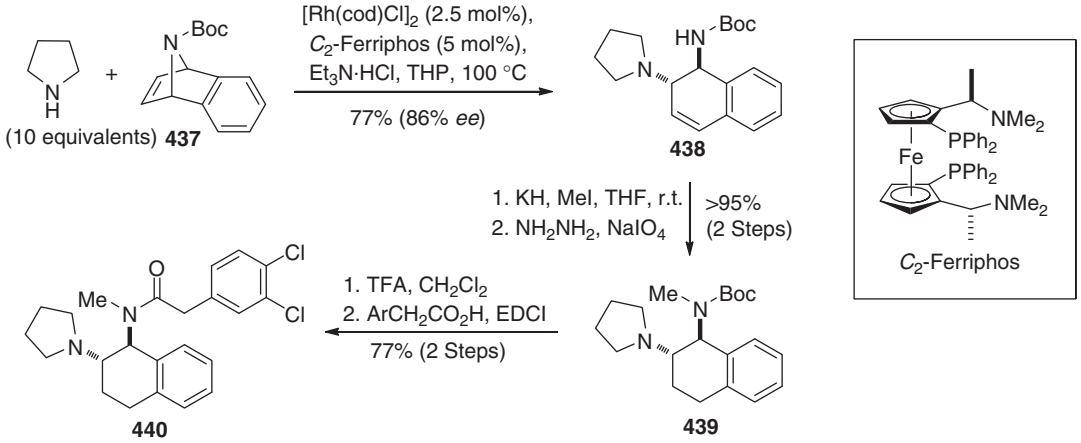
(36)

Table 22 Asymmetric ring-opening allylic amination[212,215]

Entry	*Nucleophile*	*No additives*[212]		*AgOTf, TBAI (Halogen exchange)*[215]	
		Yield (%)	ee *(%)*	*Yield (%)*	ee *(%)*
1	$PhSO_2NH_2$	86	95	–	–
2	Phthalimide	83	45	90	98
3	Indole	87	73	93	97
4	PhNHMe	96	74	97	92
5[a]	$4\text{-}MeOC_6H_4NH_2$	–	–	71	81
6[a]	$BnNH_2$	–	–	91	88

[a]CSA (1 equivalent) was added for reactions with primary amines and promotes a more rapid reaction.

[2.2.1]-Azabicyclo substrates also participate in ring-opening aminations to produce *trans*-diamines, but require the presence of an electron-withdrawing group on nitrogen (**Scheme 65**).[217] The ring opening of **437** can be achieved asymmetrically with C_2-ferriphos (86% *ee* for pyrrolidine). The cyclohexyl-1,2-diamines produced by this reaction are useful as the basis for chiral ligands, and are present in biologically active compounds. To demonstrate the value of this method, diamine **438** was elaborated in four steps to **440**, a selective κ-opioid agonist.

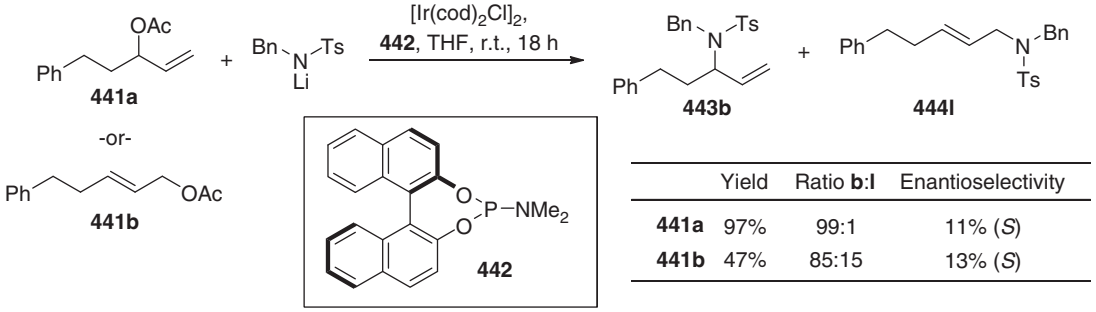


Scheme 65

6.02.3.3 Iridium-Catalyzed Allylic Amination

Ir-catalyzed allylic substitutions have attracted considerable attention since their early reports in 1997, with much of this work reviewed elsewhere.[218–223] In the context of allylic amination, this section will highlight salient features of the Ir-catalyst and ligands, and the influences of substrate and nucleophile structure, and will discuss emerging synthetic applications.

Leading work in this area involved the allylation of malonate nucleophiles,[224,225] but allylic amination has also received significant attention. Iridium catalysis favors branched allylic substitution products irrespective of whether the substrates are branched or linear. This regioselectivity complements Pd-catalysis (generally favoring linear products after equilibration of π-allyl complexes), and Rh-catalysis (product structure maps directly onto the substrate). Although branched products are favored by Ir catalysis, a modest memory effect exists (Scheme 66). Amination of both **441a** and **441b** selectively forms the branched product **443b**; however, the reaction of the linear isomer is less selective.[226] In addition to moderate differences in selectivity, it should be noted that the branched isomer reacts at a faster rate.

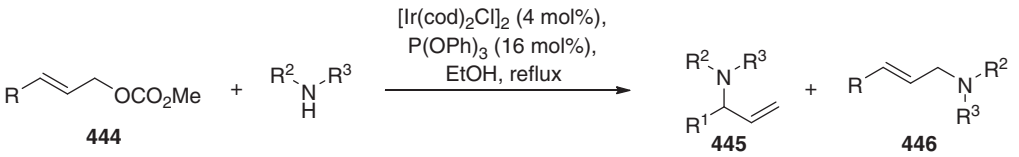


	Yield	Ratio **b**:**l**	Enantioselectivity
441a	97%	99:1	11% (*S*)
441b	47%	85:15	13% (*S*)

Scheme 66

Early studies on Ir-catalyzed allylic amination identified several key parameters that would influence subsequent reaction development. Catalyst complexes between Ir and π-acceptor ligands, specifically triphenyl phosphite, are more reactive in comparison to complexes prepared with $P(OEt)_3$ or phosphine ligands.[227,228] More rapid and higher-yielding reactions occur in polar solvents (e.g., EtOH, MeOH, Pr^iOH, acetone, MeCN, and CH_2Cl_2) versus less polar ether solvents (THF, dioxane).[228] Although branched amination products are favored, the product distribution varies according to ligand, solvent, substrate structure, and nucleophile.

The identity of the ligand appears to be most significant of these factors, although substrate and nucleophile are not inconsequential (Table 23). Highest selectivity for cinnamyl carbonate **444** was obtained for cyclic secondary amine and benzylamine nucleophiles using the catalyst generated from $[Ir(cod)_2Cl]_2$ and $P(OPh)_3$ (entries 1–3 and 5).[229] Allylic amination of **444** with Bu^tNH_2 and Et_2N proceeded in good yield, but with diminished branched selectivity (entries 3 and 4). Allyl carbonates containing an aliphatic substituent were less selective for the branched product when $[Ir(cod)_2Cl]_2$ was used as the precatalyst (entry 6 vs. entry 1). The erosion of regioselectivity was ascribed to the greater electron-donating ability of the alkyl group versus phenyl. Changing the solvent and Ir source greatly overcomes this effect and improves branched selectivity for aliphatic substrates (entries 7–9).



(37)

Table 23 Ir-catalyzed allylic amination

Entry	*Substrate*	*Amine*	*Ratio (b/l)*	*Yield (%)*
1	Ph	Pyrrolidine	96:4	95
2	Ph	Morpholine	92:8	92
3	Ph	Et_2NH	65:35	75
4	Ph	Bu^tNH_2	81:19	92
5	Ph	$BnNH_2$	96:4	89
6	Hex^n	Pyrrolidine	65:35	85
7[a,b]	Hex^n	Pyrrolidine	85:15	94
8[a]	Hex^n	$PhNH_2$	93:7	95
9[a]	Hex^c	$PhNH_2$	91:9	96

[a]With $[Ir(cod)_2OMe]_2$ as the precatalyst.

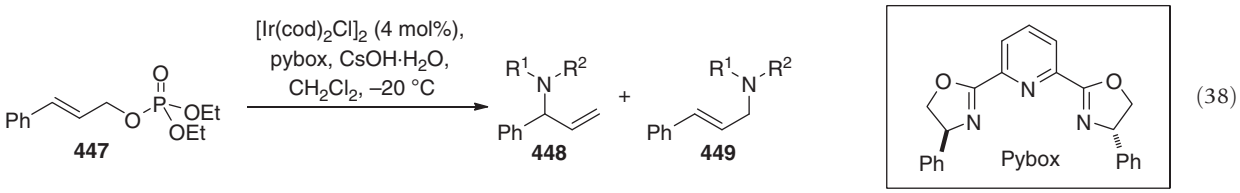
[b]With acetone as the solvent.

Source: Adapted from Tables 3 and 5 in Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525–9534, with permission from American Chemical Society.

6.02.3.3.1 Enantioselective Ir-catalyzed allylic amination

6.02.3.3.1.1 Pybox ligands

The development of an asymmetric variant of the Ir-catalyzed amination was a natural extension of this method. Pybox ligands have been widely used as chiral ligands for asymmetric reactions,[230] but have seen relatively little use for allylic substitutions. They are effective chiral ligands for Ir-catalyzed amination, but these require reactive allyl phosphates as substrates (equation 38). Linear phosphate **447** reacts with BzNHOBn to provide the **448** as the main product in 92% *ee* (Table 24, entry 1).[231] These pybox conditions also give high *ee* for the reaction of **447** with dibenzylamine and *p*-anisidine (entries 2 and 3). Although the regioselectivity for dibenzylamine was modest, it is comparable to results for other acyclic secondary amines with the Ir/P(OPh)$_3$ system (Et_2NH; 65:35 b/l). In contrast to these results, *N*-benzylbenzamide is less nucleophilic and was altogether unreactive (entry 4).



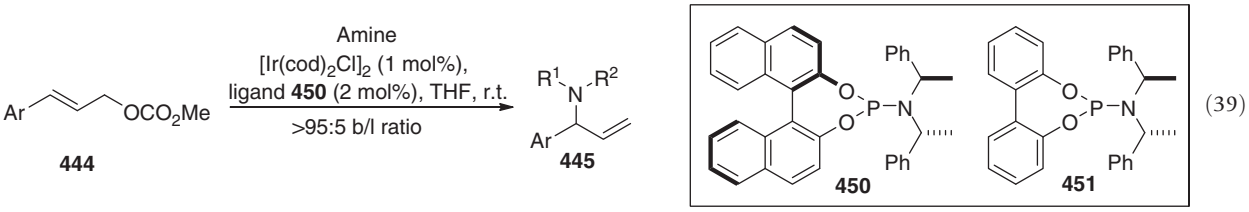
(38)

Table 24 Ir-catalyzed asymmetric allylic amination with pybox

Entry	*Amine*	*Ratio (b/l)*	*Yield (%)*	ee *(%)*
1	Bz, N, H, OBn	86:14	89	92
2	Bn, N, H, Bn	71:29	91	95
3	MeO, NH_2	90:10	86	88
4	Bz, N, H, Bn	NR	NR	NR

6.02.3.3.1.2 Phosphoramidite ligands

Hartwig reported a highly enantioselective amination catalyzed by an iridium complex with phosphoramidite ligand **450** (equation 39, Table 25).[232] These conditions provide excellent regioselectivity, with branched to linear ratios of >95:5 for most substrate and amine combinations. Even challenging acyclic nucleophiles, such as Et_2NH, were highly selective for the branched product (entry 5). The main limitation of this catalyst system is with regard to the enantioselectivity for cinnamyl substrates with *ortho*-substituents or electron-withdrawing groups (entries 6 and 7). Although most examples were run at room temperature, the reaction rates could be increased by conducting the reactions at 50 °C with essentially no loss in selectivity. Currently, the phosphoramidite conditions are more desirable compared to the pybox conditions due to better branched/linear selectivities and the ability to conduct these reactions at or above room temperature.



(39)

6.02.3.3.1.3 Identification of catalytic intermediates and ligand optimization

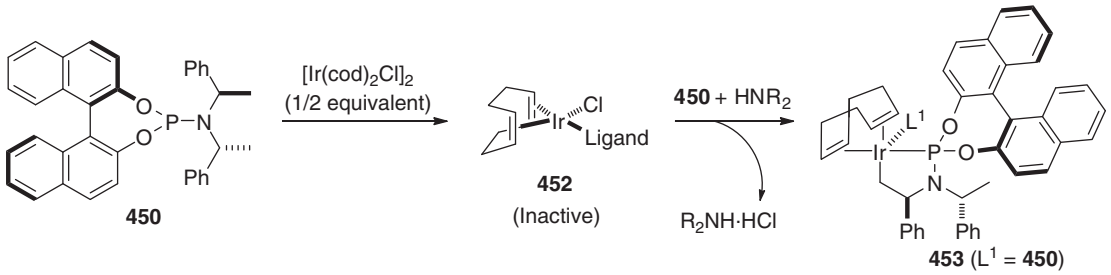
Mechanistic investigations of the reaction with phosphoramidite ligand **450** revealed a number of interesting findings and have led to additional improvements to the method. The most significant discovery was the fact that **450** does not form a C_2-symmetric complex with iridium as expected.[233] Hartwig isolated and characterized a square planar complex (**452**) formed by the 1:1 combination of phosphoramidite **450** with iridium (Scheme 67). To their surprise, allylic amination with stoichiometric complex **452** was slower than the catalytic reaction. It was then found that exposure of **452** to an amine and a second equivalent of ligand induced the formation of cyclometalated complex **453**. This cyclometalated complex (**453**) catalyzes allylic aminations at a faster rate and at lower catalyst loadings than the reaction using a 2:1 ratio of **450** and $[Ir(cod)_2Cl]_2$.

Allylic aminations using 'preactivated' cyclometalated Ir complex **453** are generally superior in terms of reaction rate, yield, *ee*, and regioselectivity. To avoid the need to prepare and isolate complex **453**, activation of the catalyst can be streamlined by heating

Table 25 Asymmetric amination with chiral phosphoramidite ligands

Entry	*Substrate (Ar =)*	*Amine*	*Yield (%)*	ee *(%)*
1	Ph	$BnNH_2$	84	95 (*R*)
2[a]	Ph	$BnNH_2$	72	87 (*R*)
3	Ph	Pyrrolidine	75	97 (–)
4	Ph	Piperidine	91	96 (–)
5[b]	Ph	Et_2NH	83	97 (–)
6[c]	4-$NO_2C_6H_4$	$BnNH_2$	67	86 (–)
7	2-$MeOC_6H_4$	$BnNH_2$	77	76 (–)
8	4-$MeOC_6H_4$	$BnNH_2$	88	96 (–)

[a]Using ligand **451**.
[b]The ratio of branched to linear to linear products was 98:2.
[c]The ratio of branched to linear products was 83:17, with the linear diallylated product representing 4% of the total.



Scheme 67

a mixture of Ir, ligand, and a basic amine to 50 °C for 20 min, removing volatiles and then redissolving the cyclometalated complex in THF.[234] Propylamine promotes cyclometalation and DABCO (1,4-diazabicyclo[2.2.2]octane) is compatible with the conditions. By preactivation of the catalyst with a sacrificial amine, less basic nucleophiles such as aniline can be used for amination.

Hartwig has continued to study the intermediates involved in the catalytic cycle. Important takeaways include the identification of **454** as the resting state of the catalyst during allylic amination (Figure 4).[235] This complex was prepared independently and it was verified that it corresponded to ^{31}P NMR signals observed during the reaction process. The allylamine that is coordinated to this complex can be displaced by other dative ligands, including ethylene, to provide **455**. Both complexes **454** and **455** are catalytically active for allylic amination, giving high yields and selectivities. Ethylene complex **455** is extraordinarily active; its catalyst loadings can be reduced to as little as 0.25 mol%.

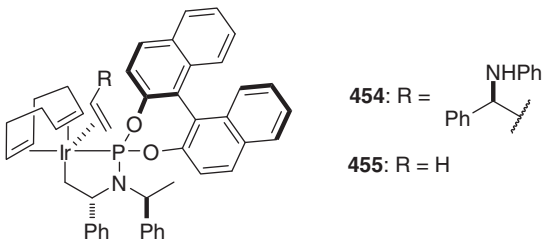


Figure 4 Resting state of the Ir-phosphoramidite catalysts.

Considering that the active catalyst is not a C_2-symmetrical complex, it was hypothesized that the distal phenethyl substituent on nitrogen could be modified to an achiral group with minimal impact on the amination reaction.[236,237] Simplifying the ligand structure is a valuable enterprise, as ligand **450** is more expensive than the precious metal component of the catalyst. Systematically altering the structure led to the simplified ligand **456**, where one phenethyl group was replaced with a cycloalkane and the chiral BINOL group was replaced by biphenol (Figure 5). The Ir complex prepared with **456** catalyzes allylic amination reactions in over 93% *ee* with branched to linear ratios of >20:1.[237] This modified ligand is relatively inexpensive to synthesize, as it contains only one asymmetric carbon derived from chiral α-benzylamine and is prepared in 60% yield via a two-step route.

Modifying the original phosphoramidite ligand **450** with sterically demanding groups significantly increases the rates of allylic amination (**457** and **458**).[238–240] The modified ligand **457**, containing naphthyl groups, boasts increased reaction rates and

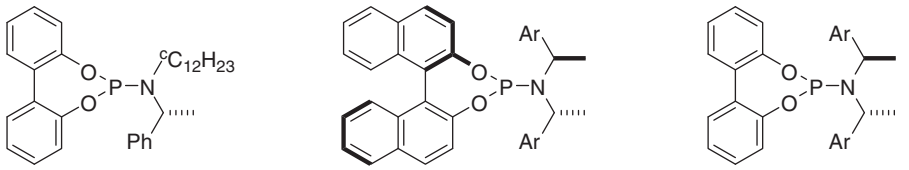


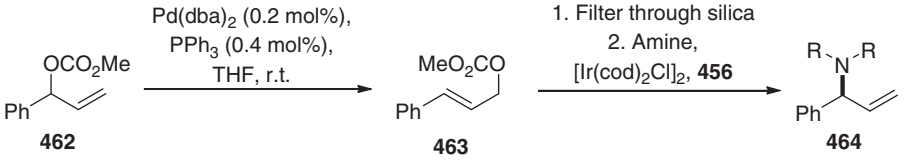
Figure 5 Phosphoramidite ligands for Ir-catalyzed asymmetric allylations.

improved yields and regioselectivities for a number of substrates. Alexakis made a direct comparison of reaction rates, noting that ligands **457–459** all gave much faster conversions for the reaction of methyl cinnamyl carbonate and benzylamine as compared to **450**.[238,241] Regioselectivity was ≥99:1 for all three ligands. Ligand **458** generally provides higher enantioselectivities than **450**, but requires an expensive chiral amine for its preparation. Some cost savings can be achieved by use of biphenol-derived ligand **461**, which gives slightly lower enantioselectivity compared to **458**.[240]

6.02.3.3.1.4 Branched allylic substrates

Racemic, branched allyl carbonates and esters are attractive substrates for asymmetric amination as they are easily prepared from the addition of a vinyl Grignard reagent to an aldehyde. Branched allyl carbonates are generally more reactive substrates for Ir-catalyzed substitutions and give better regioselectivities than their linear counterparts. Unfortunately, racemic carbonates and esters typically suffer low enantioselectivities in these reactions due to relatively slow isomerization of allyliridium intermediates via π–σ–π exchange. This slow exchange results in a significant memory effect that impedes the development of highly enantioselective reactions from branched substrates.

It is possible to conduct a kinetic resolution of racemic allyl benzoates with Ir by using a 0.5 equivalent of nucleophile.[242] An intrinsic disadvantage of any resolution process is the fact that only one half of the material is utilized. A creative solution to this problem involves a two-step process that employs both Pd- and Ir-catalysis (Scheme 68).[243] The first step takes advantage of Pd-catalyzed isomerization of carbonate **462** to a linear allyl carbonate. The crude product is then treated with an amine, $[Ir(cod)_2Cl]_2$, and **456**.



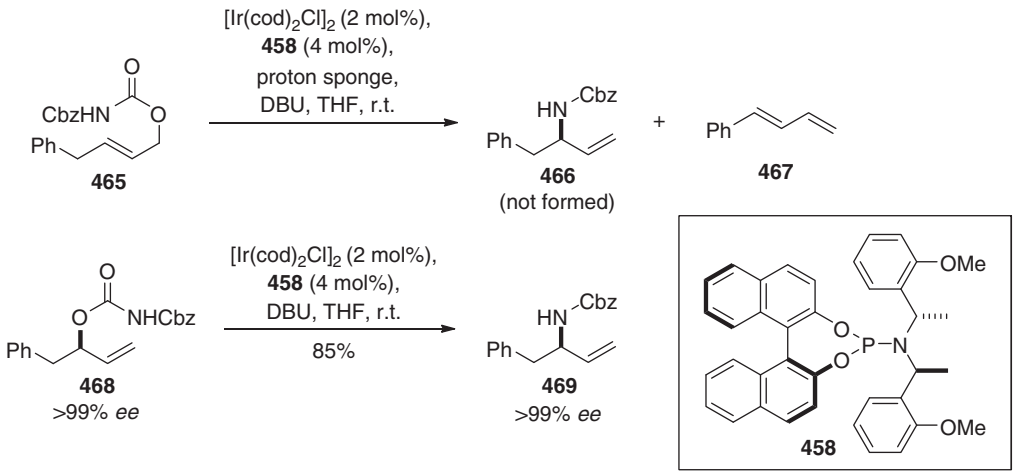
Scheme 68

The enhanced reactivity of branched allylic substrates is beneficial in certain cases where linear substrates fail to give products, or where selectivity for the branched product is especially poor. For example, **465** was a poor substrate for decarboxylative allylic amination due to a competitive elimination process (Scheme 69). This problem was overcome by switching to the branched isomer **468**.[244] A disadvantage here is the need for a chiral ligand in addition to an enantioenriched substrate. In the absence of a chiral ligand there is appreciable loss of stereochemical information.[245] Under these conditions, allyliridium complexes equilibrate by a π–σ–π process that occurs at a rate that is too slow for the stereoconvergent amination of racemic carbonates, yet is sufficiently rapid that the chirality of the starting material is lost without a chiral ligand.

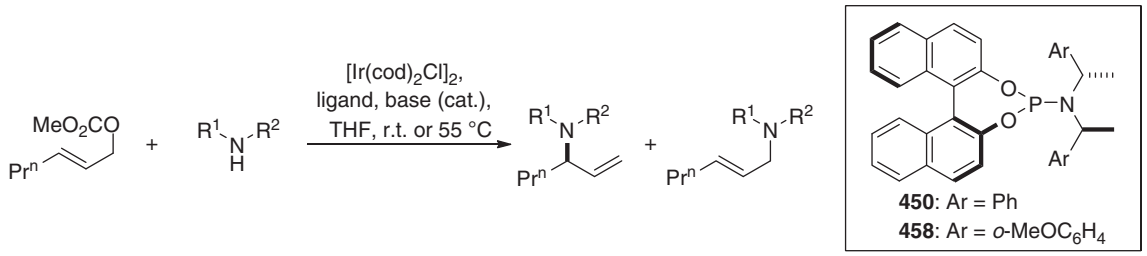
6.02.3.3.2 Allylic amination of ammonia equivalents

Various nitrogen nucleophiles have been developed as ammonia equivalents. Benzylamine is frequently used as a nucleophile to demonstrate substrate scope and validate new allylic amination conditions. Although benzylamine can be viewed as a protected form of ammonia, the hydrogenolysis conditions commonly employed to remove benzyl groups will also reduce double bonds. Thus, other ammonia equivalents are necessary so that a primary amine can be deprotected under conditions that are compatible with an alkene.

Soft nitrogen nucleophiles, such as imides and *o*-nitrobenzenesulfonamide, are attractive as ammonia equivalents due to the fact that they can be deprotected under mild conditions.[74] The results for several ammonia equivalents are shown in equation 40, Table 26.[246,247] Iridium complexes derived from ligands **450** and **458** catalyze allylation of these nucleophiles in >90% *ee*, with high branched selectivity. Where direct comparisons are possible, ligand **458** is more selective (entries 1–5). Slightly higher enantioselectivities are obtained with imide nucleophiles as compared to nitrobenzenesulfonamide.



Scheme 69



(40)

Table 26 Protected ammonia equivalents[246,247]

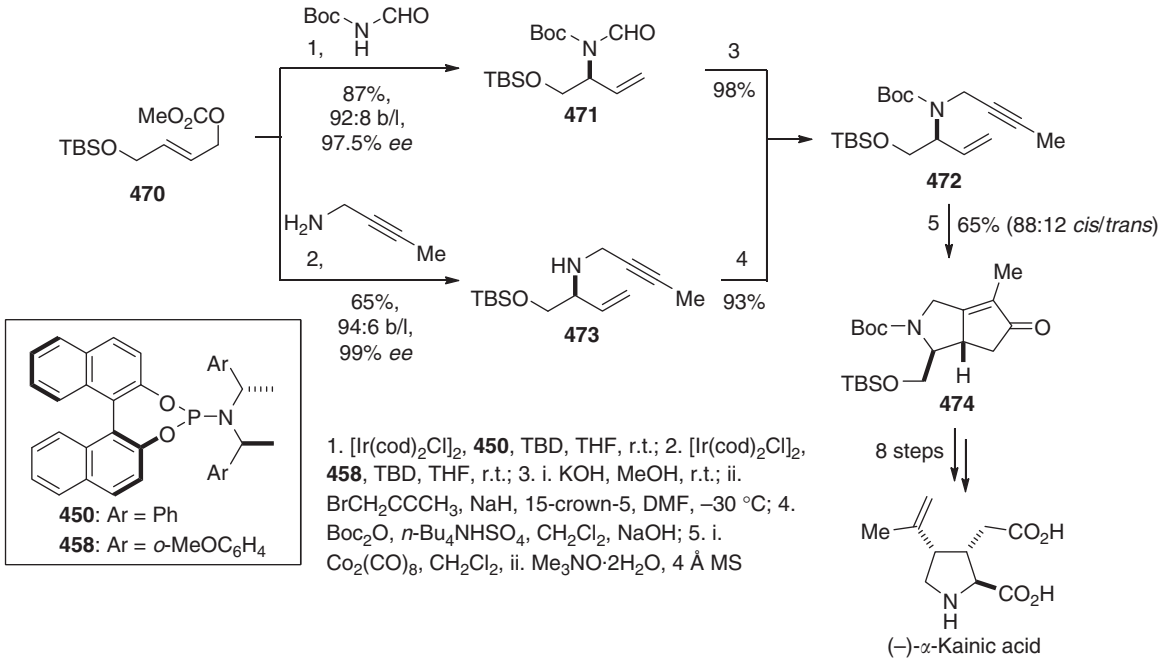
Entries	*Nucleophile*	*Base*	*Ligand*	*Yield (%)*	*Ratio (b/l)*	ee *(%)*
1	*o*-$NsNH_2$	TBD[a]	**450**	85	92:8	93
2	*o*-$NsNH_2$	TBD[a]	**458**	84	84:16	90
3	*o*-$NsNH_2$	TBD[a], Et_3N	**458**	94	93:7	94
4	Phthalimide	TBD[a]	**450**	86	90:10	95
5	Phthalimide	TBD[a]	**458**	82	94:6	96
6	HN(Boc)(CHO)	TBD[a]	**458**	98	97:3	96
7	$NaN(Boc)_2$	TBD[a]	**458**	86	96:4	99
8	$HN(Boc)_2$	DBU[b]	**458**	90	>99:1	>99
9	HN(Boc)(Ac)	DBU[b]	**458**	94	>99:1	>99
10	HN(Cbz)(Boc)	DBU[b]	**458**	92	>99:1	>99

[a]Reactions using TBD were all conducted at room temperature.
[b]Reactions with DBU were run at 55 °C. TBD = 1,5,7-triazabicyclo[4.4.0]undec-5-ene.

The key to the success of these reactions is the addition of a catalytic amount of base (TBD or DBU). This base does not serve to deprotonate the neutral pronucleophiles; that is done by carbonate (or methoxide) that formed by displacement after oxidative addition of Ir to the substrate. The role of base (TBD or DBU) is to activate the catalyst by inducing cyclometalation. Catalyst activation is especially important in these reactions with such weakly basic pro-nucleophiles. TBD and DBU give comparable results; however, better overall selectivity and yields are obtained with DBU.

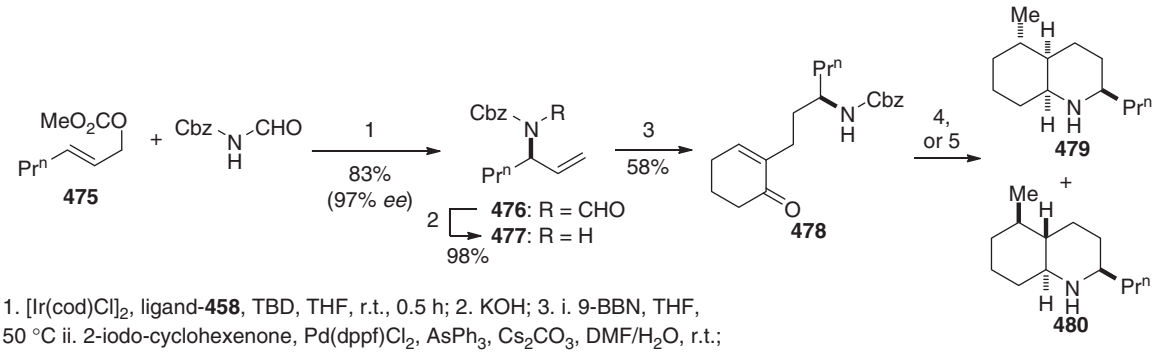
Ir-catalyzed asymmetric allylic amination is emerging as an attractive reaction for natural product synthesis due to its uniformly high enantioselectivities and the diversity of compatible nitrogen nucleophiles. Helmchen and coworkers examined two related asymmetric aminations in a synthesis of (–)-α-kainic acid (Scheme 70).[248] The amination of methyl carbonate **470** was conducted with HN(Boc)(CHO), an ammonia equivalent, and with a propargylic amine. Selectivities for both nucleophiles were comparable, but the imide [HN(Boc)(CHO)] was higher yielding.

Both amination products **471** and **473** were converted into Boc-amine **472**. A better overall yield for **472** was actually obtained via the two-step route from **471**. Methanolysis of the formamide group in **471** and alkylation provided **472** in 98% yield, which compares favorably to the yield of 93% for the *N*-Boc protection of **473**. After a Pauson–Khand reaction to give **474**, eight additional steps were required to complete kainic acid.



Scheme 70

Asymmetric allylic amination was used to establish chirality in a short and efficient synthesis of alkaloid *cis*-195 A (formerly designated pumiliotoxin C, 479).[249] (*E*)-Hex-2-enyl methyl carbonate (475) reacted with HN(Cbz)(CHO) to provide 476 (Scheme 71). The formamide group was removed by hydrolysis with KOH, and the resulting allylic carbamate 477 was subjected to hydroboration with 9-BBN. Suzuki coupling of this product with 2-iodocyclohexanone gave 478.



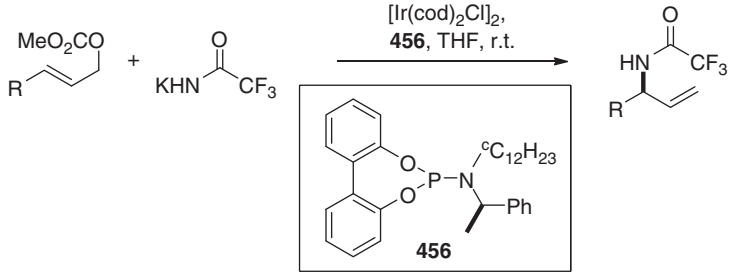
1. $[Ir(cod)Cl]_2$, ligand-**458**, TBD, THF, r.t., 0.5 h; 2. KOH; 3. i. 9-BBN, THF, 50 °C ii. 2-iodo-cyclohexenone, $Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, DMF/H_2O, r.t.; 4. i. CuCN, MeMgBr, Et_2O, –30 °C ii. aqueous NH_3 iii. H_2 (30 atm), $Pd(OH)_2/Rh/C$, MeOH r.t.; 5. i. CuTC, (*R*,*R*,a*S*)-**450**, $AlMe_3$, Et_2O, –30 °C ii. MeOH, NH_4Cl iii. H_2 (30 atm), $Pd(OH)_2/Rh/C$, MeOH r.t.

from 4: 57%, 2:1 (**479**:**480**), 97% *ee*/96% *ee*
from 5: 68%, 5:1 (**479**:**480**), >99% *ee*/80% *ee*

Scheme 71

The diastereoselective conjugate addition of a methyl group to 478 was the most challenging step of this synthesis. The preexisting stereocenter in 478 is distant from the enone group, and thus it is poorly positioned to direct the conjugate addition. Unsurprisingly, the addition of a simple organocuprate derived from CuCN and MeMgBr gave very poor diastereoselectivity (2:1). Diastereoselectivity was improved to 5:1 by using a ligand-controlled cuprate addition with chiral phosphoramidite ligand 450.[250,251] There was only a modest improvement to diastereoselectivity with the chiral copper complex, which is due to a mismatch between substrate and ligand. The same ligand catalyzed a diastereoselectivity of 99:1 for the conjugate addition to *ent*-478 (not shown). This difficult conjugate addition was further complicated by the fact that the initial addition products were inseparable by chromatography. Hydrogenation of this mixture removed the Cbz group and affected reductive amination to provide 479 and 480, at which stage these diastereomers could be separated.

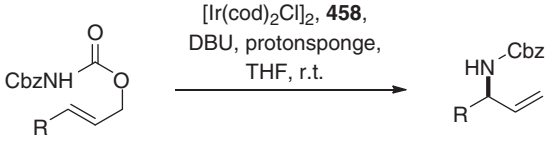
Hartwig has identified that the potassium salt of trifluoroacetamide is a viable ammonia equivalent that can be used to directly prepare monoprotected allylic amines (equation 41).[252] Although trifluoroacetamide is not as commonplace as Cbz and Boc carbamates, it is easily cleaved by methanolic K_2CO_3.[253] The substrate scope was examined with ligand **456**. Aryl- and alkyl-substituted carbonates generally worked well, although yields were lower for electron-deficient aryl groups.



R	Yield (%)	*ee* (%)
Ph	68	94
p-MeC_6H_4	74	96
p-$MeOC_6H_4$	93	98
p-BrC_6H_4,	59	92
Hex[c]	79	96

(41)

A complementary approach to protected allylic amines involves the decarboxylation of allyl carbamates (equation 42).[254] This approach is based on a decarboxylative allylic amination by Tunge that utilized Pd- and Ru-catalysis, but was not asymmetric.[255] The Ir-catalyzed reaction strongly favors the branched product by a ratio of >97:3, which is an improvement over the more modest 3:1 branched to linear ratio provided by Tunge's Ru-catalyzed conditions. As usual, chiral phosphoramidite **458** provides enantioselectivities greater than 94%. A crossover experiment demonstrated that this reaction involves the intramolecular attack of an allyliridium complex rather than an intramolecular [3,3]-sigmatropic rearrangement.



R	Yield (%)	b/l	*ee* (%)
Pr^n	90	97:3	96
Pr^i	85	90:10	96
Ph	90	>99:1	>99
2-Furyl	70	97:3	94

(42)

6.02.3.3.3 Direct allylic amination of ammonia

Direct application of ammonia as a nucleophile is challenging. There are two key complications that must be overcome. Ammonia can poison asymmetric catalysts by displacing chiral ligands to directly bind the metal. There is also a question of competitive nucleophilic attack between the allylamine product and ammonia. Allylamines are more nucleophilic than ammonia; thus, it can be difficult to obtain monoallylation products.

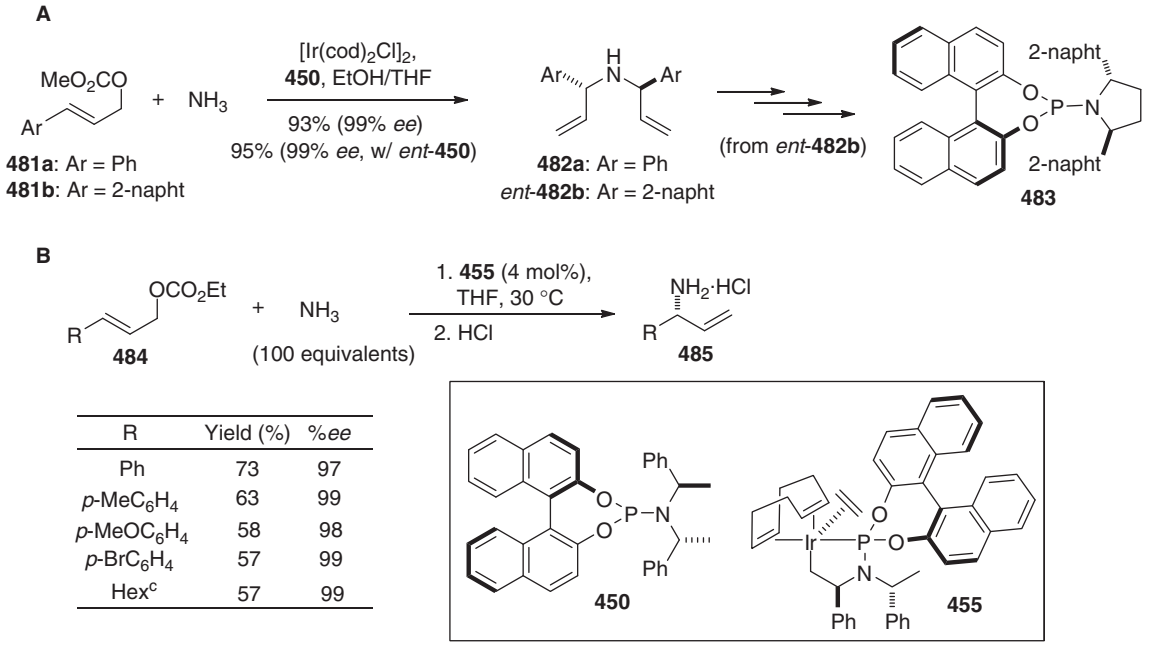
Hartwig found that the ammonia reacts with cinnamyl methyl carbonate in an ethanolic solution of ammonia (Scheme 72 A).[256] Once again, it was essential to activate the catalyst by cyclometalation before the addition of **481a** and ammonia. C_2-symmetric diallylamine **482a** is isolated as the product under these conditions. Although the monoallylated product was not obtained, the C_2-symmetric product **482a** can be useful for developing new chiral ligands. Feringa and coworkers took advantage of the diallylation of ammonia to prepare 2,5-disubstituted pyrrolidine subunits for use in phosphoramidite ligands (**483**).[257]

Selective preparation of the monoallylamine requires a large excess of ammonia.[256] The identity of the catalyst is also critical, with the single-component catalyst **455** providing the highest yields of product **485**. When the Ir-catalyst is prepared *in situ*, residual $[Ir(cod)_2Cl]_2$ is left over, which forms an insoluble species that is detrimental to the amination reaction. Ethylene complex **455** can be prepared separately and then added to the amination reaction mixture as a single discrete species. This complex was found to be stable to a large excess of ammonia, and thus avoids the formation of any insoluble Ir complexes that poison the reaction.

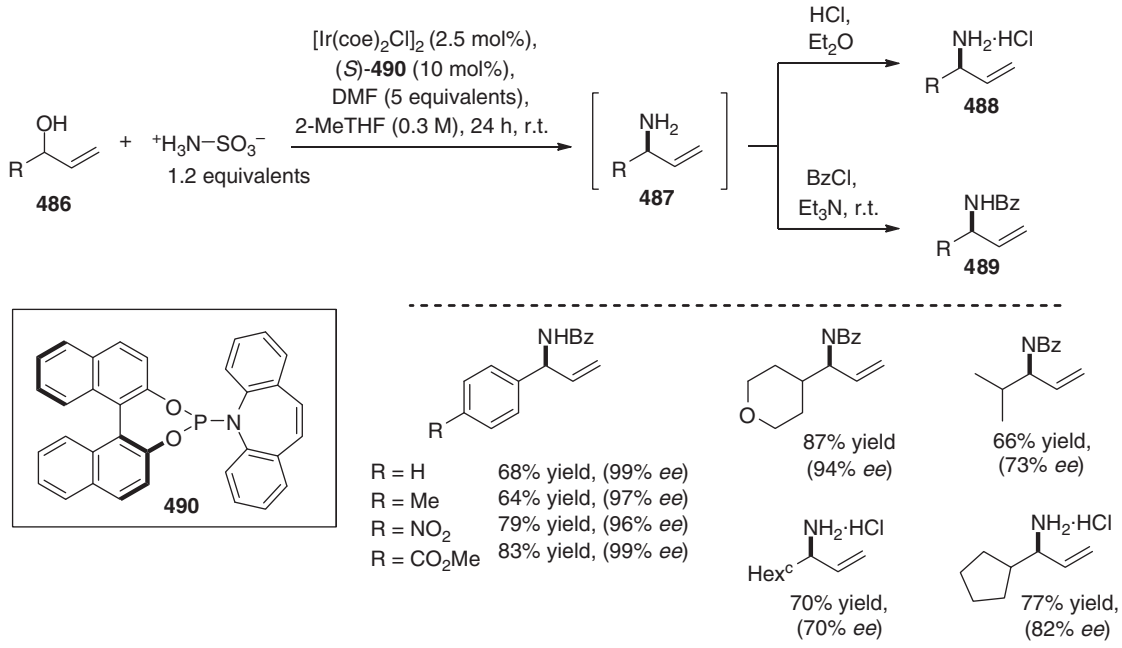
The carbonate leaving group also has a subtle effect on the direct allylation of ammonia. Empirically, it was found that conversions to **485** were better when ethyl carbonates were used instead of methyl carbonates. These conditions worked well for a variety of aryl- and alkyl-substituted allyl carbonates; albeit yields are somewhat lower than the other amination methods discussed.

Carreira has developed a method to prepare generate branched primary allylamines that employ sulfamic acid as a unique source of ammonia (Scheme 73).[258–260] Sulfamic acid is an inexpensive, easily handled solid. Unlike the reactions using ammonia, excess sulfamic acid is not required to avoid diallylated products. Primary amines are produced directly, which can then be precipitated from solution as an HCl salt or derivatized *in situ* to their protected forms. Another key advantage of this method is the fact that allyl alcohols are reactive substrates and do not require activation as an ester or carbonate.

Early reports of this method prepared racemic products,[258] or employed enantioenriched secondary allyl alcohols, which can be aminated with conservation of stereochemistry.[259] By using chiral phosphoramidite ligand **490** the stereoconvergent amination of allyl alcohols has been realized.[260] Selected results are provided in Scheme 73. Thus, easily prepared racemic allyl alcohols are converted to optically active allylamines in one step. To improve the isolation of low-molecular weight amines, the products can be protonated as their ammonium salts (**488**) or captured as benzamides (**489**). In regard to enantioselectivity, allylic alcohols



Scheme 72

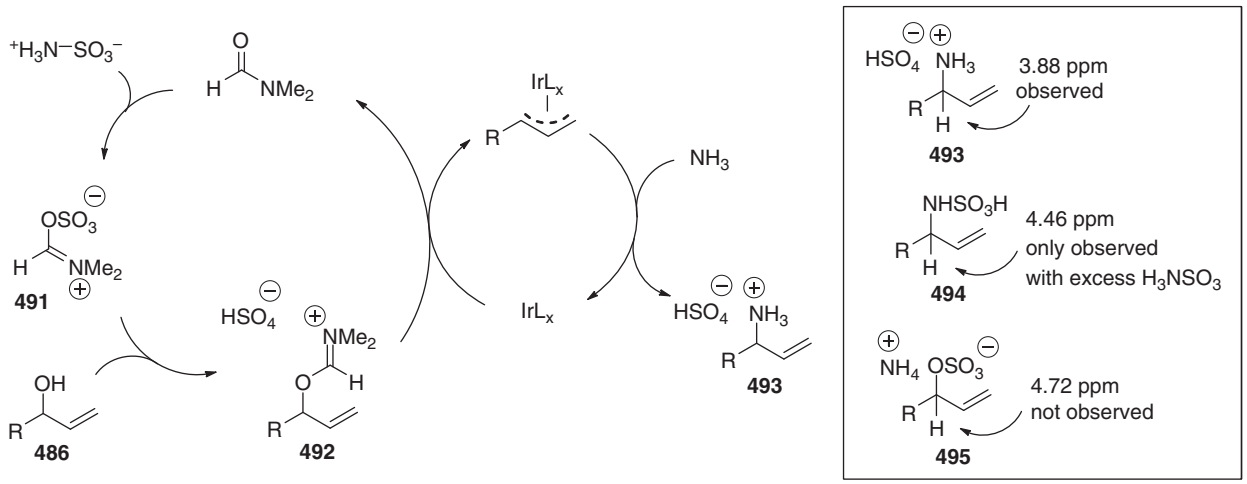


Scheme 73

that are substituted with aryl groups provide particularly high *ee*s (≥90% *ee*). Somewhat lower enantioselectivity is obtained for allyl alcohols containing only aliphatic groups (68–99% *ee*).

For synthetically useful yields, the alkene group in phosphoramidite ligand **490** is essential. Analogous saturated ligands gave ≤20% conversions, suggesting that coordination of the alkene to Ir may play an important role. Other cosolvents can be used, but a small excess of DMF is necessary for the reaction. It is hypothesized that DMF is required due to a Vilsmeier-like reaction that occurs with sulfamic acid to give **491** (Scheme 74).[258] The resulting electrophile could then capture the allylic alcohol to form **492**, which would be activated toward displacement by Ir. ^{1}H NMR analysis of the reaction provides evidence consistent with this process; **493** was the only other allyl significant component of the reaction mixture. Sulfamate **494** is not formed unless an excess

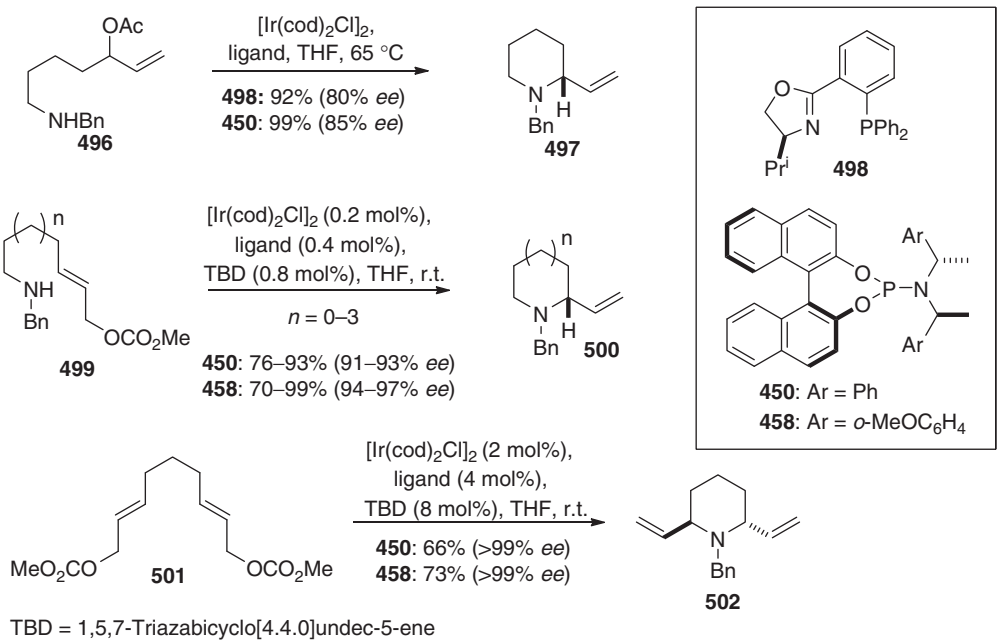
of sulfamic acid is present, and only then forms after all of the allylic alcohol has been converted to **493**. The other possible intermediate, sulfate ester **495**, was not observed.



Scheme 74 Reproduced from Table 2 in Dubovyk, I.; Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 14172–14173, with permission from American Chemical Society.

6.02.3.3.4 Intramolecular Ir-catalyzed allylic amination

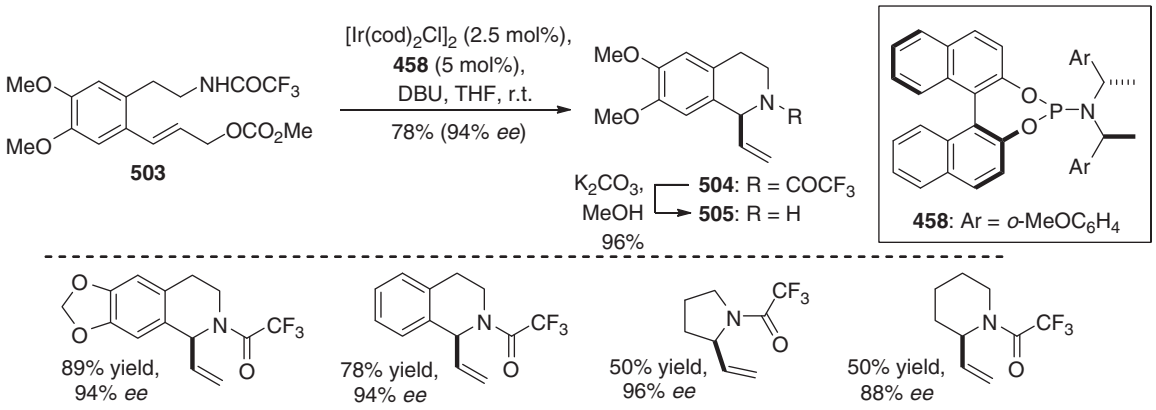
Ir-catalysis can be applied to synthesize nitrogen heterocycles by allylic amination. Several approaches have been examined, including the cyclization of achiral linear substrates and the cyclization of racemic, branched allylic acetates. Several cases are shown in Scheme 75. Oxazoline **498** and phosphoramidite **450** are both competent ligands for the asymmetric cyclization of branched acetate **496**.[261] Although respectable *ee*s are achieved from racemic **496**, linear carbonate **499** provides higher levels of enantioselectivity for 2-vinylpiperidine.[262] Five- and seven-membered azacycles were prepared from linear **499**, with phosphoramidite **458** providing optimum results with respect to *ee*. This chemistry was extended to prepare 2,6-divinylpiperidine from **501** by a sequential amination process involving both inter- and intramolecular allylic amination. *trans*-2,6-Divinylpiperidine **502** was produced in >9:1 diastereoselectivity and >99% *ee*.



TBD = 1,5,7-Triazabicyclo[4.4.0]undec-5-ene

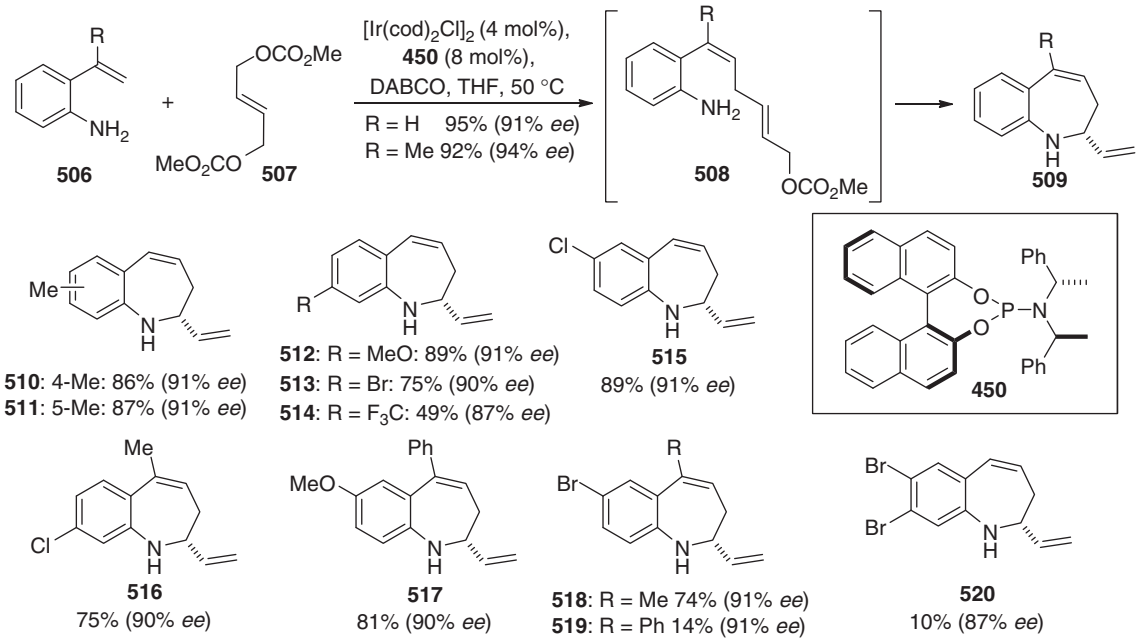
Scheme 75

A route to chiral tetrahydroisoquinolines has been developed based on the intramolecular version of the Ir-catalyzed asymmetric amination reaction (equation 43).[263] In contrast to the results above, which used amine nucleophiles, this route employed a trifluoroacetamide as the nitrogen source. Trifluoroacetamide was deemed an attractive nitrogen-protecting group since it is removed by mild hydrolysis with K_2CO_3 in methanol. Additionally, the strong electron-withdrawing nature of this group may serve to activate nitrogen, as acetamide substrates failed to cyclize. Trifluoroacetamide derivatives of pyrrolidine and piperidine could also be prepared, but the isolated yields were lower for these substrates due to their volatility.



(43)

The You group recently discovered that styrenes are viable nucleophiles for allylic substitution (Scheme 76).[264] They have further developed a tandem process to prepare chiral benzazepines involving the nucleophilic attack of a styrene on **507** followed by an intramolecular displacement of the remaining allyl carbonate.[265] Preactivation of the Ir catalyst with DABCO was superior to other bases, with ligand **450** providing the best enantioselectivities. The substrate scope for this tandem process is reasonably diverse, tolerating substitution at the 4- and 5-positions of the amino styrene. The *ee* was over 87% for all substrates examined, and yields were typically high. However, several styrenes with more strongly electron-withdrawing groups gave lower yields (see **514**, **519**, **520**).



Scheme 76

Conclusion

As seen throughout this review, displacement remains an important method for the preparation of amines. Innovative contributions continue to be made with respect to expanding the substrate scope. In particular, the development of nucleophilic ammonia

equivalents is an important area of ongoing research. Although traditional approaches to avoid polyalkylation involve the use of protecting groups, such approaches suffer from poor atom economy, and are challenged by the need for orthogonal protecting groups. The Mitsunobu reaction remains an important subset of these reactions thanks to the fact that readily available alcohols that can be converted directly to protected amine derivatives. Despite its poor atom economy, the Mitsunobu reaction has spurred considerable research, which has resulted in new reagents that have expanded the nucleophile scope and simplified the purification process.

The application of transition metal catalysis to these reactions has attracted broad activity as it provides a greener alternative to traditional stoichiometric methods. Furthermore, these catalytic methods have opened up allylic substrates containing leaving groups that otherwise would be unreactive towards displacement chemistry. Transition metal catalysis is especially powerful method when combined with chiral ligands, and there have been many creative contributions involving the stereoselective preparation of allylic amines.

There have been many outstanding contributions to this area since the publication of the first edition of Comprehensive Organic Synthesis. Even with such diverse methods available, opportunities remain for continued improvement and innovation.

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6.03 Synthesis of Nitroso, Nitro, and Related Compounds

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This chapter is a revision of the previous edition chapter by Rainer Askani, Douglass F. Taber, Vol. 6, pp 103–132, © 1991, Elsevier Ltd.

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Glossary

Building block A small molecule that reacts with other reagents to form large molecules as a result of addition, substitution, or condensation.

Cycloaddition A reaction constructing a new ring from two components. Diels–Alder reaction is one of the [4+2] cycloaddition reactions to afford a six-membered ring.

Henry reaction A reaction forming nitro alcohol from a nitroalkane and an aldehyde (or a ketone), which is also referred to as the nitro-aldol reaction.

Nitronic acid A tautomer of nitroalkane. Nitronic acid is formed by proton transfer from the α-position to the oxygen atom of a nitro group, thus it reveals high acidity.

Push-pull alkene An alkene having both electron-donating and electron-withdrawing groups, by which the electron density of the double bond is biased.

Retro-synthesis A technique for considering the synthetic schemes, in which a complex molecule is disconnected to small molecules (synthons).

Ring transformation A reaction constructing a new ring by exchanging a partial structure of the original ring with the reagent.

Synthetic equivalent A reagent undergoing a reaction instead of synthon, which cannot itself be used because of its instability.

6.03.1 Nitro Compounds

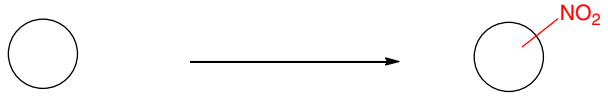
Nitro compounds constitute a large family among organic compounds and are widely used for various purposes; millions of tons of nitro compounds are synthesized and consumed every year.[1–3] A nitro group is one of the important functional groups in organic syntheses because of its strong electron-withdrawing ability and diverse chemical behavior.[1] The nitro group considerably decreases electron density of the scaffold framework by both inductive and resonance electron-withdrawing effects to facilitate reactions with nucleophiles. The α-hydrogen of a should be nitroalkane is highly acidic, leading to a stable nitronate anion, which reacts with both electrophilic and nucleophilic reagents. Furthermore, a nitro group assists the cleavage of an adjacent carbon–carbon bond, and can be transformed to versatile functional groups by the Nef reaction or by reduction.

Preparative methods for nitro compounds are generally divided into three categories, namely, (1) the direct approach to nitro compounds, (2) built-in methods using a nitrated building block, and (3) ring transformations, which are supplementary to each other. In the direct approach, three strategies are mainly employed; the most common of these is the nitration, which directly introduces a nitro group into the scaffold framework (equation 1). If other functional groups can be easily introduced, chemical transformation of the functional group into a nitro group becomes a useful method for obtaining nitro compounds (equation 2). When nitro compounds with an additional functional group are necessary, degradation of nitrated heterocyclic compounds is often employed (equation 3). The built-in method is incorporation of a nitro compound bearing an additional functional group as the building block, which is also a powerful method in elaborate syntheses (equation 4). Ring transformation is also a useful method for synthesizing complicated skeletons that are not easily available by alternative methods (equation 5).

 doi:10.1016/B978-0-08-097742-3.00604-2

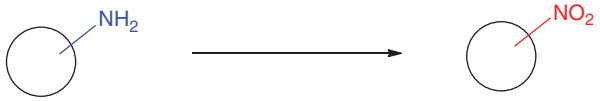
1. Direct approach

Nitration



(1)

Chemical conversion



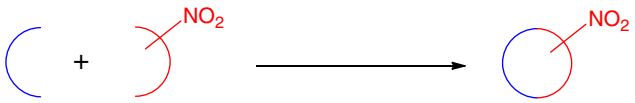
(2)

Degradation



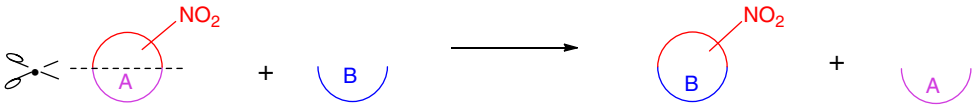
(3)

2. Built-in method



(4)

3. Ring transformation



(5)

6.03.1.1 Direct Approach to Nitro Compounds

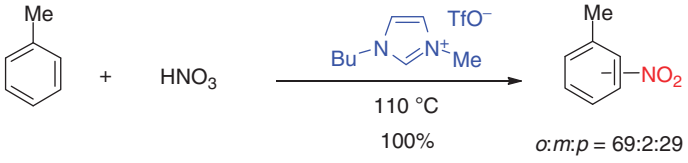
6.03.1.1.1 Nitration

This is the easiest way for introduction of a nitro group to the scaffold framework.[4] Because nitro compounds are widely used as fundamental industrial chemicals, nitration has been performed using conventional nitration processes that involve HNO_3 alone or in combination with H_2SO_4. This method has remained unchallenged for more than 160 years. In a laboratory, other nitrating agents have been employed (Table 1), however, these are not applicable to large-scale nitration. This is because harsh conditions are sometimes necessary, in which the control of the reaction is quite difficult, and a reactive functional group cannot be tolerated.

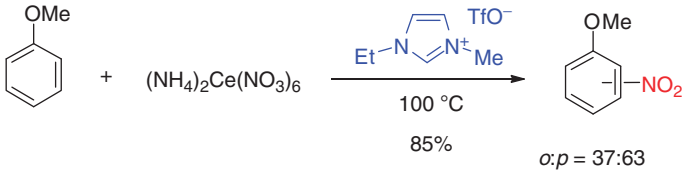
Table 1 A list of conventional nitrating agents

Nitric acid	Alone or in combination with acid			
	H_2SO_4	H_3PO_4	$HClO_4$	$HF(BF_3)$
	CF_3COOH	$MeSO_3H$	CF_3SO_3H	$FSO_3H(SbF_5)$
	Sulfonated resin	Clays	Molecular sieves	Graphite
	Nafion-H			
Nitrate salts	$AgNO_3/BF_3$	$KNO_3/AlCl_3$	$Cu(NO_3)_2/Ac_2O$	$NH_4NO_3/(CF_3CO)_2O$
	$(NH_4)_2Ce(NO_3)_6$			
Nitrate esters	$BuONO_2$/Nafion-H	$MeONO_2/BF_3$	Me_3SiONO_2	
	Acetone cyanohydrin nitrate			
Nitryl compounds	NO_2BF_4	NO_2PF_6	NO_2ClO_4	$NO_2Cl(F)$
	$MeCO_2NO_2$	$CF_3CO_2NO_2$	$PhCO_2NO_2$	
	N-nitropyridinium nitrate			
Nitrogen oxides	N_2O_3/BF_3	N_2O_4/H_2SO_4	$N_2O_4/AlCl_3$	N_2O_5
Nitroalkanes	$C(NO_2)_4$	$CH(NO_2)_3$	$(O_2N)_3CC(NO_2)_3$	

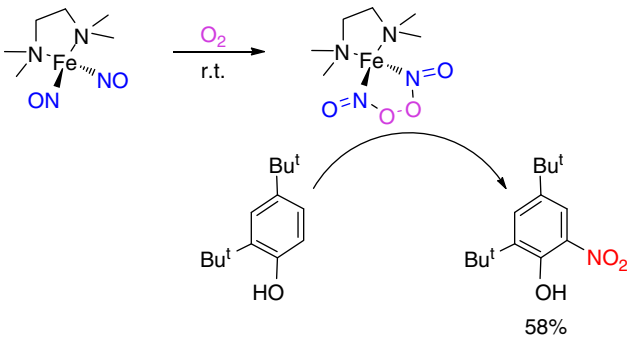
Recently, new nitrating agents have been developed that facilitate nitration under mild conditions or the nitration of deactivated aromatic compounds. Olah et al. demonstrated that a mixed acid (HNO_3 and CF_3SO_3H-$B(OSO_2CF_3)_3$) was effective for the nitration of highly deactivated benzenes.[5] The use of supercritical water[6] or ionic liquids[7,8] is found to be acceptable reaction media for the nitration (equations 6 and 7). Tran et al. achieved the nitration of a phenol derivative by the use of a dinitroso iron complex and oxygen gas (**Scheme 1**).[9] Koley et al. demonstrated that *t*-BuONO efficiently nitrates phenols at room temperature, and the reaction proceeds by a radical mechanism (equation 8).[10]



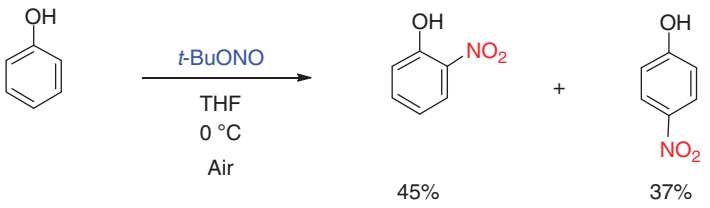
(6)



(7)

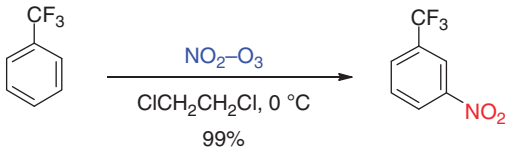


Scheme 1 Nitration using dinitroso iron complex and O_2.

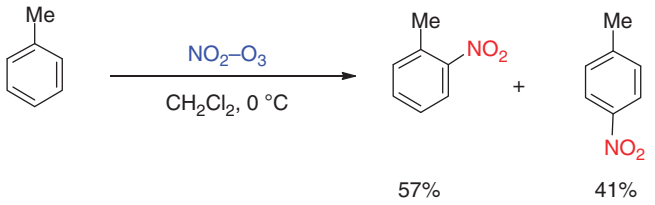


(8)

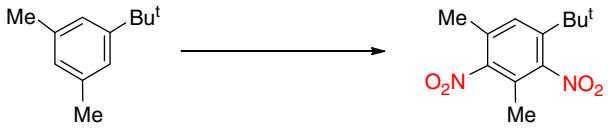
Suzuki and coworkers developed an excellent nitration method using NO_2 and O_3, and it is referred to as the Kyodai method.[11–13] This reaction proceeds efficiently even at low temperature to afford nitrated products quantitatively (equations 9 and 10). The addition of a small amount of a proton acid or Lewis acid (BF_3·OEt_2, Fe(III), etc.) enhances reactivity of the substrate to enable the polynitration (equations 11 and 12).[14,15]



(9)

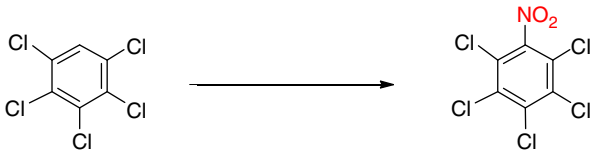


(10)



(11)

Conditions	Yield (%)
Fuming HNO_3, fuming H_2SO_4, 100 °C	80
NO_2, O_3, H^+ cat., Hexane, –10 °C	>95

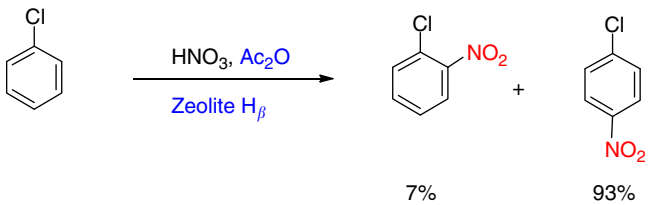


(12)

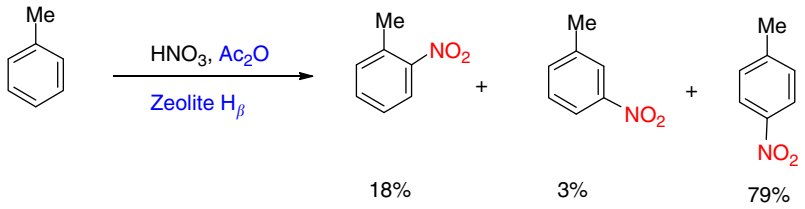
Conditions	Yield (%)
Fuming HNO_3, fuming H_2SO_4, 150 °C	89
NO_2, O_3, H^+ cat., CH_2Cl_2, 0 °C	97

In the conventional nitration method using HNO_3/H_2SO_4, large amounts of waste acids are produced, which should then be converted to an environmentally nonpoisonous form. From the economic viewpoint, solid acids such as zeolites are preferable to H_2SO_4; however, this method is less reactive than the conventional method. This is mainly because the acidic sites are poisoned by water.[16,17] This disadvantage was overcome by conducting the reaction in the presence of acetic anhydride as the water-trapping agent.

The use of solid acid catalysis realizes the regioselective nitration, which is not easily performed by the conventional nitration method. Claycop, $Cu(NO_3)_2$ supported on acidic montmorillonite clay, selectively nitrates toluene using HNO_3 and acetic anhydride to afford mononitrotoluene quantitatively with an *o*:*m*:*p* distribution of 23:1:76.[18] The higher selective nitration was achieved when tridirectional zeolites H_β and H_Y were employed instead of claycop (equations 13 and 14); these reactions proceeded within 30 min leading to nitrated products in quantitative total yields.[19,20] This reaction is considerably affected by steric hindrance of the *ortho*-substituent. When a substrate is adsorbed in the zeolite cavity, the transition state formed from *para*-attack is more stable than from *ortho*-attack, and this allows for high regioselectivity (**Figure 1**).[21] Dinitration by the Kyodai method using zeolite also proceeds with high regioselectivity even at low temperature (equation 15).[22]



(13)



(14)

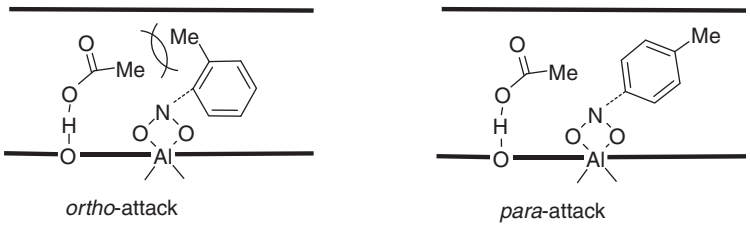
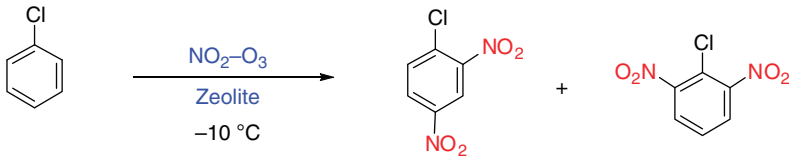
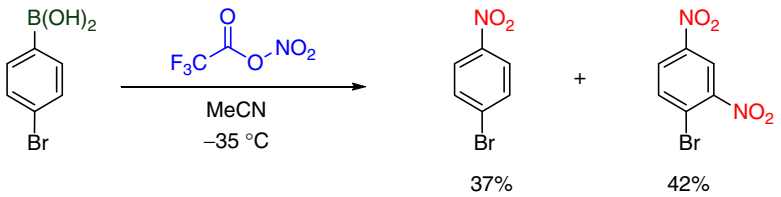


Figure 1 Two transition states in the zeolite cavity.

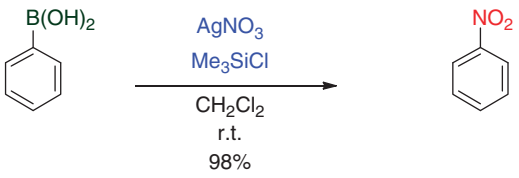


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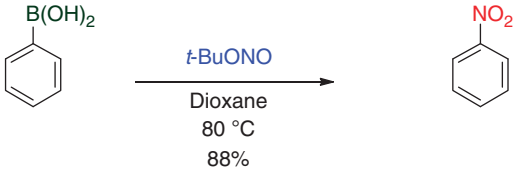
Since nitrating agents are strong oxidants, the nitrated compounds are often accompanied by oxidation products.[23] From the viewpoint of controlling regioselectivity, *ipso*-nitration methods have been developed. Olah and his coworkers demonstrated that *ipso*-nitration of *p*-bromophenylboronic acid proceeded on treatment with Crivello's reagent[24] prepared from $(CF_3CO)_2O$ and NH_4NO_3 beforehand, in which the functional group on the benzene ring can tolerate the reaction conditions (equation 16).[25] However, the relatively powerful Crivello's reagent causes competitive dinitration. The undesired side reaction is reduced by Me_3SiCl and MNO_3 (M=Ag or NH_4), in which Me_3SiONO_2 is formed *in situ* as the nitrating agent (equation 17).[26] Wu et al. showed metal-free nitration using phenylboronic acid and *t*-BuONO to afford nitrobenzene in 88% yield (equation 18).[27]



(16)



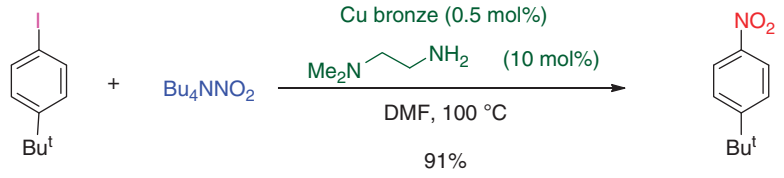
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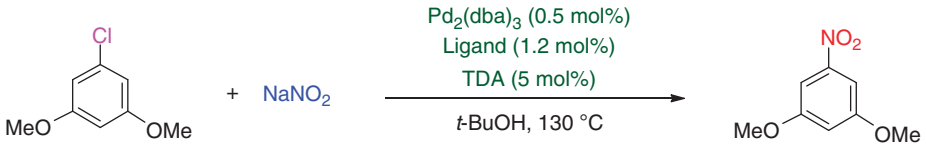
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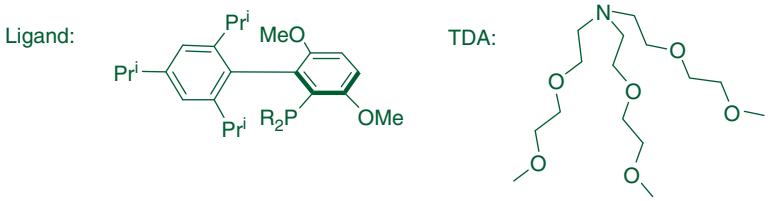
Transition metal catalysts efficiently accomplish *ipso*-nitration. Saito et al. synthesized nitrobenzenes by *ipso*-nitration of aryl halides with Bu_4NNO_2 catalyzed by a combination of Cu and diamine ligand (equation 19).[28] Furthermore, a palladium

catalyzed nitration method was reported by Buchwald et al., in which commercially available $NaNO_2$ was employed as the nitro source (equation 20).[29] In the present reaction, chloroarenes are the best substrates because they undergo transmetalation easily and have lower rates of oxidative addition with the catalyst.



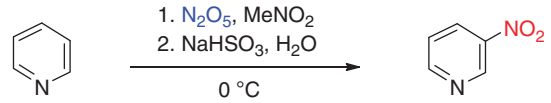
(19)



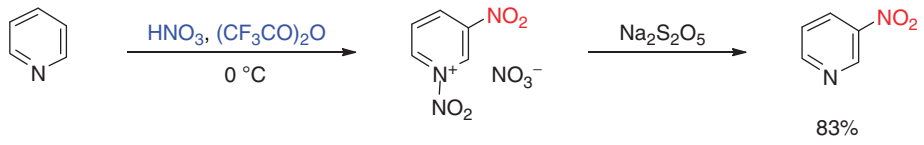


(20)

Electron-deficient compounds such as pyridine derivatives are not suitable substrates for classical nitration. Direct nitration of pyridines at the 3-position is realized when a pyridine is treated with N_2O_5 followed by addition of an aqueous solution of $NaHSO_3$ (equation 21).[30] This procedure, known as Bakke's procedure, is applicable to the Kyodai method using NO_2 and O_3, which affords 3-nitropyridine in similar yield.[31] Recently, Katritzky et al. succeeded in nitrating the pyridine nucleus by HNO_3 in $(CF_3CO)_2O$ followed by the workup with $Na_2S_2O_5$ (**Scheme 2**).[32]

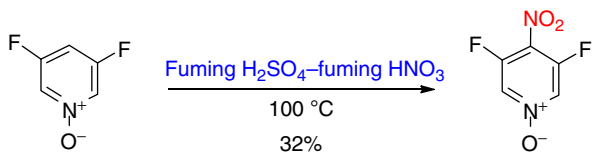


(21)

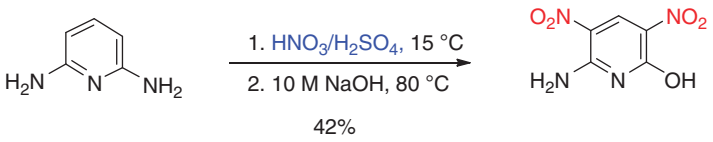


Scheme 2 Efficient nitration of pyridines by HNO_3.

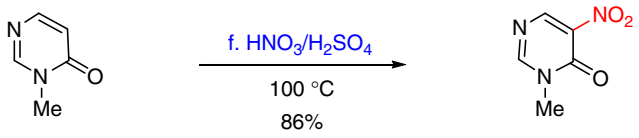
Modification of the pyridine nucleus is also effective for producing the nitration. Pyridine *N*-oxides become electron-rich by back donation of the oxygen atom, and readily undergo nitration at the 4-position by HNO_3 (equation 22).[33] In cases of 2-aminopyridines, nitration proceeds at the vicinal position to afford 2-amino-3-nitropyridines, in which *N*-nitroanminopyridines are intermediately formed and the nitro group migrates from the amino group to the pyridine ring. This reaction is applicable to synthesis of polynitropyridines (equation 23).[34] Alternatively, pyridone derivatives are easily nitrated because aromaticity of the *N*-substituted 2-pyridone is considerably decreased.[35] Similar treatment of pyrimidinone and quinolone derivatives also afforded the corresponding nitro compounds (equation 24).[36–38]



(22)

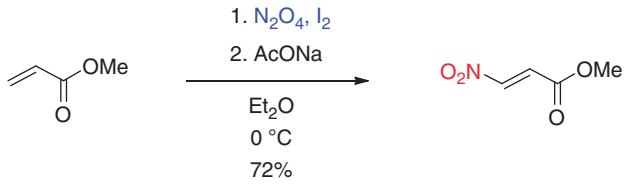


(23)

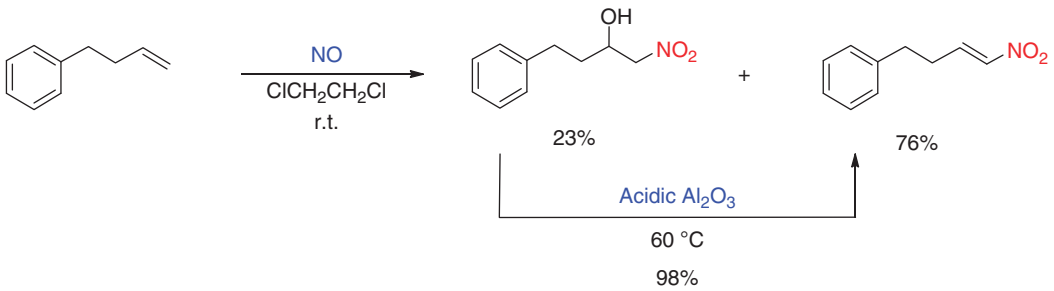


(24)

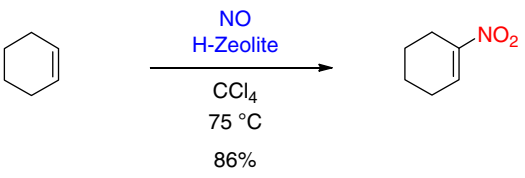
Not only aromatic compounds, but also electron-rich aliphatic compounds serve as substrates for nitration. Alkenes are readily nitrated to afford conjugated nitroalkenes, which are used as building blocks as mentioned later. However, nitration using HNO_3 often suffers from decomposition of alkenes and lack of selectivity; hence, this reaction is not employed as a general method for preparation of nitroalkenes. Instead, nitration using nitrogen oxides in the presence of an oxidant, such as I_2 (equation 25) or O_2, is conducted.[39,40] Ambient pressure of NO is also able to nitrate alkenes to afford nitroalkenes plus the nitroalcohol. Because the nitroalcohol is easily dehydrated on heating with acidic Al_2O_3, the yield of nitroalkene is increased to almost quantitative (Scheme 3).[41] When similar nitration is conducted in the presence of zeolite, the nitroalkene is efficiently afforded (equation 26).[42] The use of a combination of $NaNO_2$ and $(NH_4)_2Ce(NO_3)_6$ is effective for preparation of nitroalkenes, which is performed with only simple experimental manipulations (equation 27).[43] When a combination of Me_3SiONO_2 and CrO_3 is employed, the formed active species $NO_2OCrO_2SiMe_3$ serves both as an NO_2^+ source and as an oxidant to furnish α-nitroketones (equation 28).[44] In this reaction, a combination of Me_3SiONO_2 and DMSO is also usable, leading to nitroketones in fair yields.



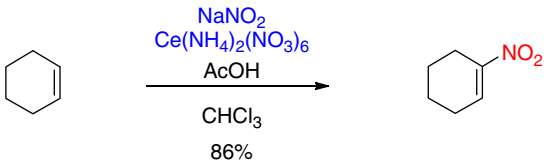
(25)



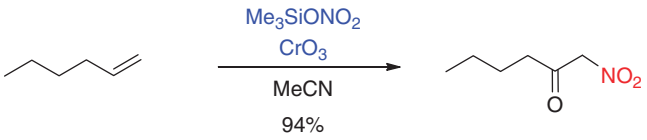
Scheme 3 Nitration of an alkene by ambient pressure of NO.



(26)

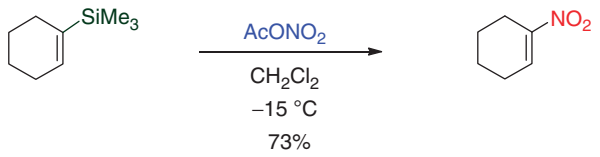


(27)

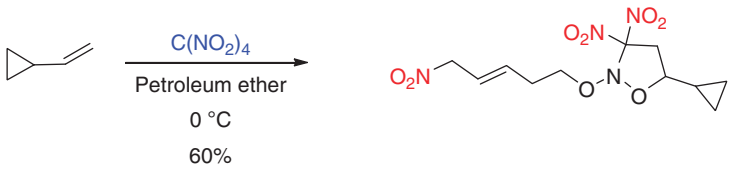


(28)

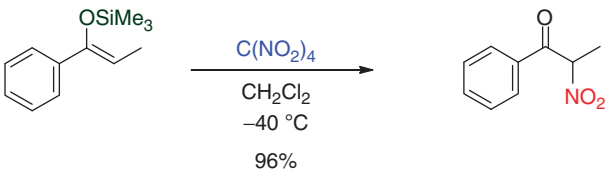
Vinylsilanes that are more reactive are easily nitrated compared with simple alkenes. For example, nitrocyclohexenes are available on treatment of cyclic vinylsilanes with acetyl nitrate (equation 29).[45] $C(NO_2)_4$ serves as both a nitrating agent and a 1,3-dipole, which is useful for construction of heterocyclic compounds (equation 30).[46] Silyl enol ethers efficiently react with $C(NO_2)_4$, accompanied by cleavage of the ether moiety, and provide an excellent method for preparation of α-nitroketones (equation 31).[47]



(29)

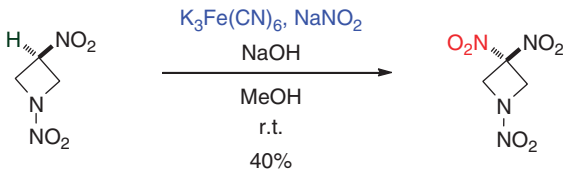


(30)

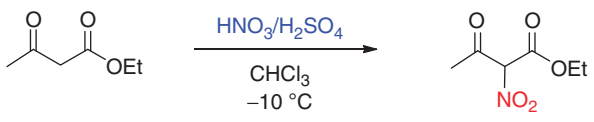


(31)

C-H acids are usable as the substrates for nitration. 1,3-Dinitroazetidine with an acidic proton at the 3-position is additionally nitrated leading to a trinitro derivative on treatment with $NaNO_2$ and $K_3Fe(CN)_6$ under basic conditions (equation 32).[48] In cases of 1,3-dicarbonyl compounds, nitration proceeds under usual nitration conditions using mixed acids, however, the reaction mixtures are considerably complicated because of polynitration and decomposition of the nitrated compounds. Laikhter et al. overcame this disadvantage by using a two-phase system ($CHCl_3$-H_2SO_4/HNO_3). The mononitro product is more soluble in $CHCl_3$ than in acids; this prevents overnitration because of removal of the mononitrated product from the nitration system into the $CHCl_3$ layer (equation 33).[49]

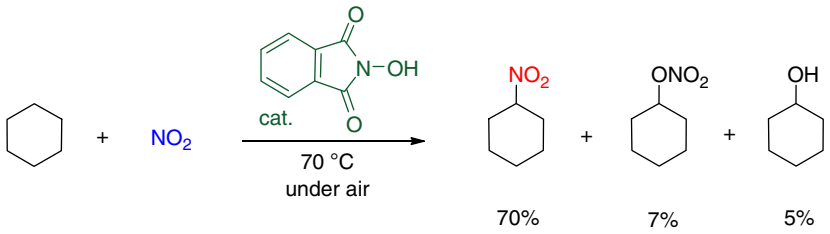


(32)



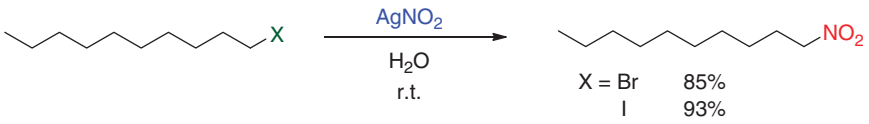
(33)

It is quite difficult to nitrate nonactivated alkanes. Currently, nitration of aliphatic hydrocarbons is performed at high temperatures (250–400 °C) using NO_2 or HNO_3 by which a free radical is formed as an active species. Ishii and coworkers succeeded in nitrating hydrocarbons under much milder conditions using NO_2 in the presence of catalytic amounts of *N*-hydroxyphtalimide (equation 34).[50]



(34)

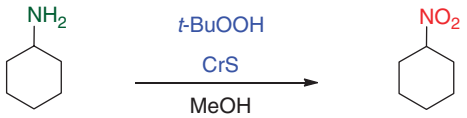
Aliphatic nitro compounds are mainly prepared by the reaction of alkyl halides with metal nitrites, in which $AgNO_2$ (Victor-Meyer reaction) and KNO_2 or $NaNO_2$ (Kornblum reaction) are often employed, and alkyl nitrites are sometimes formed as byproducts.[51] Alkyl sulfates are usable as the substrates instead of alkyl halides. This method is often applied to elaborate syntheses of versatile nitro compounds.[52,53] Although this method usually requires long reaction time, the use of DMSO or DMF, and tedious workup methods, it is promising because the reaction is performed in aqueous media (equation 35).[54]



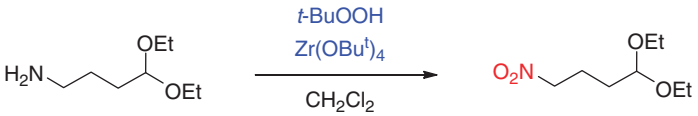
(35)

6.03.1.1.2 Formation of a nitro group by chemical conversion from other functional groups

Oxidation of an amino group to a nitro group is one of the fundamental chemical conversions. Although O_3 has been used as the oxidant, side reactions often proceed depending on the reaction conditions. The use of solid reaction media such as silica gel is effective for this conversion. Chromium containing medium pore molecular sieves (chromium silicate: CrS) effectively catalyzes the oxidation of various primary amines to the corresponding nitro compounds using *t*-BuOOH (equation 36).[55] In addition to conventional oxidants, OXONE®,[56] *m*CPBA,[57] $KMnO_4$,[58] and HOF,[59] and $Zr(OBu^t)_4$-based[60] catalytic systems have also been developed (equation 37).[55] Moreover, oxidation of amines in aqueous media can be performed using $NaBO_3$ in the presence of catalytic amount of $H_3PW{\cdot}nH_2O$.[61]

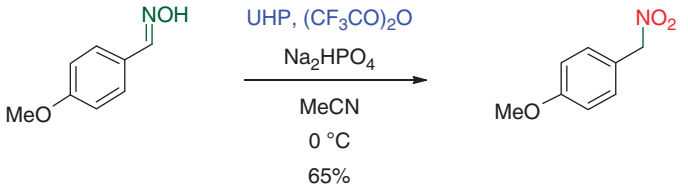


(36)

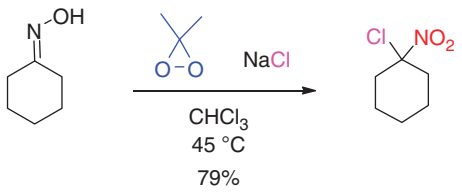


(37)

The conversion of carbonyl compounds to nitro compounds via oximes is also an important reaction, however, strong oxidants such as CF_3CO_3H should be employed for this purpose.[62] It is necessary to use H_2O_2 for preparation of peracid, which has improved to a method using the urea-H_2O_2 complex (UHP) and $(CF_3CO)_2O$ as a safer alternative (equation 38).[63] Other oxidation processes have been developed, which use *m*CPBA, $NaBO_3$/AcOH,[64] and $PhCH_2OMoO(O_2)_2^-$/*t*-Bu_4N^+.[65] When the oxidation is performed in the presence of a halogenating agent, *gem*-bis(functionalization) (halonitration) becomes possible. For example, chloronitration proceeds easily when oximes derived from ketones are oxidized with dimethyldioxirane in the presence of NaCl (equation 39).[66] The combination of H_2O_2 and HCl is also usable for the present functionalization.[67] Because reductive dehalogenation of the *gem*-bifunctional products is performed with H_2 over Pd/C, the present method is useful for the preparative method of complex nitroalkanes.

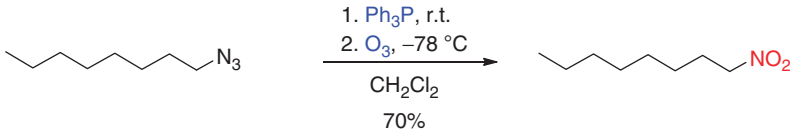


(38)

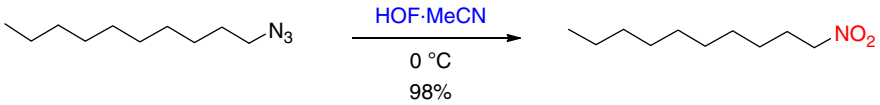


(39)

Alkyl azides also serve as precursors of nitroalkanes on oxidation. Corey et al. demonstrated a protocol for this conversion using triphenylphosphine and ozone (equation 40).[68] Carmeli and Rozen developed an oxidation method of azides with HOF-MeCN complex that is prepared by passing F_2 gas through aqueous MeCN. The oxidation efficiently proceeds at 0 °C within a few seconds (equation 41).[69]

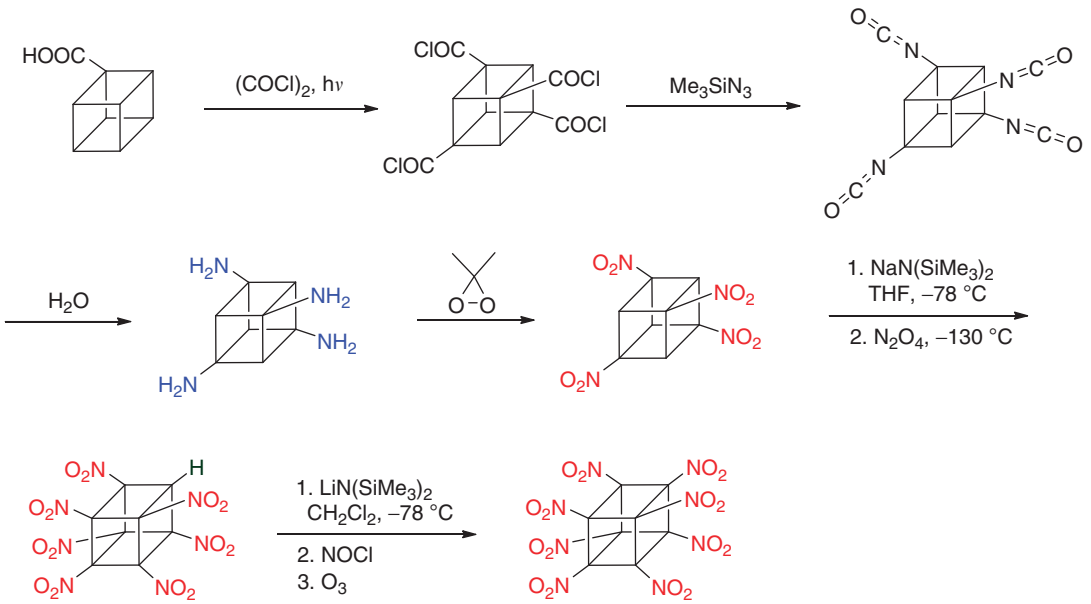


(40)



(41)

Polynitro compounds play important roles as explosives in military and commercial use. Development of more powerful and less shock-sensitive explosives is one of the demanded projects. From this viewpoint, octanitrocubane was synthesized from cubanecarboxylic acid according to **Scheme 4**, in which amino groups are introduced by Curtius rearrangement and converted to nitro groups.[70]

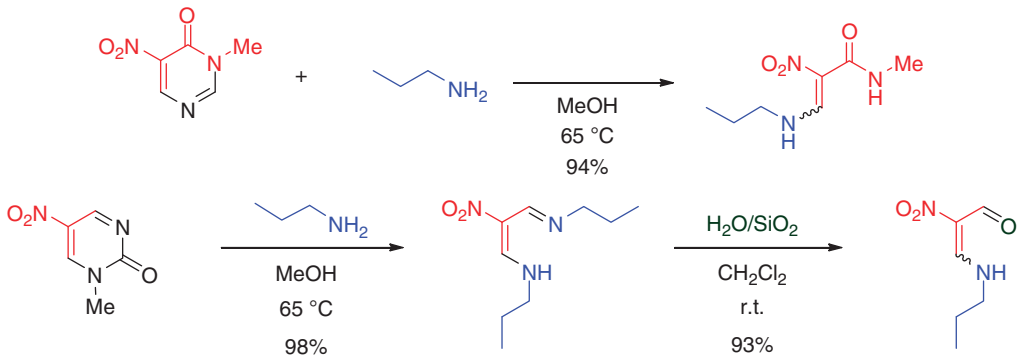


Scheme 4 Synthetic scheme for octanitrocubane.

6.03.1.1.3 Degradation of nitrated heterocyclic compounds

A benzene ring is highly stable because of the aromaticity that hardly allows it to undergo the ring-opening reaction. In contrast, heterocyclic compounds are not as inert, because of low aromaticity and polarized structure, which sometimes cause the ring-opening reaction to give degraded products. Since heteroatom(s) in the heterocyclic compound remains in the degraded products, the heterocyclic framework is regarded as the masked structure of functional groups. Hence, degradation of nitrated heterocyclic compounds furnishes multiple functionalized nitro compounds, which serve as useful building blocks for polyfunctionalized compounds as discussed in the next sections.

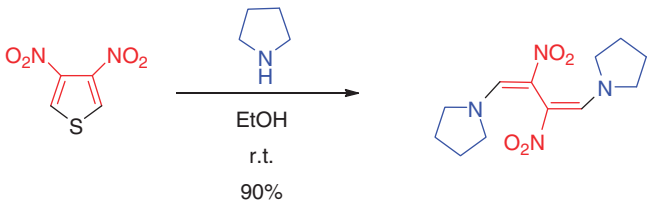
Nitropyrimidinones prepared by nitration, using HNO_3/H_2SO_4, easily undergo aminolysis. In the case of 5-nitro-4-pyrimidinone, the ring-opening reaction proceeds to afford a β-nitroenamine bearing a carbamoyl group (equation 42).[71] In contrast, aminolysis of 5-nitro-2-pyrimidinone furnishes β-imino-β-nitroenamines (azadienamines),[36] which serve as β-diketiminate ligands.[72,73] The imino moiety of the azadienamine is easily hydrolyzed leading to a formyl group, if the azadienamines is kept on a silica gel column (Scheme 5).[36]



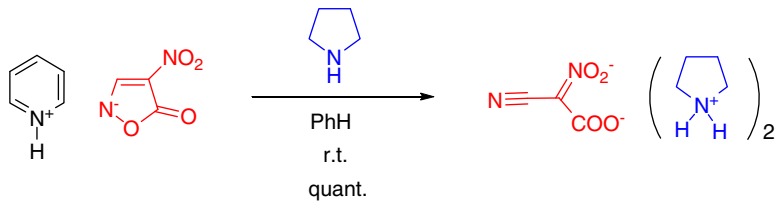
(42)

Scheme 5 Aminolysis of nitropyrimidinone leading to functionalized nitroenamines.

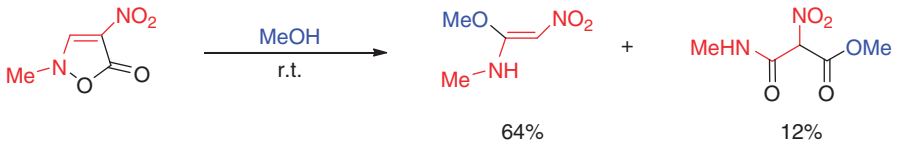
Not only six-membered heterocyclic compounds, but also five-membered ones are employed as substrates for degradation leading to functionalized nitro compounds. Aminolysis of 3,4-dinitrothiophene efficiently proceeds at room temperature to afford a bis(nitroenamine) connected between β- and β'-positions (equation 43).[74] Nitroisoxazolones show high reactivity to ring-opening reactions. Even anionic isoxazolone reacts with bases such as hydroxide and carbonate to yield dianionic trifunctionalized methane quantitatively. Pyrrolidine, an organic base, is also usable for this reaction (equation 44).[75] In the case of electronically neutral *N*-methylisoxazolone, weaker nucleophiles can trigger the ring-opening reaction to give α-amino-β-nitroenamines (ketene aminals) in the reaction with aromatic amines,[76] and to give α-methoxy-β-nitroenamine together with nitromalonic acid amide ester in the reaction with methanol (equation 45).[77]



(43)



(44)



(45)

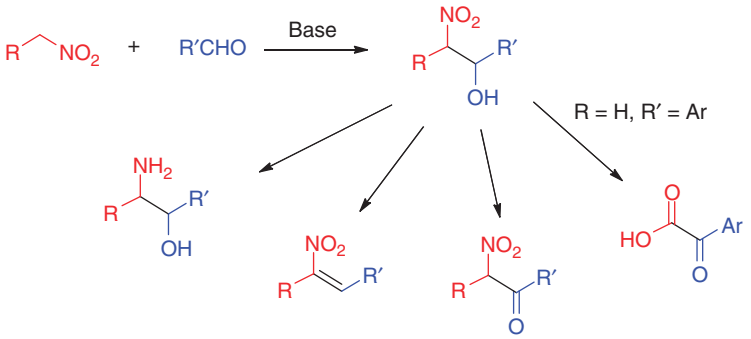
6.03.1.2 Built-in Methods using a Nitrated Building Block

6.03.1.2.1 Nitroalkanes

The strongly electron-withdrawing nitro group increases the acidity of the α-proton (pKa of $CH_3NO_2 = 10$), which enables the formation of nitronates easily using a wide variety of bases. The resultant nitronate serves as a carbon nucleophile with common electrophiles to form a C–C bond.[78]

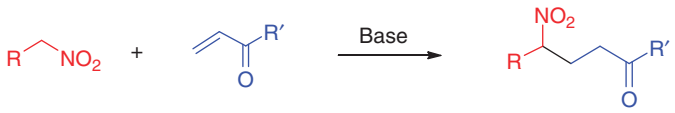
When aldehydes or ketones are used as the electrophile, β-nitroalcohols are obtained, which is referred to as the Henry (nitro-aldol) reaction (Scheme 6). The formed β-nitroalcohols are converted to β-aminoalcohols (by reduction), nitroalkenes (by dehydration), α-nitroketones (by oxidation), and α-keto carboxylic acids (by oxidation).[79] Furthermore, these products are used as precursors for versatile functional compounds. Ballini and Bosica revealed the method conducted in aqueous media.[80]

In the past decades, the enantioselective Henry reaction was developed.[81–84] Among the numerous studies, several selected works using organocatalysts are indicated in Table 2.[85–88] Both aliphatic and aromatic aldehydes undergo the Henry reaction with high enantioselectivity. Contrary to this, it is necessary to activate the carbonyl group by an adjacent electron-withdrawing group when ketones are employed instead of aldehydes. The aza-Henry reaction, referred to as the nitro-Mannich reaction, using imines as electrophiles to furnish α-amino-β-nitroalkanes is also well studied. Its asymmetrical version is shown in Table 3.[89–95] In these reactions, imines are also activated and stabilized by electron-withdrawing group at the nitrogen or the α-position.

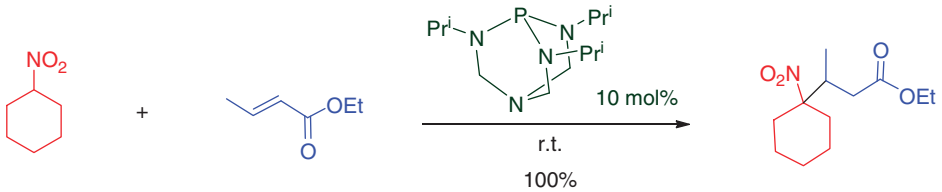


Scheme 6 Henry reaction and chemical conversions of the β-nitroalcohol.

Nitroalkanes also engage in conjugate addition to α,β-unsaturated carbonyl compounds to afford γ-nitrocarbonyl compounds (equation 46).[96] Kisanga et al. revealed that the exceedingly strong nonionic bases, proazaphosphatranes, are efficient catalysts for this reaction (equation 47).[97] Lubineau and Augé are the first to conduct the Michael addition of nitroalkanes in aqueous media, in which sugar is used as the surfactant.[98] This method was significantly improved by dilution in the presence of cetyltrimethylammonium chloride to give γ-nitroketones in good yields.[99] This method is applicable to unsaturated esters, nitriles, and sulfones although more severe conditions are required than those for unsaturated ketones.



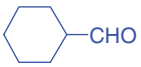
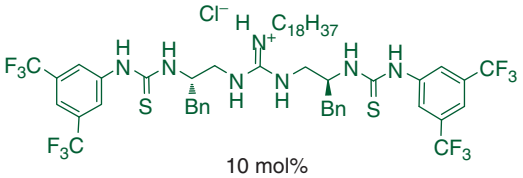
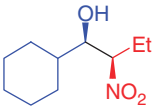
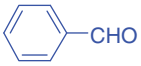
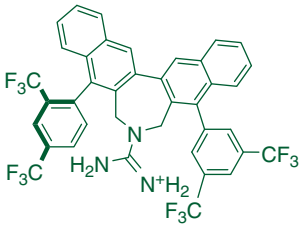
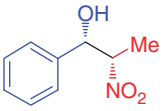
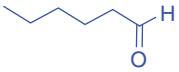
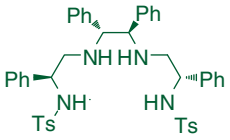
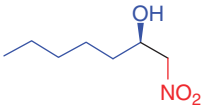
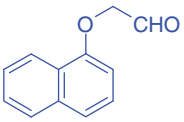
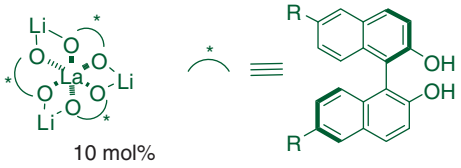
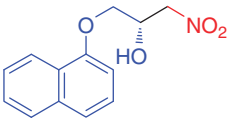
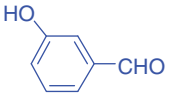
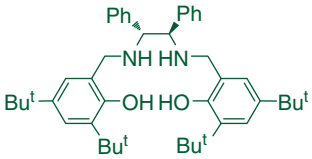
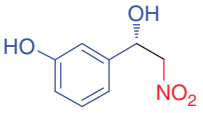
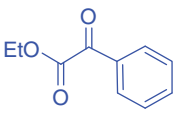
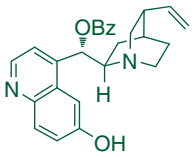
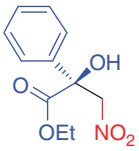
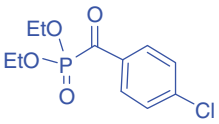
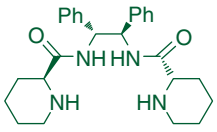
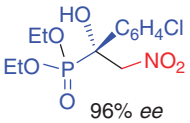
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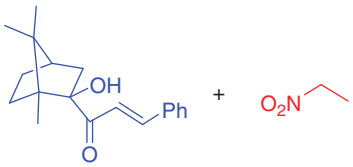


(47)

Conjugate addition of nitroalkanes to chiral unsaturated ketones or esters furnishes the corresponding adducts with high diastereoselectivity (equations 48 and 49).[100,101] The Michael adduct is used as a precursor of tetrahydropyridine derivatives (Scheme 7).[102] Enantioselective conjugate additions using chiral catalysts have also been achieved with high ee values (equations 50 and 51).[103–106]

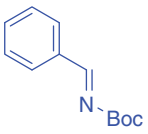
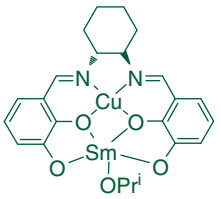
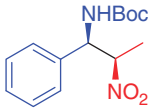
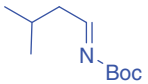
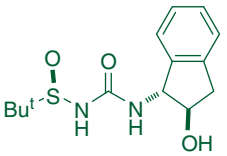
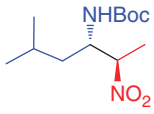
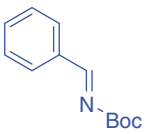
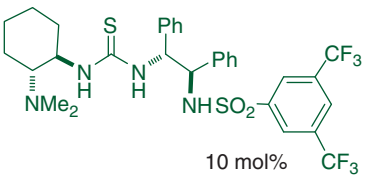
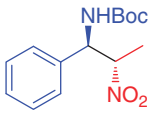
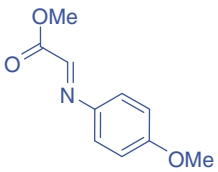
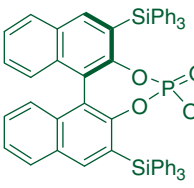
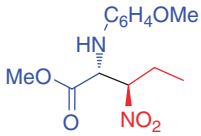
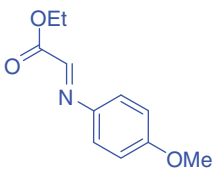
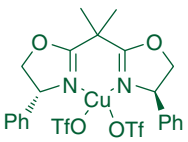
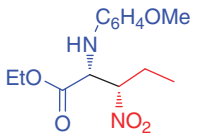
Table 2 Selected enantioselective catalytic Henry reactions

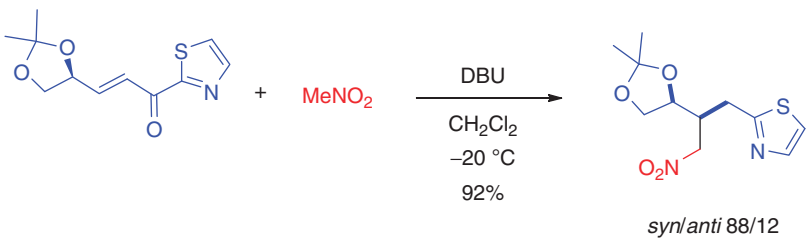
Nitroalkane	*Substrate*	*Catalyst*	*Product*
$PrNO_2$		 10 mol%	 95% *ee*
$EtNO_2$		 10 mol%	 87% *ee*
$MeNO_2$		 $Cu(OAc)_2$ 2.5 mol%	 97% *ee*
$MeNO_2$		 10 mol%	 92% *ee*
$MeNO_2$		 10 mol%	 90% *ee*
$MeNO_2$		 10 mol%	 95% *ee*
$MeNO_2$		 5 mol%	 96% *ee*



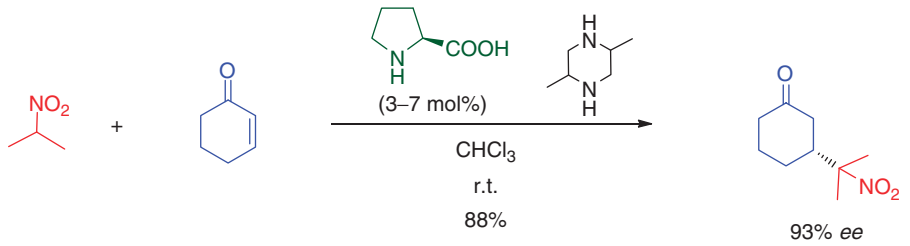
(48)

Table 3 Selected enantioselective catalytic aza-Henry reactions

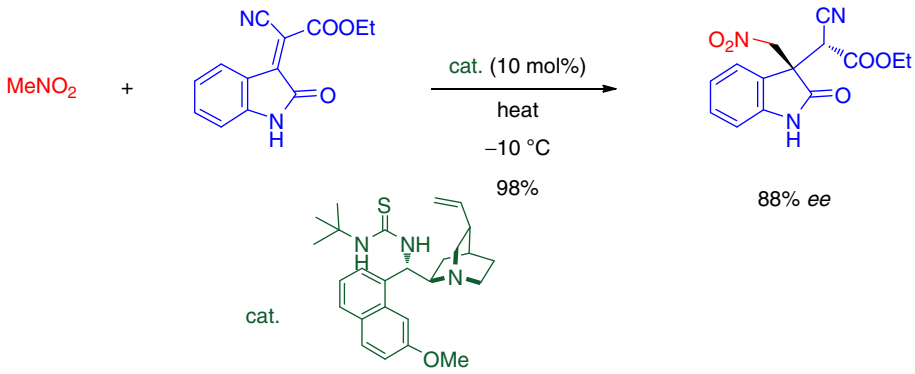
Nitroalkane	*Substrate*	*Catalyst*	*Product*
		 10 mol%	 80% *ee*
		 10 mol%	 96% *ee*
		 10 mol%	 99% *ee*
		 10 mol%	 92% *ee*
		 20 mol%	 97% *ee*



Scheme 7 Ring closure of γ-nitroketone.



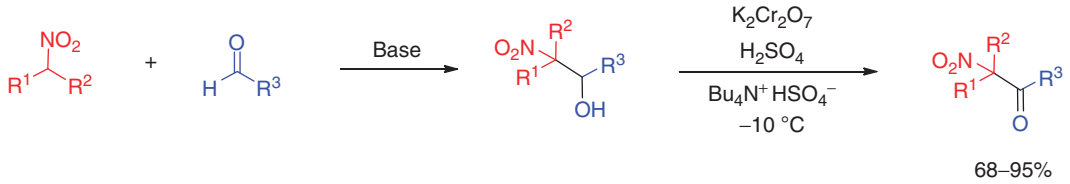
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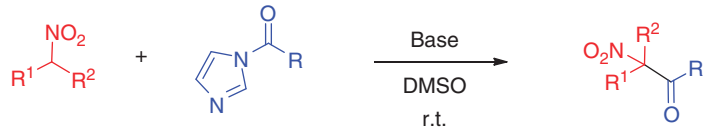
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6.03.1.2.2 α-Nitroketones and α-nitroesters

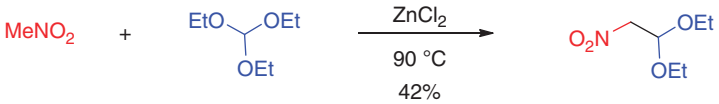
Bifunctional nitroketones and nitroesters[107] are useful building blocks for synthesizing polyfunctionalized compounds. Whereas α-nitroesters are commercially available, α-nitroketones are prepared by oxidation of β-nitroalcohols, which are obtained as products of the Henry reaction (Scheme 8).[108] Condensation of nitronates with *N*-acylimidazoles directly affords nitroketones (equation 52).[108] Zinc catalyzed condensation of nitroalkanes with orthoesters is also reported, whereby the acetal function is converted to an aldehyde or a ketone function (equation 53).[109] Nitroketones are also prepared by nitration of silyl enol ether with $C(NO_2)_4$ [47] or by oxidation of alkenes with a combination of Me_3SiNO_3 and CrO_3.[44]



Scheme 8 Synthesis of α-nitroketones via nitroalcohols.



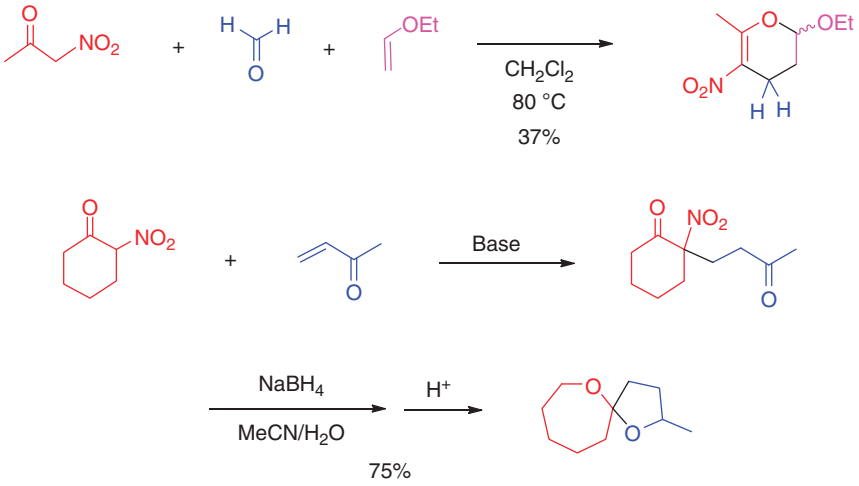
(52)



(53)

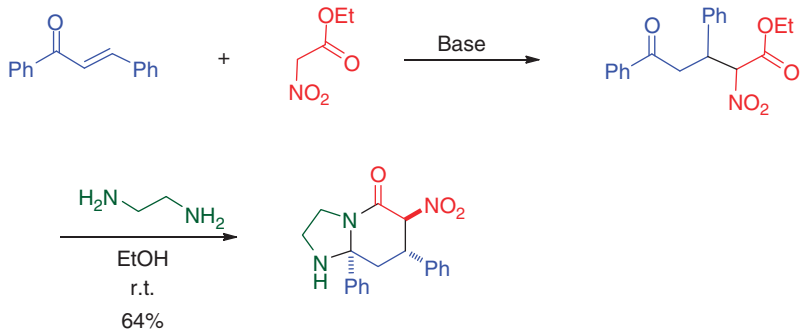
The methylene or methine group between nitro and a carbonyl group is highly activated, which enables the alkylation at that position on treatment with an alkyl halide. Formaldehyde easily reacts with nitroacetone leading to α-nitro-α,β-unsaturated ketone, which successively undergoes the hetero Diels–Alder reaction to construct a dihydropyran framework in one pot (equation 54).[110] When α-nitro carbonyl compounds are subjected to the reaction with α,β-unsaturated carbonyl compounds, conjugate

addition proceeds to afford 2-nitro-1,5-dicarbonyl frameworks.[111,112] The resultant α-substituted nitro compounds are used for elaborate syntheses such as spiro compounds (Scheme 9) and bicyclic compounds (Scheme 10, equation 55) by use of multiple functional groups.[113–116] Electrophilic fluorination is also possible when nitroacetone is treated with $FClO_3$ under basic conditions.[117]

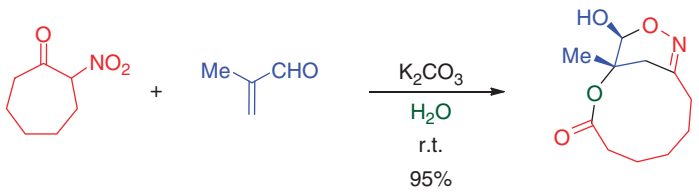


(54)

Scheme 9 Synthesis of spiro compound from α-nitro ketone.

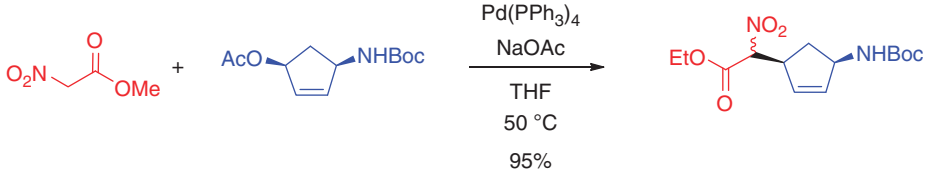


Scheme 10 Bicyclization of α-nitro-δ-keto esters.

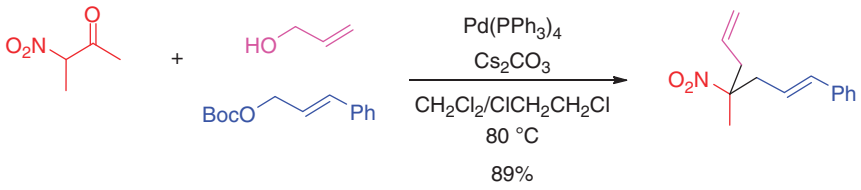


(55)

The acidic methylene group enables the palladium catalyzed C–C bond formations at the α-position (equation 56).[118,119] Wade et al. introduced a nitroacetate skeleton at the allylic position by the Tsuji–Trost reaction using palladium catalyst.[120] Recently, this method was applied to deacylative bis(allylation) of nitroketones to afford deacetylated coupling products as a result of allylation at the α-position followed by C–C bond cleavage between a carbonyl and a nitro group (equation 57).[121]

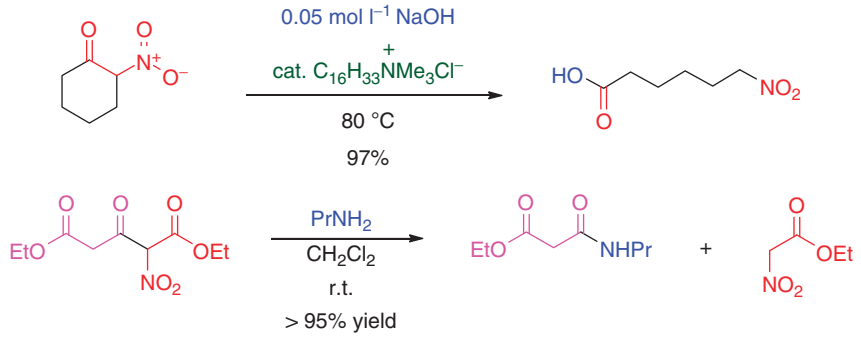


(56)



(57)

The carbonyl group of α-nitroketones is also reactive because of the strong electron-withdrawing effects of an adjacent nitro group. Moreover, nitronate serves as a good leaving group. These structural features allow nucleophilic substitution accompanied by the C–C bond cleavage. Indeed, cyclic nitroketones undergo the ring-opening reaction with water or alcohol to afford ω-nitro acid derivatives in good yields (equation 58).[122] When amines are employed as the nucleophile, aminolysis occurs quite easily to afford corresponding amides, which proceeds in the pseudo-intramolecular process via an ammonium ion pair (equation 59).[115,123,124]

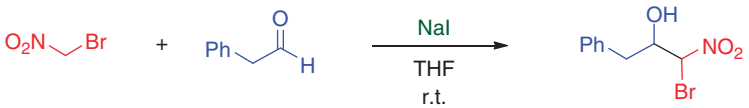


(58)

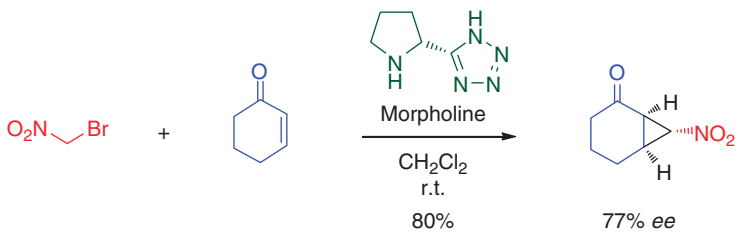
(59)

6.03.1.2.3 Bromonitromethane

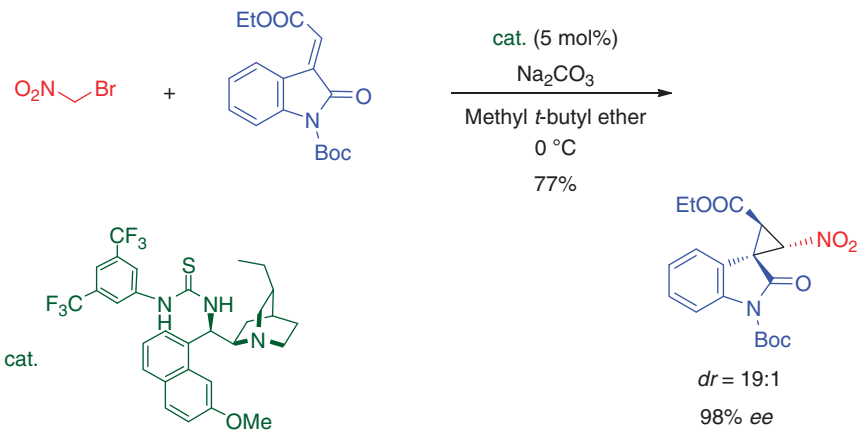
Bromonitromethane is also one of the active methylene compounds, which has both acidic hydrogens and a good leaving group. The Henry reaction with aldehydes undergoes in the presence of catalytic amount of NaI and furnishes bromonitro alcohols (equation 60).[125,126] When bromonitromethane is subjected to the reaction with cyclohexenone, nitrocyclopropanation proceeds to give the bicyclo[4.1.0]heptane derivative (equation 61).[127] This reaction is applicable to syntheses of 6-nitro-3-azabicyclo[3.1.0] hexane derivatives and spirocyclopropane systems (equation 62).[128,129]



(60)



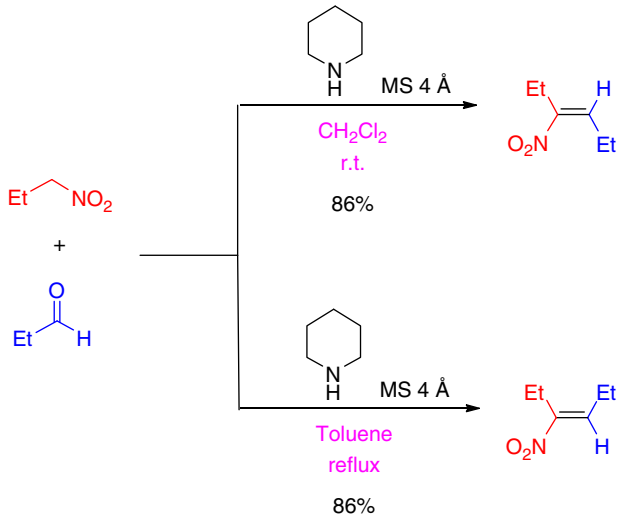
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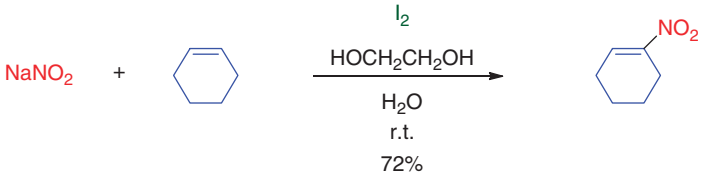
(62)

6.03.1.2.4 Nitroalkenes

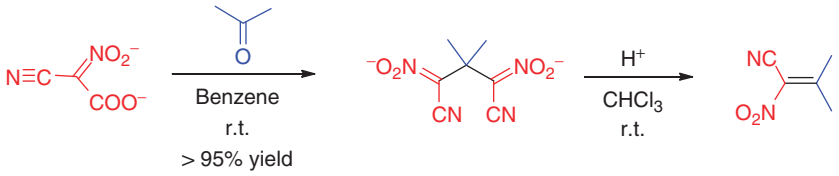
Nitroalkenes[3] are commonly synthesized by a Henry reaction followed by dehydration. Concellón et al. demonstrated the stereoselective synthesis of (*E*)-nitroalkenes promoted by SmI_2.[130] Fioravanti et al. succeeded in controlling the *E*/*Z* geometry by changing the solvent and reaction temperatures (Scheme 11).[131] Nitroalkenes are also available by the reaction of alkenes with $NaNO_2$ in the presence of I_2 as the oxidant (equation 63).[132] Active methylene compounds such as nitroacetate and nitroacetonitrile are superior coupling partners to simple aliphatic nitroalkanes, which undergo Knoevenagel-type condensation to afford α-functionalized nitroalkenes.[133] Dianionic cyano-*aci*-nitroacetate is the easily treatable synthetic equivalent of nitroacetonitrile giving α-cyanonitroalkenes via glutaronitriles as a result of condensation with ketones (Scheme 12).[134]



Scheme 11 Stereoselective synthesis of nitroalkenes.

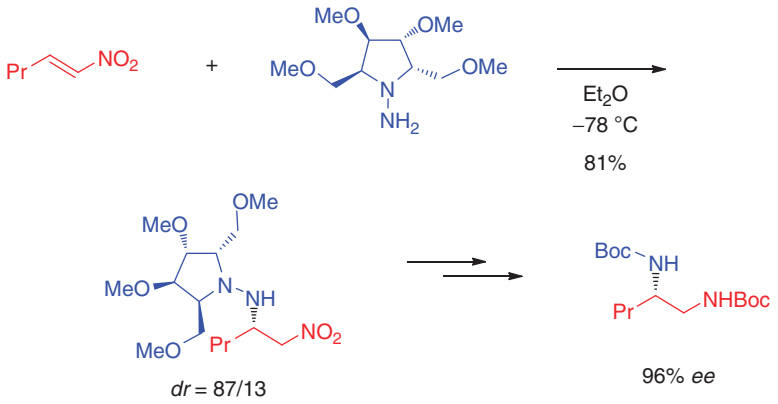


(63)

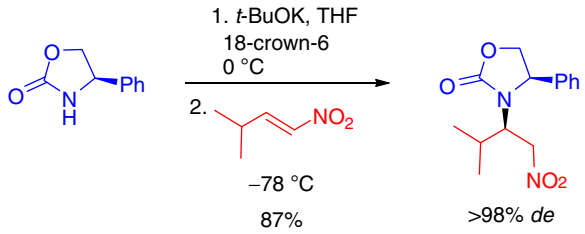


Scheme 12 Synthesis of functionalized nitroalkene via glutaronitrile.

Nitroalkenes serve as good Michael acceptors, which enables the introduction of a functional group such as a phenylthio group[135] at the β-position. Recently, stereoselective aza-Michael addition has advanced, in which *N*-aminopyrrolidine[136] and oxazolidin-2-one[137] derivatives were used as synthetic equivalents of chiral ammonia (Scheme 13, equation 64). Enantioselective catalytic additions are widely performed, some of which are shown in Table 4.[138–142] Benzophenone imine is also usable as the synthetic equivalent of ammonia.[138] When *N*-bromoacetamide is used as the nucleophile, both Michael addition and dibromination proceed, giving α,α-dibromo-β-aminonitroalkanes as a result of migration of the bromo group (equation 65).[143] A carbamate containing a nosyl group similarly serves as an *N*-nucleophile/electrophile to cause the Michael addition followed by ring-closure to form an aziridine ring (equation 66).[144]

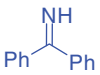
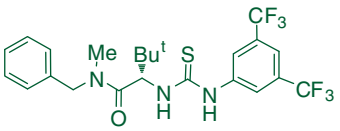
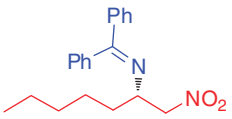
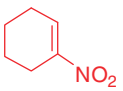
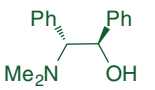
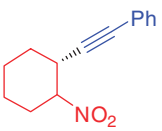
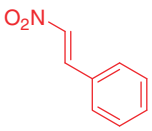
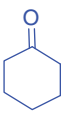
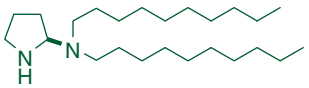
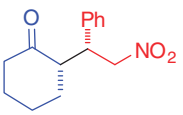
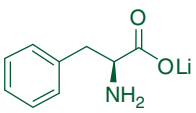
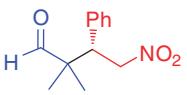
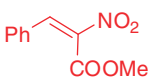
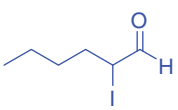
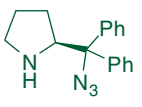
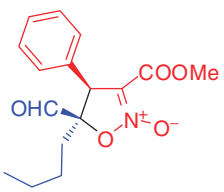


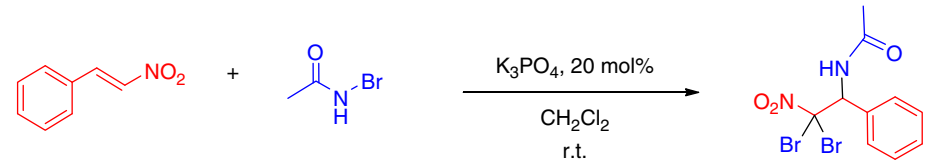
Scheme 13 Stereoselective aza-Michael additions.



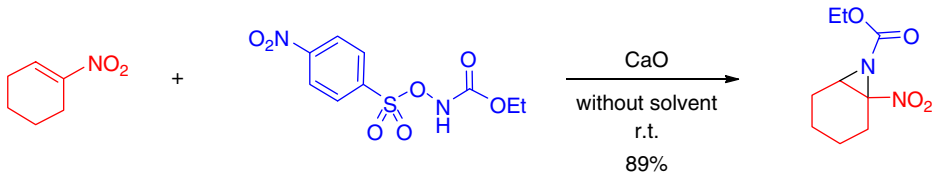
(64)

Table 4 Selected enantioselective reactions of nitroalkenes

Nitroalkane	*Substrate*	*Catalyst*	*Product*
		 10 mol%	 81% *ee*
		 3 equivalents	 97% *ee*
		 10 mol%	 *syn*/*anti* = 95/5 89% *ee*
		 20 mol%	 94% *ee*
		 10 mol%	 *cis*/*trans* = 92/8 99% *ee*

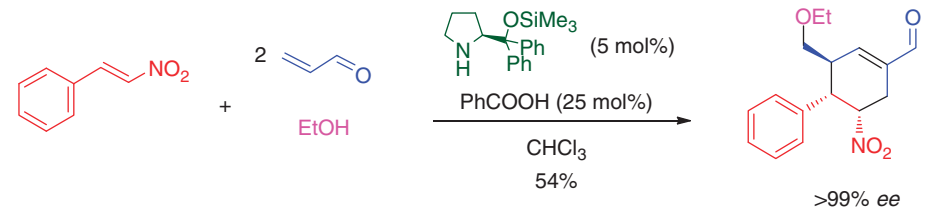


(65)

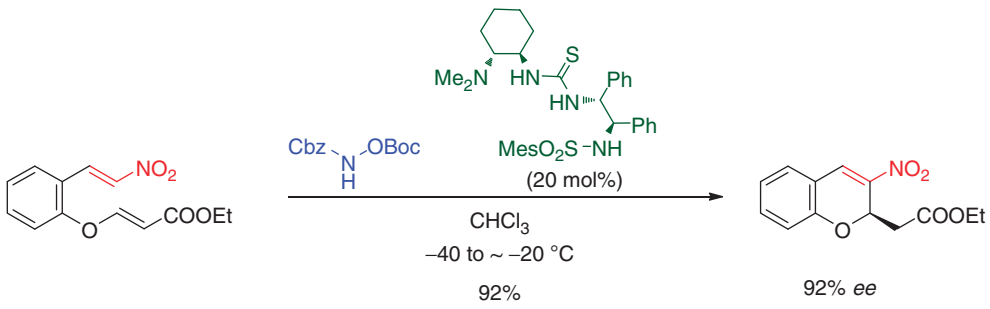


(66)

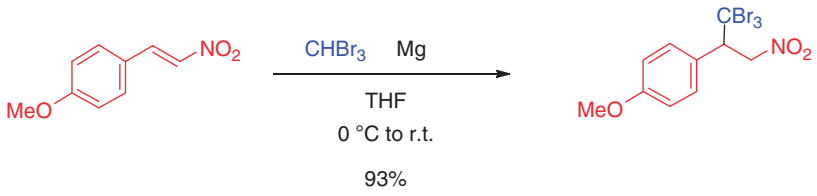
Procedures for enantioselective C–C bond formations have been developed using acetylides,[140] ketones,[139] and aldehydes[141] as the carbon nucleophiles (**Table 4**). When a combination of nitroalkenes with an ester function and α-iodoaldehyde is employed, the ring-closure proceeds after the Michael addition leading to isoxazoline *N*-oxide.[142] Recently, stereo-controlled multistep reactions including Michael addition, which proceeds with high enantioselectivities, have been reported (equations 67 and 68).[145,146] Introduction of a tribromomethyl group at the β-position is also possible when a nitroalkene is subjected to a reaction with $CHBr_3$ and Mg, in which a tribromomethyl radical is formed as the active species (equation 69).[147]



(67)

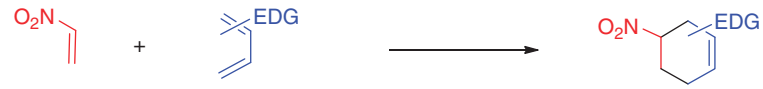


(68)

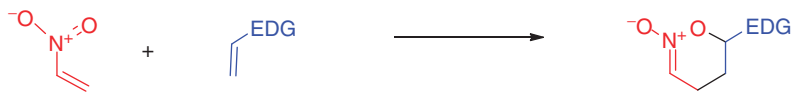


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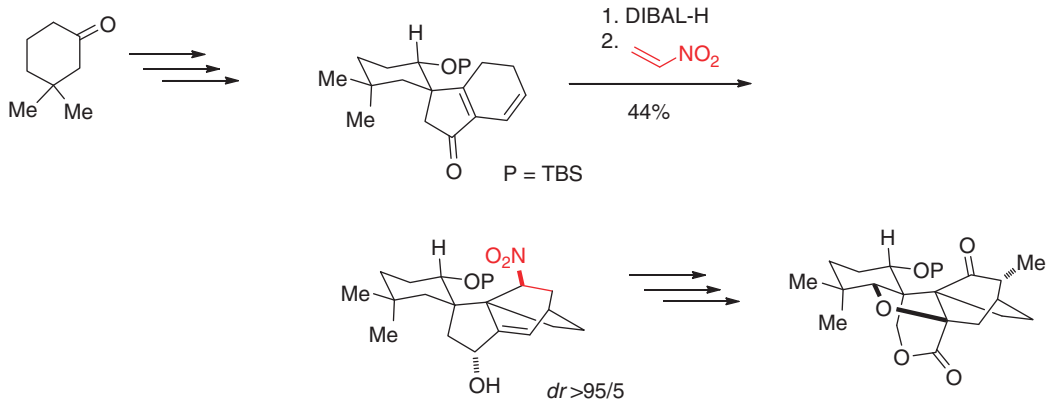
Nitroalkenes play an important role in the cycloaddition chemistry to furnish the cyclic framework with a single manipulation, in which dual reactivity is observed. In the reaction with an electron-rich diene, the carbon–carbon double bond of nitroalkene serves as an electron-poor dienophile to construct a cyclohexene ring (equation 70). In contrast, nitroalkene also serves as the electron-poor heterodiene leading to an oxazine derivative when cycloaddition is conducted with an electron-rich alkene (equation 71). The former cycloaddition is a valuable method to obtain cyclic nitro compounds, which are often found in the synthetic schemes of natural products (**Scheme 14**).[148] The advantage of this protocol is that stereochemistry of stereogenic centers is easily controlled (equations 72–74).[149–151]



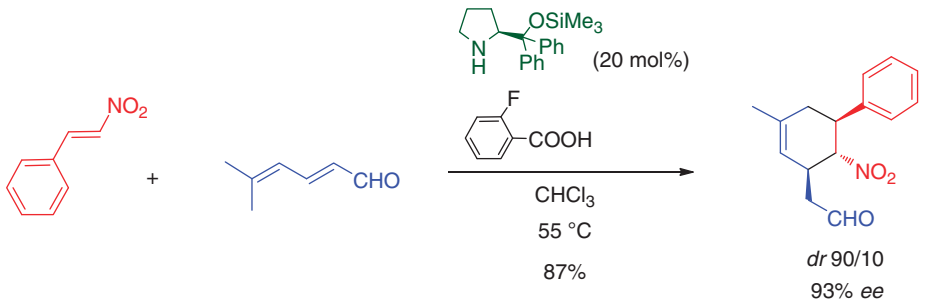
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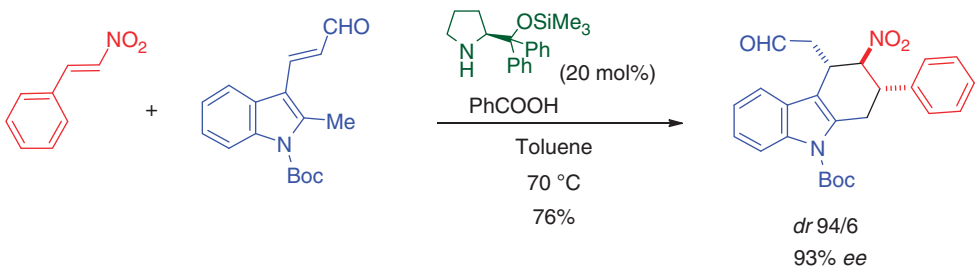
(71)



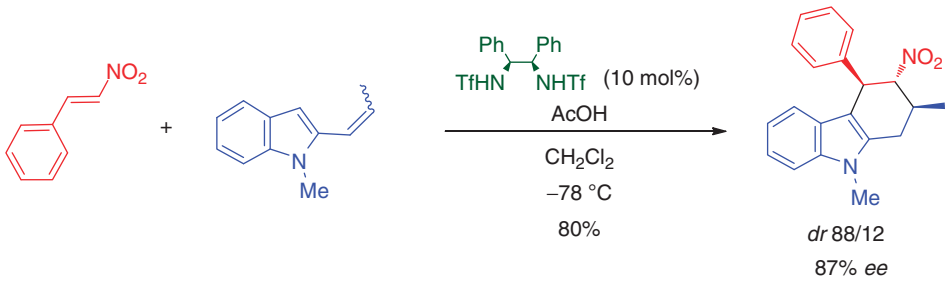
Scheme 14 Cycloaddition of nitroalkene in elaborate synthesis.



(72)

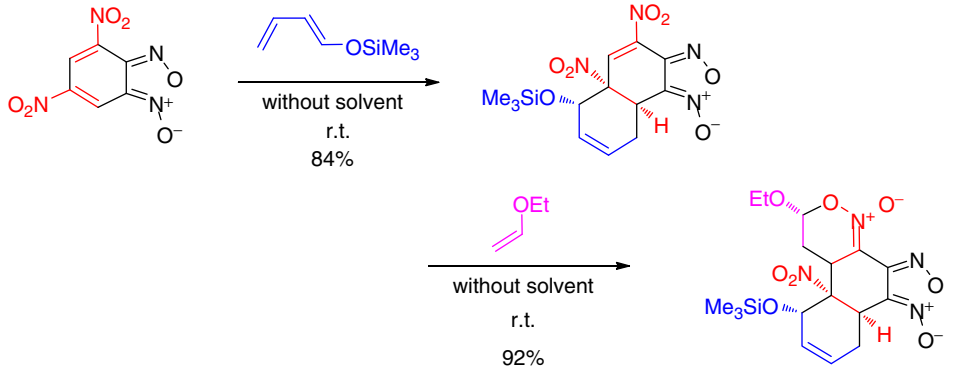


(73)

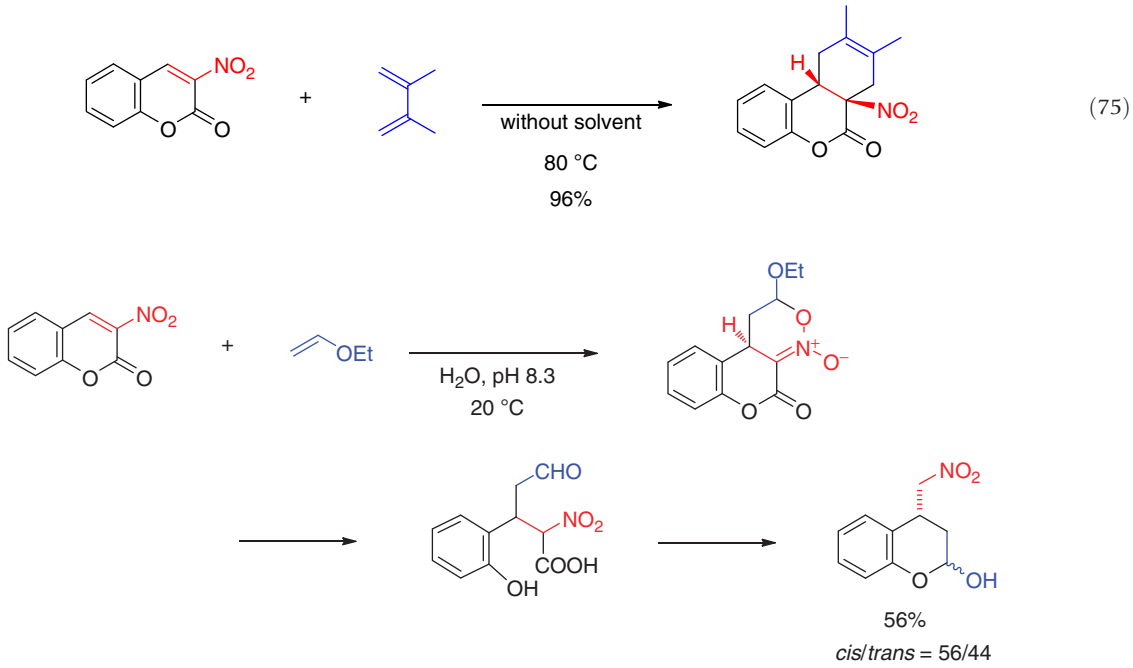


(74)

The partial structure of nitrated heterocyclic compounds often behaves as the nitroalkene because aromaticity and electron density are diminished compared with nitrobenzene derivatives. 4,6-Dinitrobenzofuroxan shows first evidence of the dual reactivity in the Diels–Alder reaction, by which new condensed rings are constructed on the six-membered ring (Scheme 15).[152] 3-Nitrocoumarin serves as a good dienophile to undergo the cycloaddition leading to [*c*]-fused condensed systems (equation 75).[153,154] When nitrocoumarin is used as a heterodiene, ring-opening and recyclization of the intermediate oxazine proceeds to afford a hemiacetal bearing a nitromethyl group at the 4-position (Scheme 16).[155]

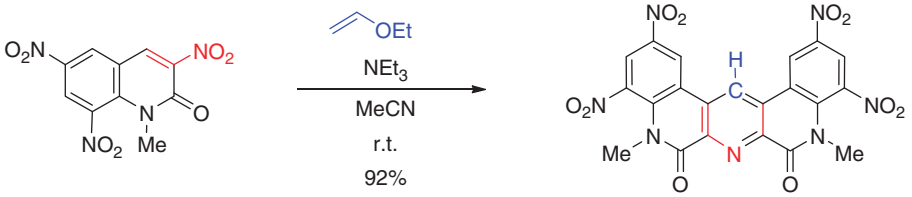


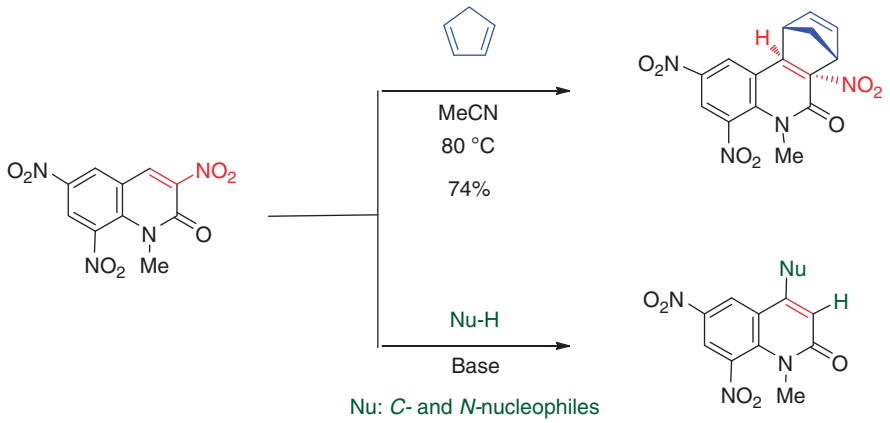
Scheme 15 Dual reactivity of nitroalkene.



Scheme 16 [4+2] Cycloaddition of nitrocoumarin with ethyl vinyl ether.

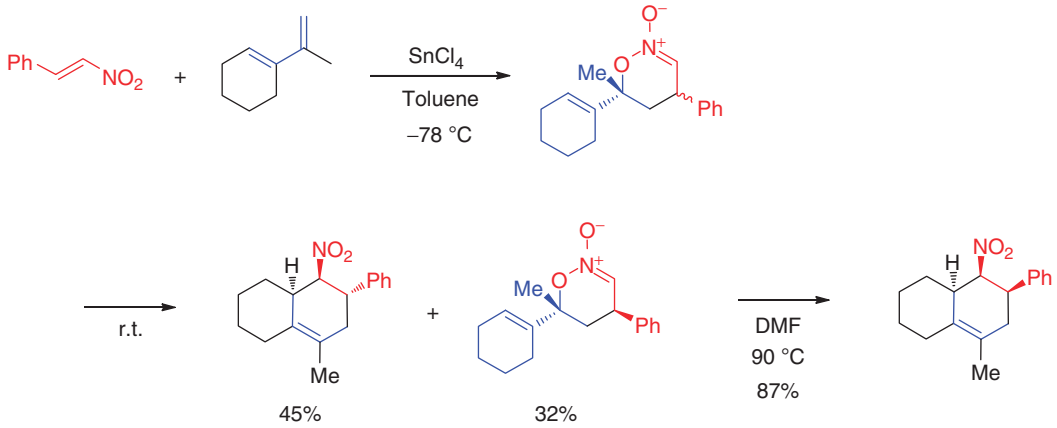
Trinitroquinolone similarly exhibits nitroalkene properties. In this case, steric repulsion between the 1-methyl and 8-nitro groups is necessary to disturb the coplanarity of the quinolone ring, which causes not only the cycloaddition, but also the *cine*-substitution (Scheme 17).[156,157] When trinitroquinolone is treated with ethyl vinyl ether, a polycyclic product is obtained (equation 76).[158] This is the first example that the dual behaviors of nitroalkene, as a heterodiene and as a dienophile, are observed in the same reaction.



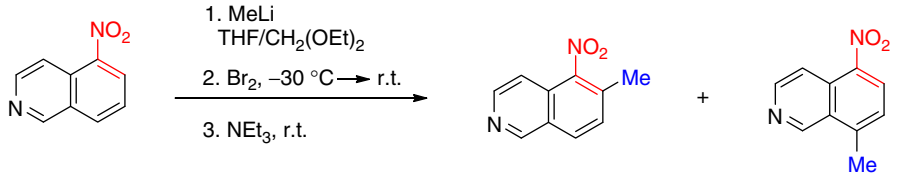


Scheme 17 Cycloaddition and *cine*-substitution of trinitroquinolone.

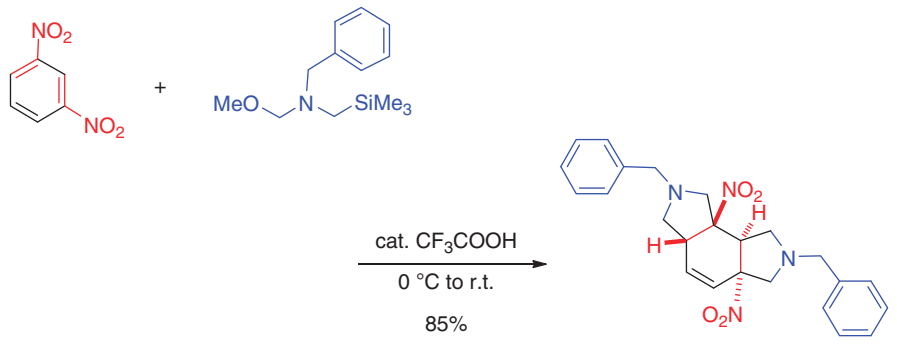
Wade et al. recently reported the [3,3]-sigmatropic rearrangement of an oxazine derivative to form the cyclohexene framework, which provides evidence for a net, indirect cycloaddition mechanism of nitroalkene reactivity (Scheme 18).[159] 5-Nitroisoquinoline also tends to lose aromaticity to cause nucleophilic substitution with MeLi at the *ortho*- and *para*-positions of the nitro group (equation 77).[160] Although nitrated fused ring systems sometimes show nitroalkene properties, nitrobenzene derivatives do not offer similar reactivity. Nitrobenzenes with an additional electron-withdrawing group, for example, 1,3-dinitrobenzene, reveal the nitroalkene reactivity to undergo the double [3+2] cycloaddition (equation 78).[161]



Scheme 18 Sigmatropic rearrangement of cycloadduct of nitroalkene.

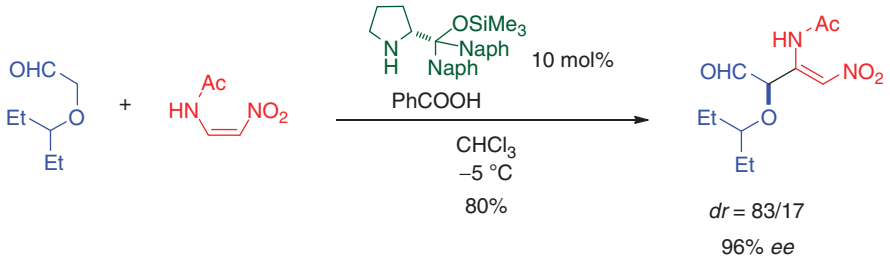


(77)

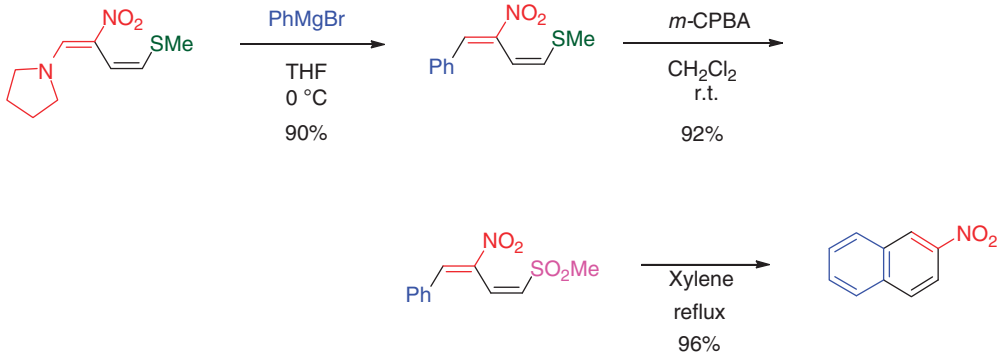


(78)

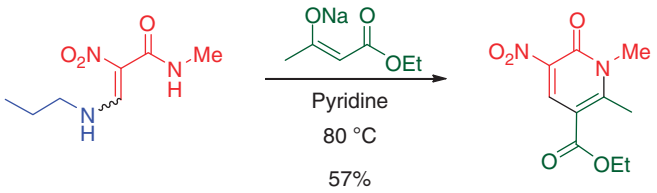
Among nitroalkenes, β-nitroenamines reveal specific reactivity because of the push-pull property. The biased electronic structure can undergo such reactions as electrophilic and nucleophilic addition-elimination, 1,3-dipolar cycloaddition, and reduction.[3,162,163] The stereoselective addition was recently reported using pyrrolidine-based catalysts (equation 79).[164] Although much work on nitroenamines is found in the literature, there are not many reports regarding those having an additional functional group. Bianchi et al. replaced an amino group of a nitroenamine with an aryl group, and the resultant phenylnitrobutadiene underwent ring-closure giving fused nitrobenzene derivatives (Scheme 19).[165] A carbamoyl substituted nitroenamine afforded bis-functionalized pyridone on treatment with the sodium enolate of acetoacetate (equation 80).[71] Nakaike et al. demonstrated that β-formyl-β-nitroenamine has multiple reaction points that cause varied reactivity. Indeed, nitroenamine serves as a useful building block for constructing nitrated frameworks such as pyridones and aminopyridines (equations 81 and 82).[166] Furthermore, the nitroenamine is used as the synthetic equivalent of nitromalonaldehyde, which is discussed in the next section.



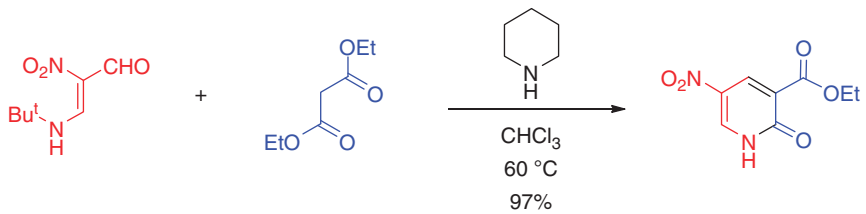
(79)



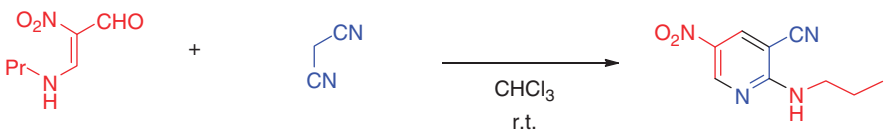
Scheme 19 Synthesis of fused nitrobenzenes using nitroenamine.



(80)



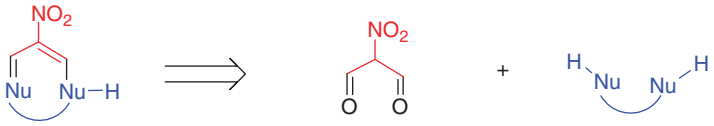
(81)



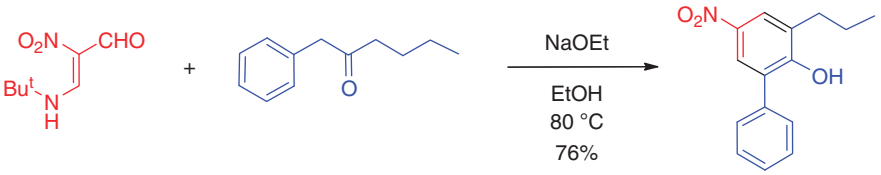
(82)

6.03.1.2.5 Nitromalonaldehyde

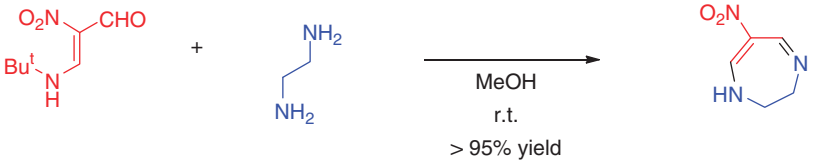
Nitromalonaldehyde is often found as a synthon in the retrosynthesis of nitro compounds (equation 83), however, it is too unstable in aqueous solutions to be isolated, presumably due to easily occurring hydrolysis accompanied by C–C bond fission.[115,123,124] Hence, the sodium salt has been used as the synthetic equivalent of nitromalonaldehyde,[167] however, it is not soluble in organic media. Therefore, several synthetic equivalents of nitromalonaldehyde usable in organic media have been developed.[168] Formylnitroenamine matches this purpose to afford nitrated phenols (equation 84),[169] pyrazoles, pyrimidines, diazepines (equation 85), etc.[170] Jędrysiak et al. demonstrated 1,4-dinitropyrazole also serves as the synthetic equivalent of nitromalonaldehyde to afford nitropyrazoles on treatment with arylhydrazines (equation 86).[171]



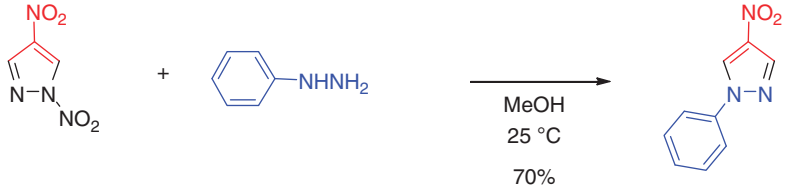
(83)



(84)



(85)

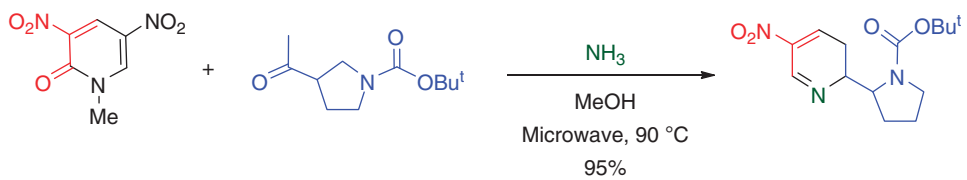


(86)

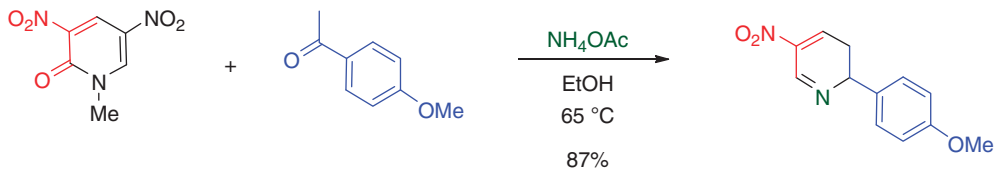
6.03.1.3 Ring Transformation

Ring transformation is one of the powerful methods for synthesis of polyfunctionalized systems that are not easily available by alternative methods. Although Diels–Alder type or degenerate type ring transformations are widely used in organic syntheses, instances of nucleophilic type ring transformations are less common. The substrates for this kind of reaction should satisfy two criteria: (1) be highly electron-deficient and (2) contain a good leaving group as the partial structure. From this viewpoint, nitrated heterocyclic compounds serve as good substrates for the present purpose, which affords nitro compounds as the products. Indeed, van der Plas and his coworkers have energetically studied this chemistry using 5-nitropyrimidine.[172]

3,5-Dinitro-2-pyridone is a superior substrate because the partial structure is easily eliminated as the stable nitroacetamide anion.[173] Recently, Henry et al. developed a direct approach to versatile nitropyridines by the three-component ring transformation of dinitropyridone with *N*-carbamate amino ketones in the presence of NH_3, which is assisted by microwave irradiation (equation 87).[174] NH_4OAc similarly serves as the nitrogen source and activates the ketone, which enables it to undergo the ring transformation under mild conditions (equation 88).[175]

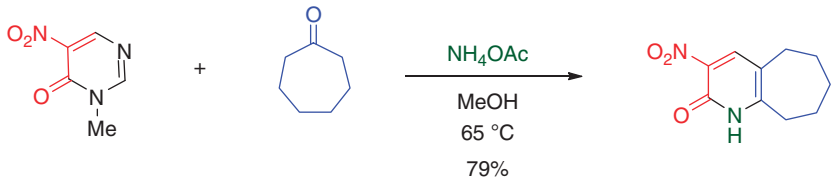


(87)

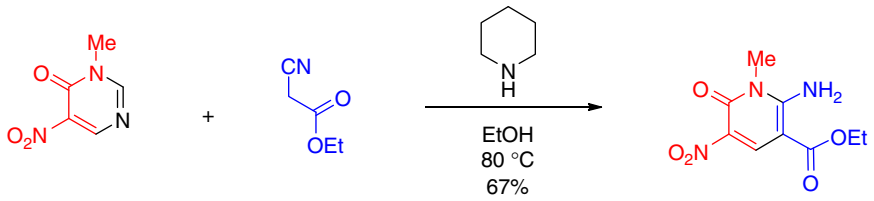


(88)

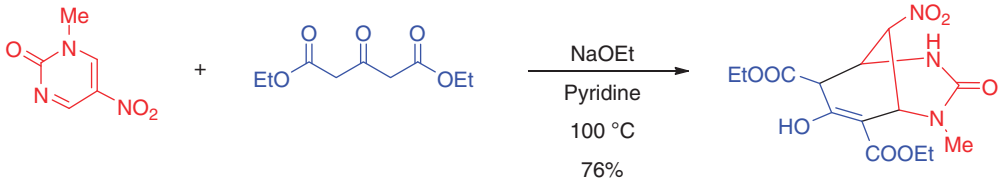
5-Nitro-4-pyrimidinone, the aza-analog of 3,5-dinitropyridone, also satisfies the above-mentioned criteria, and undergoes the three-component ring transformation with ketones in the presence of NH_4OAc leading to 5,6-disubstituted 3-nitro-2-pyridones (equation 89).[38,176] In this reaction, pyrimidinone serves as the synthetic equivalent of α-nitroformylacetic acid. Polyfunctionalized pyridones are also synthesized by the reaction of nitropyrimidinone with active methylene compounds in the presence of piperidine (equation 90).[177] However, 2-pyrimidinone is not a suitable substrate for the ring transformation because the partial structure, urea, is not easily eliminated. Thus, polyfunctionalized bicyclic compounds are isolated instead of the ring-transformed products (equation 91).[178]



(89)

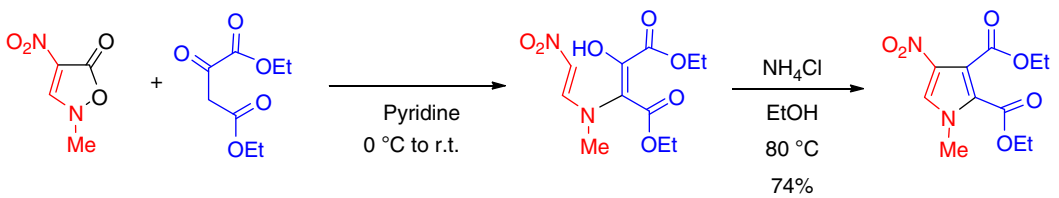


(90)

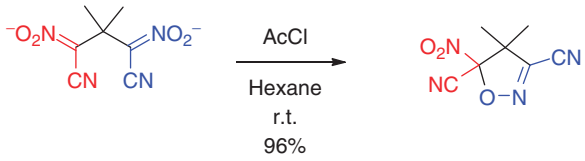


(91)

Electron-deficient nitroisoxazolone has a CO_2 unit in the molecule, which easily eliminates on treatment with nucleophiles. 2,3-Difunctionalized 4-nitropyrroles are synthesized by ring transformation of nitroisoxazolone with sodium enolate of 1,3-dicarbonyl compounds, in which the nitrogen atom behaves as the electrophile because the connected oxygen and conjugated nitro and carbonyl groups considerably diminish the electron density (**Scheme 20**).[179] *O*-Acylated nitronates show high electrophilicity, and react with weak nucleophiles easily. When dianionic glutaronitriles are treated with acetyl chloride, the ring-closure followed by intramolecular ring transformation proceeds efficiently to afford polyfunctionalized isoxazole derivatives in good yields (equation 92).[180]



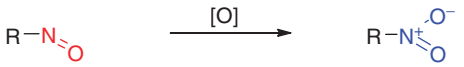
Scheme 20 Ring transformation of nitroisoxazolone leading to pyrrole derivatives.



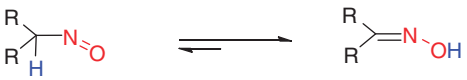
(92)

6.03.2 Nitroso Compounds

Nitroso compounds constitute a class of compounds that play an important role in biochemistry. However, synthetic methods for nitroso compounds are less efficient because they are not so stable. Nitroso compounds are readily oxidized to the nitro compounds, and are converted to the corresponding oxime by tautomerization (equations 93 and 94). Furthermore, nitroso compounds easily dimerize leading to two isomeric dimers, between which there is equilibrium via the monomeric nitroso compound (Scheme 21).



(93)

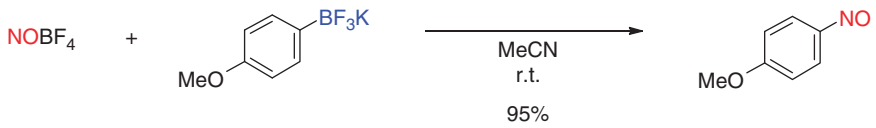


(94)

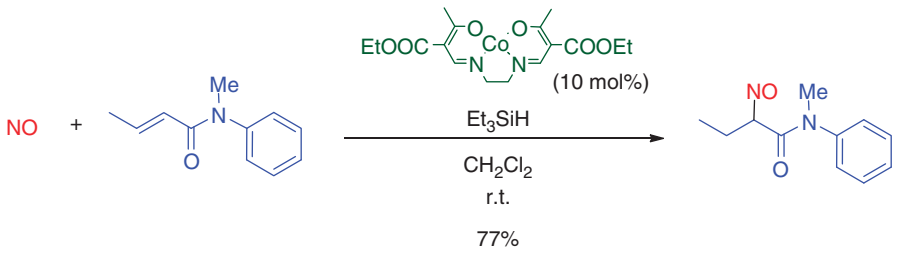


Scheme 21 Equilibrium between monomeric nitroso compound and dimeric isomers.

The conventional nitrosation methods have been comprehensively reviewed by Gowenlock and Richter-Addo, in which conventional nitrosating agents, including ClNO, alkyl nitrites, and HNO_2, are employed even now.[181,182] Recently, Molander et al. developed an excellent method for nitrosation by *ipso*-substitution of aryltrifluoroborates with nitrosonium tetrafluoroborate, which completes within 30 s at room temperature to afford versatile nitrosoarenes in good yields (equation 95).[183] When α,β-unsaturated amides are treated with NO and a Co(II) complex, nitrosation proceeds at the α-position (equation 96).[41] A nitroso function is also available by oxidation of an amino group[184] or reduction of a nitro group.[185] As mentioned in Section 6.03.1.1.2, a nitro group is prepared by oxidation, and nitroso compounds are often produced depending on reaction conditions. Hence, common preparative methods for both nitro and nitroso compounds are known. Brand et al. succeeded in synthesizing alkali dinitrosomethanide from formamidinium nitrate via two steps (Scheme 22).[186]

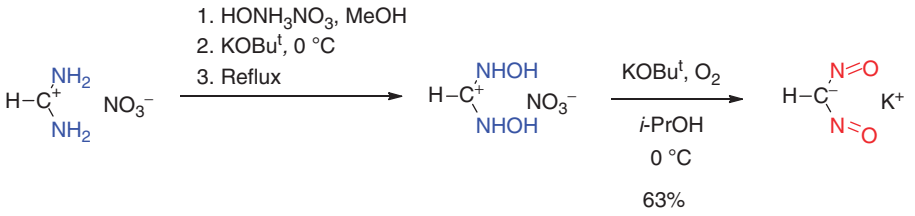


(95)



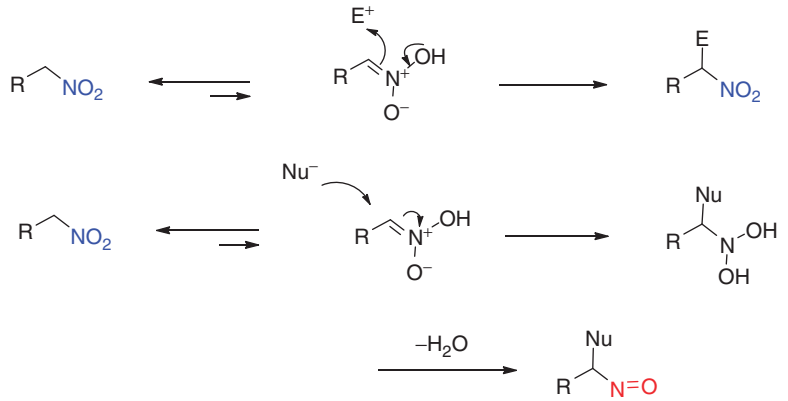
(96)

A nitro group is easily converted to a nitronic acid, which shows both nucleophilic and electrophilic properties, under equilibrium (Scheme 23). In the latter case, the formed dihydroxy product causes the dehydration to afford a nitroso group.

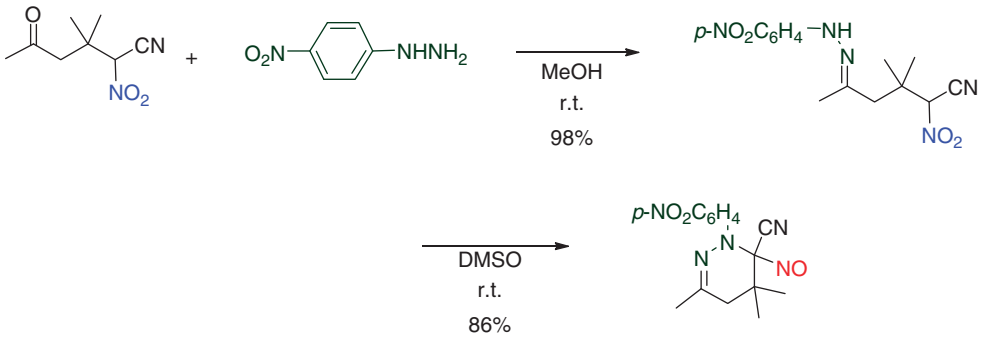


Scheme 22 Synthesis of alkali dinitrosomethanide.

Hirao et al. showed hydrazonation of α-nitro-δ-keto nitrile, which readily underwent the ring-closure via the nitronic acid tautomer to give nitrosopyridazine derivatives after loss of H_2O (Scheme 24).[187]



Scheme 23 Reactions of a nitro compound with an electrophile and a nucleophile.



Scheme 24 Synthesis of nitrosopyridazine derivative.

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6.04 Synthesis of Sulfides, Sulfoxides, and Sulfones

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This chapter is a revision of the previous edition chapter by Guy Solladie, Vol. 6, pp 133–170, © 1991, Elsevier Ltd.

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Glossary

Asymmetric synthesis A chemical procedure that starts from an achiral substrates and produces a single enantiomer of the chiral product with high selectivity using chiral reagents or catalysts.

Kinetic resolution Partial or complete resolution of a racemate into enantiomers by virtue of unequal rates of the reaction of each enantiomer with a chiral agent (reagent, catalyst, solvent, etc.).

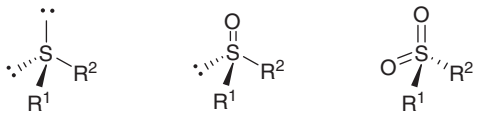
Nucleophilic substitution A reaction in which a nucleophile (a negatively charged or bearing free electron pair atom or group of atoms) attacks a positively or partially positively charged atom or group of atoms and replaces an atom or group of atoms called the leaving group.

Sulfone An organic compound, containing sulfur, in which there are two direct sulfur–carbon bonds and two sulfur–oxygen bonds.

Sulfoxide An organic compound, containing sulfur, in which there are two direct sulfur–carbon bonds and one sulfur–oxygen bond.

6.04.1 Introduction

Sulfides (structure A), sulfoxides (structure B), or sulfones (structure C) constitute the most stable groups among divalent, tetravalent, and hexavalent organic sulfur compounds, respectively.



A **B** **C**

Nonfunctionalized parent compounds and their derivatives with functionalized alkyl chains and/or aryl substituents have been a subject of interest for a long time, its beginning dating from the end of the nineteenth century. For the years, the studies devoted to their chemistry have been well documented in extremely reach original chemical literature, patent claims, and a number of monographic book chapters. The oldest monographic compilation devoted to these three groups of organic sulfur derivatives (which includes also procedures based on displacement by substitution processes) can be found in Houben–Weyl, Vol. IX. Organic sulfides are presented on pages 93–148, organic sulfoxides are mentioned on pages 207–221, and sulfones are discussed on pages 223–259. These chapters are prepared based on the earliest original and patent literature. The second edition of Houben–Weyl includes much more comprehensive chapters presenting under a single heading 'The Chemistry of Arene and Alkane Derivatives' in which the reader will also find a limited number of references to original papers devoted to procedures based on displacement by substitution processes and published between 1955 and 1982. They can be found in Houben–Weyl, Vol. E XI, pages 158–187 (for sulfides), 669–886 (for sulfoxides), and 1132–1298 (for sulfones). Similar chapters are included in 'The Chemistry of Sulfones and Sulfoxides' published in the Patai series 'Chemistry of Functional Groups.' These chapters are devoted to the synthesis of sulfones[1–2] and sulfoxides[3–4] and cyclic sulfides[5a] and also contain selected literature reports for the 1982–1992 period. The synthesis of organic sulfides is also discussed in two other review chapters.[5b–c] Brief presentations of synthetic procedures leading to organic sulfides, sulfoxides, and sulfones (which also include procedures based on displacement by substitution processes) can be found in 'Comprehensive Organic Functional Group Transformations (COFGT)'[6] published in 1995 and in COFGT II[7] published in 2005. The recent compilations devoted to these topics are included in the following: Science of Synthesis volumes: Vol. 31 (31.10.1 Product Subclass 1: Aryl Sulfones, 31.12.1 Product Subclass 1: Symmetrical and Racemic Aryl Sulfoxides, 31.12.2 Product Subclass 2: Optically Active Aryl Sulfoxides, 31.14 Product Class Aryl Sulfides, 31.18 Product Class 18: Cyclic Aryl Sulfides); Vol. 33 (33.1.2 Product Subclass 2: Alk-1-enyl Sulfones, 33.1.5 Product Subclass 5: Alk-1-enyl Sulfoxides, Sulfimides, and Related Compounds, 33.1.8 Product Subclass 8: Alk-1-enyl Sulfides); Vol. 39 (39.2.2 Product Subclass 2: Dialkyl sulfones, 39.4.2; Product Subclass 2: Acyclic Dialkyl Sulfoxides, 39.7 Product Class 7: Acyclic dialkyl sulfides; 39.11.3 Product Subclass 3: Thiiranes; 39.12.1 Product Subclass 1: Thietanes and derivatives). Therefore, in this chapter author would like to present, as comprehensively as possible, the most useful, older, and recent works describing the synthetic protocols leading to organic sulfides, sulfoxides, and sulfones based on displacement by substitution processes. In this context author would like to indicate that the original chapter included to the 1st edition of 'Comprehensive Organic Synthesis' prepared by Solladie[8] is concentrated on synthetic applications of these three classes of sulfur derivatives and the presentation of synthetic protocols is far from comprehensive.

6.04.2 Synthesis of Sulfides

6.04.2.1 Direct C–S Bond Formation

6.04.2.1.1 Direct substitution by sulfur nucleophiles

6.04.2.1.1.1 Alcohols and their derivatives

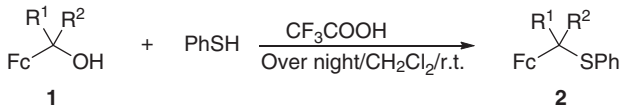
The synthesis of sulfides based on a direct nucleophilic substitution of the hydroxyl group of alcohols with a thiol requires removal of the hydroxyl radical as a leaving group with simultaneous formation of one equivalent of water (Scheme 1). Therefore,

this conversion can be effectively carried out only on activation of the hydroxyl radical which makes it a much better leaving group. The simplest way to realize such activation is based on the use of a sufficiently strong Broensted acid which is able to protonate an alcohol molecule.



Scheme 1

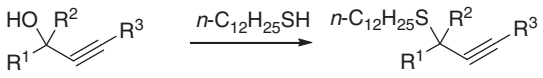
1-Ferrocenylalkyl phenyl sulfides **2** are prepared by treatment (overnight, room temperature) of the corresponding ferrocenyl alcohols **1** with benzenethiol in methylene chloride-containing trifluoroacetic acid (Scheme 2).[9]



Fc = 1-ferrocenyl
R^1,R^2 = H, alkyl, Ph
Yields = 92–96%

Scheme 2

The direct nucleophilic substitution of the hydroxyl group of propargyl alcohols **3** with *n*-dodecanethiol leading to propargyl sulfides **4** is efficiently catalyzed by *p*-toluenesulfonic acid (Scheme 3).[10]

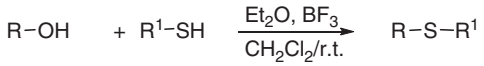


3 **4**

R^1 = Me, Ph; R^2 = H, Me; R^3 = H, *n*-Bu, Ph;
Yields = 52–80%

Scheme 3

In the presence of boron trifluoride-diethyl ether complex, various allyl alcohols **5** react with thiols (thiophenol, 1-butanethiol, trimethyl(phenylthio)silane) in dichloromethane at room temperature to give the corresponding allyl sulfides **6** in good to excellent yields (Scheme 4).[11]



5 **6**

Sulfide 6:
1. (–)Myrtenyl SPh (97%), 2. Geranyl SPh (84%),
3. Geranyl S-*n*-Bu (74%), 4. Cinamyl SPh (99%)

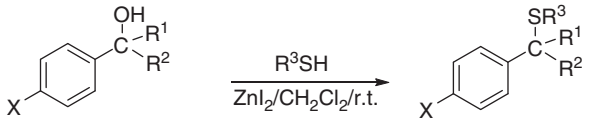
Scheme 4

Different thiols react smoothly with activated alcohols (benzylic or allylic alcohols **7**), in the presence of ZnI_2 in CH_2Cl_2 at room temperature to give the corresponding sulfides **8** in high yields (Scheme 5)[12] The low enantiomeric excess (approximately 7%) noted when PhCHMeSPh **8c** was prepared from (S)-PhCHMeOH **7c** suggests that the reaction has an S_N1-type character.

The reaction of propargyl alcohols **9** with thiols, leading to the corresponding sulfides **10** is efficiently catalyzed by iron (III) chloride (Scheme 6).[13]

A general and efficient substitution reaction of propargylic alcohols **11** with thiols leading to the formation of a C–S bond is catalyzed by copper(II) bromide giving the corresponding propargylic sulfides **12** in high yields and with excellent regioselectivity (Scheme 7).[14]

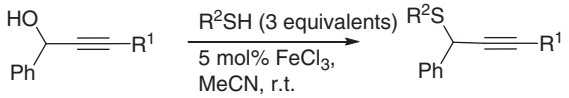
This reaction (which proceeds with both internal and terminal propargylic alcoholic systems **11**) is promoted by a cationic methanethiolate-bridged diruthenium complex [Cp*RuCl(SMe)$_2$RuCp*(OH$_2$)]OTf-**13** giving a number of propargylic sulfides **12** (Scheme 8).[15]



7 **8**

X = H, OMe, CO_2Me;
R^1 = H, Me, *n*-Bu; R^2=Me, *n*-Bu; R^3=Ar, *n*-Bu;
Yields = 81–94%

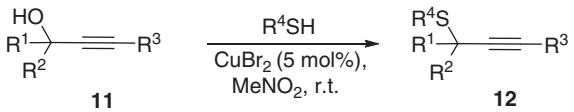
Scheme 5



9 **10**

R^1 = Ph, H; R^2 = CH_2CO_2Et, $(CH_2)_2OH$, Bn;
Yield = 41–92%

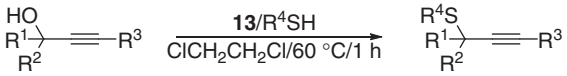
Scheme 6



11 **12**

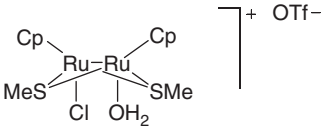
R^1 = Me; R^2 = Me; R^1R^2 = $(CH_2)_5$; R^3 = Ph;
R^4 = Et, Cy, $(CH_2)_2OH$;
Yields: 38–96%

Scheme 7



11 **12**

R^1 = Ph; R^2 = H, Me, Ph; R^3 = H, Ph, *n*-Bu, Cy;
R^4 = *n*-Bu, Ph, $PhCH_2$, $(CH_2)_3Cl$, $(CH_2)_2CO_2Me$ $(CH_2)_2OH$;
Yields: 52–90%

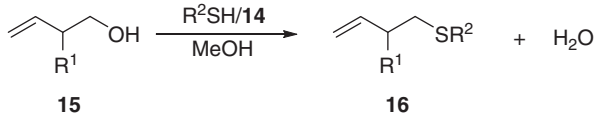


13

Scheme 8

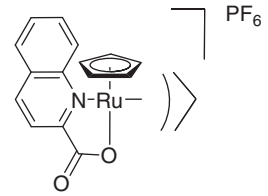
A similar SH-selective allylation procedure using [CpRu(2-quinolinecarboxylato) (η3-C_3H_5)]PF_6 **14** as a catalyst applied to allyl alcohols **15** affords a number of allyl sulfides and allyl *S*-thioates **16** (Scheme 9).[16]

Allylation of several arenethiols by allylic alcohols **17** with sterically hindered carbon of the allylic moiety is catalyzed by Pd $(OAc)_2$/TPPTS in biphasic water/hexane media under ambient conditions giving a number of allylic sulfides **18** (Scheme 10).[17]



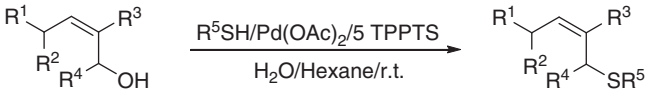
15 **16**

R^1 = H, Me, Ph; R^2 = *n*-Bu, Cy, $(CH_2)_2OH$, PhC(O), MeC(O);
Yields: 96–99%



14

Scheme 9



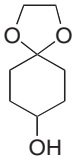
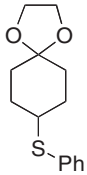
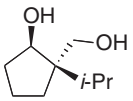
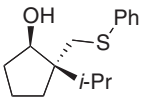
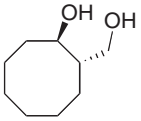
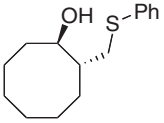
17 **18**

R^1, R^2, R^3, R^4 = H, Me; R^5 = Ph, *p*-FC_6H_4, *p*-$MeOC_6H_4$, *o*-MeC_6H_4;
TPPTS = $P[C_6H_4(SO_3Na)$-*m*$]_3$; Yields = 41–96%

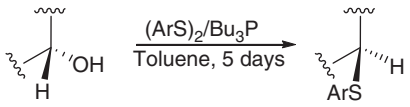
Scheme 10

The Hata reagent (combination of diphenyl disulfide and tri-*n*-butylphosphine) originally applied to the introduction of a phenylthio group to the phosphate residue of nucleotides[18–19] is a very useful reagent for converting alcohols[20] and polyhydroxylated analogs [21] into the corresponding phenyl sulfides. This reagent works also very well in the reaction of cyclic, sterically encumbered alcohols and diols **19a–c**, which are converted into the corresponding cyclic sulfides **20a–c**[22] (Table 1).

Table 1 Preparation of sulfides **20a–c** by the reaction of alcohols **19a–c** with the Hata reagent[22]

No	*Substrate*	*Conditions*				*Product Yield (%)*
		Ph_2S_2	n-*Bu_3P*	*Solvent*	*Time (h)*	
1	 **19a**	2.6	1.8	Tetrahydrofuran (THF)	15	 **20a** (65–70)
2	 **19b**	1.2	1.2	1,2-Dimethoxyethane (DME)	36	 **20b** (92)
3	 **19c**	1.1	1.1	THF	24	 **20c** (85–90)

The modification of the Hata reaction conditions $(ArS)_2/Bu_3P$ in toluene at 65 °C/sealed tube/5 days applied to the native **21** and epi-cinchona alkaloids **22** gives the corresponding aryl sulfides **23** or **24** (15 examples, 31–75%) with complete inversion of configuration at 9-C stereogenic centers (Scheme 11, Table 2).[23] Similar products are also obtained in the enantiospecific nucleophilic substitution of the 9-mesylates of alkaloids with sodium thiolates (4 examples, 73–84%) and no cinchona rearrangement is observed.[23]



9*R*-**21**
9*S*-**22**

9*S*-**23**
9*R*-**24**

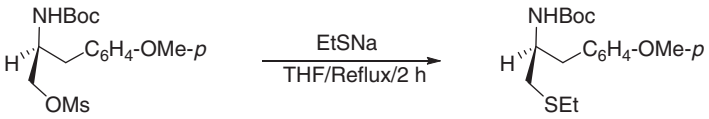
Scheme 11

Table 2 Thioetherification of various alkaloid alcohols (Scheme 11)

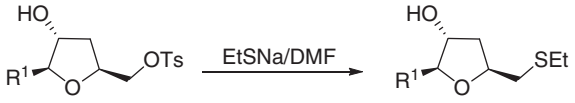
No	*Sulfide **23** or **24***	*Yield (%)*
1	*epi*-9-PhS-CD-**23a**	66
2	*epi*-9-PhS-QN-**23b**	68
3	*epi*-9-PhS-CN-**23c**	66
4	*epi*-9-PhS-QD-**23d**	72
5	*epi*-9-2-NphS-QD-**23e**	53
6	*epi*-9-4-$MeOC_6H_4$S-QD-**23f**	66
7	9-PhS-CD-**24a**	75
8	9-PhS-QN-**24b**	65

CD = cinchonidine; CN = cinchonine; QN = quinine; QD = quinidine; Nph = naphthyl.
For clarity only 9*R* epimers of 21 are shown.

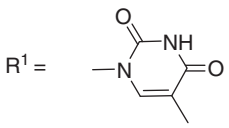
This approach was earlier applied to the preparation of *N*-(*tert*-butoxycarbonyl)-protected sulfide **26** derived from chiral aminoalcohol through the corresponding methanesulfonate **25** (equation 1)[24] and nucleotide sulfide **28** via the corresponding *p*-toluenesulfonate **27** (equation 2).[25] Similarly, a few tosylates derived from primary propargylic alcohols were used as substrates for the preparation of the corresponding aryl and heteroaryl sulfides.[26]



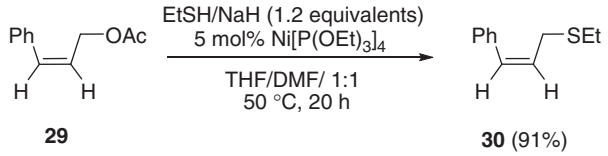
25 **26** (100%) (1)



27 **28** (50%) (2)

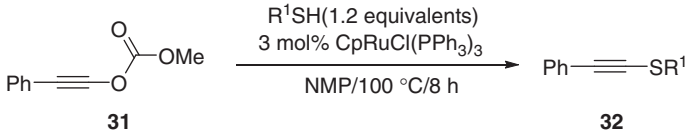


The reaction of allylic acetate **29** with ethanethiol promoted by catalytic amount of a nickel(0) triethyl phosphate produced allylic sulfide **30** with retention of configuration without allylic rearrangement (equation 3).[27a] It is interesting to note that the highly selective Pd-catalyzed kinetic resolution of the racemic cyclic allylic carbonates and racemic acyclic allylic carbonates occurs when they are used as substrates for the formation of the corresponding allylic sulfides by the reactions with 2-pyrimidinethiol by using *N*,*N*′-(1*R*,2*R*)-1,2-cyclohexanediyl bis[2-(diphenylphosphino)-benzamide] (BPA) as a ligand.[27b]



29 **30** (91%) (3)

Propargylic carbonate **31** is used as a substrate for the ruthenium-catalyzed *S*-propargylation of thiols under neutral conditions. The specific requirements allowed access to the highest yields of the corresponding sulfides **32** achieved by tuning the experimental conditions (Scheme 12).[28]

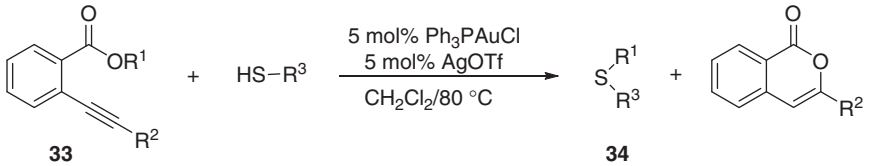


31 **32**

R^1 = *n*-C_8H_{17}, *n*-C_5H_{11}, Cy; Yields = 87–95%

Scheme 12

Alkylation of thiol derivatives by *ortho*-alkynylbenzoic acid alkyl esters **33** is catalyzed by PPh_3AuCl in combination with AgOTf in 1,2-dichloroethane at 80 °C. The corresponding sulfides **34** are obtained in good to excellent yields (Scheme 13).[29] It should be noted here that this chapter listed a number of publications reporting the preparation of aryl thioethers based on catalytic systems using transition metals such as palladium, nickel, or indium.

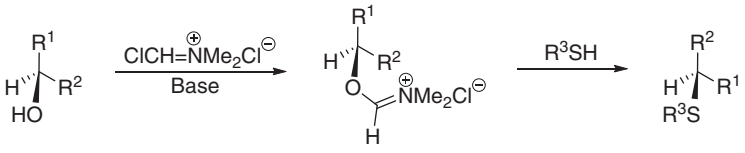


33 **34**

R^1 = Bn, *n*-Bu, *i*-Pr; R^2 = *n*-Pr, X-C_6H_4 (X = NO_2, MeO); R^3 = Ph, *p*-Tol, $PhCH_2CH_2$;
Yields = 24–85%

Scheme 13

Various alcohols on *in situ* conversion into (alkoxymethylene)methylammonium chloride **35** by treatment with (chloromethylene)dimethylammonium chloride (Vilsmeier reagent) are successfully converted into the corresponding sulfides **36** with inversion of configurations in moderate to high yields (Scheme 14).[30]



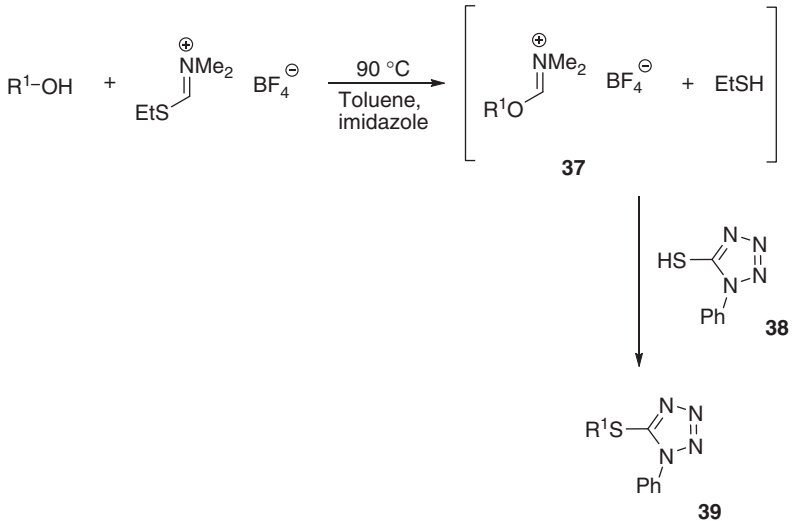
35 **36**

R^1 = Ph, $PhCH_2$; R^2 = Me; R^3 = 4-X-C_6H_4 (X = H, Cl, NO_2);
Yields = 81–98%

Scheme 14

A similar generation of (alkoxymethylene)methylammonium tetrafluoroborates **37** by treatment of primary or secondary alcohols with [(*S*-ethyl)methylene]dimethyl ammonium tetrafluoroborate, $[Me_2NCHSEt]^+ BF_4^-$ and their reaction with1-phenyl-1(H)-tetrazole-5-thiol **38** affords directly and cleanly the corresponding 1-phenyl-1(H)-tetrazol-5-yl sulfides **39** (Scheme 15).[31]

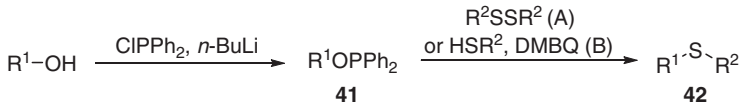
Various primary, secondary, and tertiary alcohols were successfully converted into the corresponding sulfides **42** after initial activation of the alcohols via alkoxydiphenylphosphines **41** and their reaction with aryl disulfides(Method A) or thiols (Method B) and 2,6-dimethyl-1,4-benzoquinone (DMBQ) (Scheme 16).[32a] Later on, this approach was extended for the preparation of



R^1 = $(CH_2)_5CO_2Et$, $CH_2{=}CH(CH_2)_4$, *i*-Bu, $Ph(CH_2)_2CHMe$, $BocNH(CH_2)_3$, 4-$MeC_6H_4CH_2$;
Yields = 70–91%

Scheme 15

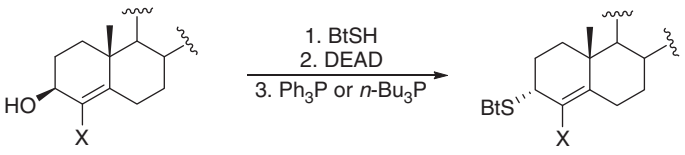
alkyl–aryl sulfides from alcohols via quinone-mediated oxidation–reduction condensation between the corresponding alkyl diphenylphosphinites and the suitably selected sulfanyl precursor.[32b–c]



R^1 = Bn, $BocNH(CH_2)_2$, $CH_2(CO)OMe$, P`Me, $PhMe_2C$;
R^2 = 4-ClC_6H_4, Ph, Py, Bt(1,3-benzothiazolyl);
Yields of 42 = 41–98%

Scheme 16

Bicyclic allylic alcohols **43** (including cholest-4-en-3β-ol) are readily transformed into benzothiazolyl sulfides **44** under the usual Mitsunobu conditions (Scheme 17).[33]



43 **44** (78–83%)

X = H, Br;
Bt = 1,3-benzothiazolyl-2

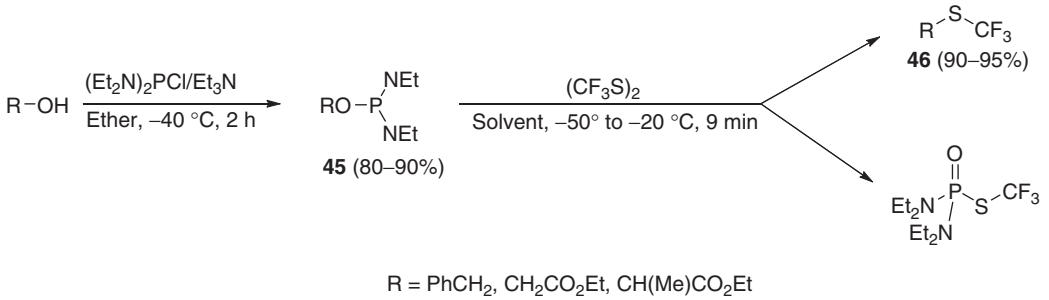
Scheme 17

A convenient method for the transformation of alcohols into alkyl trifluoromethyl sulfides **46** is based on activation of the alcohols via phosphitylation using bis-*N*, *N*-diethylaminochlorophosphine, $(Et_2N)_2PCl$, followed by reaction of diaminophosphites **45** with trifluoromethyl disulfide, $(CF_3)_2S_2$ (Scheme 18).[34]

Indole-based sulfides **48** are prepared efficiently by yttrium triflate-catalyzed chemoselective *S*-benzylation of indolin-2-thiones **47** with primary, secondary, and tertiary benzylic alcohols (Scheme 19).[35]

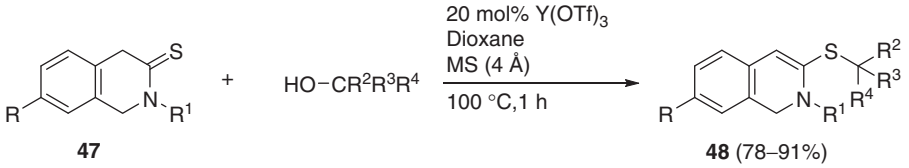
6.04.2.1.2 Alkyl halides

Formation of sulfides from alkyl halides and alkyl(aryl) thiolates (thiols) constitutes a very general method for the formation of both symmetrical and unsymmetrical dialkyl and alkyl–aryl sulfides. The advantage of this approach in the case of dialkyl sulfides



R = $PhCH_2$, CH_2CO_2Et, $CH(Me)CO_2Et$

Scheme 18



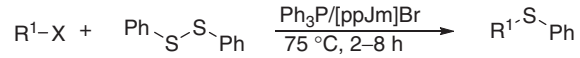
R = H, Cl; R^1 = H, Me; R^2 = Ph; R^3 = Me, Ph; R^4 = H, Ph;

Scheme 19

results from the fact that each alkyl group can in principle generate the halide or thiolate component. The thiolate is usually prepared first by treatment of the thiol with a base with the halide added subsequently. Aqueous or alcoholic solutions of sodium or potassium hydroxide or the corresponding alkoxides are commonly applied. For less acidic thiols sodium hydride, *n*-butyllithium or other organometallic base can be used. Although the substituent 'R' in alkyl halides may be varied to a large extent, the primary as well as the benzylic halides give higher yields than the secondary and tertiary ones. The formation of alkenes is often observed for tertiary halides.

The selected synthetic protocols leading to dialkyl sulfides from alkanethiols by substitution of alkyl halides are discussed in Science of Synthesis Vol. 39 (Section 39.7.1.1.1)[36a] and Science of Synthesis, Knowledge Updates 2011/3.[36b] The recent, similar, and general in scope procedures are presented in Section 6.04.2.1.2.

A convenient protocol for the one-pot synthesis of unsymmetrical sulfides by condensing *'in situ'* generated phenylthiolate with alkyl halides is based on a metal-free cleavage of diphenyl disulfide using ionic liquid/triphenylphosphine. This cleavage of diphenyl disulfide and the subsequent condensation of the thiolate anion proceed efficiently in 1-methyl-3-pentyl imidazolium bromide [pmIm]Br (40 mol%) at 75 °C, and no side products are isolated and the ionic liquid can be reused at least 5 times (Scheme 20).[37a]



R^1 = 4-Z-$C_6H_4CH_2$ (Z = H, MeO), $Ph(CH_2)_2$, CH_2=$CHCH_2$, *i*-Pr, PhCHMe, CH_2CO_2Et, PhCH=$CHCH_2$, 1-NphCH_2;
X = Cl, Br, I; Yields = 72–88%

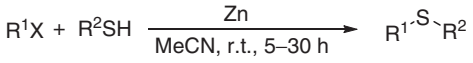
Scheme 20

This imidazolinium bromide efficiently catalyzes also the reaction of alkyl halides with thiols without any solvent, allowing the synthesis of alkyl–aryl and dialkyl sulfides in high yields (80–98% reported for 35 examples).[37b]

When primary, benzylic, and allylic alkyl halides in CH_3CN are treated with thiols in the presence of Zn powder at room temperature, the corresponding sulfides are obtained in good to excellent yields (Scheme 21).[38] Using less than stoichiometric amount of zinc powder resulted in a decrease in the yield of sulfide. Both alkyl thiols and aryl thiols react equally well, and the dihalides are also efficiently converted into their corresponding dithioethers.

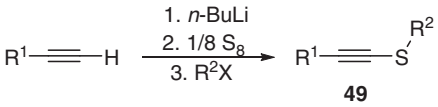
A one-pot synthesis of alkynyl sulfides **49** from terminal alkynes is based on *in situ* generation of lithium alkynyl thiolate (via lithiation of the alkyne and addition of sulfur) followed by their nucleophilic substitution reaction with various halides (Scheme 22).[39]

A similar one-pot protocol is applied to the preparation of potassium organotrifluoroborate **50**, containing the sulfide functional group, through nucleophilic substitution of potassium iodomethyltrifluoroborate by lithium *m*-methoxyphenyl thiolate generated *in situ* in the reaction of *t*-BuLi with 3-bromoanisole followed by treatment with sulfur powder (Scheme 23).[40]



R^1 = *n*-Pr, *n*-Bu, Allyl, 4-Z-$C_6H_4CH_2$ (Z = H, NO_2);
R^2 = 4-Z-C_6H_4 (Z = H, Me, Cl, Br);
Yields = 73–95%

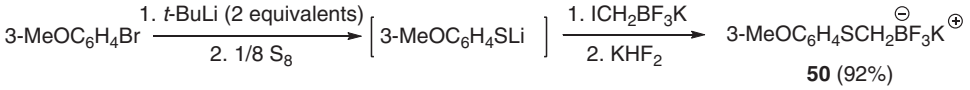
Scheme 21



49

R^1 = Ph, *n*-Bu, *n*-C_6H_{13}; R^2 = Me, Et, *n*-Pr, *n*-Bu, Bn;
X = Cl, Br, I; Yields = 56–86%

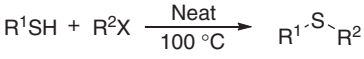
Scheme 22



50 (92%)

Scheme 23

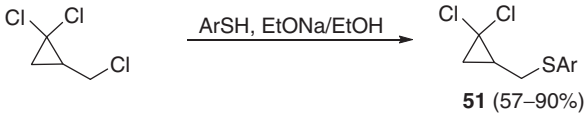
A simple, highly efficient, protocol developed for the preparation of sulfides is based on solvent-free, high temperature reaction of alkyl or aryl thiols and benzyl-, allyl-, *t*-Bu, and adamantyl halides (Scheme 24).[41]



R^1 = 4-Z-C_6H_4 (Z = H, Br, Me, Cl, MeO), *t*-Bu,
n-C_6H_{13}, *n*-C_8H_{17}; R^2 = Bn, *t*-Bu, 1-ad, allyl;
Yields = 61–90%

Scheme 24

It is interesting to note that 1,1-dichloro-2-chloromethylcyclopropane reacts with thiolates to give 2,2-dichlorocyclopropylmethyl sulfides **51** via replacement of the side-chain chlorine atom (Scheme 25).[42]

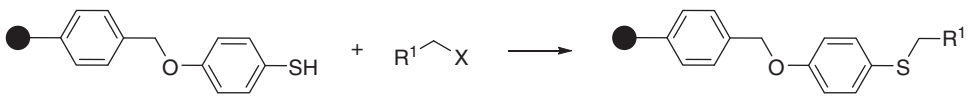


51 (57–90%)

Ar = Ph, 4-tol, 1-H-1,2,4-triazol-5-yl

Scheme 25

The resin-bound linker **52** is alkylated with alkyl halides using different bases (NaH, Cs_2CO_3, or Et_3N) and in the presence of KI, giving the corresponding resin-bound sulfides **53** in which a sulfide linkage is stable to a wide range of reaction conditions (Scheme 26).[43]

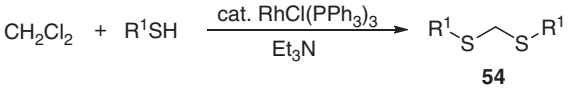


52 **53**

R^1 = $PhCH_2CH_2$, 4-$NO_2C_6H_4$, $(4\text{-}FC_6H_4)_2$ $CH(CH_2)_2$

Scheme 26

The reactions of both alkyl and aryl thiols with methylene chloride in the presence of 5% $RhCl(PPh_3)_3$ at room temperature affords the corresponding formaldehyde dithioacetals **54** in good yield (Scheme 27).[44]



54

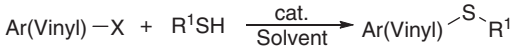
R^1 = *n*-C_8H_{17}, *n*-$C_{12}H_{25}$, Bn, $HO(CH_2)_{11}$, 4-tol;
Yields = 63–99%

Scheme 27

The similar rhodium-catalyzed reactions of thiols (*n*-octane or benzyl) proceed cleanly in Et_3N without using excess alkylating reagents when benzyl chloride or *n*-dodecyl bromide are used as an alkylating reagent.[44]

6.04.2.1.3 Aryl or vinyl halides

The coupling reaction of alkane(arene)thiols with aryl halides or vinyl halides constitutes the most efficient approach to the synthesis alkyl–aryl sulfides and diaryl sulfides and the corresponding vinyl analogs. The reactions are catalyzed by several complexes of group 3–12 metals. The older protocols are discussed in Houben–Weyl and Science of Synthesis (Volumes 31, 33, and 39) chapters mentioned in Section 6.04.2.1.2 . A number of protocols are presented briefly in Science of Synthesis, Knowledge Updates 2011/3. The selected procedures reported in the recent chemical literature, which are based on the general Scheme 28, are listed in Table 3.



Scheme 28

Transition metal-catalyzed cross-coupling reactions of aryl (vinyl) halides with thiolates are also occasionally used for the preparation of symmetrical and unsymmetrical aryl(vinyl) sulfides. Thus, indium trithiolates (derived from a variety of volatile as well as nonvolatile thiols) are effective nucleophilic coupling partners in Pd-catalyzed C–S cross-coupling reactions with a variety of aryl and vinyl bromides or iodides, producing the functionalized aryl–aryl, aryl–alkyl, aryl–vinyl, and alkyl–vinyl sulfides in excellent yields. The best catalytic systems constitutes 4 mol% of $Pd(OAc)_2$ and 4.2 mol% of Xantphos in the presence of DIPEA (1 equivalent) in dimethylformamide (DMF) (100 °C, 4 h) (Scheme 29).[64]

The nickel–bipyridine complexes is used to incorporate the SCF_3 functional group effectively in a variety of aryl and heteroaryl bromides and iodides at room temperature using tetramethylammonium trifluoromethanethiolate (Scheme 30).[65] It is interesting to note that better yields of the aryl trifluoromethyl sulfides **55** are observed for electron-rich aryl halides.

A wide range of aryl bromides is converted into aryl trifluoromethyl sulfides **55** through a palladium-catalyzed process employing silver trifluoromethanethiolate as a sulfur-containing nuclephile[66] (Scheme 31).

Nowadays the synthesis of sulfides is also based on catalytic protocols in which aryl halides activated by transition metals react with a different sulfur source.

Thus, a protocol allowing access to diaryl sulfides, starting from aryl halides, is based on the use of copper(I) iodide as a catalyst in the reaction system comprised of cesium carbonate as a base and thioacetamide as the sulfur source (Scheme 32).[67]

The very high yields of symmetrical diaryl sulfides are obtained in similar cupper-catalyzed cross-coupling reactions using thiourea[68] or potassium isothiocyanate[69] as the sulfur source. In this context it should be noted that unsymmetrical diaryl and aryl–alkyl sufides are isolated in good to excellent yields in a two-step, one-pot cross-coupling reaction of aryl and/or alkyl halides using recyclable CuO nanoparticles as a catalyst (under ligand-free conditions) and with the use of ethyl potassium xanthogenate as a sulfur source.[70] The palladium-catalyzed one-pot synthesis of symmetrical and unsymmetrical diaryl sulfides by employing potassium thioacetate as the sulfur source with aryl iodides and aryl bromides is also very effective.[71] A variety of symmetrical diaryl sulfides are synthesized in good to excellent yields by copper iodide-catalyzed C–S formation between aryl iodides and sodium sulfide as the sulfur source (Scheme 33).[72] By the sequential use of two different aryl iodides or aryl iodides and aryl bromides unsymmetrical diaryl sulfides are also obtained in moderate yields (60–85%) by a one-pot tandem process in which elemental sulfur and sodium sulfide serve as the sulfur source.[72]

A simple and efficient route for the synthesis of heteroaryl aryl sulfides is based on thermal reaction of a wide variety of heteroaryl halides and thiols carried out in aqueous medium under base- and catalyst-free conditions (Scheme 34).[73]

An efficient protocol for the C–S coupling of aryl halide with aryl thiols to the corresponding diaryl sulfides is based on the use of phosphotungstic acid as a catalyst. This one-pot synthesis does not require an inert atmosphere and produces various thioethers in high yield at room temperature (Scheme 35).[74]

Table 3 Metal-catalyzed reactions of alkane(arene)thiols with aryl(vinyl)halides (**Scheme 28**)

No	*Catalyst*	*Reaction conditions*	*Scope and limitations*	*Yield range (%)*	*References*
1	CuI with *cis*-1,2-cyclohexane diol as a ligand or *trans*-1,2-cyclohexane diol as a ligand or tris-(2-aminoethyl)amine as a ligand	*cis*-1,2-cyclohexane diol (20 mol%) as a ligand; 10 mol% of Cu(I)I, and 1.5 equivalents of K_3PO_4 in reagent-grade DMF (without drying) at 30–40 °C	Alkyl, aryl, or heterocyclic thiols with either alkyl, aryl, heterocyclic, or substituted vinyl halides	75–98	45a
		CuI (5 mol%), (±)-*trans*-1,2-cyclohexane diol (2 equivalents) and K_2CO_3 (2 equivalents) in 2-propanol	Aryl or cycloalkyl thiols with aryl bromides or iodides	32–94	45b
		CuI (0.1 mmol), ligand (0.1 mmol), aryl halide (1 mmol), thiophenol (1.02 mmol), Cs_2CO_3 (2.04 mmol), solvent (3 ml)	Aryl thiols with aryl bromides or iodides	65–90	45c
2	CuI nanoparticles in the absence of ligands	CuI nanoparticles (1.5 mol%), Ar–I (1.0 mmol), Ar–SH (1.2 mmol), 40% *n*-Bu_4 NOH aqueous (2.0 ml/3.0 equivalents) at 50 °C (for aryl thiols) or at r.t. (for alkyl thiols) under Ar for 24 h	Aryl and alkyl thiols with aryl halides	81–98	46
3	Cu_2O with 1,10-phenanthroline as a ligand or Cu_2O or Nano CuO	Cu_2O/Cs_2CO_3/DMSO at 80 °C: aryl halide (1.0 mmol), thiol (1.2 mmol), [Cu] (0.05 mmol), ligand (0.1 mmol), and base (2 equivalents) in DMSO (1 ml) under Ar for 24 h	Aliphatic and aromatic thiols; aryl iodides carrying either electron-donating or electron-withdrawing groups; activated aryl bromides and chlorides. No coupling with aryl bromides and chlorides with electron-donating groups or without any substituents. Alkyl–vinyl bromides	75–99	47a 47b
		Cu_2O(0.0025 mmol, 0.5 mol%), vinyl iodide (0.6 mmol), thiol (0.5 mmol), KOH(1 mmol), in dioxane (0.25 ml) for 12 h	Vinyl iodides	67–97	47b
		trans-β-halostyrene (1.0 mmol), thiol (1.0 mmol), catalyst (1.5 mol%), KOH (1.5 equivalents), DMSO (2.0 ml), 80 °C	*trans*-β-bromostyrenes and *trans*-β-iodostyrenes with aryl and aliphatic thiols, retention of stereochemistry	59–97	47c
4	CuCl with *trans*-1,2-diaminocyclohexane as a ligand	Stirring of both substrates (a Schlenk flask) in the presence of water at 120 °C (8.5 mol% CuCl and 3.9 equivalents of *trans*-1,2-diaminocyclohexane). The water solutions containing the copper complexes can be reused three times with any variation in the yields of the target compounds	Aryl or heterocyclic thiols with either aryl or heterocyclic halides	69–97	48
5	CuI/L-proline	An aqueous two-phase system (ATPS): thiol(5.5 mmol), halide (5 mmol), 5 mol% of	Aryl or heterocyclic thiols with either aryl or heterocyclic halides	81–97	49a

(*Continued*)

Table 3 Continued

No	Catalyst	Reaction conditions	Scope and limitations	Yield range (%)	References
		CuI, 10 mol% of L-proline, 12 mmol of K_3PO_4, 6 ml of water, and 4 ml of EtOH refluxed at 80 °C for 6 h. Or			
		3-iodo-cyclohexenone (2.0 mmol), aryl thiol (2.0 mmol), 10 mol% CuI, 20 mol% L-proline, and 1.2 equivalents of K_2CO_3 in 10 ml of 95% EtOH at reflux under nitrogenatmosphere	Aryl or heteroaryl thiols with 3-iodo-cyclohexenone	40–92	49b
6	CuI/ tetrabutylammonium bromide in water	CuI (1 mol%), thiophenol (1 mmol), aryl halide (1.1 mmol), base (1.5 mmol), and TBAB (1 mmol) /water (1 ml) in air or `CuI (5 mol%), thiol (1 mmol), iodobenzene (1.1 mmol), KOH (1.5 mmol), and TBAB (1 mmol)/water at 80 °C in air	Aryl thiols that have electron-withdrawing and -donating substituents with aryl chlorides, bromides or iodides	21–99	50
7	CuBr or CuI/ with 1,2,3,4-tetrahydroquinoline-8-ol as a ligand	Aryl halides (0.75 mmol), thiols (0.5 mmol), CuBr (20 mol%), ligand (20 mol%), Cs_2CO_3 (1 mmol), and DMF (1.5 ml) stirred at 130 °C for 48 h under argon	Aryl thiols that have electron-withdrawing and -donating substituents with aryl chlorides, bromides, or iodides	57–99	51
8	Basic alumina-supported copper sulfate, $CuSO_4$. The authors suggest Cu/Al_2O_3 as an active catalyst	Aryl halide (1.0 mmol), thiol (1.1 mmol), [Cu] (0.05 mmol), and base (2 mmol.) in DMF (3 ml) heated at 110 °C	Alkyl, aryl, or heteroaryl thiols with either aryl or heteroaryl bromides or iodides. Unsymmetrical bis-sulfides are available by base controlled differential reaction of thiols with iodo- and bromo-substituents in an aromatic halide	69–97	52
9	nano-Fe_3O_4 -DOPA-Cu catalyst (nano-Fe-DOPA-Cu). DOPA=dopamine hydro-chloride or nano – CuFe2O4 or /Cu(OAc)2] with TMEDA as a ligand	1.2 mmol of aryl thiol, 1.0 mmol of aryl halide, 100 mg of nano–FeDOPACu catalyst, 120 °C, MW irradiation. Easy recovery of the catalyst using an external magnet, efficient recycling, and the high stability of the catalyst.	Aryl thiols with aryl bromides or iodides.	88–96	53a
		Aryl halide (1.0 mmol), benzenethiol (1.0 mmol), $CuFe_2O_4$ (5 mol%, 12 mg), Cs_2CO_3 (1.0 equivalent), DMSO (2.0 ml), N2, 100 °C, 24 h.	Aryl bromides or iodides with benzene thiol	70–98	53b
		Aryl halide (1.2 equivalents), thiophenol (1.0 equivalent), base (2.0 equivalents), TMEDA (0.2 equivalent), [Fe] (0.2 equivalent), [Cu] (0.1 equivalent), DMF, microwave, 135 °C, 10 min	Aryl bromides or iodides or heterocyclic halides with aliphatic thiols, heterocyclic thiols and substituted aryl thiols	26–95	53c

(*Continued*)

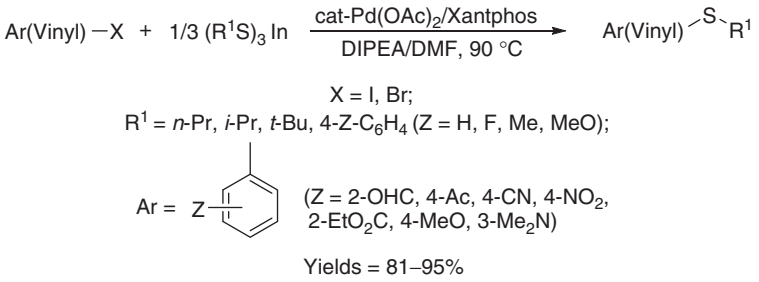
Table 3 Continued

No	*Catalyst*	*Reaction conditions*	*Scope and limitations*	*Yield range (%)*	*References*
10	Palladium *N*-carbene complex [(NHC)Pd(PPh3)Cl2]	Palladium complex (2.5×10^{-3} mmol), aryl halide (0.4 mmol), thiol (0.25 mmol), and potassium *t*-butoxide (0.4 mmol) in solvent (0.5 ml)	Aryl bromides or iodides with aromatic thiols	48–99	54
11	Palladium on charcol	Aryl halide (2 mmol), thiol (2 mmol), 2 mol% Pd/C (5 wt. %), KOH (3 mmol), DMSO (2 ml), 110 °C; catalyst can be reused for five runs	Aryl and heteroaryl halides with aryl and aliphatic thiols	53–99	55
12	$Pd(OAc)_2$	Aryl halide (1 mmol), NaF (1 mmol), TBAB (1 mmol), Pd (OAc)2 (5 mol%), water (15 ml), heating to 150 °C	Aryl iodides and aryl bromides bearing electron-withdrawing groups with aryl thiols: formation of disulfides as byproducts (from 0 to 20%)	65–88	56
13	$Pd_2(dba)_3$ with 1,1′-bis (diphenylphosphino)ferrocene(DPPF) as a ligand	Thiol (1.0 equivalent), $[Pd_2(dba)_3]$ (1 mol%), DPPF (2 mol%), diisopropyloethyl amine (DIPEA) (1.1 equivalents), reflux under nitrogen	Aryl and heteroaryl bromides with aryl and aliphatic thiols	60–99	57
14	Lanthanum oxide (La_2O_3)/ TMEDA	Vinyl bromide (iodide) (1.0 mmol), thiols (1.0 mmol), La_2O_3 (10 mol%), TMEDA (20 mol %), KOH (1.5 equivalents), and DMSO (2.0 ml), at 90 °C; lanthanum oxide can be reused for four runs	Vinyl bromides and iodides with aliphatic and aromatic thiols	55–96	58
15	Lanthanum oxide La_2O_3/ *N,N*'-dimethylethylenediamine (DMEDA)	Aryl halide (1.1 mmol), benzenethiol (1.0 mmol), La_2O_3 (10 mol %), DMEDA (20 mol%), KOH (2.0 equivalents), DMSO (2.0 ml), 110 °C, under a nitrogen atmosphere	Aryl iodides with aryl and aliphatic thiols		59
16	Nano Indium Oxide, In_2O_3	Aryl halides (1.1 mmol), benzenethiols (1.0 mmol), In_2O_3 (3.0 mol%), KOH (2.0 equivalents), DMSO (2.0 ml), 135 °C, under a nitrogen atmosphere	Aryl iodides and bromides with aryl and aliphatic thiols	55–94	60
17	$In(OTf)_3$ with tetramethylethylenediamine (TMEDA) as a ligand	Thiol(1.0 mmol), aryl halide (1.1 mmol), 0.1 equivalent of, In(OTf)3, 0.2 equivalent of TMEDA, 2.0 equivalents of KOH, DMSO (2.0 ml), 135 °C, nitrogen atmosphere	Aryl iodides and bromides with aryl and aliphatic thiols	51–96	61
18	$MnCl_2 \times 4H_2O$ with tetramethylethylenediamine (TMEDA) as a ligand	Aryl (vinyl) halide (1.2 mmol), thiol (1.0 mmol), $MnCl_2 \times 4H_2O$ (15 mol%), KOH (1.5 equivalents), TMEDA (1 mol%), DMSO (2.0 ml) at 110 °C	Aryl iodides and bromides and vinyl iodides with aryl and aliphatic thiols	60–82	62

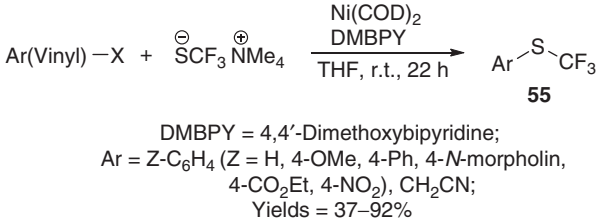
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Table 3 Continued

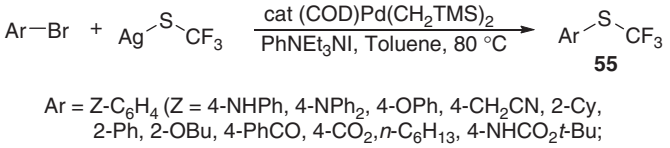
No	*Catalyst*	*Reaction conditions*	*Scope and limitations*	*Yield range (%)*	*References*
19	Cobalt iodide, CoI_2/dppe complex	0.50 mmol of aryl halide, 0.50 mmol of thiole, 0.0050 mmol of CoI_2(dppe), 0.750 mmol of Zn, and 0.50 mmol of pyridine in 2 ml of CH_3CN at 80 °C. For arylbromides, 0.010 mmol of CoI_2(dppe) was used	Aryl and heteroaryl iodides and bromides with aryl and aliphatic thiols	29–99	63



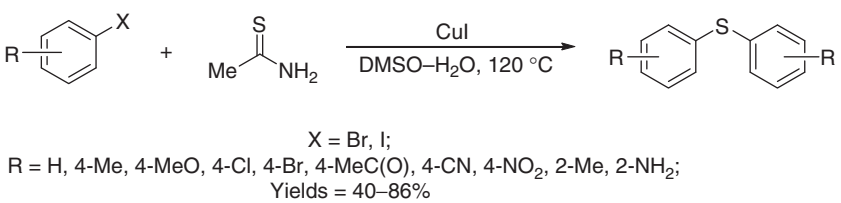
Scheme 29



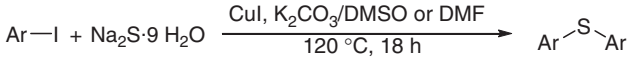
Scheme 30



Scheme 31

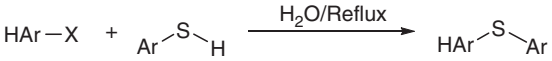


Scheme 32



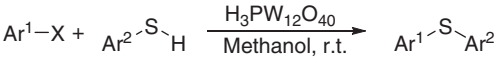
Ar = 4-Z-C_6H_4 (Z = H, 4-Me, 2-Me, 4-Br, 2-Br, 4-NH_2, 4-NO_2, 4-MeO), 1-Nph, 4-Pyridyl;
Yields = 81–94%

Scheme 33



X = Cl, Br;
HAr = 2-Py, 4-Me-2-Py, 3-CN-2-Py, 5-NO_2-2-Py, 3-Py, 2-quinoyl, 1-isoquinoyl and radical derived from pyrimidine,quinazaline and 9*H*-purine;
Ar = 4-Z-C_6H_4 (Z = H, Me, Cl, Br), 2-Z-C_6H_4 (Z = Me, MeO); 2-Nph;
Yields = 61–95%

Scheme 34

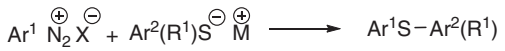


X = F, Cl, Br, I;
Ar^1 = Z-C_6H_4 (Z = H, 2-MeO, 2-NO_2-5-NH_2, 2-NO_2-4-NO_2, 2-Py);
Ar^2 = Z-C_6H_4 (Z = H, MeO);
Yields = 74–91%

Scheme 35

6.04.2.1.4 Miscellaneous procedures

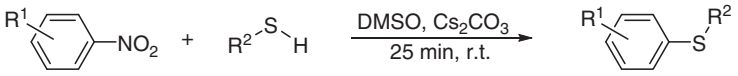
Arenediazonium salts react with arenethiolates to form unsymmetrical diaryl sulfides (Scheme 36).[75] In this context unsuccessful attempts to react fullerene C_{60} with sodium (tetrabutylamonnium) *t*-butylarenethiphosphinate, *t*-BuPhP(O)S^-, should be mentioned.[75d]



Ar^1 = Z-C_6H_4 (Z = H,2,3,4-halo, NO_2), Nph;
Ar^2 = Ph, 2,4,6-$Me_3C_6H_2$, 4-Cl-C_6H_4, 4-Tol; R^1 = *n*-Pr
Yields = 55–85%

Scheme 36

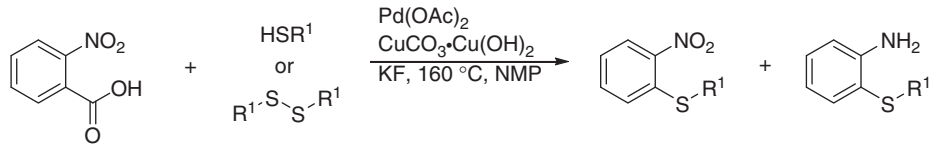
Treatment of nitroarenes having electron-withdrawing groups at the *ortho* or *para* position with alkanethiol in the presence of cesium carbonate in dimethyl sulfoxide at 25 °C leads, via nucleophilic displacement of the nitro group with the alkylthio group, to the corresponding aryl–alkyl(phenyl) sulfides (Scheme 37).[76]



R^1 = 4-CHO, 2-CHO, 4-NO_2, 4-COMe, 4-CN, 4-F;
R^2 = *n*-$C_{12}H_{25}$, Ph, Allyl, PhCH=$CHCH_2$, *t*-Bu, $HO(CH_2)_2$;
Yields = 69–98%

Scheme 37

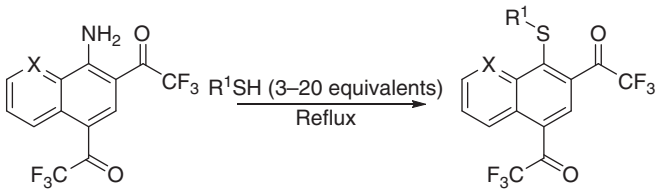
However, the coupling reactions of 2-nitrobenzoic acid with an alkanethiol (disulfide) carried out in the presence of different combinations of transition-metal catalysts at elevated temperatures leads, via a decarboxylative C–S cross-couplings, to the corresponding nitrobenzene alkyl sulfides (or a mixture of nitrobenzene and aminobenzene alkyl sulfides) (Scheme 38).[77]



R^1 = *n*-$C_{12}H_{25}$, *n*-Bu, $Ph(CH_2)_2$, Z-C_6H_4(Z = H, 4-Me, 4-MeO), Nph;
Yields = 68–75% (nitrobenzenes), 70–85% (aminobenzenes)

Scheme 38

N,*N*-Dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine **56a** and *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine **56b** react in excellent yields by aromatic nucleophilic N–S exchange reactions with thiols to afford various 5,7-bis (trifluoroacetyl)-1-naphthyl(8-quinolyl)sulfides **57a–b** (Scheme 39).[78]

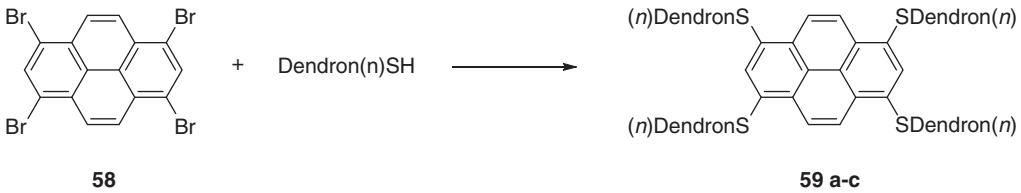


56 **57 a** (X = C)
57 b (X = N)

R^1 = *n*-Pr, *n*-Bu, *n*-C_6H_{13}, Bn, Z-C_6H_4 (Z = H, 4-Me, 4-MeO, 4-Cl);
Yields = 81–100%

Scheme 39

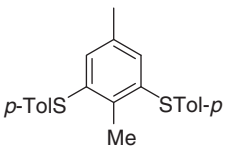
The polysulfuration of 1,3,6,8-tetrabromopyrene **58** by using simple nucleophilic aromatic Br-S substitutions with thiolate anions derived from *p*-toluenethiol and its dendrimeric analogs **59 b–c** in DMF or in DMI (1,3-dimethyl-2-imidazolidinone affords a novel class of dendrimers **60a–c**, consisting of a polysulfurated pyrene core with appended poly(thiophenylene) dendrons (Scheme 40).[79]



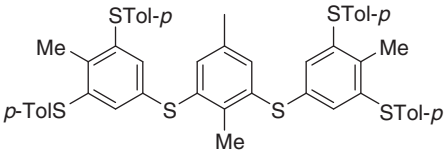
58 **59 a-c**

59 a Dendron (*n*=1) = *p*-Tol

59 b Dendron (*n*=2) =



59 c Dendron (*n*=3) =

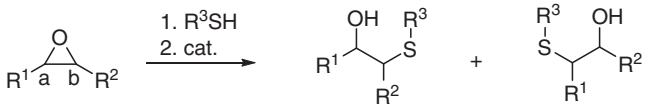


Scheme 40

6.04.2.2 Oxirane Ring Opening by Sulfur Nucleophiles

Thiolysis of epoxides constitutes practically the most useful protocols for the synthesis of *β*-hydroxy sulfides, which serve as important intermediates for the synthesis of a rich family of molecules of biological interest and natural products. A number of convenient procedures to realize this reaction are based on the use of bases or Lewis acids. Others are carried out in the presence of heterogenous catalysts or using microwave activation. The importance of these compounds in organic synthesis and some limitations from which already existing procedures suffer (such as a very strong acidic nature, lack of selectivity, toxicity of reagents,

low yield, lack of regioselectivity, and long reaction times) make a search for new procedures of their preparation still important synthetic challenge. The selected, most recent protocols devoted to this general conversion (Scheme 41) are presented in Section 6.04.2.2.



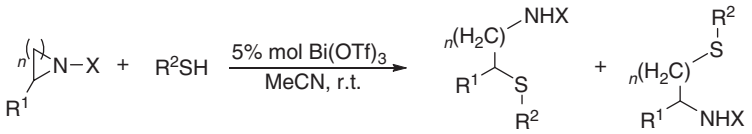
R^1 = $ClCH_2$, $ArOCH_2$ (Ar = Ph, 4-ClC_6H_4), Ph;
R^2 = H;
R^3 = Z-C_6H_4 (Z = H, 4-Me, 4-Br, 2-MeO, 4-F, 3-OH);
$Ga(OTf)_3$ - α/β up to 98/2, yields up to 91%, *ee* up to 96%
water - α/β up to 100, yields up to 95%
$[emim]BF_4$ - α/β up to 99/1, yields up to 98%

Scheme 41

Thus, the ring-opening reaction of epoxides with thiols carried out with the use of $SbCl_3$-supported on Kieselguhr under solvent-free conditions affords high yields of β-hydroxy sulfides formed by regioselective nucleophilic attack of the thiols at the less hindered site of the epoxides.[80] A convenient reaction condition for the regioselective, high yield thiolysis of epoxides using a series of thiols are based on the use of water as a solvent without applying any catalyst.[81a,b] A similar, highly effective and mild protocols for ring opening of epoxides with thiols under solvent-free conditions are based on the use of catalytic amounts of HBF_4 supported on SiO_2,[82] gallium(III) triflate,[83a] erbium(III) triflate,[83b] and polystyrene-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene.[84] It is interesting to note that the activity of the latter catalyst is remarkably reduced in MeCN, and the reactions are totally anti-diastereoselective and generally highly C-β-regioselective. Clean thiolysis reaction of various epoxides in ionic liquids ($[emim]BF_4$), without catalyst generates β-hydroxy sulfides in excellent yields (up to 98%) with high regioselectivity.[85] The desymmetrization of meso-epoxides with thiols proceeds smoothly in dichloromethane or dichloroethane in the presence of a catalytic amount of a chiral scandium complex consisting of $Sc(OTf)_3$ and chiral bipyridine derivatives. The corresponding cyclic β-hydroxy sulfides are formed in high yields with high enantioselectivities.[86]

6.04.2.3 Nitrogen-Containing Rings Opening by Sulfur Nucleophiles

The regioselective ring opening of aziridines with thiols constitutes also the simplest and most straightforward route to β-aminosulfides, which are very useful as intermediates for the synthesis of biologically interesting amino acids and heterocycles, including alkaloids. The existing procedures are based on the use of Lewis (boron trifluoride etherate or zinc chloride) or Bronsted acids (trifluoromethanesulfonic) or base as catalysts. Among them there is a very efficient protocol based on the use of bismuth triflate. It affords the corresponding β-aminosulfides under mild conditions in excellent yields (Scheme 42).[87]



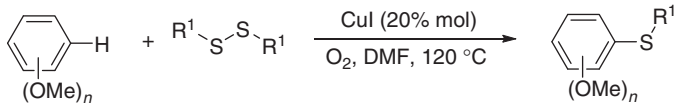
n = 1,3,5; X = Tos, Bn;
R^1 = Ph, 4-Tol, *n*-C_6H_{13}, *n*-C_9H_{19};
R^2 = Ph, 4-Tol, 4-$MeOC_6H_4$, *n*-Bu, 4-ClC_6H_4, 2-Nph;
Yields = 82–90%

Scheme 42

A simple, mild protocol for preparation of β-amino sulfides in a one-pot operation is based on the ring opening of aziridines by the thiolate generated *in situ* by treatment diaryl disulfides with rongalite (NaO_2SCH_2OH).[88] A similar, efficient synthesis of amino sulfides is achieved via the ring cleavage of *N*-tosylazetidines with thiols in the presence of various Lewis acids (boron trifluoride etherate is the most efficient). The products are obtained in modest to good yields under very mild conditions in 5–15 min.[89]

6.04.2.4 Reaction of Disulfides with Carbon Nucleophiles

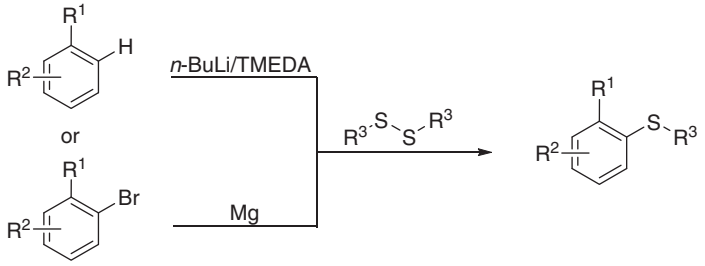
A CuI-catalyzed C–H bond cleavage of di- or trimethoxybenzenes occurring in the presence of disulfides and oxygen opens an access to a variety of unsymmetrical sulfides (Scheme 43).[90]



n = 2,3; R^1 = aryl, alkyl, Bn, allyl;
Yields = 40–98%

Scheme 43

Similarly, Cu(II) salts catalyze thiolation of 2-phenylpyridine with dimethyl disulfide[91] and benzoxazole C–H bond with diaryl disulfides.[92] Iron-catalyzed sulfenylation of an indole C–H bond with diaryl disulfides is also effective.[93] Organometallic reagents, generated *in situ* by an *ortho*-lithiation of the suitably substituted arene derivatives or a bromine–lithium exchange reaction of selected aryl halides, react with disulfides giving the corresponding unsymmetrical sulfides (Scheme 44).[94a–c]

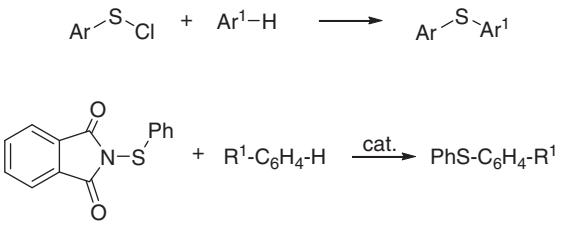


R^1 = SH, $CONHMe_2$, CH_2NMe_2, $C(CF_3)_2(OH)$, Me;
R^2 = H, Me;
R^3 = Me, Et, *n*-Pr, *i*-Pr, Ph, 4-Tol, Me_2N;
Yields = 60–90%

Scheme 44

6.04.2.5 Sulfenylation Reactions

The preparation of unsymmetrical diaryl sulfides is based on the low-temperature reactions of aresulfenyl chlorides with arenes (Scheme 45-top equation).[95a–c] The use of Lewis acids leads to a substantial increase of the yields.



R^1 = H, 2-PhO, 4-MeO, Me;
catalysts: $AlCl_3$, $TiCl_4$;
Yields = 49–94%

Scheme 45

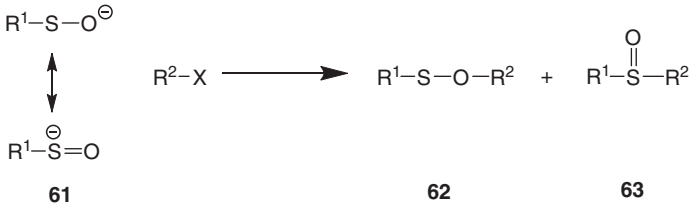
This approach is also extended to the synthesis of sulfides of the azulene series by reaction of chamazulene with aliphatic, aromatic, and heterocyclic sulfenyl chlorides.[96] Another approach to the preparation of unsymmetrical diaryl sulfides is based on a sulfenylation reaction between of *N*-(phenylsulfanyl)phthalimide with a variety of arenes (Scheme 45).[97]

6.04.3 Synthesis of Sulfoxides

6.04.3.1 Direct C–S Bond Formation

6.04.3.1.1 Direct substitution by sulfenic acid anions

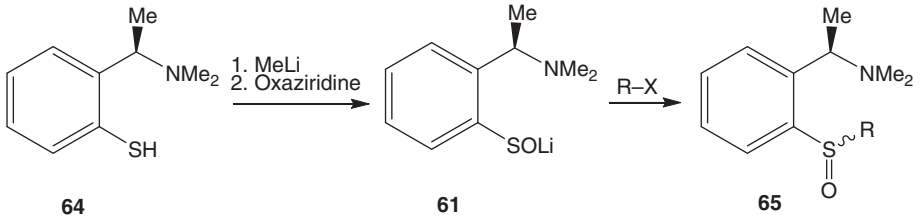
Anions of sulfenic acids can be described by two canonical resonance structures, in which the negative charge is located either on the sulfur or the oxygen atom **61**. Hence, they can show a typical ambident reactivity. It is obvious, that the direction of their alkylation depends on the kind of the alkylating agent: the 'hard' alkylating agents lead to the predominant formation of the O-alkylation products, that is, alkyl sulfenates **62**, whereas the 'soft' agents – to the *S*-alkylation products, that is, sulfoxides **63** (Scheme 46). Early reports are summarized in References 3 and 4.



Scheme 46

One of the important issues that remains is the preparation of the sulfenate anions, which is usually not a straightforward operation.[98] Nevertheless, several attempts have been successfully made which resulted in the formation of anions bearing various counterions. In each case, the main goal was the subsequent S–C bond formation leading to the desired sulfoxides.

The first protocol involved initial oxidation of sulfur in the appropriate precursor. Thus, the sulfenate anions were obtained by oxidation of properly substituted thiolates with the Davis oxaziridine and treated *in situ* with alkyl halides to give sulfoxides.[99] The same procedure was later repeated using thiol **64**, bearing a chiral auxiliary, to obtain diastereomerically enriched sulfoxides **65** (Scheme 47, Table 4).[100]



Scheme 47

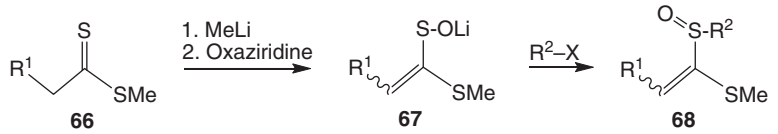
Table 4 Diastereoselective sulfenate anion alkylation (Scheme 47)

No	*R–X*	*Sulfoxide **65***	
		Diastereomer ratio	*Overall yield (%)*
1	MeI	84:16	70
2	EtI	84:16	86
3	AllylBr	81:19	70
4	$PhCH_2Br$	98:2	43

Enethiolates derived from dithioesters **66** were efficiently converted into the corresponding alkenylsulfenates **67** by oxidation with a sulfonyloxaziridine. Subsequent alkylation with alkyl halides led to ketene dithioacetal *S*-oxides **68** in good to excellent yields (Scheme 48).[101]

Similarly, lithium 1-alkynylsulfenates **69**, derived from 1,2,3-thiadiazoles, were reacted with alkyl halides to give alkynyl sulfoxides **70** (Scheme 49).[102]

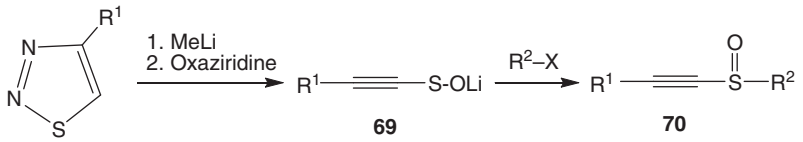
However, the most frequently used procedures of the preparation of sulfenate anions were based on the fragmentation of properly substituted sulfoxides, during which sulfenate anions are released. Thus, when β-sulfinylesters **71** were treated with a base, the corresponding sulfenate anions were formed as a result of a retro-Michael reaction.[103,104] As in the cases shown before



R^1 = H, Me, *n*-Pr, *n*-Oct, Ph
R^2 = Me, Et, Bn

Yield: 26–85%

Scheme 48

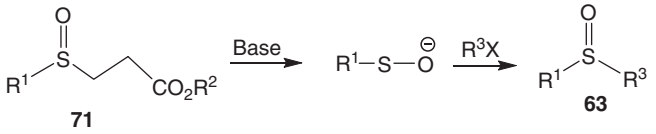


R^1= *t*-Bu, Ph, Me
R^2–X = BnBr, EtI, MeI, $BrCH_2CO_2Et$

Yield: 5–85%

Scheme 49

(see Section 6.04.3.1.1), their treatment with alkyl halides led to the corresponding sulfoxides which were formed in various yields, depending on the base and conditions used (Scheme 50).

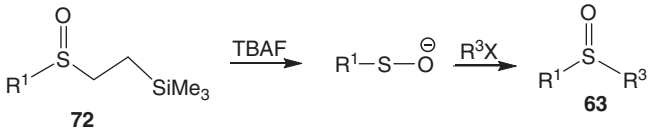


R^1 = Aryl, Alkyl, Cycloalkyl, [2.2]Paracyclophane
Base: NaHMDS, KHMDS, LDA, BuLi, *t*-BuOK, NaH
R^3 = Me, Et, Bn

Yield 57–95%

Scheme 50

Another approach utilized 2-trimethylsilylethyl sulfoxides **72**, which under the treatment with a fluoride source underwent eliminative cleavage to give sulfenate anions. The latter were trapped, as usual, by alkylating agents (Scheme 51).[105]



R^1 = Aryl, Pyridyl, *t*-Butylethynyl, 2-Methylethenyl
R^3 = Me, Et, Bn,

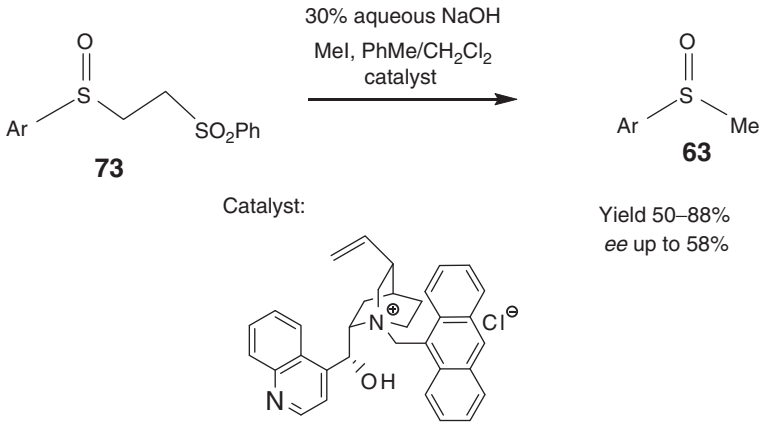
Yield 49–84%

Scheme 51

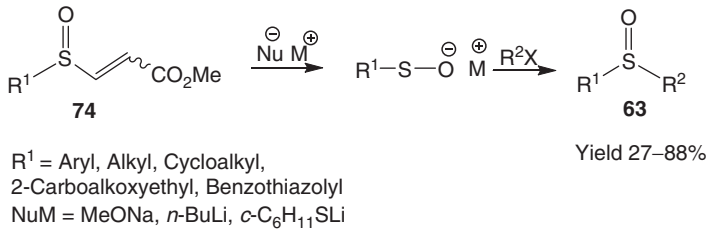
In turn, aryl 2-(benzenesulfonyl)ethyl sulfoxides **73** were used as a sulfenate anion source in the asymmetric synthesis of sulfoxides under phase transfer catalysis (PTC) conditions using cinchona-based chiral phase-transfer catalysts. The final sulfoxides were obtained in good yields and with moderate enantiomeric excess (Scheme 52).[106]

Finally, 2-sulfinylacrylates **74** were used as substrates to produce sulfenate anions in a Smiles-like rearrangement. This approach made it possible to obtain a large variety of sulfenate anions and hence sulfoxides (Scheme 53),[107,108] including the one derived from protected cysteine *S*-oxide **75**. In the latter case, the final alkylation proceeded with high diastereoselectivity (Scheme 54).[109]

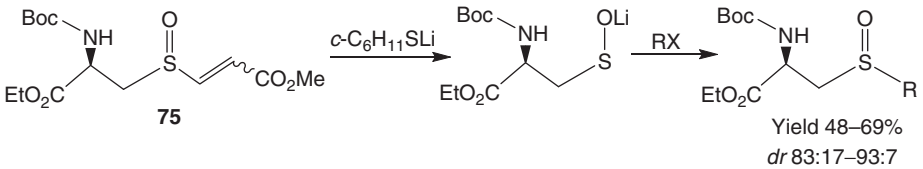
The sufenate anions, prepared as describe in Section 6.04.3.1.1, were also used in the palladium-catalyzed formation of allyl sulfoxides **76**,**77** (Scheme 55)[110,111] and aryl sulfoxides **78** (Scheme 56)[110,112]. In the latter case, the use of various chiral ligands allowed the formation of the final sulfoxides in the enantiomerically enriched form (*ee* up to 80%).[113]



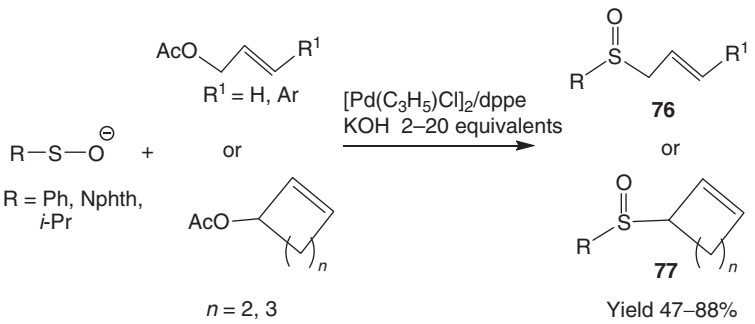
Scheme 52



Scheme 53



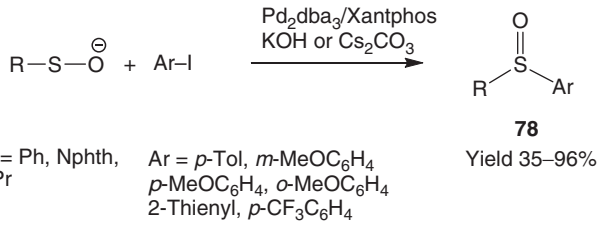
Scheme 54



Scheme 55

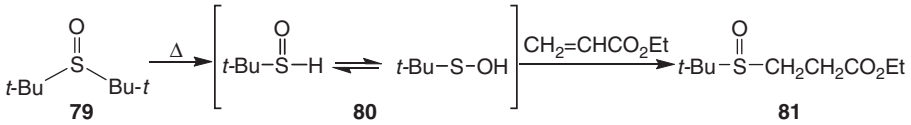
6.04.3.1.2 Addition of sulfenic acids to alkenes, and alkynes

Properly substituted sulfoxides undergo thermal fragmentation and, after elimination of stable byproducts, yield the corresponding, generally unstable, sulfenic acids, which can exist as a mixture of two tautomeric forms. To avoid their decomposition, trapping agents such as electrophilic alkenes or alkynes are used which constitutes a convenient method of the synthesis of the corresponding saturated and α-alkenyl sulfoxides, respectively.



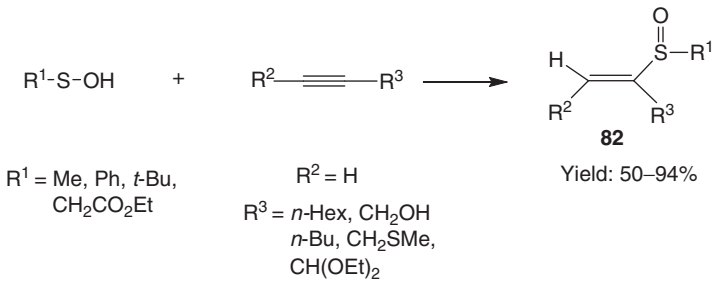
Scheme 56

Thus, thermolysis of di-*tert*-butyl sulfoxide **79** led to *tert*-butylsulfenic acid **80** which added readily to ethyl acrylate to give ethyl *β*-*tert*-butanesulfinylpropionate **81** (Scheme 57).[114] Other precursors which were used to give sulfenic acids on pyrolysis were *S*-alkyl thiosulfinates,[115] *N*-alkylidenearenesulfinamides,[116] and *β*-cyanoethyl sulfoxides.[117]

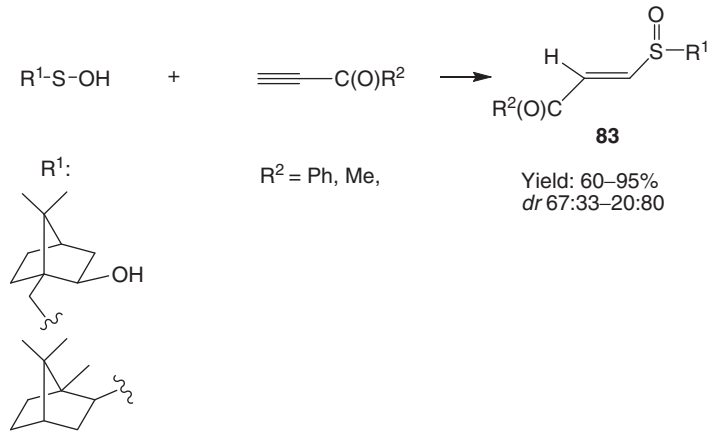


Scheme 57

Sulfenic acids add readily to alkynes according to a stereospecific *syn*-addition mechanism, to give *α*-alkenyl sulfoxides.[118] The regioselectivity was determined to depend on the alkyne nature. For example, in the case of nonactivated alkynes, the Markovnikov products **82** were obtained (Scheme 58),[119] whereas for those bearing electron-withdrawing substituents the opposite regioselectivity was observed[115]; interestingly, introduction of various chiral substituents into the sulfenic acid molecules led to different diastereomeric ratio of the final sulfoxides **83** (Scheme 59).[120]



Scheme 58

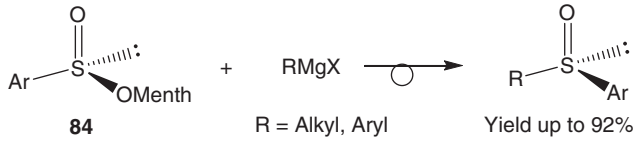


Scheme 59

6.04.3.2 Reaction of Sulfinyl Derivatives with Organometallic Reagents

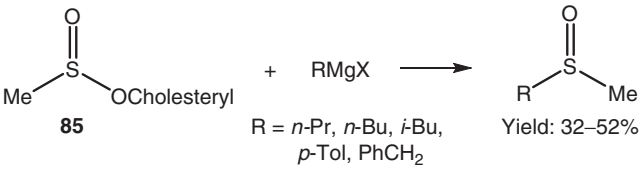
6.04.3.2.1 Sulfinic esters

Reaction of sulfinate esters with various organometallic reagents is one of the most important and frequently used methods of the synthesis of sulfoxides in which the direct formation of the C–S bond is involved.[3,4] It is particularly useful in the preparation of optically active sulfoxides.[121] The stereoselective synthesis of enantiomerically pure sulfoxides developed by Andersen in 1962, which was based on the reaction of Grignard reagents with diastereomerically pure menthyl arenesulfinates **84** (Scheme 60),[122,123] was a milestone in this area and has since then been widely used and in many ways improved. The attempts at the improvements were mainly directed toward development of new, more versatile sulfinate esters.

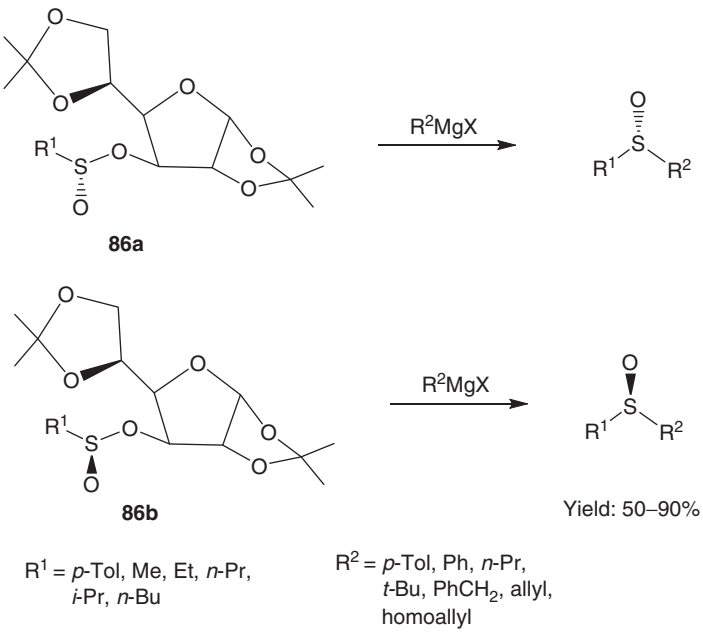


Scheme 60

Thus, the difficulties in the preparation of diastereomerically pure menthyl alkanesulfinates, which was a limitation of the original method, were resolved by using the corresponding cholesteryl esters, for example, **85**. The yields were, however, only moderate (Scheme 61).[124] Other approaches used, instead of menthyl and cholesteryl esters, chiral *trans*-2-phenylcyclohexyl sulfinates[125] or chiral sulfinates derived from easily accessible diacetone-D-glucose (DAG) **86a,b**, which allowed synthesis of a large variety of enantiomerically pure sulfoxides. (Scheme 62).[126,127]

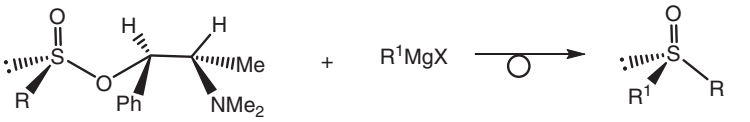


Scheme 61



Scheme 62

Diastereomeric sulfinates obtained from *N*-methylephedrine **87** were other interesting examples. Their reaction with Grignard reagents gave sulfoxides in high yields and with high enantiomeric excess (Scheme 63).[128]



87

R = Me, *t*-Bu

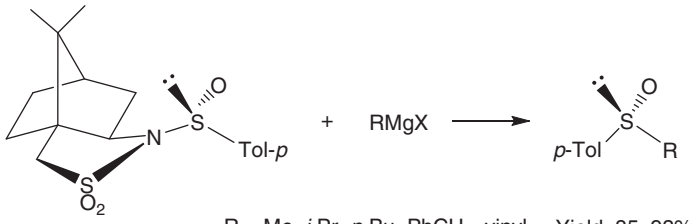
R^1 = *p*-Tol, Ph, *t*-Bu, $PhCH_2$

Yield: 58–85%
ee 96.8–100%

Scheme 63

6.04.3.2.2 Sulfinamides

Chiral sulfinamides were also used as chiral auxiliaries in nucleophilic substitutions at sulfinyl sulfur. Particularly important were those bearing the Oppolzer's sultam residue **88**, which on treatment with Grignard reagents gave almost enantiomerically pure sulfoxides in high yields (Scheme 64).[129]



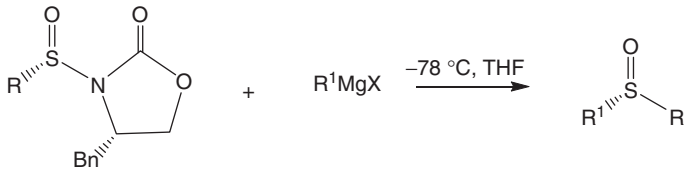
88

R = Me, *i*-Pr, *n*-Bu, $PhCH_2$, vinyl, 1-propenyl, 2-propenyl, allyl, 2-thienyl, 3-furyl, 1-pentynyl

Yield: 85–93%
ee 96 to >99%

Scheme 64

N-Sulfinyl oxazolidinones **89** were also successfully applied in the preparation of highly enantiomerically enriched or pure dialkyl and alkyl–aryl sulfoxides (Scheme 65).[130]



89

R = Me, *t*-Bu, *p*-Tol

R′ = Me, Et, *n*-Bu, *t*-Bu, octyl Ph, $PhCH_2$,

Yield: 78–92%
ee 90–100%

Scheme 65

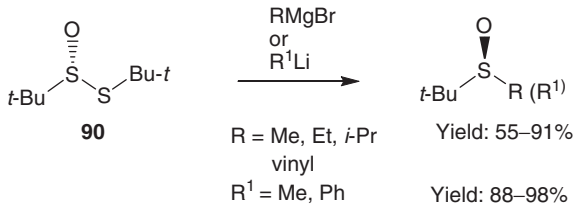
6.04.3.2.3 Thiosulfinates

Enantiopure *S*-*tert*-butyl *tert*-butanesulfinate ester **90**, obtained by asymmetric oxidation of the corresponding disulfide, was used as a chiral auxiliary. Its reaction with Grignard or organolithium reagents led to sulfoxides with inversion of configuration and without racemization (Scheme 66).[131]

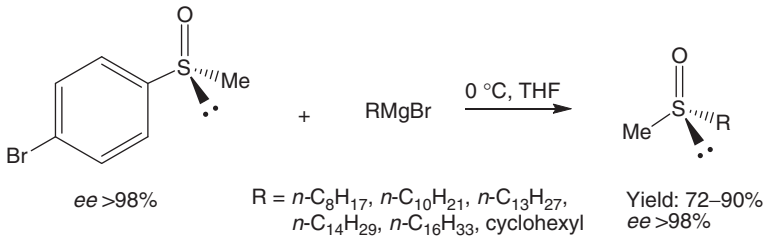
6.04.3.2.4 Sulfoxides

This approach involves a carbon for carbon substitution at the sulfinyl sulfur atom in sulfoxides.[132] Alkyllithium, alkylsodium, and Grignard reagents were found to be capable of displacing a carbanionic leaving group from a chiral sulfoxide to produce the unsymmetrical enantiopure dialkyl sulfoxide. Thus, *p*-bromophenyl methyl sulfoxide on treatment with alkyl Grignard reagents yielded alkyl methyl sulfoxides in good isolated yield (72–90%). The reaction was stereospecific and proceeded with full inversion of configuration at sulfur (Scheme 67).[133]

When diethyl sulfinylmethylphosphonates **91** were subjected to the reaction with various Grignard reagents, the measured enantiomeric excesses of the resulting sulfoxides were high (91−>98% *ee*). The yields, which were originally moderate because of

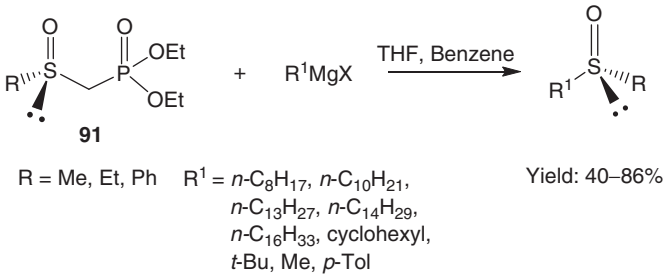


Scheme 66



Scheme 67

the competing metalation of the starting material by the organometallic reagent, were finally improved by methylation of the metalated species (Scheme 68).[134]



Scheme 68

6.04.3.3 Reaction of Sulfurous Acid Derivatives with Organometallic Reagents

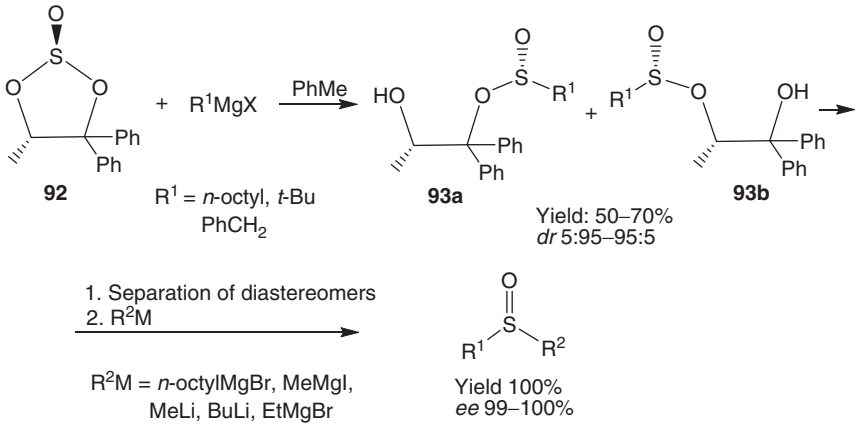
6.04.3.3.1 Sulfites

Reaction of dialkyl or diaryl sulfites with arylmagnesium bromide has been known for many years to lead to the corresponding symmetric diaryl sulfoxides.[135] Recently, the reaction of diastereomeric cyclic sulfites **92**, obtained from chiral 1,1-diphenylpropane-1,2-diol, was used in the preparation of enantiomerically enriched sulfoxides. The procedure consisted of two subsequent substitution reactions using different organometallic reagents, mainly organomagnesium halides. The first reaction led to an open-chain β-hydroxy sulfinate **93**, usually formed as a mixture of two regioisomers **93a** and **93b** which had to be separated, the second – to the final asymmetric sulfoxide. The usefulness of this method depends on the size of the organometallic reagent applied in the first step, which has a decisive impact on the diastereomer ratio of the regioisomers formed. Hence, it is particularly suitable for the synthesis of *tert*-butyl sulfoxides (Scheme 69).[136,137]

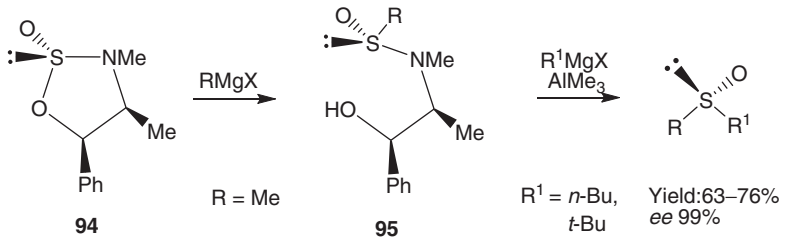
6.04.3.3.2 Amidosulfites

The use of chiral cyclic amidosulfites, synthesized from thionyl chloride and appropriate 2-amino alcohols, is advantageous with respect to cyclic sulfites presented above because of the presence of two different leaving groups at the sulfinyl moiety which can be replaced subsequently by organometallic reagents.

Various enantiomeric amino alcohols were applied in the synthesis of amidosulfites. The first one was based on ephedrine as a chiral source.[138,139] In this case the reaction of the amidosulfite **94** with Grignard reagents led to the formation of sulfinamide **95**, thus the S–O bond was broken. Owing to a lower reactivity of the S–N bond it was necessary to add trimethylaluminum before addition of the next organometallic reagent to obtain sulfoxides (Scheme 70).

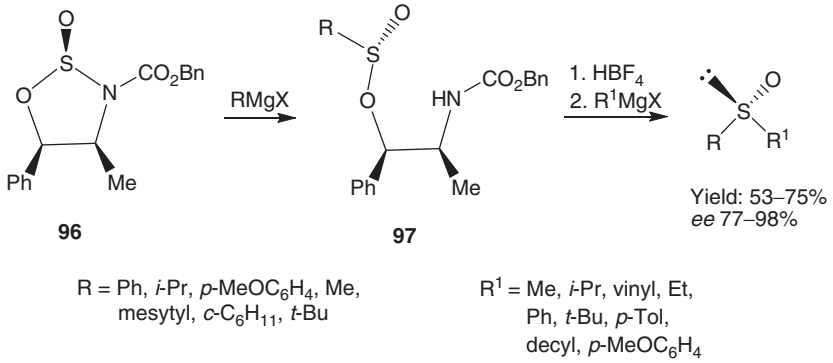


Scheme 69



Scheme 70

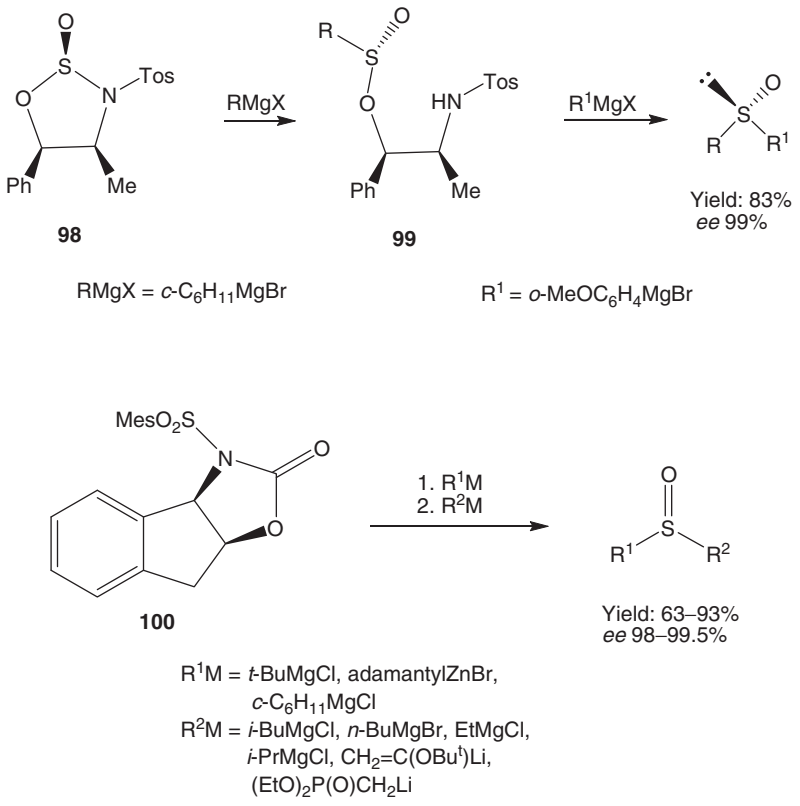
Later on, some structural modifications were made which rested on introduction of electron-withdrawing substituents bonded to nitrogen. The reason was to increase the ability of the amino moiety as a leaving group and, in this way, to reverse the reactivity. Thus, the amidosulfite **96** bearing *N*-benzyloxycarbonyl group proved to react as expected, to produce sulfinate **97** after the treatment with the first organometallic reagent. Its reaction with the next organometallic reagent proceeded smoothly to give the desired sulfoxides in reasonable yields and high enantiomeric excess. On this basis, a one-pot procedure was developed. Tetrafluoroboric acid was added after the first stage to avoid O–*N*-sulfinyl group migration (Scheme 71).[140]



Scheme 71

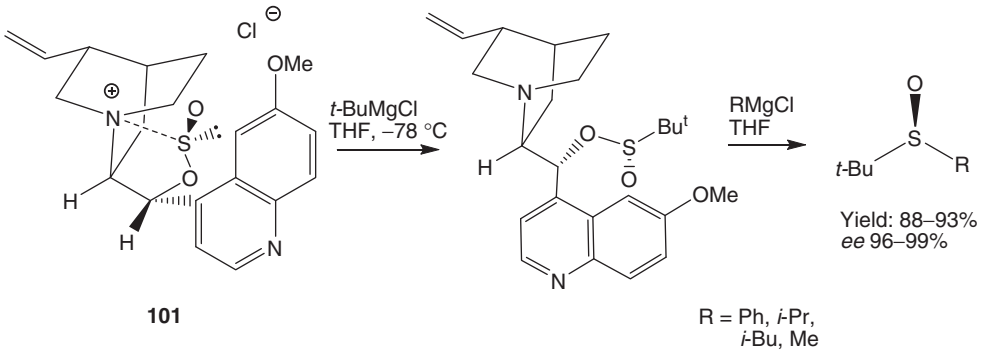
The *N*-tosyl analog **98** behaved similarly (Scheme 72) and so did the aminoindanol derivative **100** (Scheme 72). In both cases a one-pot procedure was also developed which allowed the synthesis of unique chiral sulfoxides in excellent yields and with high enantiomeric excess.[141,142]

The most recent approach was based on the use of cinchona alkaloids as the source of chirality. The ability of the nitrogen part in **101** to serve as a good leaving group was enhanced by the formation of a pseudo-five-membered oxathiazolidine ring



Scheme 72

containing a noncovalent S–N bond. In this way, the corresponding sulfoxides were obtained in high yields and with high enantiomeric excess (Scheme 73).[143]

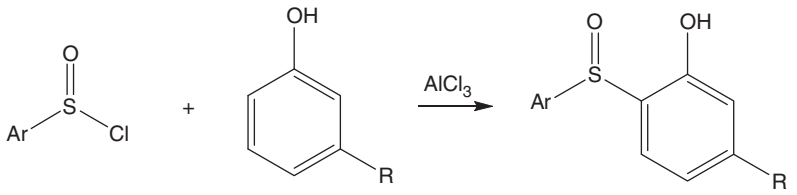


Scheme 73

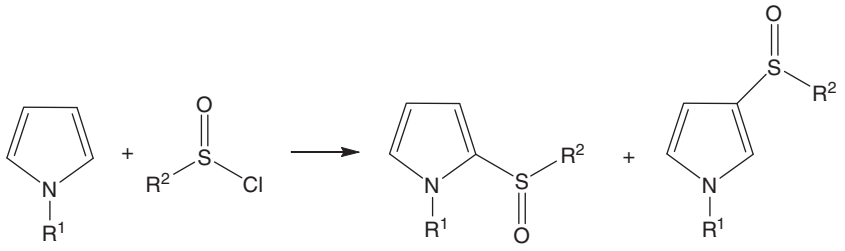
6.04.3.4 Reaction of Sulfinyl Chlorides with Aromatic Derivatives and Alkenes

Sulfinyl chlorides react with arenes in the presence of aluminum trichloride according to a Friedel–Crafts mechanism. It was found that sulfinyl chlorides are very weak electrophiles giving reactions of high selectivity with the aromatic substrates. In all cases the *para* isomer prevailed, however, no yields of the sulfoxides were given.[144] Hydroxy-substituted diaryl sulfoxides were also prepared in fairly good yields by the reaction of arenesulfinyl chlorides with 3-substituted phenols (Scheme 74).[145]

Reaction of pyrrole and *N*-methylpyrrole with arene and alkanesulfinyl chlorides gave the corresponding 2-sulfinylpyrroles **102**, when hydrogen chloride was excluded and 3-sulfinylpyrroles **103** as a result of a rearrangement caused by the presence of hydrogen chloride (Scheme 75).[146]



Scheme 74



102 **103**

R^1 = H, Me R^2 = Ph, *p*-Tol, *n*-Bu, $PhCH_2$ Yield: 35–91% Yield: 41–71%

Scheme 75

6.04.4 Synthesis of Sulfones

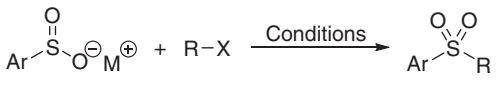
6.04.4.1 Direct C–S Bond Formation

6.04.4.1.1 Direct substitution by sulfinic acid anion

Direct substitution in a wide variety of electrophiles with the use of sulfinic acid salts **104** and various reaction conditions has been extensively investigated for relatively long time and still is found to be an attractive synthetic method Therefore, it can be considered as a one of the most popular and important methods of the synthesis of sulfones.

6.04.4.1.2 Alkyl halides

Alkyl halides **105** have been successfully and probably most often used as electrophile precursors in this type of reaction. *S*-Alkylation is a general rule in the nucleophilic substitution by sulfinic acid anions in halides bearing halogen atom bonded to an sp^3 carbon atom. Hence, these reactions give sulfones **106**. The results are presented in Scheme 76 and in Table 5. On the contrary, the use of hard alkylating agents (e.g., dimethyl sulfate, Meerwein reagent, diazomethane, etc.) leads to *O*-alkylation.



104 **105** **106**

Scheme 76

First attempts to synthesize sulfones by this method comprised the use of alkali metal or silver salts **104** (M = Li, Na, K, or Ag) in alcohols, polyglycols, THF, or DMF. However, the reactions were rather slow and usually gave moderate yields of sulfones because of side reactions, for example, *O*-alkylation.[147,148] The employment of tetrabutylammonium salt **104** (Ar = *p*-Tol, M = *n*-Bu_4N) slightly improved the process (Scheme 76, Table 5, No. 1–8).[147,149] Nevertheless, the preparation of tetrabutylammonium *p*-toluenesulfinate from sodium *p*-toluenesulfinate by the treatment with tetrabutylammonium bromide was not convenient. It required twofold excess of the sodium salt, and the product obtained was only 50% pure (starting tetrabutylammonium bromide constituted *c.* 50% of the crude product).

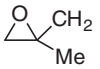
For this reason Savoia and coworkers decided to apply an anion exchange resin – Amberlyst A-26 – instead of tetrabutylammonium bromide, which resulted in the formation of pure ammonium salt **107**. When it was treated with selected alkyl halides (in the ratio of 1.3–1 equivalents) in refluxing benzene or toluene, the expected sulfones were obtained in high yields

Table 5 Reaction of sulfinic acid salts with alkyl halides (**Scheme 76**)

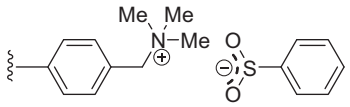
No	*Ar*	*M*	*R*	*X*	*Conditions*	*Yield (%)*	*References*
1	*p*-Tol	*n*-Bu_4N	Me	I	THF, 20 °C, 3 h	93	1,147,149
2	*p*-Tol	*n*-Bu_4N	*p*-$ClC_6H_4CH_2$	Br	THF, 20 °C, 2 h	93	1,147,149
3	*p*-Tol	*n*-Bu_4N	Allyl	Br	THF, 20 °C, 2.5 h	80	1,147,149
4	*p*-Tol	*n*-Bu_4N	$NCCH_2$	Cl	THF, 30 °C, 3 h	85	1,147,149
5	*p*-Tol	*n*-Bu_4N	EtO_2CCH_2	Br	THF, 20 °C, 2 h	80	1,147,149
6	*p*-Tol	*n*-Bu_4N	$BzCH_2$	Br	THF, 20 °C, 2 h	81	1,147,149
7	*p*-Tol	*n*-Bu_4N	$PhCH=CHCOCH_2$	Cl	THF, 20 °C, 2 h	85	1,147,149
8	*p*-Tol	*n*-Bu_4N	$BrCH_2$	Br	THF, 20 °C, 4 h	89	1,147,149
9	Ph	Amberlyst A-26	Me	I	Benzene, reflux, 3 h	95	1,2,4,150
10	Ph	Amberlyst A-26	*n*-Pr	I	Benzene, reflux, 3 h	94	1,2,150
11	Ph	Amberlyst A-26	*n*-C_6H_{13}	Br	Benzene, reflux, 3 h	92	1,2,150
12	Ph	Amberlyst A-26	*n*-C_8H_{17}	Br	Benzene, reflux, 3 h	92	1,2,150
13	Ph	Amberlyst A-26	*n*-$C_6H_{13}CH(Me)$	Br	Toluene, reflux, 3 h	60	1,2,150
14	Ph	Amberlyst A-26	Bn	Cl	Benzene, reflux, 2 h	93	1,2,150
15	Ph	Amberlyst A-26	$Me_2C=CHCH_2$	Br	Benzene, reflux, 1.5 h	95	1,2,150
16	Ph	Amberlyst A-26	(*E*)-$MeO_2CC(Me)=CHCH_2$	Br	Benzene, reflux, 1.5 h	93	1,2,150
17	Ph	Amberlyst A-26	EtO_2CCH_2	Cl	Benzene, reflux, 2 h	91	1,2,150
18	Ph	Amberlyst A-26	$NCCH_2$	Cl	Benzene, reflux, 2 h	95	1,2,150
19	Ph	Na	*o*-$TolCH_2$	Br	DME, 20 °C, 24 h, 2 mol% of *n*-Bu_4NBr	97	1,2,149,151
20	Ph	Na	2-MeNaphthyl-3-CH_2	Br	DME, 20 °C, 5 h, 2 mol% of *n*-Bu_4NBr	97	1,2,149,151
21	*p*-Tol	Na	*o*-NCBn	Br	DME, 20 °C, 24 h, 2 mol% of *n*-Bu_4NBr	96	1,2,149,151
22	*p*-Tol	Na	Bn	Br, Cl	DME, 85 °C, 0.5 h, 5 mol% of *n*-Bu_4NBr	98	1,2,149,151
23	*p*-Tol	Na	Allyl	Br	DME, 85 °C, 0.5 h, 5 mol% of *n*-Bu_4NBr	90	1,2,149,151
24	*p*-Tol	Na	$BzCH_2$	Cl	DME, 85 °C, 0.5 h, 5 mol% of *n*-Bu_4NBr	96	1,2,149,151
25	*p*-Tol	Na	EtO_2CCH_2	Cl	DME, 85 °C, 0.5 h, 5 mol% of *n*-Bu_4NBr	90	1,2,149,151
26	*p*-Tol	Na	*n*-Bu	Br	DME, 85 °C, 4 h, 5 mol% of *n*-Bu_4NBr	94	1,2,149,151
27	*p*-Tol	Na	*i*-Pr	Br	DME, 85 °C, 48 h, 10 mol% of *n*-Bu_4NBr	68	1,2,149,151
28	*p*-Tol	Na	*n*-C_7H_{15}	Br	Water/benzene/acetone (4:3:3, v/v/v), 80–85 °C, 8 h, 6.7 mol% of *n*-Bu_4NBr or *n*-Bu_4NI	85	1,2,152
29	*p*-Tol	Na	Et	I	Water/benzene/acetone (4:3:3, v/v/v), 80–85 °C, 6 h, 6.7 mol% of *n*-Bu_4NBr or *n*-Bu_4NI	89	1,2,152
30	*p*-Tol	Na	*i*-Pr	I	Water/benzene/acetone (4:3:3, v/v/v), 80–85 °C, 12 h, 6.7 mol% of *n*-Bu_4NBr or *n*-Bu_4NI	65	1,2,152
31	*p*-Tol	Na	Bn	Cl	Water/benzene/acetone (4:3:3, v/v/v), 80–85 °C, 8 h, 6.7 mol% of *n*-Bu_4NBr or *n*-Bu_4NI	93	1,2,152
32	*p*-Tol	Na	$H_2C=C(Me)CH_2$	Cl	Water/benzene/acetone (4:3:3, v/v/v), 80–85 °C, 12 h, 6.7 mol% of *n*-Bu_4NBr or *n*-Bu_4NI	71	1,2,152

(*Continued*)

Table 5 Continued

No	Ar	M	R	X	Conditions	Yield (%)	References
33	*p*-Tol	Na	$Me_2C{=}CHCH_2$	Br	Water/benzene/acetone (4:3:3, v/v/v), 80–85 °C, 12 h, 6.7 mol% of *n*-Bu_4NBr or *n*-Bu_4NI	87	1,2,152
34	*p*-Tol	Na	$AcCH_2$	Cl	Water/benzene/acetone (4:3:3, v/v/v), 80–85 °C, 6 h, 6.7 mol% of *n*-Bu_4NBr or *n*-Bu_4NI	94	1,2,152
35	*p*-Tol	Na	$MeCHCO_2Et$	Br	Water/benzene/acetone (4:3:3, v/v/v), 80–85 °C, 8 h, 6.7 mol% of *n*-Bu_4NBr or *n*-Bu_4NI	79	1,2,152
36	*p*-Tol	Na	ICH_2	I	Water/benzene/acetone (4:3:3, v/v/v), 80–85 °C, 24 h, 6.7 mol% of *n*-Bu_4NBr or *n*-Bu_4NI	55	1,2,152
37	*p*-Tol	Na		Cl	Water/benzene/acetone (4:3:3, v/v/v), 80–85 °C, 12 h, 6.7 mol% of *n*-Bu_4NBr or *n*-Bu_4NI	95	1,2,152

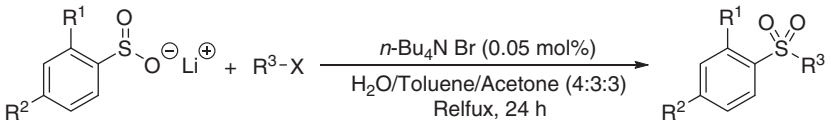
91–95% (Table 5, No. 9–12 and 14–18) in the case of primary halides, and only in moderate yield (60%) in the case of secondary halides (Scheme 76, Table 5, No. 13).[1,2,150]



107

To improve the synthetic method, the solid–liquid PTC was applied. It allowed avoidance of the initial preparation of tetrabutylammonium sulfinate or use the equimolar amount of tetrabutylammonium bromide without loss of the yield. The suspension of 1.05 equivalents of corresponding sodium sulfinates **104** (Ar=Ph, *p*-Tol, M=Na) in 1,2-dimethoxyethane (DME) was treated with 1 equivalent of various alkyl halides in the presence of a catalytic amount of tetrabutylammonium bromide (2–10 mol%) (Scheme 76, Table 5, No. 19–27).[1,2,149,151]

The liquid–liquid PTC can be considered as a complementary method to that mentioned above. The process included treatment of 1.5 equivalents of sodium sulfinate **104** (Ar=*p*-Tol, M=Na) with 1 equivalent of selected alkyl halides in the presence of a catalytic amount of tetrabutylammonium bromide or iodide (6.7 mol%) in a two-phase system – water/benzene/acetone (Scheme 76, Table 5, No. 28–37).[1,2,152] No reaction was observed in the absence of a catalyst. The influence of the metal cation was also studied and showed that the yields decreased in the order of sodium, potassium, and lithium.[152] Nevertheless, Beslin and coworkers utilized lithium sulfinates in the above method to synthesize in good to high yield a series of aryl–alkyl sulfones using several alkyl halides in the presence of the same catalyst – tetrabutylammonium bromide – in water/toluene/acetone solvent system (Scheme 77, Table 6). Syntheses occurred without any side reactions, except for EtI, where <10% of *O*-alkylation products were observed.[153]



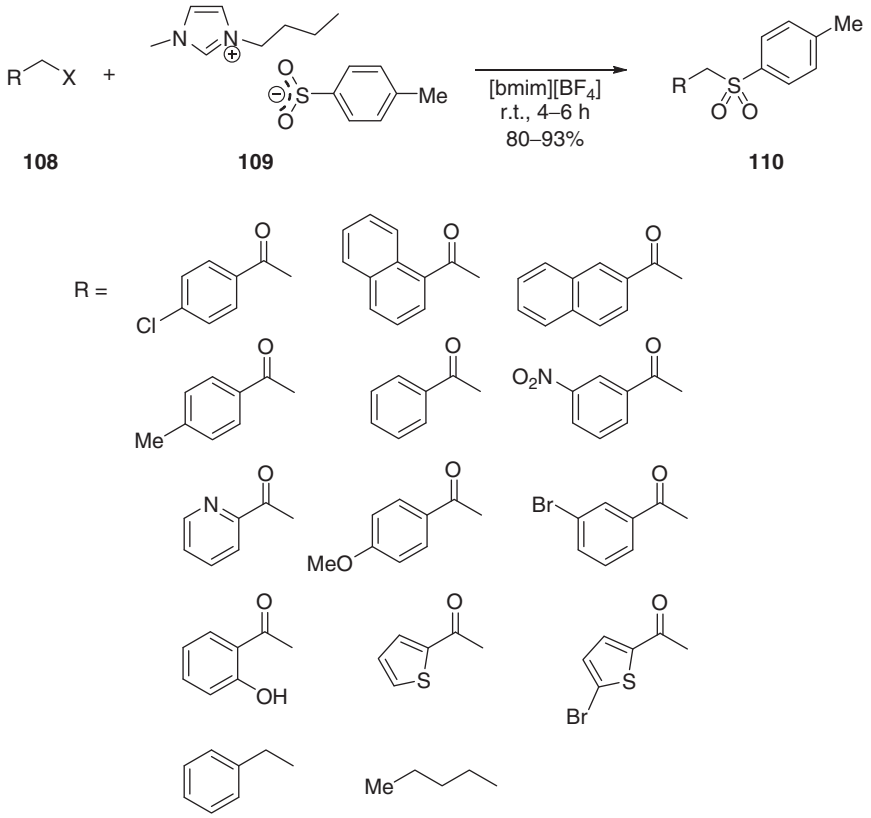
Scheme 77

Recently, another modification of the method was developed. It included the treatment of various alkyl and *β*-ketoalkyl halides **108** with previously prepared 1-butyl-3-methylimidazolium *p*-toluenesulfinate [bmim][*p*-$TolSO_2$] **109** in ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF_4], at room temperature. Expected sulfones **110** were obtained in 80–93% yield (Scheme 78).[154] The use of the ionic liquid as a reaction medium made the process more environmentally friendly. Moreover, it gave best results among tested solvents (THF, DMSO, EtOH, MeOH, [bmim][Br], [bmim][BF4]). This may be explained in terms of the noncoordinating nature of this ionic liquid resulting in the enhancement of nucleophilicity of sulfinic acid anion.

Table 6 Synthesis of aryl–alkyl sulfones from lithium sulfinates (**Scheme 77**)[153]

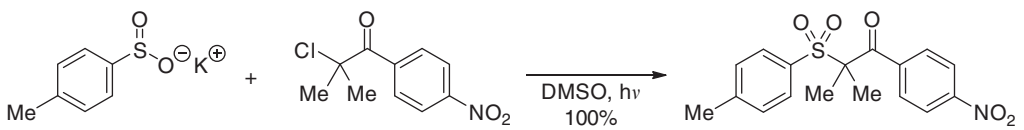
No	*R^1*	*R^2*	*R^3–X*	*Yield (%)*
1	H	H	MeI	75
2	H	H	EtI	75
3	H	H	AllylBr	91
4	H	H	BnBr	85
5	H	H	$Me_2C{=}CCH_2Br$	79
6	CO_2Me	H	MeI	77
7	Me	H	EtI	74
8	OMe	H	EtI	80
9	H	F	EtI	76
10	H	SEt	MeI	71

A comparative analysis also showed that [bmim] as a counterion made *p*-toluenesulfinate anion most reactive at presented reaction conditions.[154]



Scheme 78

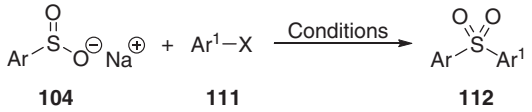
It was established that the processes mentioned above occur according to the S_N2 mechanism. However, in the case of alkyl halides bearing additional electron-withdrawing substituents a radical substitution pathway has been detected (equation 4).[1,2]



(4)

6.04.4.1.3 Aryl halides and arylboronic acids

Aryl halides and arylboronic acids **111**, except for the highly activated ones, do not react with sulfinates **104** at the conditions presented in previous subchapter. They require a use of transition-metal complex catalysts to furnish diaryl sulfones **112** in high yield (Scheme 79, Table 7).[149]



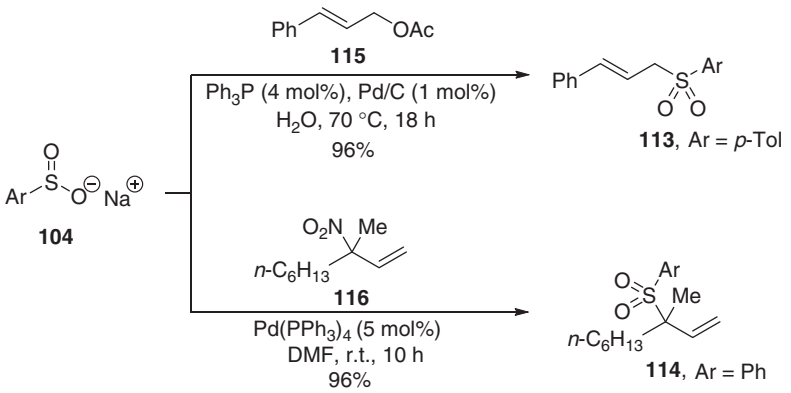
Scheme 79

Table 7 Reaction of aryl halides or arylboronic acids with sodium arenesulfinates (Scheme 79)

No	*Ar*	*Ar*^{1}	*X*	*Conditions*	*Yield (%)*
1	*p*-Tol	Ph	Br	$Pd_2(dba)_3$ (5 mol%), Xantphos, Cs_2CO_3, TBACl, toluene, 80 °C, 1–22 h	91
2	*p*-Tol	Ph	I	$Pd_2(dba)_3$ (5 mol%), Xantphos, Cs_2CO_3, TBACl, toluene, 80 °C, 1–22 h	90
3	Ph	*p*-OHC_6H_4	I	CuI (5 mol%), L-proline sodium salt (20 mol%), DMSO, 90 °C, 36 h	90
4	Ph	*p*-ClC_6H_4	$B(OH)_2$	$Cu(OAc)_2$, K_2CO_3, 4 Å molecular sieves, DMSO, r.t.	60

6.04.4.1.4 Catalytic substitution on allylic, vinylic, or sp carbon atom

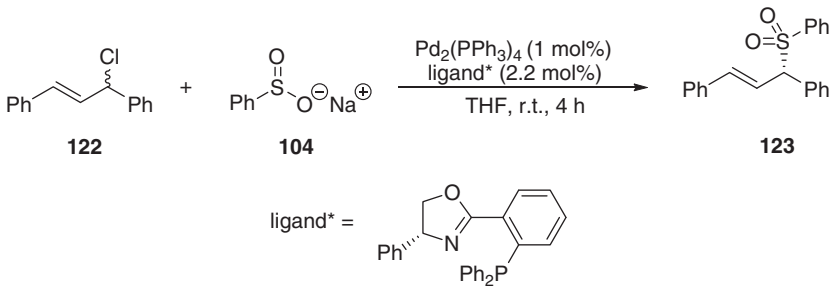
Allyl sulfones **113** and **114** can be obtained by the treatment of sodium arenesulfinates **104** (Ar=Ph, *p*-Tol) with allylic compounds **115** and **116**, in the presence of palladium catalyst in polar solvents (Scheme 80).[149]



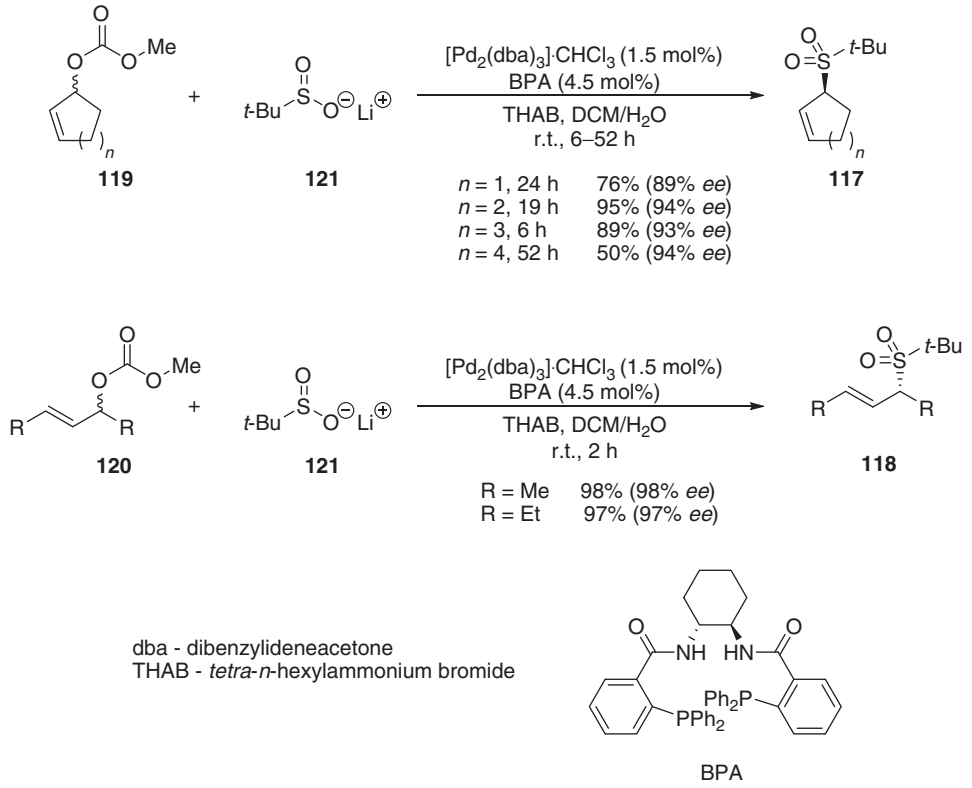
Scheme 80

Optically active sulfones **117** and **118** were conveniently prepared in high yield and enantiomeric excess from racemic cyclic **119** and more reactive acyclic **120** allyl carbonates, respectively, and lithium *tert*-butanesulfinate **121** in the presence of palladium chiral catalyst at PTC conditions (Scheme 81).[155] In the case of cyclooctenyl carbonate **119** ($n=4$), the selectivity of kinetic resolution was so high that the synthesis of the corresponding sulfone **117** ($n=4$) was achieved only in 50% yield together with enantiomerically pure corresponding carbonate. For other substrates asymmetric synthesis was observed.[155]

A similar method was used for the asymmetric conversion of racemic chloride **122** into the corresponding sulfone **123** in high yield and enantiomeric excess (equation 5).[149]

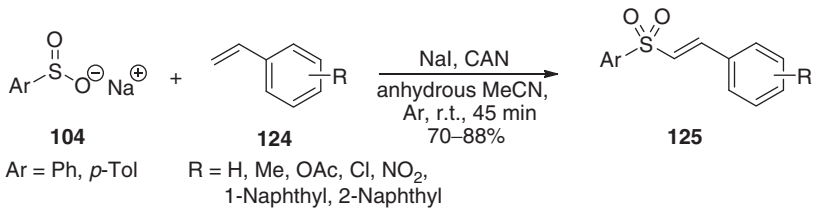


(5)



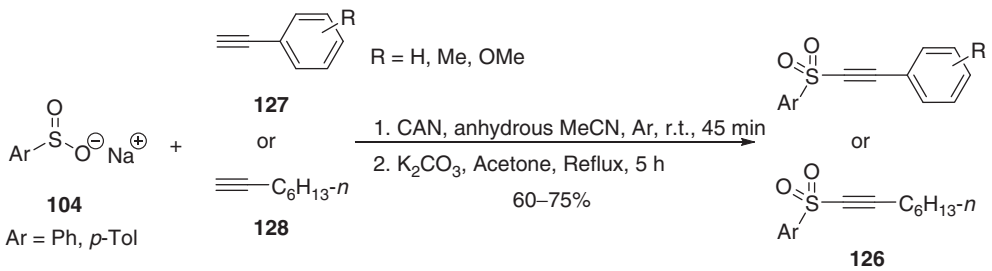
Scheme 81

The formal substitution on sp^2 vinylic carbon atom of selected styrene derivatives **124** by the treatment with sodium sulfinates **104** (Ar=Ph, *p*-Tol) in the presence of NaI and cerium(IV) ammonium nitrate (CAN) was also presented. The one-pot process furnished the corresponding vinyl sulfones **125** in good yield (Scheme 82). It was established that reaction proceeded according to a radical mechanism.[149,156]



Scheme 82

Analogously, acetylenic sulfones **126** were synthesized from **104** and phenylacetylene derivatives **127** or 1-octyne **128** (Scheme 83). In these cases an additional step of refluxing of the crude product in K_2CO_3 acetonic solution was performed.[156]

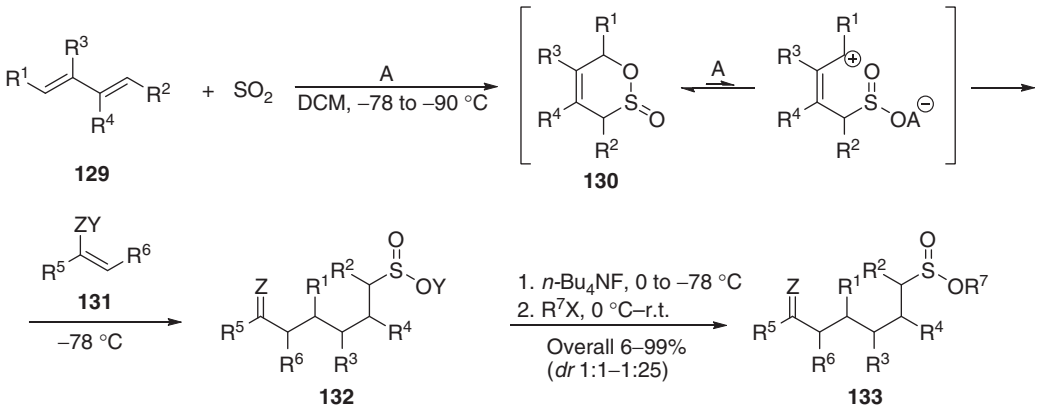


Scheme 83

6.04.4.2 Direct Substitution by Sulfinic Acid Anion Generated *In Situ* from Sulfur Dioxide

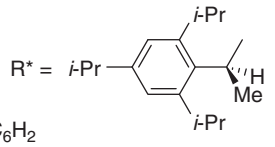
Owing to its electrophilic character, SO_2 is well known to react with organometallic compounds to give metal sulfinates, which undergo further reaction with appropriate electrophiles to furnish sulfones.[1,2]

Recently, Vogel and coworkers developed the one-pot synthesis of chiral sulfones. The reversible hetero Diels–Alder addition of SO_2 to 1,3-dienes **129** in the presence of suitable Lewis acid (LA) or proton acid resulted in formation of unstable sultine **130**. Its treatment with appropriate sila-ene **131** also gave unstable silyl sulfinates **132**, which were treated with TBAF and subsequently with various electrophiles to furnish expected sulfones **133** (Scheme 84).[157,158]



A = $Yb(OTf)_3$, $Sc(OTf)_3$, $Sn(OTf)_3$, Me_3SiOTf, (*t*-Bu)Me_2SiOTf, Tf_2NH, Tf_2NTMS

R^1 = OMe, OBn, OTMS, OTBDMS, OCH_2CH_2TMS, OR*
R^2 = H, Me
R^3 = H, Me
R^4 = H, OAc, OBz
R^5 = Me, Et, *t*-Bu, CH_2TMS, $CH_2Si(n\text{-}Bu)_3$, Ph, *p*-$MeOC_6H_4$, 2,4,6-$(MeO)_3C_6H_2$
R^6 = H, Me
R^7 = Me, *i*-Bu, Allyl, 2-MeAllyl, *m*-ClBn, EtO_2CCH_2
X = Br, I, OAc
Y = TMS, *n*-Bu_3Si
Z = O,CH_2

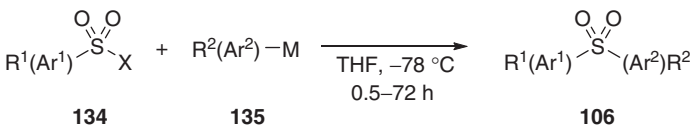


Scheme 84

6.04.4.3 Reactions with Organometallic Reagents

6.04.4.3.1 Sulfonyl halides

Reactions of alkyl or aryl sulfonyl halides **134** with great variety of organometallic *C*-nucleophiles **135** leading to the formation of sulfones **106** has been well documented (Scheme 85, Table 8).[1,2,159] As can be noticed, aryl Grignard reagents gave better yields than their lithium analogs (Table 8, compare No. 7 and 8, 15, and 19). On the contrary, alkyl reagents furnished opposite results (Table 8, compare No. 9 and 17, 12, and 18). Moreover, the bulkiness of alkyllithium compounds did not influence the yield (Table 8, No. 21–24), but for analogous Grignard reagents (Table 8, No. 27, 28, and 21) and alkylcopper (Table 8, No. 33–35), and alkylcopperlithium (Table 8, No. 25–27) compounds this dependence was significant. The lowest yield was observed for triphenylmethyllithium, vinylmagnesium bromide, and ethynylmagnesium bromide (Table 8, No. 16, 23, and 20, respectively). This result can be explained by good stabilization of negative charge on the nucleophilic carbon atom. The influence of the temperature was also shown (Table 8, No. 18).[159]



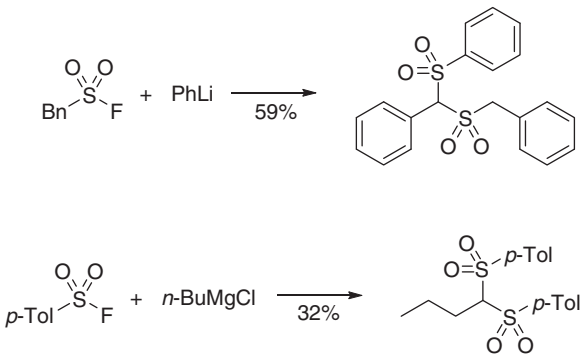
Scheme 85

Table 8 Reaction of sulfonyl halides with organometallic reagents (**Scheme 85**)

No	$R^1(Ar^1)$	*X*	$R^2(Ar^2)$	*M*	*Yield (%)*	*References*
1	Me	Cl	$(MeO_2C)_2CH$	Na	58	1,2,159
2	CF_3	F	$(EtO_2C)_2CH$	Na	68	1,2,159
3	CF_3	F	$MeSO_2CH_2$	MgBr	70	1,2,159
4	*n*-Bu	F	$(EtO_2C)_2CH$	Na	80	1,2,159
5	Bn	F	Ph	MgBr	88	1,2,159
6	*p*-BrC_6H_4	F	Ph	MgBr	91	1,2,159
7	Ph	F	Ph	Li	67	1,2,159
8	Ph	F	Ph	MgBr	95	1,2,159
9	*p*-Tol	F	Bz_2CH	Na	26	1,2,159
10	*p*-Tol	F	Et	MgBr	83	1,2,159
11	*p*-Tol	F	Me	Li	94	1,2,159
12	*p*-Tol	F	*n*-Bu	Li	92	1,2,159
13	*p*-Tol	F	*s*-Bu	Li	91	1,2,159
14	*p*-Tol	F	*t*-Bu	Li	94	1,2,159
15	*p*-Tol	F	Ph	Li	76	1,2,159
16	*p*-Tol	F	Ph_3C	Li	0	1,2,159
17	*p*-Tol	F	Me	MgCl	87	1,2,159
18	*p*-Tol	F	*n*-Bu	MgCl	0[a], 59[b], 26[c]	1,2,159
19	*p*-Tol	F	Ph	MgBr	95	1,2,159
20	*p*-Tol	F	HC≡C	MgBr	12	1,2,159
21	*p*-Tol	F	*i*-Bu	MgCl	13	1,2,159
22	*p*-Tol	F	Allyl	MgCl	99	1,2,159
23	*p*-Tol	F	Vinyl	MgBr	0	1,2,159
24	*p*-Tol	F	Me_2	CuLi	71	1,2,159
25	*p*-Tol	F	*n*-Bu_2	CuLi	99	1,2,159
26	*p*-Tol	F	*s*-Bu_2	CuLi	83	1,2,159
27	*p*-Tol	F	*t*-Bu_2	CuLi	69	1,2,159
28	*p*-Tol	F	Ph_2	CuLi	84	1,2,159
29	*p*-Tol	F	*n*-Bu_2	CuMgCl	8	1,2,159
30	*p*-Tol	F	Ph_2	CuMgCl	79	1,2,159
31	*p*-Tol	F	$Allyl_2$	CuMgCl	86	1,2,159
32	*p*-Tol	F	Me	Cu	86	1,2,159
33	*p*-Tol	F	*n*-Bu	Cu	88	1,2,159
34	*p*-Tol	F	*s*-Bu	Cu	34	1,2,159
35	*p*-Tol	F	*t*-Bu	Cu	17	1,2,159
36	*p*-Tol	F	Ph	Cu	94	1,2,159
37	*p*-Tol	F	Allyl	Cu	20	1,2,159

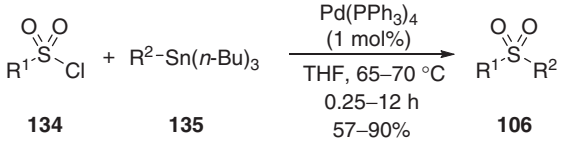
[a]At – 78 °C.
[b]At 0 °C.
[c]At r.t.

It was proven that in some cases considerable amounts of bissulfones are produced (**Scheme 86**).[1,2,159] These results were because of basic properties of the nucleophiles used which caused deprotonation at the α carbon atom of the initially formed monosulfone. The new carbanion reacted further with another molecule of sulfonyl halide.[159]



Scheme 86

Another route, which was complementary to the one presented in Section 6.04.4.3.1, included treatment of sulfonyl chlorides **134** (X=Cl) with vinyl and allylstannanes **135** [M=Sn(*n*-Bu)$_3$] in the presence of a catalytic amount (1 mol%) of Pd(PPh$_3$)$_4$ and led to sulfones **106** in good yield (Scheme 87).[160] The reaction for vinylstannanes always gave sulfone with (*E*) configuration of the double bond, irrespective of a configuration of the stannane used.[160] Moreover, this method allowed to avoid the use of LA and highly toxic sulfonyl fluorides.

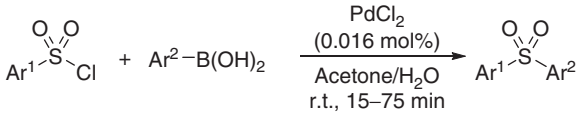


134 **135** **106**

R^1 = Me, *p*-MeC$_6$H$_4$, *p*-MeOC$_6$H$_4$, *p*-ClC$_6$H$_4$, *m*-HO$_2$CC$_6$H$_4$, 2-Naphthyl
R^2 = (*E*)-PhCH=CH, (*E*)-*n*-C$_6$H$_{13}$CH=CH, (*E*)-THPOCH=CH, (*E*/*Z*)-THPOCH=CH, (*E*)-EtO$_2$CCH=CH, (*Z*)-EtO$_2$CCH=CH, (*E*)-MeCH=CH,

Scheme 87

The utilization of selected arylboronic acids **136** instead of compounds **135** in the presence of PdCl$_2$ (0.016 mol%) and K$_2$CO$_3$ in acetone/water at room temperature also gave the corresponding sulfones **106** in excellent yield (Scheme 88).[149,161]



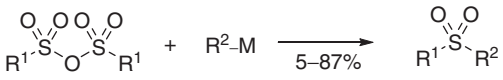
134 **136** **106**

Ar^1 = Ph, *p*-Tol
Ar^2 = Ph, *p*-Tol, *p*-MeOC$_6$H$_4$, *p*-BnOC$_6$H$_4$, *o*-MeC$_6$H$_4$, *o*-MeOC$_6$H$_4$, *o*-FC$_6$H$_4$, 2-Thienyl, 3-Pyridyl

Scheme 88

6.04.4.3.2 Sulfonic acid anhydrides and esters

The reaction of sulfonic acid anhydrides **137** with organometallic compounds **135** was convenient for the preparation of acetylenic sulfones **106** (Scheme 89), which were difficult to obtain by previous methods. However, some halogenation side reactions were observed for Grignard reagents.[1,2]



137 **136** **106**

R^1 = CF$_3$, *n*-C$_6$F$_9$
R^2 = Bn, PhC≡C
M = Li, MgCl, MgBr

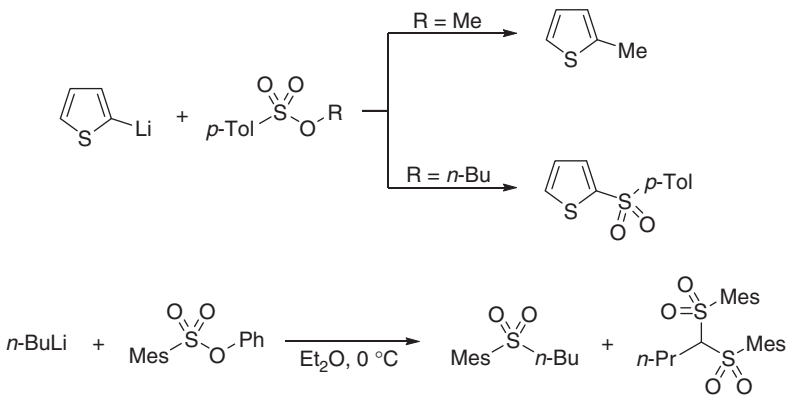
Scheme 89

The use of sulfonates instead of anhydrides eliminated this side process, although alkylation or twofold sulfonylation could occur depending on reagents used and conditions (Scheme 90).[1,2]

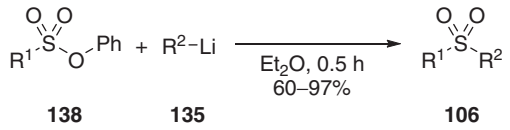
Nevertheless, some phenyl arenesulfonates **138** gave the corresponding sulfones **106** in good to high yield in the reaction with organolithium compounds **135** (Scheme 91).[149]

6.04.4.3.3 β-Sultones

β-Sultones **139** treated with selected Grignard reagents **135** followed by water furnished β-hydroxysulfones **140** in reasonable to high yield (Scheme 92).[1,2]



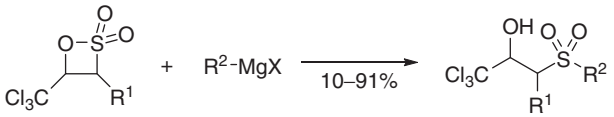
Scheme 90



138 **135** **106**

R^1 = Ph, *p*-tol, 2-naphthyl
R^2 = *n*-Bu, allyl, 2-thienyl, Ph

Scheme 91



139 **135** **140**

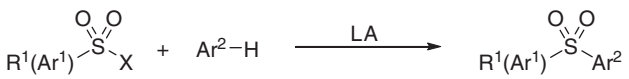
R^1 = H, Me, Cl
R^2 = Me, Et, *n*-Pr, Allyl, Bn, Ph, *p*-Tol, *p*-ClC_6H_4

Scheme 92

6.04.4.4 Sulfonylation of Arenes

6.04.4.4.1 Sulfonyl halides

Sulfonylation of arenes **141** with sulfonyl halides **134** in the presence of a stoichiometric or higher amount of LA, leading to the corresponding arenesulfones **106** in high yield (Scheme 93, Table 9), can be regarded as a modified Friedel–Crafts electrophilic substitution in aromatic systems. It is suitable for both alkene- and arenesulfonyl halides and is well documented.[1,2,149] Generally, arenesulfonyl halides gave better yields than alkene analogs. Interestingly, alkanesulfonyl fluorides are more reactive than chlorides (Table 9, No. 8 and 9).



134 **141** **106**

Scheme 93

Table 9 Sulfonylation of arenes with sulfonyl halides (**Scheme 93**)

No	$R^1(Ar^1)$	*X*	Ar^2	*LA*	*Yield (%)*
1	Ph	Cl	Ph	$AlCl_3$	90
2	Ph	Cl	Mes	$AlCl_3$	70
3	Ph	Cl	2-(*p*-Xylenyl)	$AlCl_3$	92
4	Ph	Cl	*p*-ClC_6H_4	$AlCl_3$	80
5	Ph	Cl	Ph	$SbCl_5$	89
6	Ph	F	Ph	SbF_5	92
7	CF_3	Cl	Ph	$AlCl_3$	70
8	CF_3	Cl	Mes	$AlCl_3$	5
9	CF_3	F	Mes	$AlCl_3$	70
10	*n*-$C_{16}H_{33}$	F	2-(*p*-Xylenyl)	$AlCl_3$	86

The use of stoichiometric amounts of LAs created problems with reaction regioselectivity, product purification, and significant amounts of solid waste. Therefore, efforts were made to develop more convenient, inexpensive, and environmentally friendly catalytic methods.

Replacement of LA with catalytic amount of Fe^{3+} exchanged montmorillonite in nitrobenzene at elevated temperature allowed access to the desired sulfones **106** in high yield (**Scheme 94**, **Table 10**, No. 1). The reaction was regiospecific for most cases. The method is operationally simple, relatively environmentally nonarduous, and noncorrosive.[162]



134 **141** **106**

Scheme 94

Table 10 Catalytic sulfonylation of arenes with sulfonyl halides (**Scheme 94**)

No	$R^1(Ar^1)$	Ar^2	*Conditions*	*Yield (%)*	*References*
1	Ph, *p*-Tol	Ph, *p*-Tol, 6-(*m*-Xylenyl), Mes, Naphthyl	Fe^{3+}-montmorillonite, nitrobenzene, 80–200 °C, 3–12 h	84–92	162
2	Ph, *p*-Tol, *p*-(*t*-Bu)C_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-FC_6H_4, *n*-Bu, CF_3	Tol, $MeOC_6H_4$, FC_6H_4, ClC_6H_4, BrC_6H_4, Xylenyl	$BiCl_3$ (5 mol%), 120 °C, 5–6 h, or $Bi(OTf)_3$ (1–10 mol%), 90–120 °C, 1–7 h	8–60 35–90	17,149,163
3	Ph, *p*-Tol, Me, *n*-Bu	Tol, $MeOC_6H_4$, FC_6H_4, ClC_6H_4, BrC_6H_4, *m*-Xylenyl, Mes	$In(OTf)_3$ (5–10 mol%), 120 °C, 2–24 h	66–98	149,164
4	*p*-Tol	Ph, *p*-Tol, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4,4-(*o*-Xylenyl), 6-(*m*-Xylenyl), 3-Thienyl	$NaClO_4$ (20 mol%), reflux, 4–9 h	73–88	165

The use of bismuth(III) chloride or bismuth(III) triflate also gave good results (**Scheme 94**, **Table 10**, No. 2).[149,163] Bismuth (III) triflate appeared to be a better catalyst – it furnished higher yield and regioselectivity. An isomer ratio was *c.* 1:1 (*ortho*: *para*) for $BiCl_3$, and in the case of $Bi(OTf)_3$ in general the *para* isomer was the major product for arenesulfonyl chlorides, whereas for alkenesulfonyl chlorides contributions of the *ortho* and *para* isomers were almost equal.[163]

Better results were obtained when indium(III) triflate was used as a catalyst (**Scheme 94**, **Table 10**, No. 3).[149,164] Besides excellent yield, for halobenzenes reaction was completely regiospecific and furnished only *para* isomers.[164]

The sulfonylation reaction in the presence of sodium perchlorate under neutral conditions (pH 6.9) (**Scheme 94**, **Table 10**, No. 4) resulted in slightly worse yields of sulfones **106**, but complete regioselectivity – *para* isomers were obtained as the only products.[165]

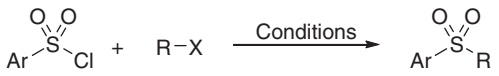
6.04.4.4.2 Sulfonic acid anhydrides

Reactions of catalytic electrophilic substitution of arenes **141** with sulfonic acid anhydrides **137** also constitute a pathway for the synthesis of sulfones **106**.[163,164,166] Processes were carried out in the presence of bismuth(III) chloride,[163] bismuth(III) triflate,[163]

indium(III) triflate,[164] and cation-exchange zeolite β[166]. Although it is an alternative for sulfonyl halides, the method characterized itself with usually poorer yields and comparable regioselectivity.

6.04.4.5 Reaction of Sulfonyl Chlorides with Alkyl Halides

Another alternative method for preparation of sulfones **106** is metal-catalyzed reaction of sulfonyl chlorides **134** with alkyl halides **105** (Scheme 95, Table 11). Zhang and coworkers presented that kind of transformation with use of zinc powder as a catalyst leading to the formation of the desired sulfones **106** in aqueous media in moderate to good yields (Scheme 95, Table 11, No. 1).[167] The reaction time in aqueous media was shorter than in THF. The method was ineffective for alkanesulfonyl chlorides.



134 **135** **106**

Scheme 95

Table 11 Metal-mediated reaction of sulfonyl chlorides with alkyl halides (Scheme 95)

No	*Ar*	*R*	*X*	*Conditions*	*Yield (%)*	*References*
1	Ph, *p*-Tol	Me, *i*-Pr, allyl, $PhCH=CHCH_2$, Bn, EtO_2CCH_2, $BzCH_2$, *p*-$BrC_6H_4COCH_2$	Br, I	Zinc dust, THF/$NH_4Cl_{(aqueous)}$ (4:1) or THF/H_2O (4:1) or THF, 2–8 h, 0 °C or r.t.	51–82	167
2	Ph, *p*-Tol	Allyl, $PhCH=CHCH_2$, Bn, EtO_2CCH_2, $BzCH_2$, *p*-$BrC_6H_4COCH_2$	Br	Indium, H_2O, 4–5 h, 0 °C	55–84	168
3	Ph, *p*-Tol	Me, allyl, EtO_2CCH_2, $PhCH=CHCH_2$, Bn, $BzCH_2$, *p*-$BrC_6H_4COCH_2$, *p*-$O_2NC_6H_4COCH_2$	Br, I	$Sm/HgCl_2$, THF, 2.5 h, 50–60 °C	51–75	169
4	Ph, *p*-Tol	Me, EtO_2CCH_2, $PhNHCOCH_2$, Bn, $BzCH_2$, $NCCH_2$	Cl, Br	$(EtO)_2P(O)TeNa$, TEBA, THF/EtOH, reflux, 2–4 h	77–94	170

The replacement of zinc with indium in water slightly improved the yield of the process (Scheme 95, Table 11, No. 2).[168] Nevertheless, no reaction occurred in the case of alkanesulfonyl chlorides even after prolongation of the reaction time.

The use of samarium/mercury(II) chloride bimetallic system in THF (Scheme 95, Table 11, No. 3) did not further improve the yield nor did it allow access to dialkyl sulfones, although it did led to selected sulfones in shorter reaction times.[169]

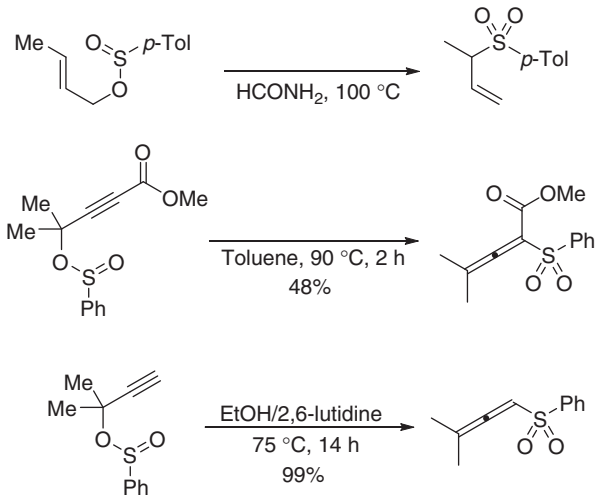
Also known is the utilization of *O*,*O*-diethyl phosphorotellurite ion as a catalyst in the presence of a catalytic amount of benzyltriethylammonium chloride in this type of reactions. It allowed access to selected sulfones **106** in high yield (Scheme 95, Table 11, No. 4).[170]

6.04.4.6 Miscellaneous Procedures

The treatment of *p*-toluenesulfonylhydrazide with various alkyl or aryl halides in the presence of sodium acetate resulted in the formation of the corresponding *p*-tolyl alkyl or *p*-tolyl aryl sulfones in 80–95% yield.[171]

Allyl and crotyl sulfinates underwent [2,3]-sigmatropic rearrangement furnishing the corresponding sulfones, quite often in high yield, at various condition (Scheme 96).[1,2,149] By this method some enantiomerically enriched sulfones could be obtained with the use of appropriate catalyst.[3]

Moreover, arylsulfonanilides can undergo 1,3- and 1,5-shift of sulfonyl group to give *ortho*- and *para*-(arylsulfonyl)anilines.[1,2]



Scheme 96

Acknowledgments

Preparation of this chapter was financially supported by the National Science Center fund awarded based on the decisions: DEC-2011/01/M/ST5/05240 (to JD) and UMO-2011/03/B/ST5/03233 (to JD).

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6.05 Synthesis of Phosphonium Ylides

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Glossary

Carbodiphosphorane A particular example of phosphorus double ylides that are considered as divalent carbon(0) derivatives; the central carbon(0) atom has two electron pairs and is additionally stabilized by two neutral phosphine ligands to attain an electron octet.

Cumulene A hydrocarbon with three or more *cumulative* (consecutive) double bonds. Unlike most alkanes and alkenes, cumulenes tend to be rigid.

Phosphacumulene ylides Molecules combining the conjugated phosphorus ylide group and a cumulene moiety.

Phosphine-mediated reactions Sequential cascade phosphine-catalyzed reactions allowing facile synthesis of a range of compounds, usually heterocyclic ones, which proceeds via the intermediate formation of ylidic intermediate.

Phosphorus ylides A subclass of ylides where a heteroatom bearing a positive charge presents a phosphorus one having three additional substituents. Although they are often referred to as the Wittig reagents, they are also applied for dipolar cycloadditions, allylic, and sigmatropic rearrangements.

Wittig reaction A method used to convert carbonyl compounds into alkenes via reaction with phosphorus ylides.

Ylide A neutral dipolar molecule containing a formally negatively charged atom (usually a carbanion) directly attached to a heteroatom with a formal positive charge (usually nitrogen, phosphorus, or sulfur), with both of these atoms having electron octets. Ylides are thus 1,2-dipolar compounds.

6.05.1 Introduction

The class of phosphorus ylides belongs to one of the most outstanding achievements in the chemistry of the previous century, the importance of which is increasing in various fields ranging from medicinal chemistry, organic synthesis, coordination chemistry to materials science. These compounds have attained great significance as versatile reagents for linking synthetic building blocks with the formation of carbon–carbon double bonds and the development of new routes to heterocyclic systems; they are especially useful in the synthesis of natural products and compounds with biological and pharmacological activity where development of new methods is impossible without phosphorus ylides. This review covers the most significant advances during the past 20 years in this area. The first section mainly deals with synthetic approaches to phosphorus ylides having exclusively P–C bonds, including *C*-substituted by an electron-withdrawing group (COR, CO_2R, CN, etc.) or heteroatom-containing functional groups, which found permanent applications in the Wittig carbonyl olefination (*see* Chapter 1.15). Just this type of compounds was the main subject of the corresponding chapter by Bestmann and Zimmerman in the first edition of Comprehensive Organic Synthesis[1] in 1991. For the reader's convenience, the authors have tried to retain in general the form of the previous version. In this area the general approaches, for example, synthesis from phosphonium salts, by addition of trivalent phosphorus compounds to a range of

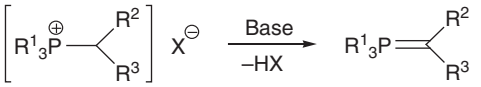
substrates, or by conversion of other phosphorus ylides do not change principally, but application of novel methods, for example, environmentally benign conditions or new reactants have provided novel possibilities for the synthesis of compounds with a particular structure. Therefore, these new methods will be reviewed in the context of the previous data. The principally new developed routes refer to the preparation of stabilized phosphorus ylides via addition of tertiary phosphines to activated alkynes in the presence of EH-nucleophiles (E = N, S, O, C), reduction of phosphonium salts, transformation of two-coordinated phosphorus compounds, and synthetic approaches to carbodiphosphoranes and cumulated ylides. The other new trends in the synthesis of phosphorus ylides deal with the synthesis and chemistry of phosphorus ylides *C*-substituted by metal, metalloids, and nonmetals. The data up to 1998 in this area are well discussed in the review on this topic of Oleg I. Kolodiazhnyi[2] and in his book 'Phosphorus Ylides, Chemistry and Application in Organic Synthesis,' published in 1999,[3] as well as in the subsequent review of M. Taillefer and H.-J. Cristau[4] (data up to 2002). The detailed peculiarities of structure, stability, conformations, and chemical bonding in phosphorus ylides in terms of a resonance hybrid between a dipolar form and double bond form (usually the dipolar form is considered to be more important from the standpoint of chemical reactivity) have been thoroughly discussed by Gilheany.[5]

6.05.2 Alkylidenephosphoranes

6.05.2.1 Synthesis from Phosphonium Salts

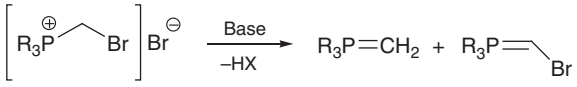
6.05.2.1.1 Generation with bases

The most important, effective, and convenient method for obtaining phosphorus ylides is still deprotonation with suitable bases of the corresponding phosphonium salts (equation 1), for which a lot of efficient and general strategies allowing the introduction of different substituents to the phosphorus atom as well as other functional groups have been developed. Generation of ylides *in situ* via deprotonation of the corresponding phosphonium salts is often used in the Wittig reaction, which, along with the related Horner–Wadsworth–Emmons olefination, is probably the best known example of the use of organophosphorus reactants in the preparation of organic compounds and one of the most popular methods for C–C bond construction.



(1)

It should be taken into account that triarylalkylphosphonium salts as ylide precursors unambiguously lead to alkylidenetriphenylphosphoranes, while, in the case of tetraalkylphosphonium salts, ylide formation may take place principally at different α-positions relative to the phosphorus, yielding isomeric ylides (equation 2). Moreover, isomeric ylides may result from the intramolecular transylidation process. A mixture of ylides may be also formed if the phosphonium salt carries another positively charged substituent in the α-position, such as, for example, a halide atom, where the reaction afforded the mixture of methylide and halomethylide, but it can be controlled by the variation of a halide and base. Thus, using PhLi, the ratio of these products was 1:99, 50:50, and 75:25 for chlorine, bromine, and iodine, respectively. At the same time, application of BuLi in the case of bromine provided methylide as a major product, while Lipip led to an opposite result.[6]



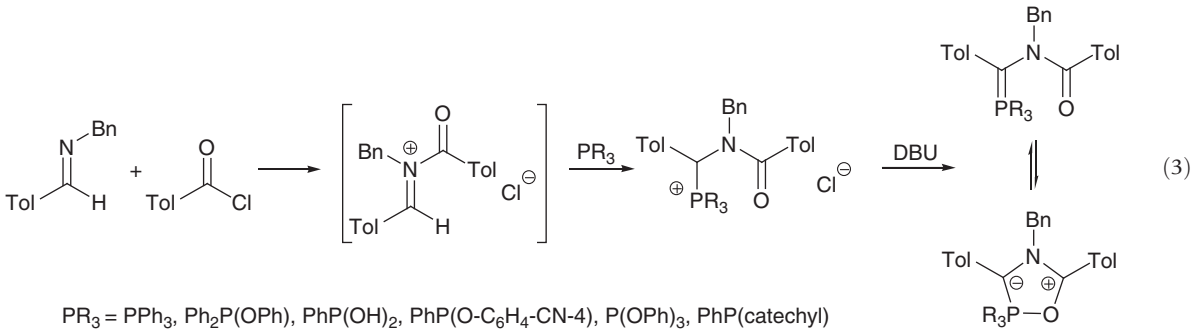
(2)

Over the deprotonation of cyclic amino phosphonium salts, the result depends on the nature of the substituents at the phosphorus atom and on the ring size, so cyclic phosphorus ylides can either be stable or undergo fragmentation into the corresponding phosphine and transient species.[7] Note that cyclic phosphorus ylides can be prepared not only by deprotonation of the corresponding β-amino phosphonium salts but also by intramolecular addition of a carbanion to the carbene center of (amino)(phosphonio)carbene.[7]

The salt deprotonation approach can be used in the case of vinylphosphonium salts,[1,8] where the abstraction of a proton proceeds from the γ-position to the phosphorus atom. However, this procedure does not provide good yields of the final ylides if the salt bears a good leaving group in the β-position (generation of vinylphosphonium salt as a side product) or if the β-proton is too acidic (Hofmann elimination side process). Therefore, to the best of our knowledge, for these compounds the deprotonation strategy is used very rarely nowadays.

The choice of the appropriate base/solvent system for the ylide generation depends on the acidity of the corresponding salt, stability of the resulting ylide in the reaction medium, and intended application of the ylide. A great variety of bases have been used to generate ylides from the corresponding phosphonium salts: various nitrogen bases, alkoxides, alkali metal hydrides, carbanionic bases, alkali metal hydroxides and carbonates, alkali metal bis(trimethylsilyl)amides, ethylene oxides, basic ylides (transylidation reaction), and others.[1] Thus, phosphonium salts with electron-withdrawing groups at the α-carbon, which are capable of stabilizing a negative charge, are deprotonated by relatively weak bases, such as dilute aqueous alkali or ammonia. In some cases phosphonium salts of this type can be deprotonated by tertiary amines, as, for example, α-cyano-vinylphoshonium

salts where triethylamine was applied,[9] or *N*-acyl-substituted phosphonium salts derived from a range of phosphorus(III) species (phosphines, phosphites, phosphonites, and phosphinites), imines, and acid chlorides where DBU was used (equation 3).[10] This reaction resulted in a family of phosphorus ylides existing as resonance hybrid forms and having similarity with 1,3-oxazolium-5-oxides, commonly known as Münchnones. Ylides of this type possess great potential (especially catechyl-substituted compound) as 1,3-dipoles for heterocycle synthesis with high regioselectivity via one-pot reactions, such as cycloadditions with alkynes followed by loss of phosphine oxides to form pyrroles.



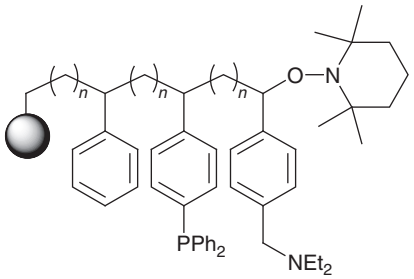
(3)

PR_3 = PPh_3, $Ph_2P(OPh)$, $PhP(OH)_2$, $PhP(O\text{-}C_6H_4\text{-}CN\text{-}4)$, $P(OPh)_3$, PhP(catechyl)

If there are electron-donating substituents at the α-carbon, stronger bases, such as alkyllithium, are required. Highly reactive phosphonium ylides are usually generated in an aprotic medium and are mostly not isolated but further reacted *in situ* (typically with carbonyl compounds to give the corresponding olefins via the Wittig reaction).

As mentioned above, aqueous alkali metal hydroxides and carbonates are suitable for the generation of stabilized ylides from phosphonium salts which carry strongly electron-withdrawing groups (e.g., acyl, alkoxycarbonyl, cyano, fluorenyl, nitrophenyl, and others) at the α-carbon and are usually sufficiently stable in water. These aqueous bases may also be applied to the synthesis of reactive ylides both by perfoming the reaction under phase-transfer conditions[11] and by using water as a sole solvent[12] in the presence of an aldehyde which undergoes the Wittig reaction with *in situ* generated ylide. In water, the reaction can be carried out in micellar systems formed in the presence of sodium dodecyl sulfate (SDS)[13] or in the absence of any additive.[14] Furthermore, semistabilized ylides can be generated in water from the reaction of trialkylbenzyl- or trialkylallylphosphonium salts and metal hydroxide followed by immediate reaction with aromatic and aliphatic aldehydes, providing high-yielding synthesis of *E*-stilbenes with high selectivity and alkenes, respectively.[15] The above procedure allows a gram-scale synthesis of the anticancer agent DMU-212 utilizing no organic solvent at any stage. The salt precursor useful for this ecologically friendly P=O olefination in water may be formed from the reaction of benzyl or allyl alcohol and air-stable and easy-to-handle triethylphosphine hydrobromide instead of using direct alkylation of odoriferous free trialkylphosphines which are inclined to oxidation.[16]

For the purpose of combinatorial chemistry, the salts for the Wittig olefination may be generated *in situ* using polystyrene beads bearing two distinct reactive groups, namely, the phosphine and amine functions.[17]



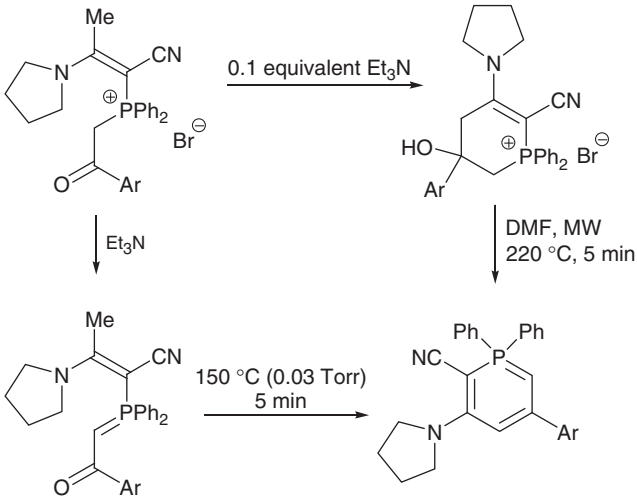
In the reaction, the phosphine groups of the polymeric matrix react with halocarbonyl compounds to form the corresponding phosphonium salt which would be deprotonated intramolecularly by the amine groups to form the reactive phosphorane moieties. Due to the heterogeneous nature of the polymer, the desired alkene product formed in the subsequent Wittig olefination with stereoselectivities ranging from *E*/*Z*=83/17 to 99/1 could be isolated in excellent yield in essentially pure form only after filtration and solvent removal.

The above approach to phosphoranes may be realized in the absence of a solvent using alumina or potassium fluoride supported on alumina[18] or by mechanochemical means (via high-energy ball-milling) using potassium carbonate as a base.[19] In the latter case, three major types of phosphorus ylides, namely, stabilized, semistabilized, and nonstabilized are generated, and the addition of a carbonyl compound allows for the synthesis of the corresponding alkenes via the subsequent Wittig reaction.

Taking into account that the reaction of tertiary phosphines with electrophiles is the most popular and convenient procedure for the creation of phosphonium salts, generation of ylides can be also realized as a two-step, one-pot process starting directly from R_3P without isolation of the intermediate salt. This one-pot method can be carried out in the conventional organic solvents,[20] realized by mechanochemistry means,[18] and even performed in water where the aqueous Wittig reaction was accomplished as a one-pot process using the mixtures of tertiary phosphine (Ph_3P or nBu_3P), bromoesters $BrCH_2CO_2R$ (R=Et, ^{t}Bu, CH_2Ph), and

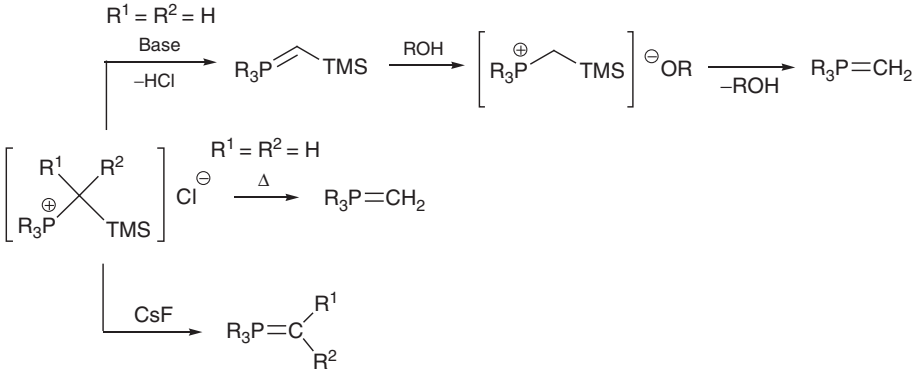
aldehyde in saturated sodium bicarbonate solution (at 20 °C for 40 min to 3 h) to provide the Wittig products in up to 99% yield and 98% *E*-selectivity.[14]

Besides the generation of phosphonium ylides by deprotonation of phosphonium salts with bases, in some instances ylides may be formed from pyrolysis (mostly of silylated salts),[1] electrolysis (*see* Chapter 9.14)[1,6] of phosphonium salts, or under microwave irradiation (*see* Chapter 9.10). This approach may be applied for vinylphosphonium salts as well. For example, cyclic phosphonium salts generated from linear precursors in benzene at reflux in the presence of a catalytic amount of bases such as triethylamine or Hunig's base underwent MW-induced transformation, affording phosphinines.[8] These endocyclic ylides can be also obtained by the flash vacuum pyrolysis of the corresponding stabilized vinylphosphonium ylides obtained from the same linear precursors by deprotonation (equation 4). Nevertheless, these procedures have not generally gained ground.



(4)

Desilylation of phosphonium salts has proved to be a useful alternative for the synthesis of really salt-free nonstabilized ylides. Desilylation may be performed as a two-step process comprising formation of trimethylsilyl substituted ylide followed by the transformation to a salt bearing alkoxide group and subsequent desilylation, but this route is applicable to methylides only or as a fluoride-induced reaction where cesium fluoride is the best source of fluoride ions (equation 5).[1,6] Furthermore, for the desilylation process, methanol or trimethylsilanol (substitution of trimethylsilyl by hydrogen), heterosiloxanes (substitution of trimethylsilyl by organoelement groups), acid chlorides, thioesters, anhydrides and trimethylsilyl esters (acylation), and halogenosilanes (transsilylation) can be used.[1]



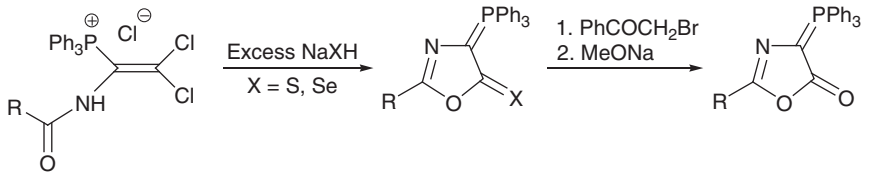
(5)

This general approach via desilylation to phosphonium, ammonium, and sulfonium ylides, which formation via deprotonation is complicated by both thermodynamic and kinetic factors, is also discussed by Vedejs and West.[21]

6.05.2.1.2 Preparation by addition of nucleophiles to vinyltriphenylphosphonium salts

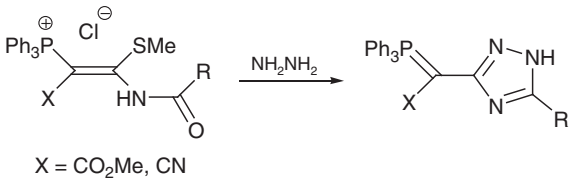
An approach to phosphonium ylides via nucleophilic attack at the β-position of vinylphosphonium salt was developed by Schweizer in the 1970s.[1] Note that the related method based on the nucleophilic ring-opening of cyclopropylphosphonium salts did not attract much attention due to low availability of the starting substrates. The synthesis via vinylphosphonium salt, especially commercially available vinyltriphenylphosphonium bromide known as Schweizer's reagent, despite the complications due to side reactions in some cases, has been successfully employed in the addition of a variety of anionic derivatives of alcohols, thiols, amines, etc. For example, alkyl, alkenyl, and aryl cuprates readily add to vinyltriphenylphosphonium bromide to provide phosphoranes.[22] Furthermore, α-acylamino vinylphosphonium salts proved to be very efficient in the synthesis of mesomeric 4-phosphoranylidene-5(4*H*)-oxazolones. The synthesis was accomplished via treatment of the starting salts with an excess of

sodium sulfide (hydrosulfide) or the corresponding selenide (equation 6).[23] Subsequent treatment of the thio-derivative with phenacyl bromide and sodium methoxide allowed obtaining the corresponding oxygen-containing product.

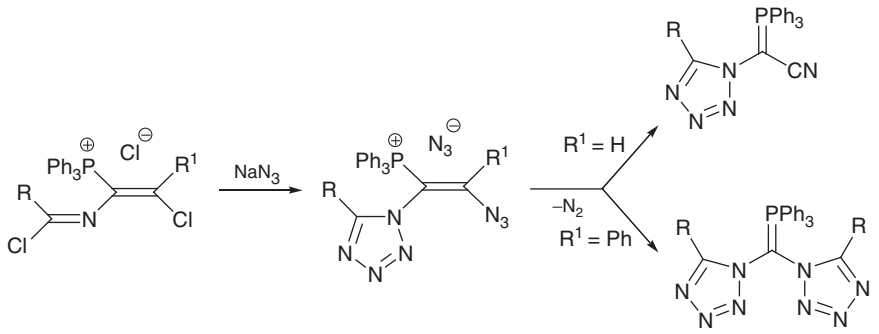


(6)

Methylmercapto-substituted β-acylamino vinylphosphonium salts readily react with hydrazine to give in high yields 1,2,4-triazoles bearing an ylidic function (equation 7).[24] For the synthesis of 1,2,3,4-tetrazolyl ylides, the reaction of the related imidoyl chlorides with sodium azide was used. Depending on the substituent at the vinyl group, the product bearing either one ($R^1 = H$) or two ($R^1 = Ph$) heterocyclic rings can be isolated due to the difference in the rearrangements of the intermediates generated (equation 8).[25]



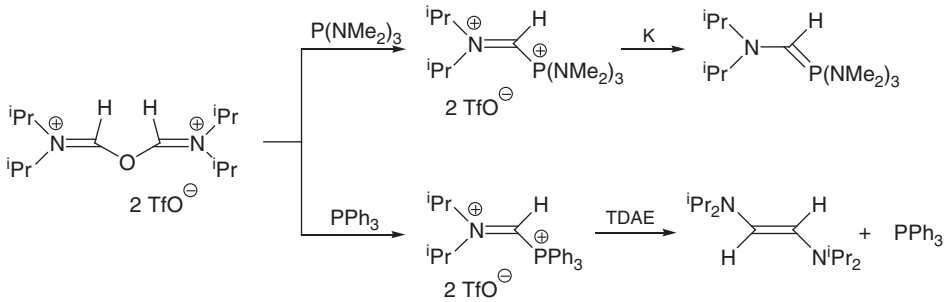
(7)



(8)

6.05.2.1.3 Preparation by reduction of phosphonium salts

An original synthetic route to stable and transient *C*-amino phosphorus ylides was suggested by Bertrand and coworkers.[26] The synthesis is based on the two-electron reduction of phosphonio-substituted aldiminium, iminium, and imidazolidinium salts (*see* Chapters 8.02, 8.03, and 8.05) with either potassium metal or tetrakis(dimethylamino)ethylene (equation 9). The starting compounds can be readily prepared by the addition of a range of phosphines to the Alder dimer or by treatment of the corresponding chloroiminium salt with the phosphine/trimethylsilyl triflate adduct generated *in situ*. The stability of these phosphorus ylides depends on the nature of the substituents at the phosphorus atom – ylides can be isolated only when basic phosphines, such as tris(dimethylamino)phosphine, are used, otherwise the reduction results in carbene and phosphine as the fragmentation products.



(9)

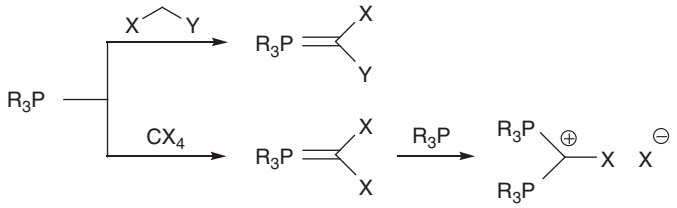
The synthesis of this stable linear *C*-amino phosphorus ylide can also be performed via deprotonation with butyllithium of 1:1 salt adduct [$^iPr_2N$-CH_2-$P^+(NMe_2)_3$][TfO^-] of tris(dimethylamino)phosphine and *N*,*N*-diisopropyliminium salt [$^iPr_2N^+ = CH_2$][TfO^-], but this approach is limited to basic phosphorus(III) derivatives such as $P(NMe_2)_3$.[7] Otherwise, no salt formation is observed (as in the case of triphenylphosphine) or the salt readily undergoes fragmentation (as with methyldiphenylphosphonium derivative).

Note that *C*-amino phosphorus ylides both of linear and cyclic structure[27] readily act as aminocarbene/phosphine transfer agents toward various transition metal centers in contrast to stabilized, semistabilized, and even nonstabilized phosphorus ylides.

6.05.2.2 Preparation by Addition of Phosphorus(III) Reagents to Different Compounds

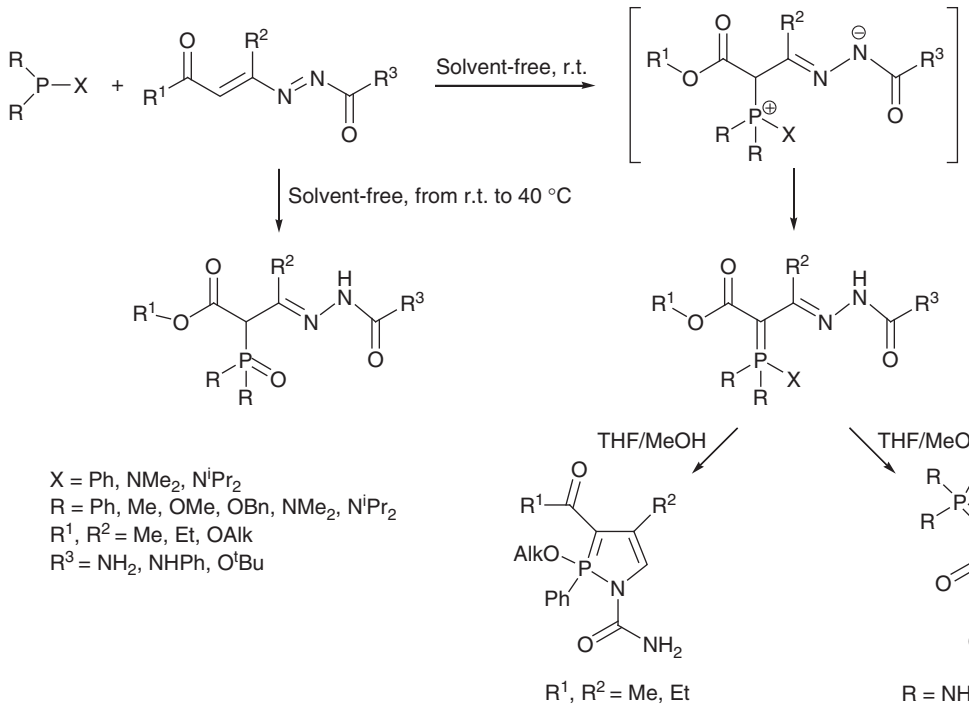
A wide range of phosphorus(III) derivatives (especially tertiary phosphines, such as triphenylphosphine) give rise to functionalized alkylidenephosphoranes, reacting with various compounds.[1] Among such compounds are carbenes and carbenoids, generated from di- or tri-halomethanes with bases (organolithium compounds or alkoxides, aqueous sodium hydroxide solution under phase-transfer conditions) or resulting from the decomposition of sodium trihaloacetates in the presence of a tertiary phosphine; tetrahalomethanes; aliphatic diazo compounds in the presence of Cu(I) salts; epoxides; nitrilimines; sulfuranes; amidines; compounds with multiple C–C bonds, etc.

This approach was well developed mainly for the synthesis of haloalkylidenephosphoranes bearing either one or two halogen atoms at the α-carbon atom (equation 10).[1] The corresponding haloalkylidenephosphoranes were usually not isolated but reacted with added carbonyl compounds to give alkenes and dichloroacetals. Note also that dihalophosphoranes may undergo subsequent reaction with tertiary phosphine, yielding the formation of a semiylide salt.



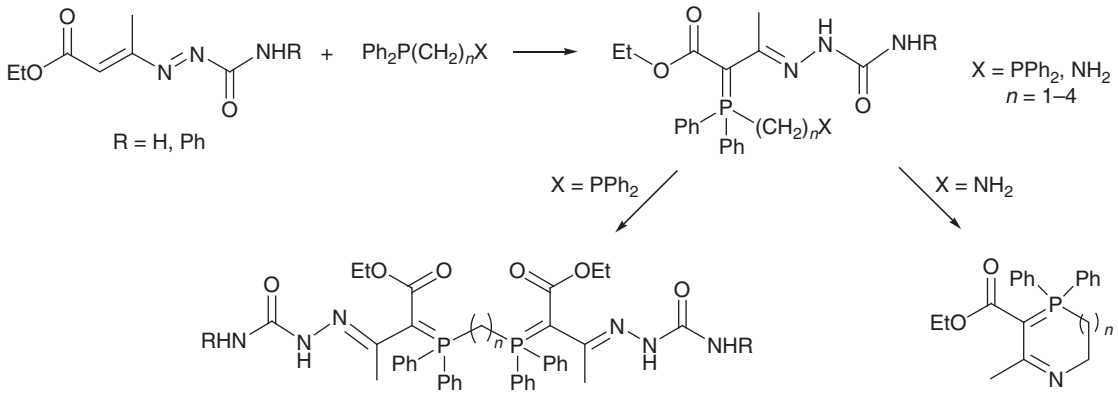
(10)

Although the additions to other substrates were not used earlier as generally applicable methods for the synthesis of phosphonium ylides,[1] the scope of this reaction was significantly expanded over the last two decades. Thus, the reactions of different phosphorus nucleophiles with 1,2-diaza-1,3-butadienes proceeded under very mild conditions, for example, under solvent-free conditions (*see* Chapter 9.11) and in the presence of atmospheric moisture, and spontaneously afforded ylides from the zwitterionic adducts formed by the 1,4-Michael-type attack on diazabutadienes. For example, the use of tertiary phosphines, dialkylphosphonites, trialkylphosphites, or a range of phosphorus(III) amides (phosphoramidites, phosphorodiamidites, or tris(dimethylamino)phosphines) gave stable α-phosphoranylidene-hydrazones (equation 11).[28] Note that a slight increase of the reaction temperature up to 40 °C in the case of starting phosphorus substrate bearing at least one alkoxy moiety changed the reaction course toward the corresponding phosphonate derivative. The linear ylides in the mixed THF/MeOH solution undergo further intramolecular transformations to give 1,2,3λ^5-diazaphospholes bearing endocyclic *P*-ylide moiety in the case of phenylphosphinite as a starting substrate or 5-oxo-4-phosphoranylidene-4,5-dihydro-1*H*-pyrazoles with exocyclic *P*-ylide function when trialkyl-, triarylphosphines, and tris(dialkylamino)phosphines are used.



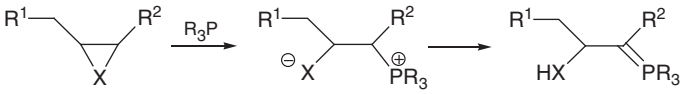
(11)

Similarly, the reactions between 1,2-diazabutadienes and diphosphines in a 2:1 molar ratio in ethyl acetate gave, after about 15 min, the stable bisylide derivatives in almost quantitative yields (equation 12).[29] The reaction proceeded via intermediate monoylide derivatives, which, however, were not isolated in a pure form. Vice versa, in the case of phosphinoamines, the reaction yielded the corresponding monoylides stable in a solid state but undergoing spontaneous cyclization in chloroform solution to give the cyclic ylides, obviously due to the internal nucleophilic attack of the amine nitrogen atom on the imine carbon atom with displacement of a semicarbazide molecule (equation 12).



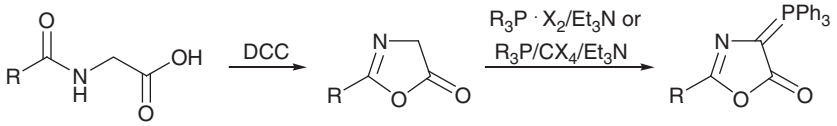
(12)

The addition of tertiary phosphines to epoxides was expanded over the past two decades for other small heterocycles, such as aziridines. In both cases, the reaction afforded the corresponding betaine intermediate followed by inter- or intramolecular hydrogen shift to afford the corresponding ylide, which was used subsequently in the Wittig reaction (equation 13).[30]



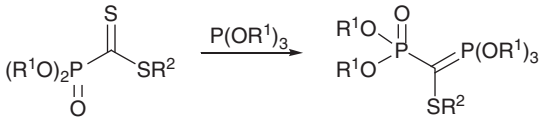
(13)

The treatment of 4-unsubstituted 5(4*H*)-oxazolones, obtained in turn by the dehydration of *N*-acylglycines with DCC in CH_2Cl_2 (at ambient temperature) with $R_3P{\cdot}Br_2$ adducts in the presence of triethylamine or with the mixture of tertiary phosphine, tetrahalomethane, and triethylamine presents a convenient approach to mesomeric 4-phosphoranylidene-5(4*H*)-oxazolones isolated in up to 96% yield in the case of bromine adducts (equation 14).[31] The procedure suggested is more effective than the synthesis of similar ylides via nucleophilic addition to vinylphosphonium salts (see equation 6), but allows the synthesis of keto-derivatives only.



(14)

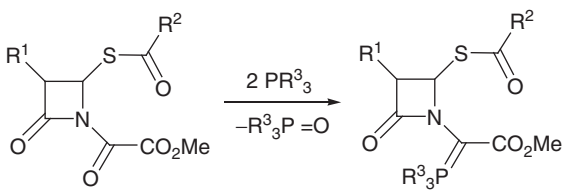
In some reactions within the scope of the above approach, P(III) derivatives other than tertiary phosphines can be also utilized. For example, the addition of trialkylphosphites (two equivalents, THF solution) to phosphonodithioformates presents a suitable synthesis of *α*-sulfanyl-*α*-phosphonyl phosphonium ylides, providing the final products in quantitative yields (equation 15).[32] The reaction proceeds by a thiophilic addition followed by desulfurization, and trialkyl thiophosphate, which is also generated in the reaction, can be efficiently removed under vacuum.



(15)

R^1 = Et, R^2 = Me
R^1 = Me, R^2 = CD_3
R^1 = ^{i}Pr, R^2 = Me

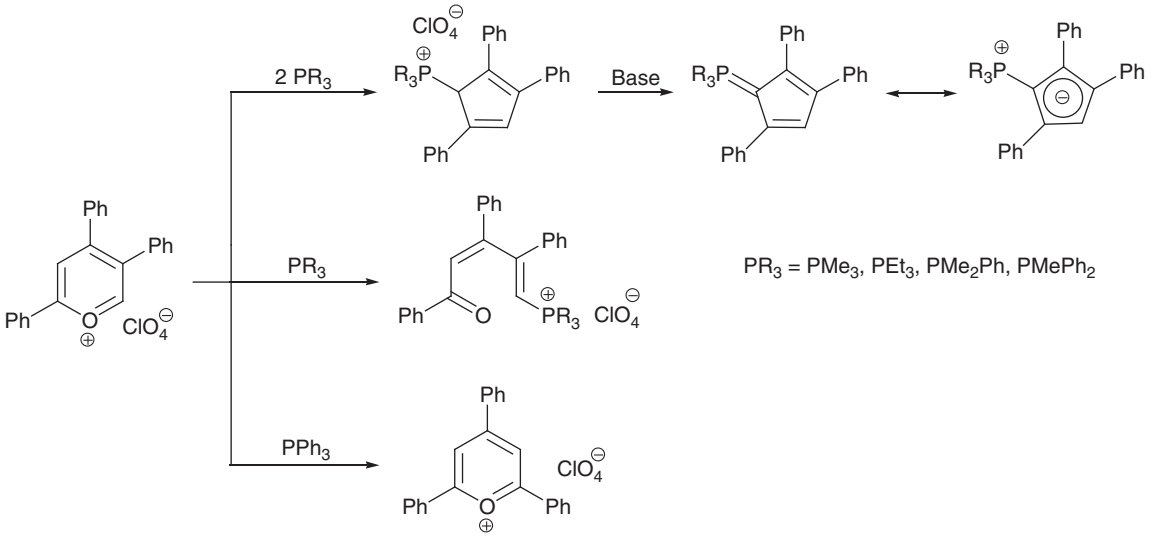
Note that, as developed by Woodward et al.,[33] synthesis of the ylides containing the 4-acylthioazetidin-2-one group based on the phosphine addition and its further modifications using not only tertiary phosphines but also phosphites and phosphinites (equation 16),[34] is of industrial importance for the preparation of the *β*-lactame antibiotics.



(16)

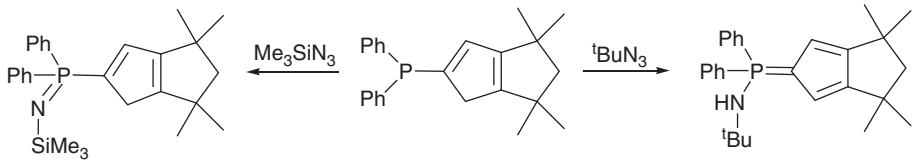
PR^3_3 = $P(OEt)_3$, P(OEt)Me, PPh_3

A ring contraction of an α-reactive 2,4,5-triphenylpyrylium salt in the reaction with phosphines, such as PMe_3, PEt_3, PMe_2Ph, and $PMePh_2$ (at least two equivalents), offers an effective approach to aryl and alkylphosphonium triphenylcyclopentadienylides (63–75% yield) (equation 17). The preliminary results supported a plausible mechanism of the tandem conjugate addition followed by the intramolecular Wittig reaction.[35] Note that the reaction of an equimolar amount of phosphines yielded only the ring-opening phosphonium salt, while the reaction with PPh_3 gave the corresponding more stable 2,4,6-triphenyl pyrylium salt as a sole product (equation 17).



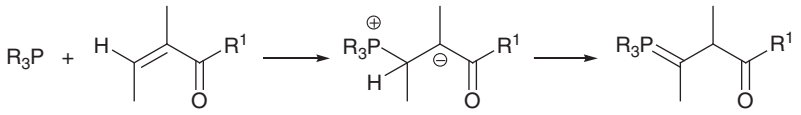
(17)

Even the Staudinger reaction can afford the ylidic product existing exclusively in the *P*-aminocyclopentadienylidenephosphorane tautomeric form, but it is limited to a special case of annelated tetramethylpentalenyl-substituted phosphine Ph_2P-Cp^{TM}H and addition of $^tBuN_3$ (equation 18).[36] Change of $^tBuN_3$ for Me_3SiN_3 resulted in the formation of typical *P*-imino-cyclopentadienylphosphine.



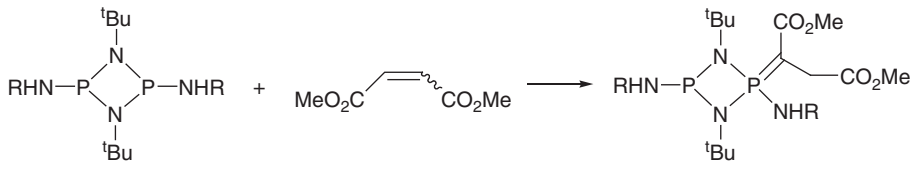
(18)

Phosphonium ylides are also available from the reactions of trivalent phosphorus derivatives with compounds bearing activated C–C multiple bonds (*see* Chapter 4.01). Thus, phosphines add to the activated C=C double bond of α,β-unsaturated ketones or carboxylic acid derivatives to yield the zwitterionic intermediates (generally phosphonioenolates), which may undergo 1,2-prototropic shift, giving rise to alkylidenephosphoranes (equation 19).[1]



(19)

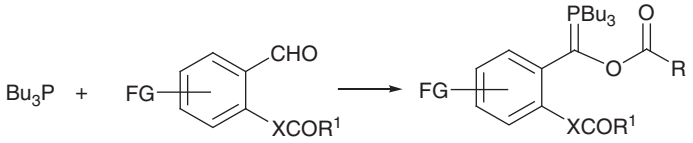
Recent examples of this type of transformation include the reactions of cyclodiphosph(III)azanes with dimethyl maleate (or dimetyl fumarate), which proceed without opening of the phosphazane cycle[37] (equation 20), as well as the addition of tertiary phosphines to one of the double bonds in neutral porphyrins.[38]



R = ^{i}Pr, ^{t}Bu

(20)

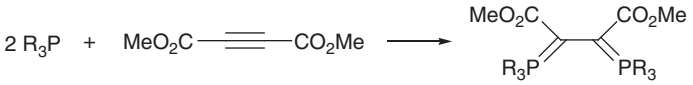
It should be noted that in some cases the intermediate phosphorus ylides may result from the addition of tertiary phosphines to C═E double bond (*see* Chapter 1.17), as, for example, the aldehyde function; therewith, ylides are stabilized by subsequent acylation (equation 21).[39]



X = O, S, NAlk, NAr
FG = Cl, Br, NO_2, CH_3, ^{i}Pr

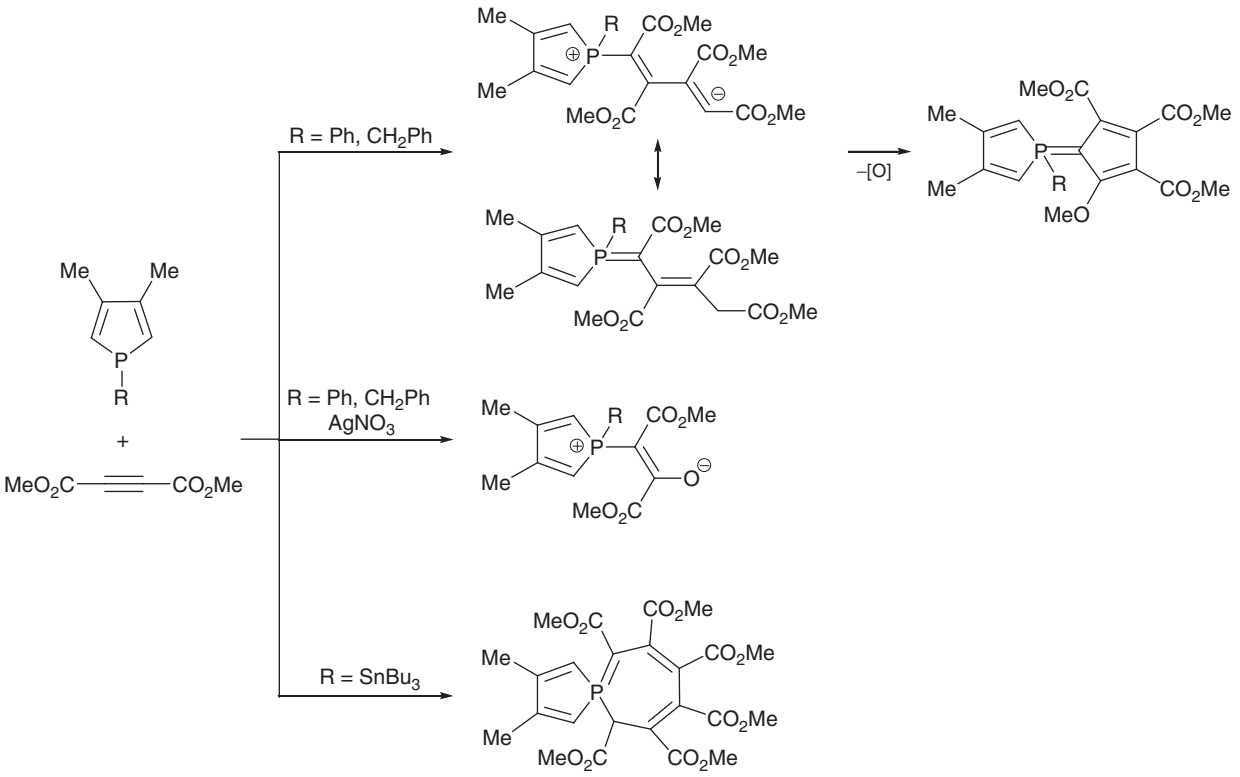
(21)

The addition of tertiary phosphines to alkynes having activated C≡C triple bonds, originating from the pioneering work of Tebby[40] on the reactions of triphenylphosphine with dimethyl acetylenedicarboxylate (DMAD), is also a suitable route to ylidic compounds. Thus, used in a 2:1 molar ratio, tertiary phosphines gave rise to 1,2-bisylides (equation 22).[1]



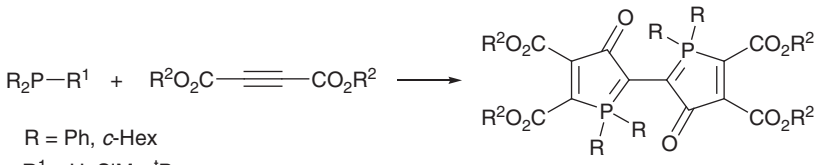
(22)

The application of some phospholes as tertiary phosphines in the reaction with dimethyl acetylenedicarboxylate (DMAD) is also known to yield a variety of ylides having sometimes ring-expanded or ring-fused structures, depending on the reaction conditions (equation 23). Thus, in the presence of DMAD excess, the interaction of 1-phenyl(benzyl)-3,4-dimethylphosphole with DMAD provided stable ylides being [1:2] adduct. Deoxygenation of the methoxycarbonyl substituent at the α-carbon of the $(DMAD)_2$ chain of this adduct afforded cyclization with the formation of cyclopentadienylidenephosphorane. At the same time, when the reaction was performed in the presence of $AgNO_3$, an oxo-ylide was formed due to oxidation.[41] Replacing the substituent at the phosphorus atom in the starting phosphole by a stannyl group yielded quite a different result, namely, the formation of a 1:3 adduct with a seven-membered ring.[42]



(23)

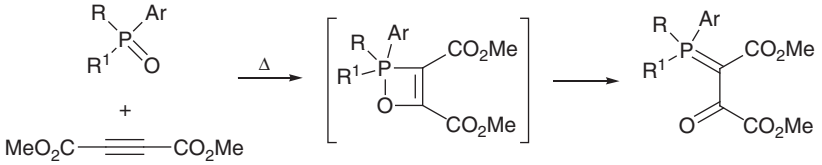
The reaction of a secondary phosphine (or silylphosphine) and DAAD under ambient conditions, which is believed to proceed as a complicated condensation of five molecules into a single one (one-pot cascade reaction) starting, most likely, from the nucleophilic attack of phosphine at DAAD, resulted in a new class of phosphorus ylides containing conjugate heterocycles – bis(3-oxo-λ5-phospholes) (equation 24); however, the procedure seems to be limited to the mentioned substituents at the phosphorus atom.[43] Note that reacting with propiolates and alkynyl ketones, trimethylsilyl- and dimethyl-*tert*-butyl-phosphines, either without any catalyst or in a Lewis acid–mediated version, give only the corresponding 3-phosphino-2-silyl-prop-2-enes, i.e., 3,4-addition products.[44]



R = Ph, *c*-Hex
R^1 = H, $SiMe_2{}^tBu$
R^2 = Me, Et

(24)

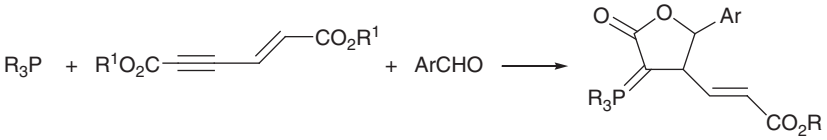
The addition of phosphine oxides to DMAD affords stabilized phosphonium ylides featuring two electron-withdrawing substituents at the ylidic carbon atom in variable yields (19–85%), but the requirement of the presence of an overcrowded 2,4,6-trisubstituted aryl group seems to be the limitation of this procedure (equation 25).[45] The reaction was suggested to proceed via a kind of the 'inverse Wittig reaction,' corresponding to the thermal dissociation of an oxaphosphetene resulting from the [2+2] cycloaddition between phosphine oxide and activated acetylenic compounds.



R, R^1 = Alk or *c*-Alk
Ar = 2,4,6-trisubstituted phenyl

(25)

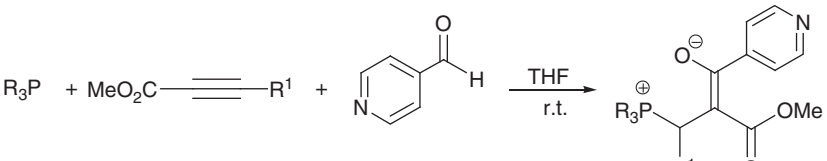
The cyclic ylides, presenting γ-lactones with an exocyclic α-phosphorus ylide moiety, may be generated in up to 92% yield via the addition of triarylphosphines to hex-2-en-4-ynedioic acid dialkyl esters in the presence of aromatic aldehydes as electrophiles (THF, 60 °C) (equation 26). However, this three-component, one-pot reaction is limited to aldehydes bearing electron-withdrawing groups in the phenyl rings. In the case of more electron-rich aromatic or aliphatic aldehydes, the CH proton of the intermediate species is less reactive for deprotonation and thus did not form the final ylidic lactone.[46]



R = Ph, 4-Cl-Ph, 4-F-Ph, 4-MeO-Ph, $4\text{-}CH_3$-Ph, 2-Th etc.

(26)

Furthermore, the related reaction of phosphines bearing at least one electron-donating alkyl group at the phosphorus atom with alkyl propiolates and dimethyl acetylenedicarboxylate in the presence of 4-pyridinecarboxaldehyde afforded different types of stable zwitterionic phosphonium-enolates (equation 27).[47] In contrast, no reaction was observed for triphenylphosphine, even at elevated temperature (80 °C) and over longer reaction times. The possible mechanism of such transformations was suggested to involve the nucleophilic addition of the reactive intermediate *P*-vinyl anion to the aldehyde followed by two successive proton transfers.

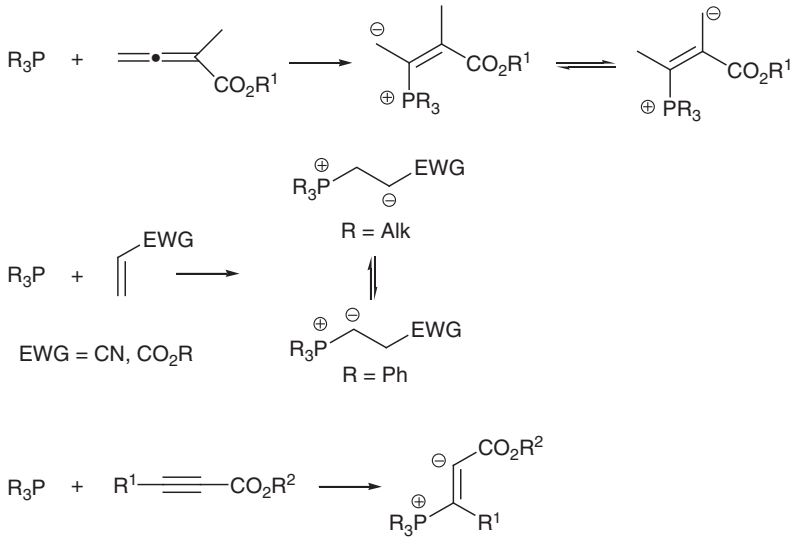


R_3P = Me_3P, Bu_3P, Me_2PhP, $MePh_2P$
R^1 = H, Me, Ph, CO_2Me

(27)

Note that the *in situ* generation of reactive zwitterionic intermediates from phosphines, used either in catalytic or in stoichiometric amount, and compounds with activated carbon–carbon multiple bonds (olefins, allenes, and alkynes) followed by one-pot reaction with electrophiles usually proceeding with loss of a phosphine moiety has become a powerful tool for the synthesis of a variety of carbo- and heterocycles from readily available starting materials (the so-called phosphine-mediated reactions or nucleophilic phosphine organocatalysis), which is illustrated by an increasing range of publications.[48] In general, nucleophilicity, steric, and electronic properties of phosphines may be altered to achieve the reaction regioselectivity, and chiral phosphines may be used for enantioselective synthesis.[49] Although the intermediate zwitterionic species were both isolated and their structures were established on the basis of NMR data, occasionally in a variety of cases their formation was proposed from a general

chemistry point of view. The accepted mechanisms for the phosphine-mediated reactions with alkynes or allenoates comprise the phosphine attack at the β-carbon of these substrates, formation of zwitterionic carbenoid species followed by the subsequent steps.



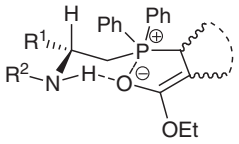
(28)

Discussing further the mechanism of similar reactions, it should be noted that in the phosphine-mediated reaction of alkyl α-methylallenoate with various aldehydes, a classic case of equilibrium between phosphonium dienolates and vinylogous phosphorus ylides was established, and the reaction course depended on the nature of the phosphine along with the presence/absence of a Lewis acid. Thus, vinylogous Wittig olefination was observed in the reaction of ethyl 2-methyl-2,3-butadienoate with electron-deficient aromatic aldehydes in the presence of a stoichiometric amount of electron-deficient triarylphosphine $(4\text{-}RC_6H_4)_3P$ (R=CN, CF_3) and a catalytic amount of a Lewis acid (e.g., $BF_3{\cdot}Et_2O$ or $TiCl_4$), while in the absence of a Lewis acid, triphenylphosphine promoted the aldol addition accompanied by 1,2-aryl phosphorus-to-carbon migration. At the same time, in reactions with electron-deficient alkenes, electron-donating trialkylphosphines are believed to form or facilitate the reactions of the β-zwitterionic intermediate, whereas electron-deficient triarylphosphines favor the ylide intermediate, i.e., stabilized α-anion.[50] Ylidic intermediates were aslo proposed in a general procedure for the syntheses of tetrasubstituted furans starting from Michael acceptors, tributylphosphine, and acyl chlorides followed by the intramolecular Wittig-type reactions.[51]

Nucleophilic phosphine catalysis played a significant role in the development of cycloaddition chemistry, which regio- and stereoselectively generates carbo- and heterocyclic motifs. The representative examples include the well-reviewed Morita–Baylis–Hillman reaction,[52] including its asymmetric version,[53,54] Trost's intramolecular γ-addition of oxygen nucleophiles to 2-alkynoates,[55] the [3+2] annulation reaction (*see* Chapter 5.08),[56] PPh_3-catalyzed (4+1) and (4+2) annulations of bis(nucleophiles) and 2-(acetoxymethyl)-buta-2,3-dienoates that efficiently provide facile access to cyclopentene and tetrahydropyridazine derivatives,[57] and the Rauhut–Currier reaction,[58] i.e., the phosphine-catalyzed dimerization of electron-deficient alkenes, acrylonitrile, and ethyl acrylate. In the latter case, the transformation is believed to proceed via reversible conjugate addition of a nucleophilic catalyst, i.e., trialkylphosphine or triarylphosphine to an alkene, yielding zwitterionic species, followed by the Michael addition of the second equivalent of activated alkene and subsequent prototropic shift, and extrusion of the phosphine catalyst to generate the coupling product. Some other useful examples of phosphine-mediated reactions include the triphenylphosphine-induced Biginelli synthesis of 3,4-dihydropyrimidin-2-(1H)-ones(thiones),[59] annulation of allylic compounds with *N*-tosylimines, affording either 3-pyrrolines or (*E*)-dienylimines, depending on the reaction conditions and nature of the starting substrate,[60] annulations of alkyl allenoate in the presence of Ph_3P with a variety of aromatic aldehydes, leading to 2-pyrones[61] and alkylidenemalononitriles to give highly functionalized cyclopentenones,[62] creation of the tetrahydrofuran ring from propargyl alcohol and Michael acceptors,[63] and catalytic cyanomethylation using highly basic tris(2,4,6-trimethoxyphenyl)phosphine,[64] synthesis of *trans*-2,3-dihydrobenzofurans by the reaction of salicyl *N*-thiophosphinyl imines and allylic carbonates in the presence of 5–10 mol% of Ph_3P,[65] three-component, one-pot reaction of aldehyde, hydrazones, and azodicarboxylates in the presence of 1 mol l^{-1} equivalent of triphenylphosphine, for the synthesis of substituted 4-amino-1,2,4-triazol-3-ones,[66] etc.

For the asymmetric version of the phosphine-mediated reaction, phosphines bearing additional donor sites are of high interest. Thus, excellent enantioselectivities were achieved in the allenoate–imine cycloadditions catalyzed by bifunctional phosphine-containing thioureas.[67] Miller and coworkers[68] used α-amino acid-derived phosphines as efficient catalysts for the allenoate–enone cycloadditions, which provided high *ee* values and regioselectivity, in contrast to those obtained with monodentate phosphine catalysts in the related reactions. Similarly, good to excellent enantioselectivities were observed in the case of the asymmetric organocatalytic [3+2] cycloaddition between allenoates and double activated olefins in the presence of *N*-acyl aminophosphines.[69] In the last two cases, the asymmetric induction was explained by a zwitterionic transition state organization

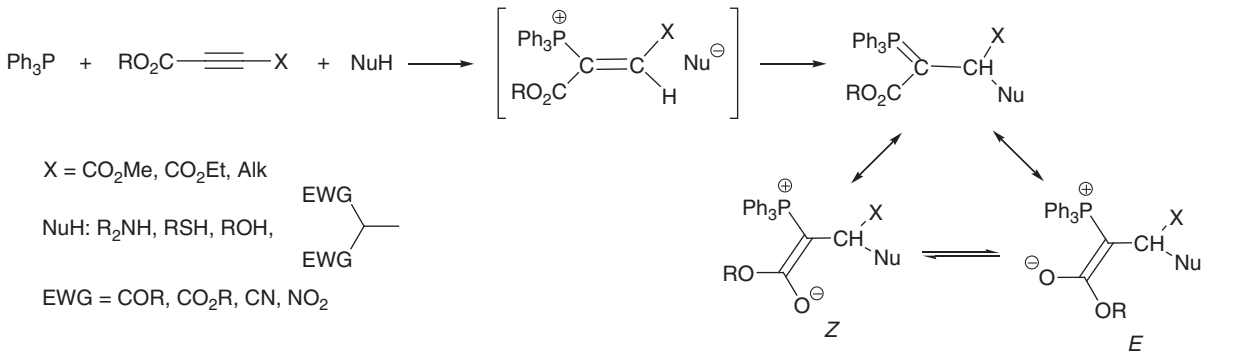
stabilized by H-bonds, which requires the approach of the dipolarophile to the zwitterion from the π-face opposite to one of the catalyst Ph rings.



As mentioned above, in the phosphine-mediated reactions, the nature of substituents at phosphorus influences the reaction course. Thus, PPh_3 acts as both a nucleophilic trigger and a deoxygenating agent in reductive cyclopropanation between R-substituted allenoates and aldehydes.[70] Employing more nucleophilic phosphines, such as PBu_3, led to the formation of another product, 1,2,3,4-tetrasubstituted conjugated 1,3-diene, in high yield and excellent diastereoselectivity (up to *dr* 20:1), together with only traces of cyclopropanes,[71] while both $P(OMe)_3$ and $P(NMe_2)_3$ mediate neither cyclopropanation nor olefination. Note that another crucial factor in this reaction is the structure of aldehyde; *o*-substituted aromatic aldehydes (except for salicylaldehyde) exclusively afforded cyclopropanation products in 51–99% yields. At the same time, aliphatic aldehydes, being unreactive under cyclopropanation conditions, successfully undergo PBu_3-mediated olefination. In this particular case the mechanism of the reaction confirmed based on the ^{31}P NMR and deuterium-labeling experiments the formation of a resonance-stabilized zwitterionic phosphonium intermediate reversibly converting into the allylic phosphorus ylide via a water-assisted hydrogen shift.

6.05.2.3 Preparation by Addition of Tertiary Phosphines to Activated Acetylenic Compounds in the Presence of Acidic Compounds

The three-component reactions of tertiary phosphines, dialkyl acetylenedicarboxylates (DAAD) or alkyl propiolates, and various OH-, NH-, SH-, and CH-nucleophiles is nowadays a well-established route to highly functionalized stabilized phosphorus ylides existing mostly as zwitterionic vinylphosphonium enolates in which the ratio of *Z*- and *E*-isomers depends on the substituents in the molecule. The reaction mechanism involves the Michael addition of phosphine to the activated triple bond of an akyne component, stabilization of the resulting reactive intermediate by protonation with a nucleophile, and, finally, addition of a conjugated base to the vinyltriphenylphosphonium salt formed (equation 29). In other words, the method is based on the *β*-additions of nucleophiles to the vinyl group of vinyphosphonium salt, which is generated *in situ*. Recent achievements in this area, including theoretical, NMR, kinetic, and mechanistic investigation of the reaction, have been discussed in reviews of Iranian researchers, who made a notable contribution to this area.[72]



(29)

Introduction of new nucleophiles (in a practically boundless series) into this reaction from year to year gave rise to novel representatives of the above general structure. The nucleophiles which can be used comprise those with N–H bond (aromatic primary amines and aromatic amides,[73,74] azole heterocycles,[75,76,77] e.g., phenothiazine and 1,3-diaryl-1-triazenes,[78] semicarbazones,[79] urethanes,[80] arylsulfonylhydrazides, aryl hydrazines,[81] etc.), S–H bond (SH-heterocyclic compounds, such as arylmercaptanes,[76,82] 5-mercaptotetrazoles,[83] 2-mercapto-1-methyl imidazole,[84] 2-mercapto-4,6-dimethyl pyrimidine,[85] and so on), *O*-nucleophiles (e.g., 2-hydroxy-4-methoxybenzaldehyde,[86] 5-hydroxy-2-hydroxymethyl-4H-pyran-4-one (kojic acid),[87] 2-nitrophenol[88]), as well as CH-acids, such as malonodinitrile,[89] ethylcyanoacetate,[90] 5-acyl Meldrum's acid,[91] and 1,3-butadiones.[92,93] A related preparation of specific stabilized phosphonium ylides corresponds to the reaction of triarylphosphines with acetylene dicarboxylic esters in the presence of fullerene, which affords cyclopropanyl-fullerene substituted stabilized phosphonium ylide[94] or the corresponding evolution products.[95]

The reactions can be performed at room temperature or even at −10 °C[96] in conventional organic solvents, under solvent-free conditions (*see* Chapter 9.11), or in water as a sole medium. The latter procedure is especially advantageous from the viewpoint of 'green chemistry,' minimizing the cost of operational hazards by performing the reaction under environmentally benign conditions. Examples of water reactions include the application of sodium dodecyl sulfate as a surfactant[97] as well as in the presence of polyethyleneglycol (PEG), β-cyclodextrin (β-CD), glycerin (Gly), or ethyleneglycol (EG).[98] Under aqueous conditions the corresponding ylides were obtained using a range of N–H, C–H, or S–H acids including different NH-heterocyclic systems, for example, 2-benzoxazolinone, pyrrole-2-carboxaldehyde, benzotriazole, 5-methylbenzotriazole, and 5-chlorobenzo-triazole[26,75] diethyl malonate, acetylacetone and cyclohexane-1,3-dione,[93] and 2-thiazoline-2-thiol.[26] No doubt this ecologically friendly procedure may be used for a variety of other E–H nucleophiles.

Typically, triphenylphosphine is used in these transformations, but other phosphines bearing at least one electron-donating alkyl group can be also utilized.[47] Attempts to introduce other trivalent phosphorus derivatives revealed that the reaction of triphenylphosphite with halogenated anilines leads to phosphonates due to the elimination of PhOH from the intermediate quasiphosphonium salt in the presence of residual moisture.[99] At the same time, ylides produced from trialkylphosphites (2-indolinone was used as a nucleophile) were stable under ambient conditions both in a solid state and in solution.[100] Recently, hexamethyl phosphorous triamide was successfully introduced into the reaction with dimethyl acetylenedicarboxylate and various NH- and CH-acids.[101]

Generally, functionalized *P*-ylides obtained via this three-component, one-pot procedure are stable and can be isolated in high yields, but some undergo further transformations, affording both phosphorus-containing products and some which have lost the triphenylphosphine group. Often such transformations comprise the intramolecular Wittig reaction (but not intermolecular P=O olefinations), as, for example, in the synthesis of dialkyl 5-oxo-1,2-dihydro-5Y-chromeno[4,3-b]pyridine-2,3-dicarboxylates using enaminocarbaldehydes as the third component,[102] or in the reaction of PPh_3, diaroylacetates, and arylidenemalononitriles, affording 3-aroyl-2,5-diaryl-2,4-cyclopentadiene-1,1-dicarbonitriles.[103] The normal intermolecular Wittig reactions are typical only for *P*-ylides of the above structure bearing highly electron-poor carbonyl groups. In the other way of transformation, consisting of 1,2- or 1,3-proton[104] shift and elimination of PPh_3, when the products formed are the desired ones, triphenylphosphine can be used in catalytic amounts (3–5 mol%). In such cases the reactions are often performed under solvent-free conditions (*see* Chapter 9.11) in the presence of silica gel, powdered K_2HPO_4, KH_2PO_4, or KI[105] under thermal induction, or using microwave assistance (*see* Chapter 9.10).[106]

Finally, it should be noted that the synthetic possibilities of this approach to functionalized *P*-ylides, generated in the reaction of PPh_3 and acetylene derivatives in the presence of an acid, were further expanded to form heterocyclic systems using a one-pot, four-component reaction. Examples include synthesis of tetrasubstituted pyrroles using butane-2,3-dione in combination with ammonium acetate,[107] 2,5-bis(amino)furans and electron-poor imides from benzoic acid and alkylisocyanide,[108] pyrazol-4-yl-2-butenedioates using acetylacetone and phenylhydrazine,[109] bisfuramides using α,ω-alkylenediamines and diketene (pseudo-five component synthesis),[110] as well as a diastereoselective route to 2H-indeno[2,1-b]furans in the presence of different alcohols as an acid and subsequent intermolecular Wittig reaction with ninhydrin, etc.[111]

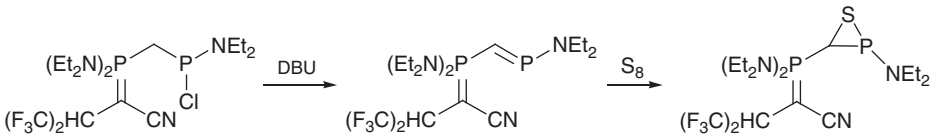
6.05.2.4 Preparation by Conversion of Other Phosphonium Ylides

Principally, alkylidenephosphoranes can be transformed into new phosphonium ylides either by reactions taking place in a side chain of the parent ylide, without implication of the ylide group α-C atom, or by introduction of additional substituents at the above carbon.

6.05.2.4.1 By transformation of a side chain in the parent ylide

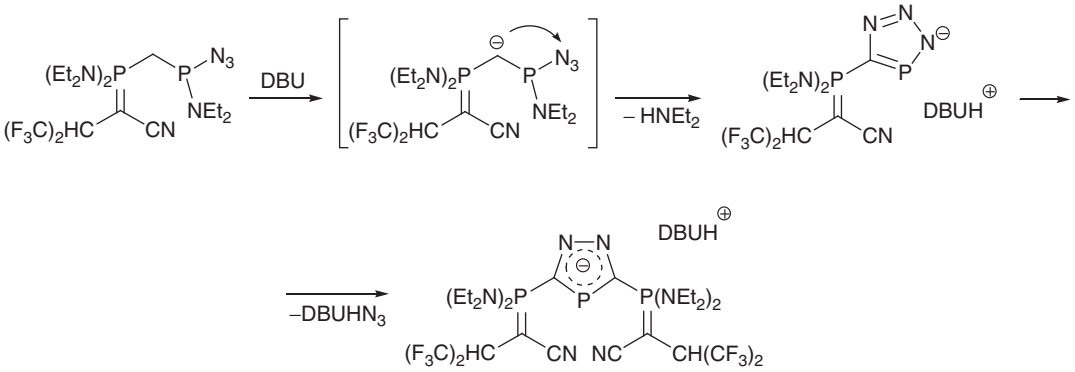
Reactions of the first type are not very popular inasmuch as they are often accompanied by side reactions, and it seems much easier to introduce the desired substituted chain to the phosphorus atom at the early stages of ylide synthesis. Examples known from the previous century involve reaction of allylidenetriphenylphosphoranes (*see* Chapter 2.04) with different chlorinating agents, such as alkyl chloroformates, acyl chlorides, 3-chloroacrylates, 2-chlorovinyl ketones, phosphorus chlorides, or other electrophilic compounds, followed by the proton abstraction (via transylidation) or proton migration to afford the corresponding derivatives functionalized at the γ-C atom of the side chain.[1] Also known are substitution at the second position of the cyclopentadienyl ring in cyclopentadienylidenetriphenylphosphorane under the action of electrophiles, a route limited to a single starting substrate, as well as substitution at the γ-C atom of α-keto-stabilized ylides or γ,δ-unsaturated acylphosphoranes via reaction of their lithiated derivatives with a range of electrophilic compounds (alkyl halides, aldehydes, ketones, benzoate esters, etc., and, in the second case, mainly alkyl halides). Furthermore, transformation of the side chain can be performed for additional functional groups, such as second ylide function, additional phosphonate group, halogen atom, and so on of the parent ylide.[1]

As a particular example, stabilized chlorophosphine ylide can be almost quantitatively transformed into the derivative having a two-coordinated phosphorus atom by dechlorination (equation 30). The addition of sulfur to the phosphaalkene double bond in this compound affords the corresponding $1,2\lambda^3,\sigma^3$-thiaphosphirane.[112]



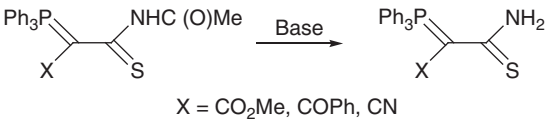
(30)

The above-mentioned chlorophosphine ylide can be also converted into the ylide derivative bearing phosphine azide group via treatment with sodium azide.[113] The addition of DBU to this product resulted in the intramolecular cyclization into triazaphosphole, having a two-coordinated phosphorus atom, in 85% yield. Over the isolation, the latter rearranges spontaneously into 1,2,4-diazaphosphole with two ylidic moieties. This transformation is likely to present a more general reaction that can be used for the synthesis of other 1,2,3,4-triazaphospholes.[113]

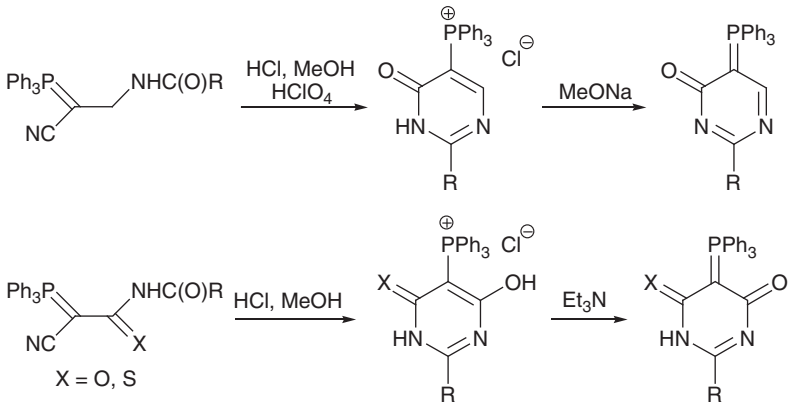


(31)

Recently it has been found that deacylation of *β*-acylamino-substituted ylides can be readily performed with sodium methylate, alkaline metal hydroxides, or ammonia (equation 32).[2,114] A modification of such transformation by the successive treatment of acylamino-substituted phosphorane with acid affording the intermediate cyclic phosphonium salt followed by deprotonation yielded polycentric pyrimidine-ylides (equation 33).[3,115]

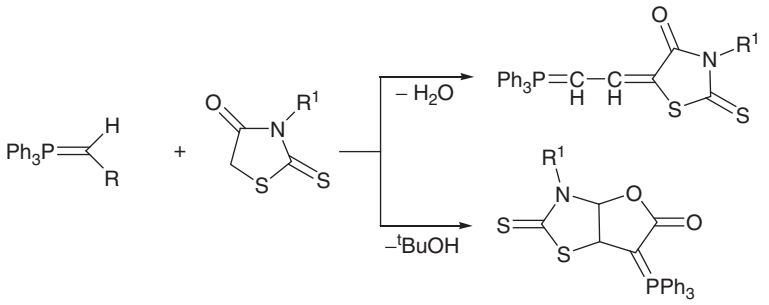


(32)



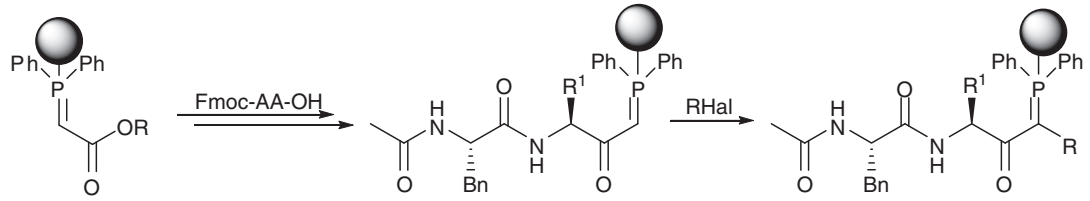
(33)

A side chain of some stabilized ylides may be transformed using the reaction with heterocycles bearing an activated methylene group, such as 2-thioxo-4-thiazolidinones (equation 34). However, this reaction is limited to formylmethylenephosphorane and *tert*-butoxycarboxyl derivative, while in the case of other substituents at the *C*-ylidic atom the nonphosphorylated products were isolated.[116]



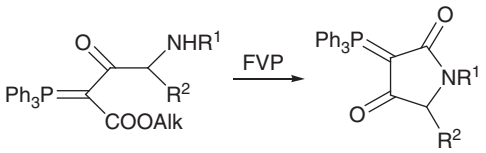
(34)

Note that transformation of a side chain can be performed using polymer-supported ylides. For example, α-keto-stabilized phosphorus ylides (trimethylsilylethyl or *tert*-butyl esters) easily undergo acylation with Fmoc-protected amino acid followed by peptide elongation under standard conditions and deprotection of ester groups with methyl iodide or benzyl bromide, which is accompanied by selective *C*-alkylation at the ylidic carbon atom leading to the decarboxylated peptidyl phosphoranes (equation 35).[117]



(35)

In some cases the transformation of a side chain yielding the new ylide may be performed by thermolysis, as, for example, in the synthesis of cyclic products from the corresponding linear phosphonium ylides bearing an acyl residue derived from amino acids (equation 36). At the same time, the presence of *N*-protected group in the precursors leads to the formation of alkyne derivatives via pyrolysis.[118]



(36)

6.05.2.4.2 By introduction of a substituent at the ylide carbon atom

The synthesis of novel ylides bearing additional heteroelement substituents at the α-C atom are typically accomplished by the interaction of parent phosphonium ylides bearing at least one proton at this carbon atom with a range of electrophilic reagents. These reactions lead to α-substituted phosphonium salts or zwitterionic intermediates, from which the corresponding substituted ylides are generated by deprotonation with an external base or via proton migration if the proton is sufficiently acidic.

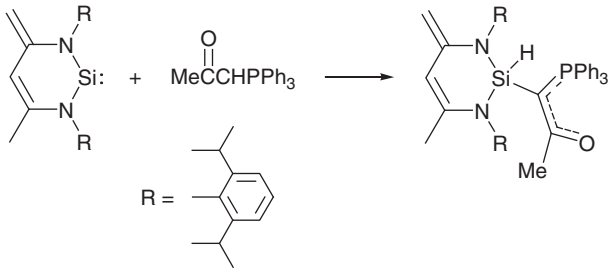
These reactions leading to substitution products were mainly developed in the 1970s–1980s (the known procedures are discussed in details in comprehensive reviews[1–3,6]) and involved synthesis of halogenated ylides from stabilized ylides and free halogen or halogen-containing derivatives. Among the latter type of reagents are bromo cyanide (in the presence of triethylamine); dichloro- and difluoro-iodobenzene; chloramine T; iodo bromide and perchloryl fluoride; 1-sulfur- and 1-selenium-substituted ylides, for example, alkyl(aryl)thio- and sulfonyl-alkylidenephosphoranes and their selenium analogs, available from the reaction of the related ylides with sulfenyl chlorides (selenyl halides) and sulfonic acid halides or anhydrides; 1-nitrogen substituted ylides, obtained form the reactions with azo-compounds; 1-silyl-, 1-germanium-, and 1-tin-substituted ylides, prepared by the reactions of ylide precursors with silicon, germanium, and tin halides (at a 2:1 ratio of the reagents) or by the reactions of ylide carbanions with element halides in a 1:1 ratio; 1-boron substituted ylides or bis(ylides) obtained by a similar approach via the reaction of ylides with dialkylchloroboranes, alkyldichloroboranes, and trialkylborates or (or *C*-trimethylsilylsubstituted

phosphinocarbene with trialkylborane[119]); and 1-phosphorus-substituted ylides, readily synthesized from the parent ylides and phosphorus(III) or phosphorus(V) acid halides. Note that the reactions of phosphorus acid chlorides having different surrounding at the phosphorus atom with nonstabilized phosphorus ylides can afford the products bearing one, two, or three phosphorus ylide groups at the trivalent[120] or pentavalent[121] phosphorus atom, depending on the nature of the initial reactant (equation 37).

$$R^1{}_3P{=}CHR^2 \xrightarrow[[R^1{}_3P^+CH_2R^2]Cl^-]{X \\ \| \\ R^3{}_nPCl_{3-n}} (R^1{}_3P{=}CR^2)_{3-n}\overset{X}{\overset{\|}{P}}R^3{}_n \qquad (37)$$

R^1 = Ph, $NAlk_2$, R^2 = H, Alk, R^3 = Alk, Ar, $NAlk_2$, Cl
X = O, S
n = 0–2

Quite recently it has been demonstrated that keto-stabilized phosphorus ylide reacts readily with silylene (equation 38). The reaction proceeded as the regiospecific activation of the ylide C(alkyl)–H bond to afford the corresponding *C*-silylated derivative.[122]



(38)

Of note also is the recently reported dehydrocoupling of triphenylphosphonium methylide with phenylsilane, leading to the silylated ylide $Ph_3PCHSiH_2Ph$, which is catalyzed by $[Y((N(SiMe_3)_2)_3]$.[123]

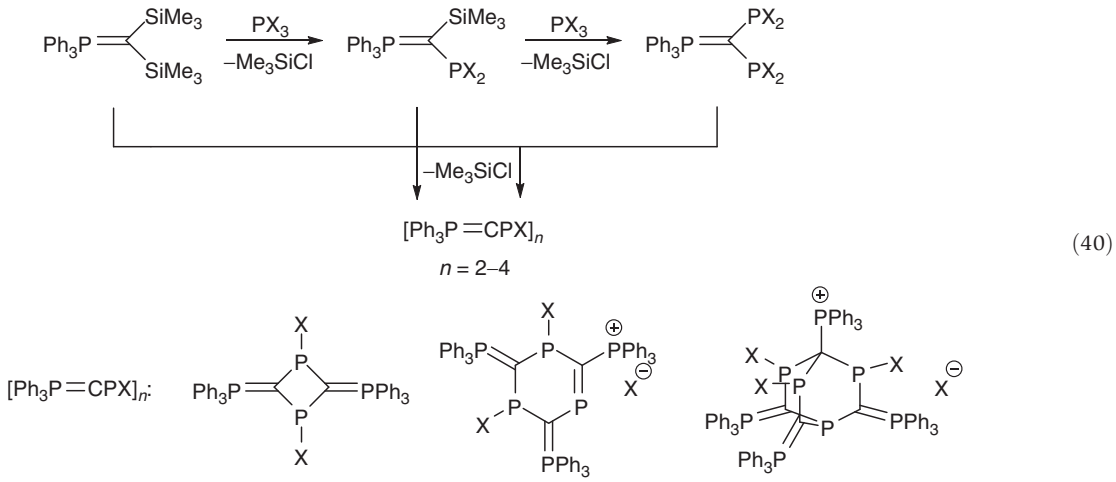
It should be noted that in some cases the application of ylide anions instead of neutral forms is more preferable, as the metal atoms in them are readily substituted for various groups in reactions with electrophiles, even those which do not react, or react with difficulty, with phosphorus ylides. Moreover, it is possible to perform further substitution in element-substituted phosphoranes, such as the displacement of one halogen atom for another halogen, thioisocyanato,[124] or organyl group (under the action of organometallic compounds), and, more conveniently, substitution of trimethylsilyl group at the α-carbon atom for a number of substituents using chlorine-containing electrophiles (e.g., chlorophosphines, chloroarsines, and chlorostilbines) to yield phosphorus-, arsenic-, and antimony-substituted ylides (equation 39).[125]

$$R^1{}_3P{=}C(R^2)SiMe_3 \xrightarrow[-\ Me_3SiCl]{R^3{}_2ECl} R^1{}_3P{=}CR^2ER^3{}_2 \qquad (39)$$

E = P, As, Sb

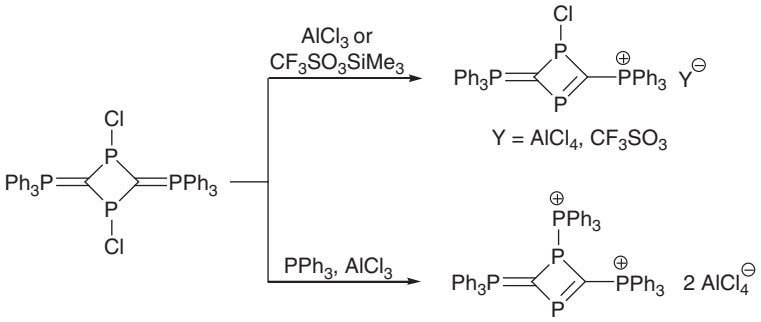
The three-valent phosphorus atom in the novel ylides also can undergo further reactions to afford stable compounds,[120b] including those having unusual structure, bearing the phosphonium group or the phosphorus atom in an unusual coordination, such as two-coordinated trivalent[126] and three-coordinated pentavalent phosphorus atoms.[127] Note that the ylide moiety effectively stabilizes the low coordination of phosphorus as long as it is bonded with an electronegative group, while ylide-substituted $Ph_3P{=}C(R)\text{-}P{=}P\text{-}(R)$ undergo dimerization.[126c]

Treatment of *C*-trimethylsilyl substituted ylides with phosphorus trihalides (X=Cl, Br) affords the dihalophosphanyl ylides, which can be oxidized by sulfur and selenium and are converted to ylidyl-chlorophosphenium (= chloro-phosphaalkenyl-phosphonium) salts $[Ph_3P\text{-}CR{=}PCl][AlCl_4]$.[128] In solutions, dihalophosphanyl ylides undergo self-condensation, affording mono- and bicyclic oligomers $(Ph_3PCPX)_n$ (n=2, 3, 4) (equation 40).[128a] A type of the dominating oligomer is determined by small changes in reaction conditions, such as starting substrate, solvent, concentration, and temperature. If a mixture of oligomers is obtained, the components can be separated by their different solubilities.[128a]



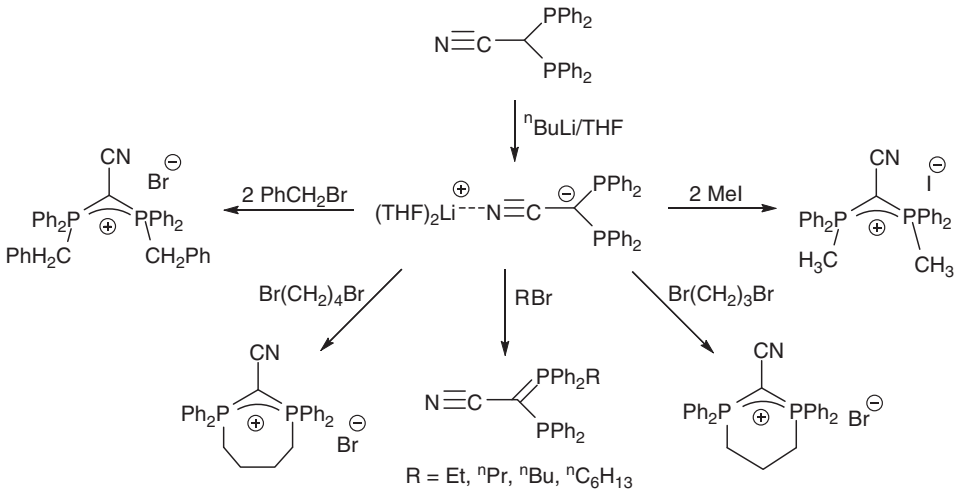
(40)

The reaction of a four-membered dimer with aluminum trichloride or trimethylsilyl trifluoromethanesulfonate causes dissociation of the P–Cl bond, and in the presence of triphenylphosphine an ylide-substituted cyclic dication is formed (equation 41).



(41)

A nontypical approach to phosphine-substituted ylides is based on the alkylation of THF-stabilized monomeric lithiobis-(diphenylphosphinyl)acetonitrile with alkyl bromides (R = Et, ^{n}Pr, ^{n}Bu, ^{n}Hex) which react selectively at one phosphorus atom of the substrate (equation 42).[129] However, more reactive methyl iodide or benzyl bromide resulted in the alkylation at both phosphorus atoms to give delocalized bis(phosphonium) ylides. Similarly, alkylation with 1,3- and 1,4-dibromoalkanes afforded six- and seven-membered heterocyclic bis(phosphonium) ylides (equation 42). The presence of delocalized $Ph_2RP–C(CN)–PRPh_2$ substructures in the latter two cases was unambiguously confirmed by NMR spectroscopy and X-ray diffraction analysis.



(42)

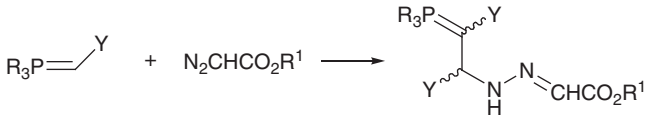
The area of phosphorus ylides substituted at the α-carbon atom by transition metal atoms relating to their coordination chemistry has been also well reviewed.[2,4] Furthermore, recent findings in the ylide coordination chemistry (up to 2008) are

covered in a review of Urriolabeitia,[130] which is focused on the bonding properties of ylides (*C*- versus *X*-coordination), their redox features and behavior in C–C coupling reactions, as well as participation in bond activation processes (C–H and C–P activation). The coordination properties of phosphonium ylide ligands in comparison with diaminocarbenes have been investigated systematically through a test family of *C,C*-chelating ligands containing two moieties of either kind fixed at 1,2-positions of the phenyl ring.[131] The typical synthesis of these metal-containing ylidic compounds is based on the reaction of ylides with the corresponding metal precursor. The peculiarities of recent examples of such reactions can be also found in the corresponding chapters of annual volumes of `SPR-Organophosphorus Chemistry.'[132]

As for the introduction of an alkyl group instead of the α-proton, two alternative routes are typically used.[1] The first is based on the reaction with an alkylating agent followed by deprotonation of the resulting phosphonium salt either with the second mole of the original ylide or with an external base. It should be mentioned that not only alkyl halides (often containing additional functional groups) but also such reactants as Mannich bases, strained cyclic compounds (epoxides or aziridines), pyrylium salts, and others can be used as alkylating agents. The second route comprises the Michael addition of a phosphorane to the activated C=C double bonds, which was developed at the same period of time.

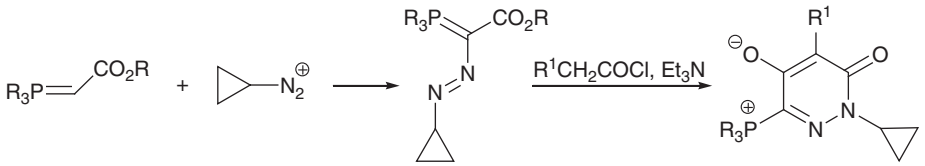
Similarly, the alkenylation of alkylidenephosphoranes may be performed by the reaction of the starting phosphorane with conjugated alkynes and allenes (but the Michael addition is restricted to stabilized ylides) or with alkenylating reagents.[1]

Alternatively, phosphorus ylides can be reacted with diazo esters, leading to novel phosphorus ylides bearing a polyfunctional substituent at the α-carbon (equation 43). The multistep process was found to proceed via bonding of the starting ylide α-carbon with the terminal *N*-atom of the diazo component at the first stage followed by elimination of the ylide-forming molecule and successive addition of the second ylide fragment.[133]



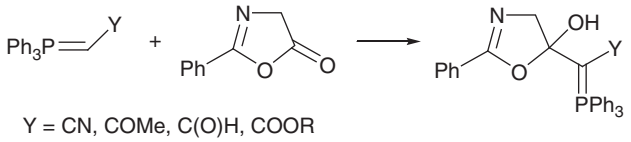
(43)

In contrast to diazo esters, the reaction of stabilized ylides with diazocyclopropane generated *in situ* affords only *N*-substituted cyclopropylazophosphorane (equation 44). This stable ylide can be further used in the reactions of side-chain transformation yielding cyclopropyl-substituted heterocyclic betaines.



(44)

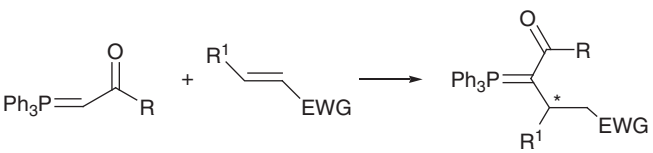
Furthermore, the reaction of stabilized ylides $Ph_3P{=}CH{-}Y$ (Y=COOMe, COOEt, CN, CHO) at the keto-function of such heterocycles as 2-phenyl-5-(4*H*)-oxazolone yields β-hydroxy-substituted cyclic phosphoranes with an exocyclic phosphorus atom (equation 45).[134]



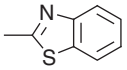
Y = CN, COMe, C(O)H, COOR

(45)

The addition of stabilized ylides via formation of the Michael addition product, often followed by prototropic shift, proceeded also in the case of alkenes activated by an electron-withdrawing group (without the γ-hydroxy group), resulting in new functionalized ylides (equation 46).[135] If the reaction was performed in the presence of chiral amine salts, generated *in situ* as catalysts (the best combination was *N*-Boc-L-proline plus (9*S*)-6′-methoxycinchonan-9-amine), it provided, after proton shift, stabilized phosphorus ylides in up to 82% *ee*, and enantiopure products were isolated by recrystallization.[136]

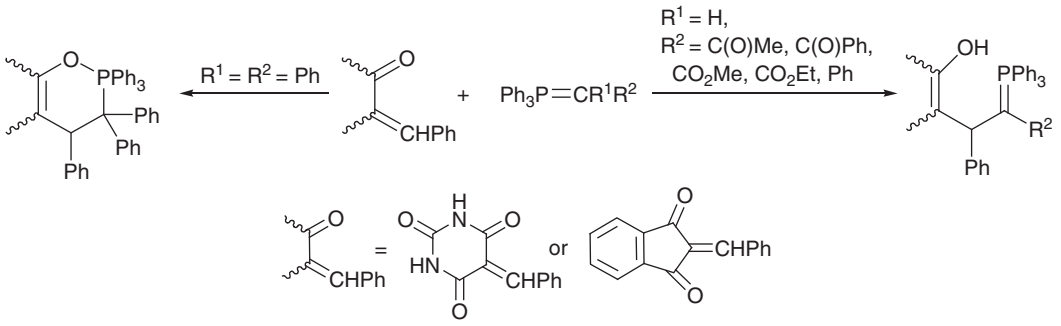


EWG = COAlk, COPh, COOAlk,



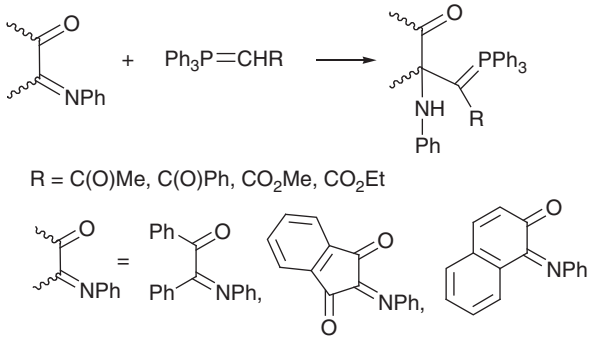
(46)

This reaction strategy for the synthesis of highly functionalized phosphorus ylides was also realized using *o*- and *p*-quinones,[137] niclosamide Mannich bases,[138] and 2-benzylidene-1,3-indandione 5-benzylidenebarbituric acid,[139] where in the case of the starting ylide lacking the proton at the *α*-carbon atom, fused cyclic products were formed (equation 47).



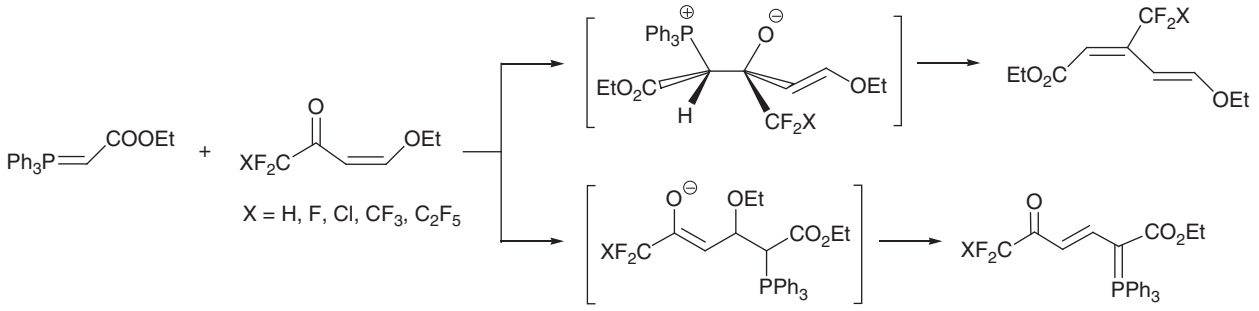
(47)

The reaction of stabilized ylides proceeds analogously in the case of unsaturated starting derivatives bearing C=N double bond instead of C=C, for example, quinone monoanils, to afford novel *β*-aminosubstituted ylides (equation 48).[140]



(48)

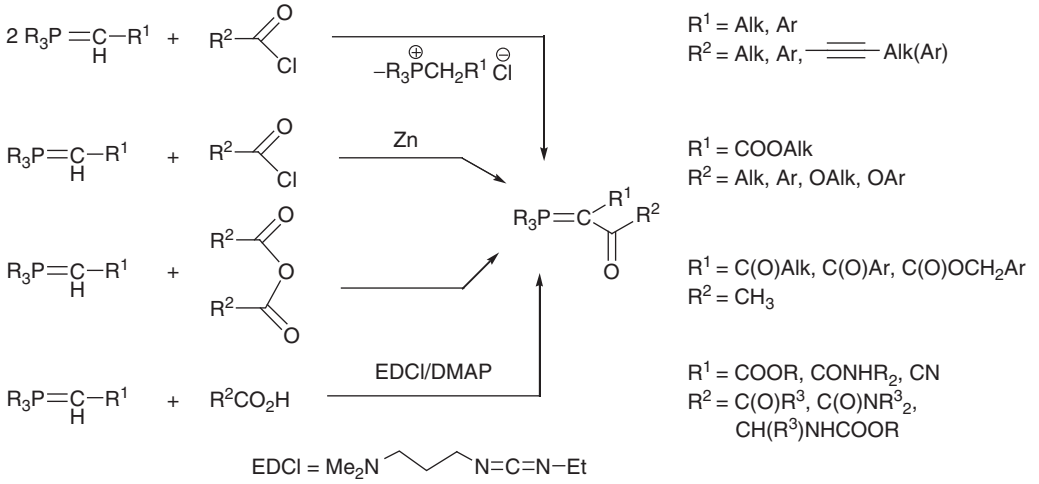
In the case of *β*-alkoxyvinyl polyfluoroalkyl ketones, a mixture of alkoxydienes (the Wittig reaction product) and polyfluoroacyl vinyl ylides (the Michael addition products) was formed due to the concurrent 1,2- and 1,4-addition of the starting phosphorus substrate (equation 49). The yield of the first reaction product decreased with an increase of the polyfluoroalkyl group volume and its electron-withdrawing effect.[141]



(49)

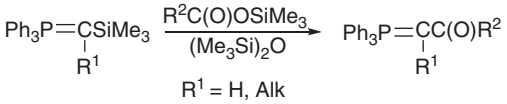
A widely known process introduced by H. J. Bestmann and coworkers as early as in the 1960s represents the transformation of the parent phosphonium ylides to the corresponding *β*-oxophosphonium derivatives via acylation (equation 50). In this case the acidity of the salt obtained is greater than that of the starting phosphorane, and it reacts with the second mole of the starting ylide according to the transylidation scheme (the second mole of the starting ylide necessary for the transylidation may be substituted for the tertiary amine if the latter is the stronger base than the ylide) to give *α*-substituted ylide and the conjugated salt of the original ylide.[1] Recently, the reaction was suggested to perform using as acylating agents acyl chlorides and *in situ* transylidation,[142] methyl chloro(xo)acetate,[143] the corresponding zinc promoted version,[144] allowing one to avoid the application of an extra equivalent of the starting ylide as a consequence of the transylidation reaction, acetic anhydride,[145] and direct acylation of stabilized phosphonium ylides by carboxylic acids, including *a*-aminoacids, in the presence of EDCI/DMAP.[146] Furthermore,

chiral *N*-Boc- and Cbz-protected (α-aminoacyl)benzotriazoles (derived from L-Ala, L-Val, L-Phe, L-Asp(OMe), L-Trp) can be used as acylation reagents, and the reaction can be promoted by microwave induction to afford, starting from ethyl (triphenylphosphoranylidene)acetate, chiral phosphorus ylides in 65–90% yield. Note that the reactions of diastereomeric chiral phosphorus ylides demonstrated the preservation of chirality.[147]



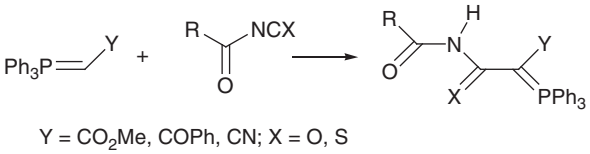
(50)

Moreover, acyl-substituted ylides can be synthesized via the reaction of *C*-silyl-substituted phosphorus ylides with trimethylsilyl carboxylates, which is accompanied by the elimination of hexamethyldisiloxane (equation 51).[148]



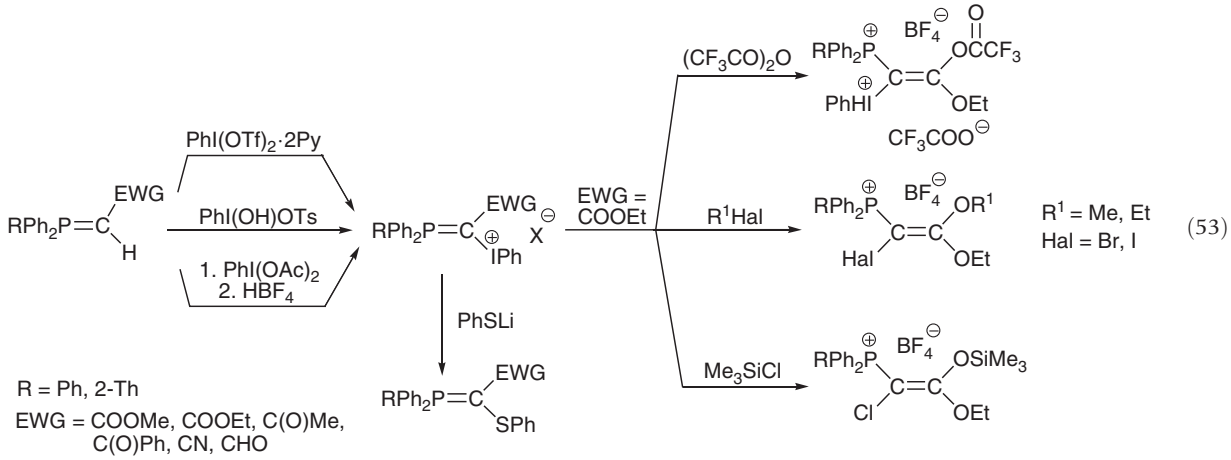
(51)

Among the developed routes to substituted ylides bearing functional groups derived from the carboxy group (alkoxycarbonyl, alkylthiocarbonyl, carbamoyl, etc.), the approach based on the addition of stabilized ylides to isocyanates and their thioanalogs should be mentioned.[149] Independently of the structure of the final products, which depends on the nature of the ylide and cumulene as well as reaction conditions, the first reaction step resulted in the formation of 1:1 adducts via the electrophilic center of the –N=C=X (X=O, S) moiety. Sometimes the adducts formed were stabilized by the transformation into heterocyclic compounds. More recently, this approach was used for the synthesis of stable β-acylamino-substituted ylides by the reaction of acyliso(thio)cyanates (equation 52).[23,150]



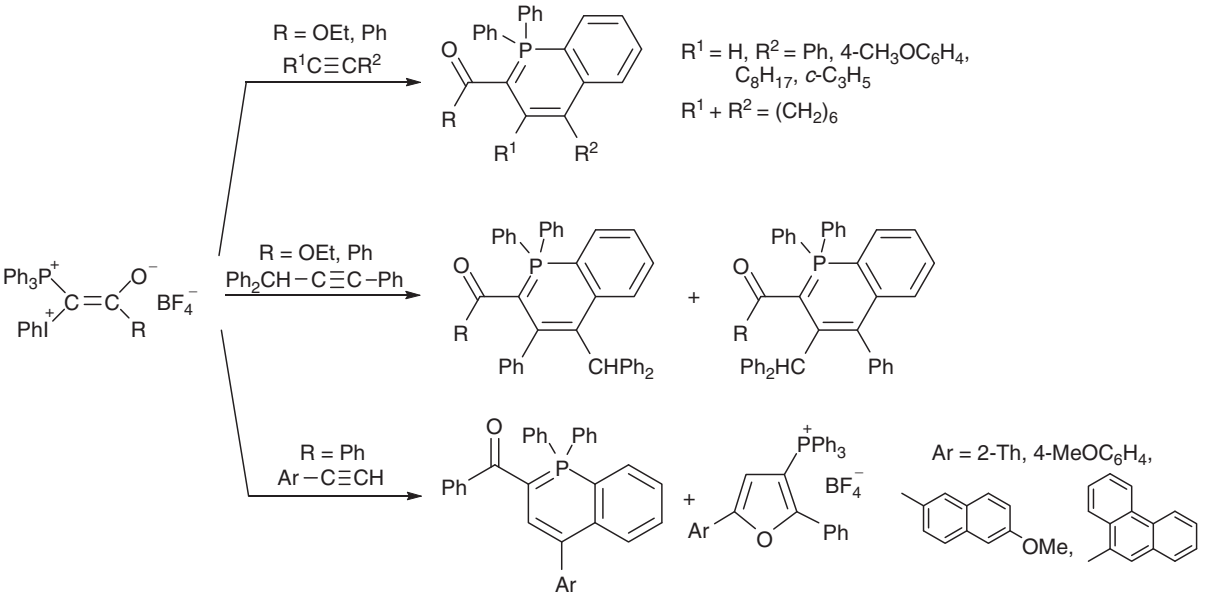
(52)

Suitable substrates for the preparation of novel phosphorus ylides by this synthetic strategy present mixed phenyliodonio α-substituted phosphonium ylides, also obtained via transformation of stabilized ylides under the action of phenyliodine ditriflate, hydroxytosylate, or diacetate, followed by treatment with HBF_4 (equation 53).[151] The iodonium group in these ylides can be further substituted by nucleophiles, such as PhSLi, to give mercaptosubstituted phosphorus ylides.[151a] Furthermore, these reactive ylides readily undergo further acylations, alkylations, and silylation to give highly functionalized phosphonium derivatives[152] (equation 53). Note that for such modifications, tetrafluoroborates, being the more stable in this series, are more convenient than tosylates, which, in turn, are more stable than triflates.



(53)

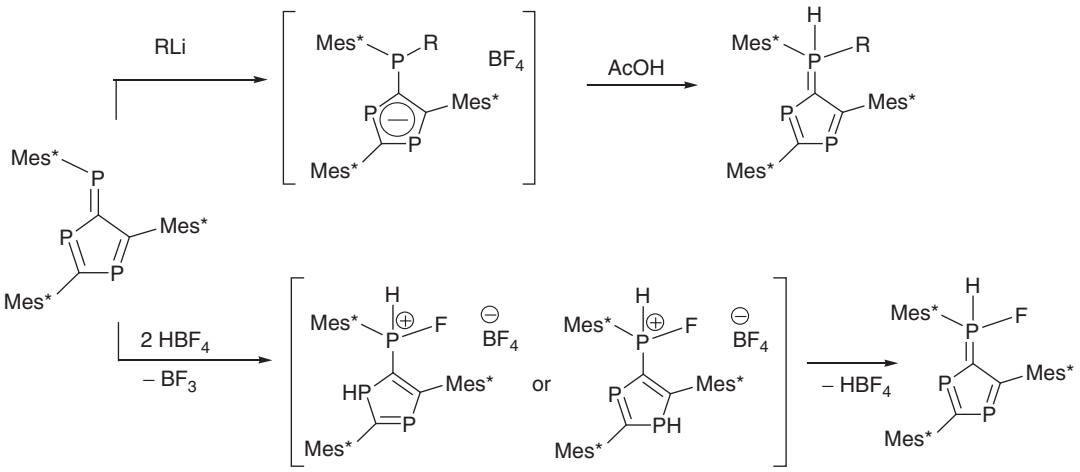
A photochemical reaction of the mixed phosphonium-iodonium ylides with aryl-, alkyl-, cyclopropyl substituted terminal, conjugated, and cyclic acetylenes afforded λ^5-phosphinolines in 35–80% yields; these belong to a rare class of phosphorus heterocycles with endocyclic ylide moiety hardly accessible by other methods (equation 54).[153] Mostly, the reaction proceeds regiospecifically; however, benzoyl-substituted ylide reacted with 1,3,3-triphenylpropyne, yielding two regioisomers, while reaction with aromatic terminal acetylenes afforded two heterocyclic systems, namely, λ^5-phosphinolines and phosphonium-substituted furans.[154]



(54)

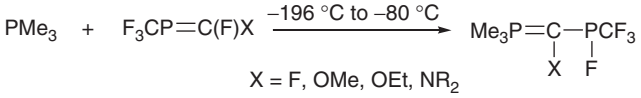
6.05.2.5 Synthesis from Two-Coordinated Phosphorus Compounds

The oxidative addition of the R–H bond to the sp^2-phosphorus atom allows one to obtain phosphorus ylides from phosphaalkenes, which can be exemplified by the corresponding transformations of MesP=CPh_2 (Mes=2,4,6-$Me_3C_6H_2$)[155] and 1,3,6-triphosphafulvene (equation 55).[156] In the latter case, lithiation followed by treatment with acetic acid occurred at the *exo* sp^2-phosphorus atoms, affording 1,3-diphosphacyclopentadienylidene-phosphoranes, i.e., phosphorus ylide bearing P–H bond, while the reaction with hydrogen tetrafluoroborate yielded the phosphorus ylide bearing both P–H and P–F bonds. In contrast to their linear analogs, these ylides did not isomerize through H-migration into the corresponding phosphinodiphospholes, probably due to the π-accepting ability of the unsaturated P–C bonds and aromaticity of the C_3P_2 ring.



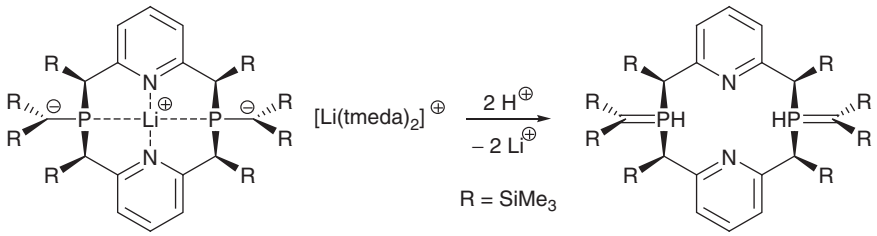
(55)

Phosphorus ylides substituted by the trivalent phosphorus atom can be also obtained from the addition of trimethylphosphine to fluorinated phosphaalkenes (equation 56). The formation of ylides was explained by the electrophilic character of the two-coordinated phosphorus atom.[157] This reaction is accompanied by the substitution of the fluorine atom at the sp^2-hybridized carbon atom with the phosphonium group and subsequent migration of the fluorine.



(56)

Recently, Niecke and coworkers[158] have succeeded in isolating a cyclic phosphorus ylide where trimethylsilyl and pyridyl groups stabilize the >P(H)=C< system instead of the expected and thermodynamically more favorable phosphine (equation 57). This PH-ylide was formed via the kinetically controlled protonation of the cyclic phosphamethanide complex. As the electrostatic potential on the surfaces of the Li derivative shows, the attack of the proton on the sterically well-shielded methanide carbon atom, and thus the formation of the phosphine form, is hindered.



(57)

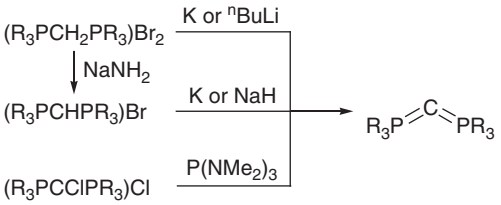
6.05.3 Cumulated Phosphoranes: Synthesis and Transformation into Alkylidenephosphoranes

6.05.3.1 Carbodiphosphoranes

Carbodiphosphoranes ($1\sigma^4,3\sigma^4$-diphosphaallenes) $C(PR_3)_2$ (CDP) are particular examples of phosphorus double ylides that are considered as divalent carbon(0) derivatives having peculiar donor properties: the central carbon(0) atom has two electron pairs and is additionally stabilized by two neutral phosphine ligands to attain an electron octet. Thus, the bonding situation in CDP is best described by the formula $R_3P{\rightarrow}C{\leftarrow}PR_3$. Like *N*-heterocyclic carbenes (NHC), carbodiphosphoranes have a bent conformation, but the donor-acceptor character of C–P interactions conceptually distinguishes these divalent carbon derivatives from carbenes CR_2 in which the central carbon atom contributes two electrons to form electron-sharing C–R bonds and formally possesses an electron sextet. The compounds of the general type CL_2 (L=PPh_3, NHC, etc.), in which L is a neutral donor molecule, are often termed carbones. The electronic structure of CDPs was also studied by quantum chemical methods including NBO analysis, which confirmed the presence of two high-lying occupied MO of σ and π symmetry (HOMO and HOMO-1) at the sp^2-carbon atom.[159]

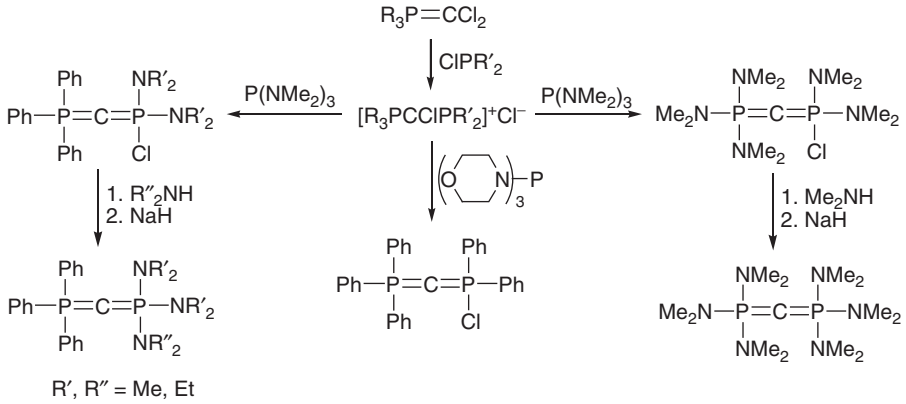
Since the synthesis of the first carbodiphosphorane, $C(PPh_3)_2$, as early as in 1961 by Ramirez et al.,[160] the chemistry of CDPs has attracted considerable interest among several research groups, and numerous compounds containing the CDP moieties were isolated.[3,161] A recent comprehensive review considers CDPs both as free molecules and as ligands in transition metal complexes.[162]

Developed in the 1960s and 1970s the general synthetic routes to hexaorganocarbodiphosphoranes include dehydrohalogenation or dehalogenation of suitable phosphonium salt precursors (equation 58). Thus, a series of symmetrical alkyl/phenyl-substituted carbodiphosphoranes CL_2 were produced, where L is PPh_3,[160,163,164] PMe_3,[120c,165] $PPhMe_2$,[165] or PPh_2Me.[166] The application of mixed phosphonium salts, such as $[R_3PCHPPh_3]Cl$ or $[R_3PCClPPh_3]Cl$ (R = Et, ^{n}Pr, ^{n}Bu), afforded unsymmetrical carbodiphosphoranes.[167] The latter may also result from the skeletal rearrangements of other bis(ylide) precursors.[168] Note that the choice of a base for the deprotonation depends on the nature of the starting phosphonium salt, and suitable bases include sodium amide, alkali metal hydrides, alkylidenetrialkylphosphoranes, potassium, or organolithium compounds.[161,162] A list of all known symmetrical and unsymmetrical (both cyclic and acyclic) CDP derivatives up to 1983 was summarized in a publication by Schmidbaur et al.[169]



(58)

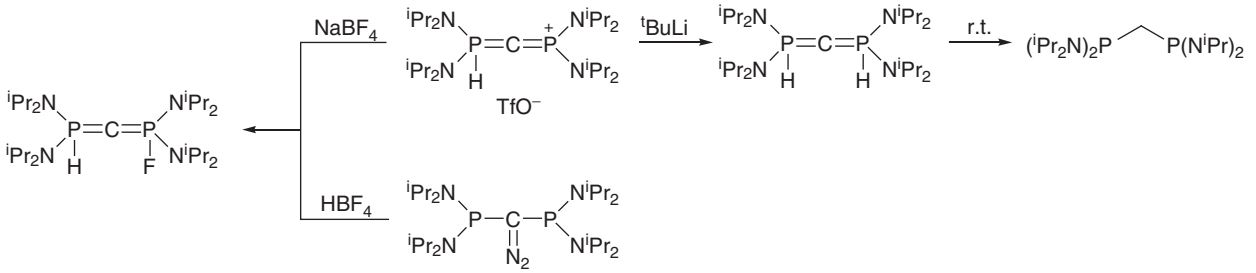
Dechlorination of appropriate phosphonium salts may also give access to heterosubstituted carbodiphosphoranes. Thus, a number of amino- and chlorosubstituted CDPs were produced from $[R_3PCClPR'_2]Cl$ under the action of triaminophosphines (equation 59).[170,171] The corresponding starting phosphonium derivatives were obtained, in turn, by the reaction of dichloromethylenephosphoranes with phosphorous or phosphinous acid chlorides. The resulting monochlorine amino-substituted CDPs can be further transformed by the introduction of an additional NR''_2 group either into symmetrical hexakis (dimethylamino)-carbodiphosphorane or unsymmetrical tris(amino)[(triphenylphosphoranylidene)methylene]phosphoranes.[165]



(59)

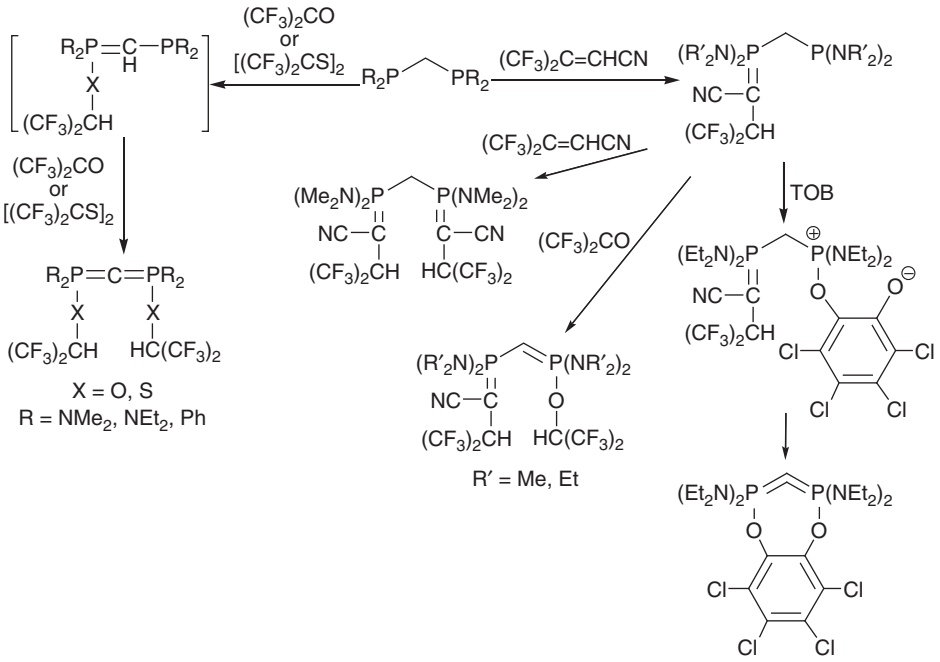
The symmetrically halogenated species $C(PClPh_2)_2$ were synthesized by the reaction of CCl_4 with $Ph_2P–CH(SiMe_3)–PPh_2$.[172] The treatment of methylenebis(difluorophosphoranes) $R_2F_2PCH_2PR_2F_2$ (R = Ph, NMe_2) with ^{n}BuLi afforded fluorinated CDPs.[173] However, both methods have no general character and relate to these particular examples.

Over the last two decades, the main advances were made in the field of heterosubstituted carbodiphosphorane derivatives. Thus, Bertrand et al.[174] introduced the first CDP with a P–H bond, which was obtained by the nucleophilic attack at the phosphonioyl(phosphoranediyl)carbene $[(^iPr_2N)_2P(H)CP(N^iPr_2)_2]^+$ bearing bulky diisopropylamino groups or generated directly from the corresponding diphosphinodiazomethane under the action of tetrafluoroboric acid (equation 60). Moreover, treatment of the starting (phosphino)(phosphonio)carbene with ^{t}BuLi led to CDP featuring two P–H bonds, which was characterized in solution (equation 60).[175] However, this carbodiphosphorane readily rearranges at room temperature into diphosphinomethane as a result of prototropic shifts.



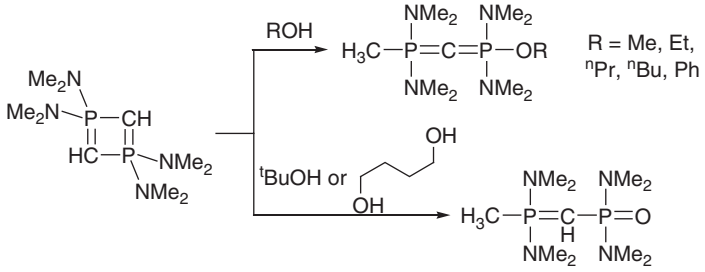
(60)

A facile synthesis of 1-fluoroalkoxy- or l-fluoroalkylmercapto-substituted carbodiphosphoranes in quantitative yields was accomplished by the treatment of methylene diphosphines with hexafluoroacetone or its thioanalog (equation 61).[176,177,178] Interesting as an unusual reaction leading to carbodiphosphoranes instead of the expected phospholane derivatives, this route is limited by the above electrophilic (thio)carbonyl reactants only. Thus, the substitution of the (thio)carbonyl function with a C=C double bond of bis(trifluoromethyl)acrylonitrile yields only monoylide products, which nevertheless can be used as suitable precursors for symmetrical and unsymmetrical bis(ylide) derivatives.[179] Moreover, the oxidation of such monoylide derivative with tetrachloroorthobenzoquinone (TOB) does not afford the expected 1,2,3-dioxaphospholane but terminated at the formation of unusually stable intermediate zwitterion, which converts in solution at T > 15 °C into symmetrical cyclic CDP eliminating hexafluoroisovaleronitrile.[180]



(61)

Alcoholysis of 1,1′,3,3′-tetrakis(dimethylamino)-1λ^5,3λ^5-diphosphete, representing a dimeric derivative of a three-coordinated phosphorus compound, with aliphatic and aromatic alcohols ROH (R=Me, Et, ^{n}Pr, ^{n}Bu, and Ph) yielded the alk(phen)oxy substituted carbodiphosphoranes (equation 62). Note that in the case of *tert*-butanol or 1,4-butanediol, the unstable primary products eliminate isobutene or tetrahydrofuran to give phosphoryl-substituted monoylides.[181]

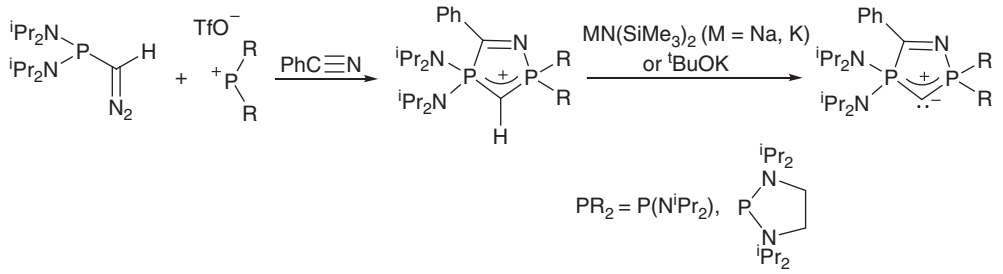


(62)

The cyclic carbodiphosphoranes with five-, six-, and seven-membered rings, described for the first time by Schmidbaur et al.,[182,183] can be generated by the quaternization of methylenebis(diphenylphosphine) with dibromoalkanes Br$(CH_2)_n$Br (n=2–4) followed by the mild dehydrohalogenation of the resulting bis(phosphonium salts) using $Me_3P{=}CH_2$ as a transylidating agent. A cyclic CDP derivative with a 1,3-diphosphaindane skeleton was also synthesized by the deprotonation of the corresponding bis(phosphonium) precursor.[184] Other ring-strained cyclic carbodiphosphoranes with an annulated *o*-phenylene moiety resulted from the unusual intramolecular rearrangement of methylenebis(methyldimesitylphosphonium iodide), $[CH_2(PMes_2(CH_3)_2]I_2$, under the action of bases, accompanied by the elimination of mesitylene.[185] Note that the stability of cyclic CDPs is markedly influenced not only by the nature of the substituents at the phosphorus atom, but also by the ring sizes, and most of the previously reported examples were found to be very unstable.

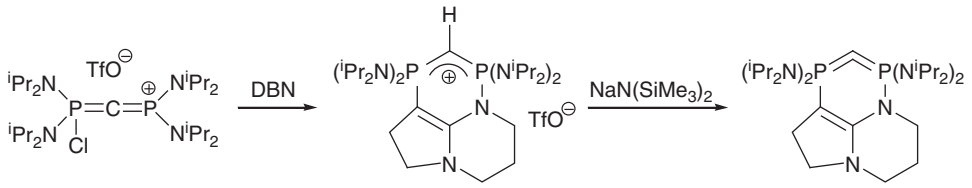
Recently, Baceiredo et al.[186] described the rare examples of stable cyclic carbodiphosphoranes stabilized by bulky substituents at the phosphorus atoms, which were readily generated by the deprotonation of the corresponding cationic precursors with

potassium or sodium hexamethyldisilazide (equation 63). The key five-membered heterocyclic cations, in turn, were prepared by the previously reported method that exploits the reactivity of transient diphosphino carbocations as 1,3-dipoles. Thus, the reaction of bis(diisopropyl)phosphine diazomethane with a bis(dialkylamino)phosphenium salt in the presence of a large excess of benzonitrile leads cleanly, after evolution of nitrogen, to the desired heterocyclic cations in good yields.[187] The cyclization is totally regioselective in the case of diazaphospholidine derivative and gives the product in which the imine nitrogen atom is bound to the less hindered phosphorus atom. Deprotonation with potassium *tert*-butoxide in THF at −78 °C followed by the addition of CuCl and AuCl(Me_2S) cleanly yields the corresponding complexes.[188]



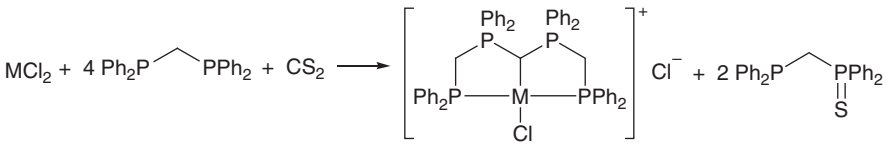
(63)

1,3-Dinucleophilic attack of DBN on the (phosphino)(*P*-chlorophosphonio)carbene followed by deprotonation with sodium hexamethyldisilazide afforded another example of stable cyclic carbodiphosphoranes (equation 64).[189]



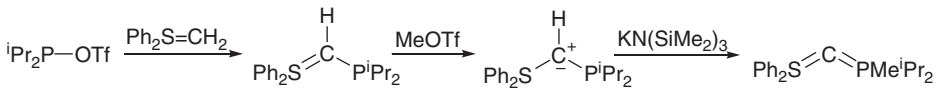
(64)

Finally, an elegant route to carbodiphosphoranes consists in the template assembling of CDP ligand in the 10 group metal coordination sphere.[190] Thus, the one-pot reaction of $Ph_2PCH_2PPh_2$ (dppm), CS_2, and MCl_2 (M = Pd, Ni, Pt) smoothly gave PCP pincer complexes with a central carbodiphosphorane moiety, accompanied by the release of $Ph_2PCH_2P(S)Ph_2$ (equation 65). Although the reaction mechanism is still not fully understood, of special note is the double role of CS_2 as both a C_1 source and a single sulfur acceptor, which was found to be irreplaceable to enable the overall process (e.g., application of Ph_3P as a desulfurization agent was unsuccessful).



(65)

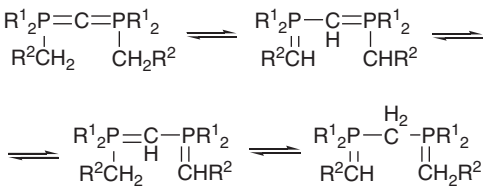
Among the related carbone derivatives, of particular interest is the unique mixed phosphonium-sulfonium double ylide, $C(PMeR_2)(SPh_2)$, which was prepared by the deprotonation of a suitable phosphonium salt already featuring the phosphorus–carbon–sulfur skeleton (equation 66). The latter was synthesized from $^iPr_2POTf$ and diphenylsulfonium ylide via treatment of the intermediate phosphorus-substituted sulfonium ylide with MeOTf.[191]



(66)

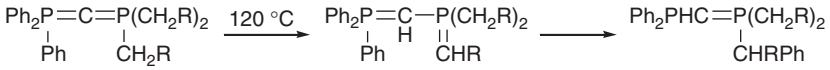
The above P=C=S cumulene is stable for days at T > −20 °C, but it decomposes at room temperature ($t_{1/2}$ = 10 h in C_6D_6). The formation of this phosphorane was confirmed along with the NMR data by its chemical reactivity.

It should be underlined that CDPs bearing alkyl groups at the phosphorus atom exist as prototropic tautomers due to intramolecular prototropic exchange, and electron-donating substituents shift the equilibrium toward the carbodiphosphorane form (equation 67).[168,183,192]



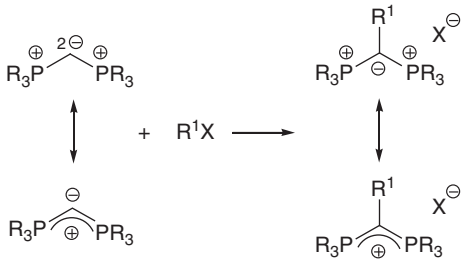
(67)

Using this peculiarity of alkyl-substituted CDPs, the nonsymmetric carbodiphosphoranes were converted under thermal heating into phosphino-substituted ylides via the intermediate formation of bis-ylide as a result of phenyl group migration from the phosphorus atom to the ylide carbon atom (equation 68).[193]



(68)

Finally, a typical route for transformation of carbodiphosphoranes to 'more simple' ylides is based on reactions with a range of electrophilic agents such as alkyl halides, acyl chlorides, phosphorus acid halides, chlorotrimethylsilane, and so on, which can proceed as substitution both at the central carbon atom or in the side chain depending on the electrophile[1,2] (equation 69). Thus, the reactions with alkyl halides, chlorophosphines, and acid chlorides afford the ylides substituted by phosphonium groups, which could be described as salts of diphosphaallyl cations, while hexamethylcarbodiphosphorane reacts with chlorotrimethylsilane to give the ylide containing a trimethylsilyl group at the side carbon atom. The related reactions involve sulfur or selenium addition followed by alkylation.



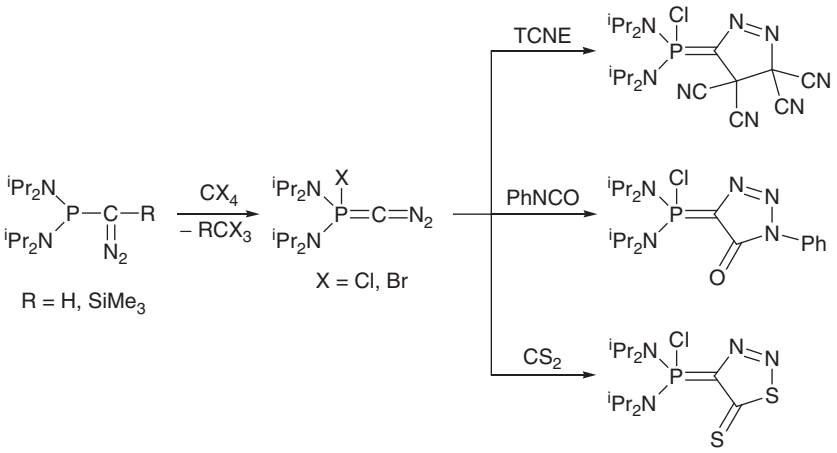
(69)

6.05.3.2 Phosphacumulenes

Known since the 1960s from the pioneer works of Birum, phosphacumulene ylides of the type $R_3P{=}C{=}C{=}X$ and those of the type $R_3P{=}C{=}CR'_2$, designated phosphaallene ylides, which combine in one molecule the conjugated phosphorus ylide group and cumulene moiety, became a versatile tool in synthetic organic and organophosphorus chemistry due to their strongly nucleophilic electron system and ability to participate in a variety of (cyclo)addition reactions which can occur both at the polar C–P ylide bond and at the C=C double bond.

The most obvious route to phosphacumulenes, similar to 'more simple' ylides, consists in the deprotonation of vinylphosphonium salts by suitable (strong) bases or dehydrohalogenation of 2,3-dihalogeno-2-propenyl phosphonium salts.[1,194,195] Deprotonation may also be applied for substituted ylide precursors (under the action of sodium hexamethyldisilazide), but has not found widespread application. Birum et al.[196,197] reported the method based on the reaction of hexaphenylcarbodiphosphorane with carbon dioxide, carbon disulfide, and isothiocyanates, followed by thermolysis of the intermediate betaines to yield oxovinylidene-, thioxovinylidene-, and iminovinylidenetriphenylphosphoranes. Another widely used strategy, well developed by Bestmann et al.,[149a] involves the interaction of three equivalents of methylenetriphenylphosphorane with geminal dihalo compounds (isocyanide dichlorides, thiophosgene, 1,1-dihalo-1-alkenes); therewith, $Ph_3P{=}CH_2$ goes into the formation of phosphonium salt, its transylidation, and dehydrohalogenation of the resulting derivative. A special case is the synthesis of diethoxyvinylidenetriphenylphosphorane – a versatile reagent for further transformations, which can be obtained by *O*-alkylation of carboethoxy-substituted phosphorane by triethyloxonium tetrafluoroborate, followed by deprotonation of the intermediate phosphonium tetrafluoroborate salt.[149a] These routes provided the corresponding phosphacumulenes $R_3P{=}C{=}C{=}X$ bearing C=S, C=O, and C=N–Ph functional groups and phenyl groups at the phosphorus atom, which became in time useful synthetic tools for design of 'more simple ylides' as well as a variety of heterocyclic compounds,[198] including those having exocyclic phosphonium or *P*-ylidic moieties.

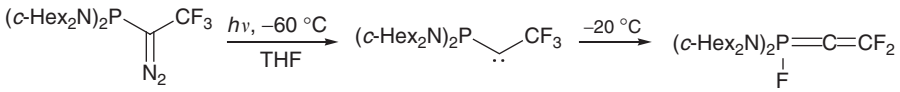
The development of this area over the past two decades is mainly associated with the synthetic strategies for heterocumulenes featuring other PCX sequence and especially those with a PCP skeleton. Thus, addition of a stoichiometric amount of carbon tetrahalide to (bis(diisopropy1amino)phosphino)diazomethane at room temperature leads, after loss of chloroform (or trimethylsilylchloroform), to diazomethylenephosphoranes having a $P{=}C{=}N_2$ scaffold (equation 70).[199]



(70)

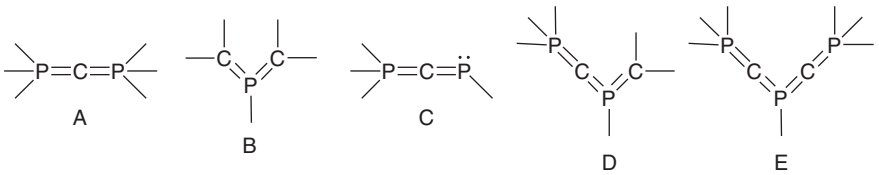
Interestingly, these compounds are stable in solution for several weeks but decompose slowly in the absence of a solvent. Their reactions with tetracyanoethylene (TCNE), carbon disulfide, and phenyl isocyanate afford phosphoranes with heterocyclic moieties at the α-carbon atom (equation 70), which are the adducts of [2+3] cycloaddition on the diazo group.

An interesting route to phosphacumulene with a PCC scaffold, introduced by G. Bertrand et al.,[200] has been based on the phosphinodiazomethane derivative bearing trifluoromethyl group as a starting substrate. This compound readily transforms to (phosphinyl)(trifluoromethyl)carbene under UV irradiation followed by rearrangement upon warming of the THF solution from −60 °C to −20 °C, which presumably includes two successive fluorine migration (equation 71).



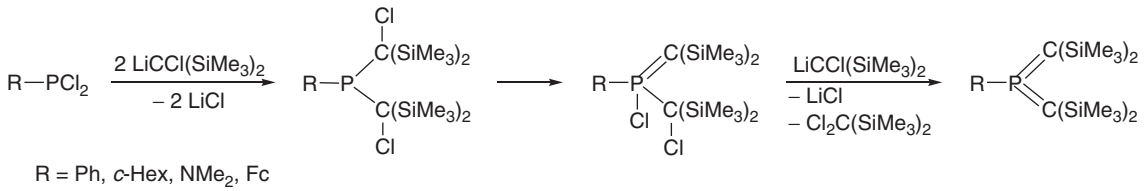
(71)

Phosphacumulenes with a PCP scaffold and at least one ylidic phosphorus atom can be divided into a few types, namely, carbodiphosphoranes A (discussed in Section 6.05.3.1), bis-(methylene)phosphoranes B, phosphine-substituted compounds C, and prolonged conjugated systems D and E (equation 72).

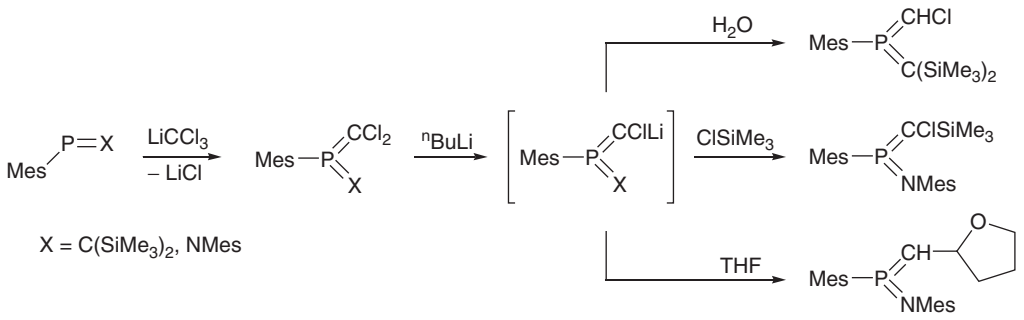


(72)

Bis(methylene)phosphoranes B are usually prepared by the addition of two equivalents of a carbenoid to dichlorophosphine[201] (equation 73) or from two-coordinated phosphorus derivatives (equation 74).[202]

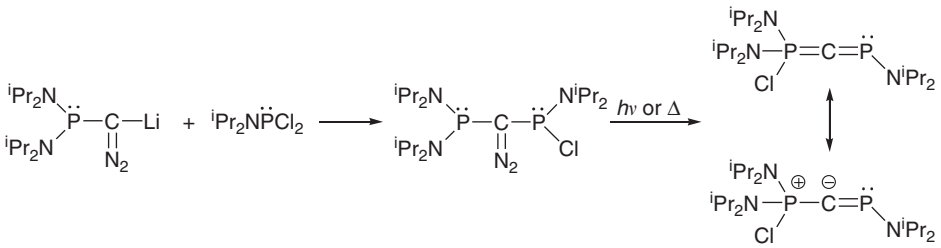


(73)



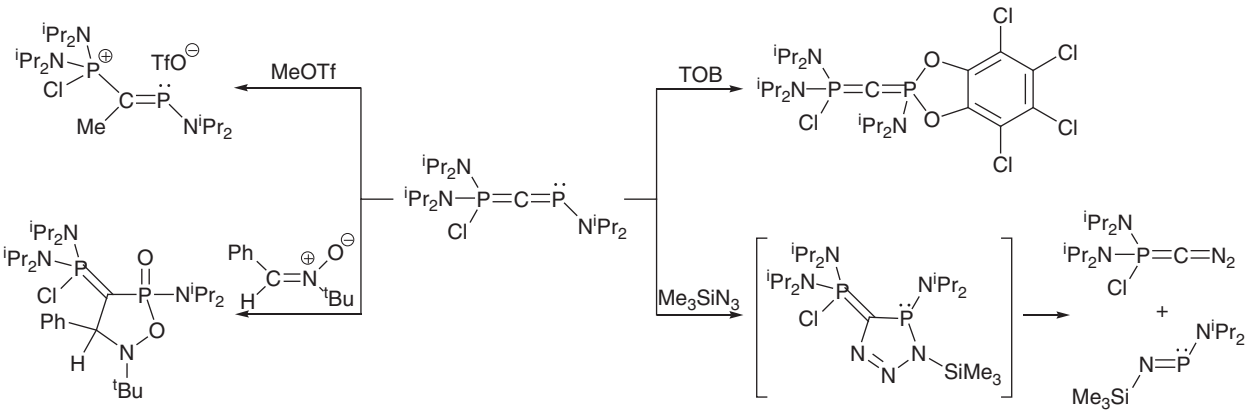
(74)

The elimination of N_2 from phosphinyl(chlorophosphinyl)diazomethane, which first leads to the corresponding transient carbene followed by a stepwise 1,3-chlorine shift from one phosphorus to the other, opens up the way to $1\sigma^4,3\sigma^2$-diphosphaallenes (compounds C in equation 72) having two different types of phosphorus–carbon 'double' bonds in the PCP scaffold (equation 75).[203]



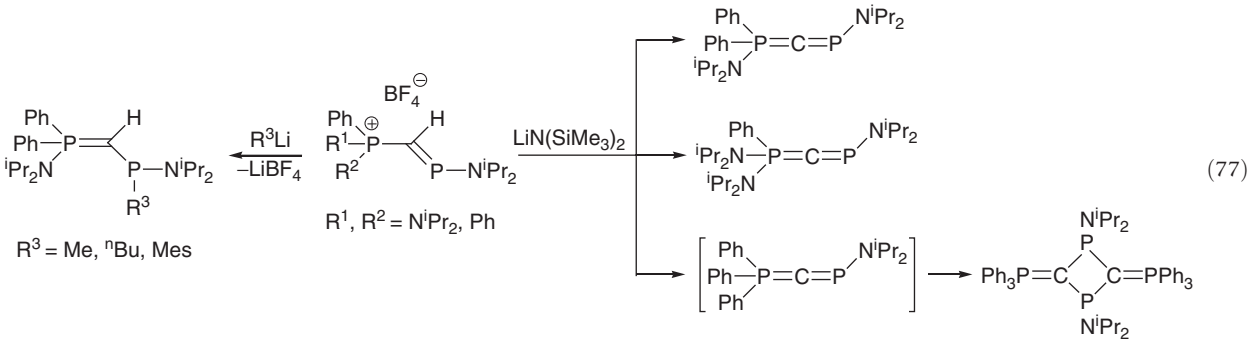
(75)

Although this approach is very limited in terms of starting materials, further reactions of these reactive cumulenes give access to a variety of products possessing phosphonium salt, ylidic, and cumulene structure (equation 76).[203]



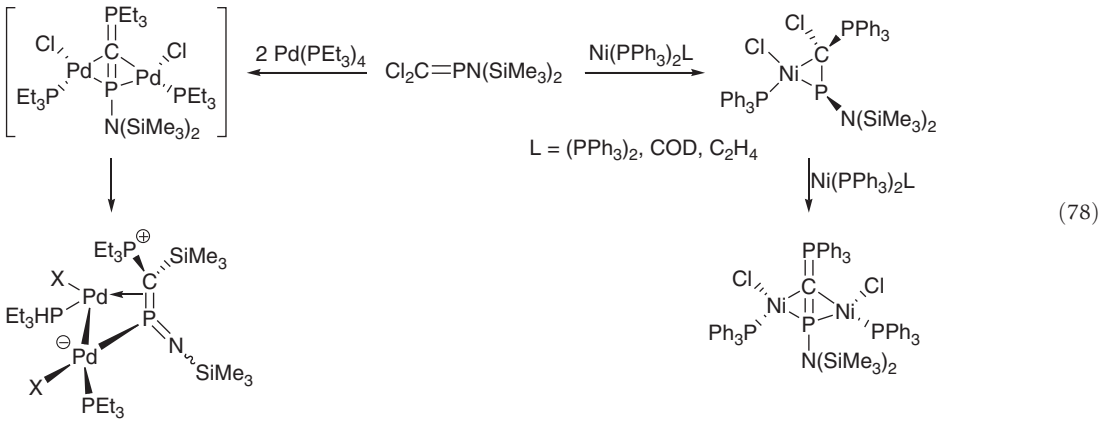
(76)

Another synthetic strategy for phosphacumulenes of type C is based on the deprotonation of phosphonio-phosphaalkenes,[204] which can be regarded as phosphenium salts substituted by a phosphonium ylide fragment. While alkyllithium (methyl-, *n*-butyl-, and mesityllithium) reagents were shown to lead quantitatively to *C*-phosphinylphosphonium ylides instead of the expected cumulenes, the application of bulky, but not reducing lithium hexamethyldisilazide resulted in a mixture of *C*-phosphinylphosphonium ylides with the desired diphosphaallenes, the latter being the major product in the case of diphenyl(diisopropylamino)phosphonium derivative (equation 77).[205] Note that with more acidic phosphonio-phosphaalkene having three phenyl groups at the σ^4-phosphorus center the corresponding diphosphaallene underwent dimerization to give a four-membered heterocycle.



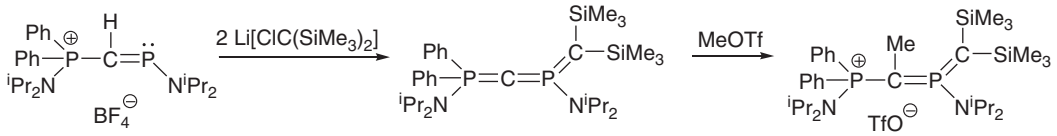
(77)

The synthesis of cumulenes C was also accomplished in the transition metal coordination sphere via oxidative addition of $Cl_2C{=}PN(SiMe_3)_2$ to nickel precursors $Ni(PPh_3)_2L$ (L=COD, PPh_3, C_2H_4) in a 1:2 ratio (equation 78).[206] The reaction initially afforded the phosphavinyl phosphonium adduct, which upon addition of the second equivalent of Ni(0) reagent quantitatively transformed into dinuclear phosphavinylidene–phosphorane complex bearing $Ph_3P{=}C{=}PN(SiMe_3)_2$ ligand bridged between two nickel atoms (equation 78). The related palladium complex was proposed to be an intermediate in the reaction of $Cl_2C{=}PN(SiMe_3)_2$ with $Pd(PEt_3)_4$, which yielded phosphonio–methylene(imino)metallophosphorane as a mixture of *E*- and *Z*-isomers (equation 76).[207]



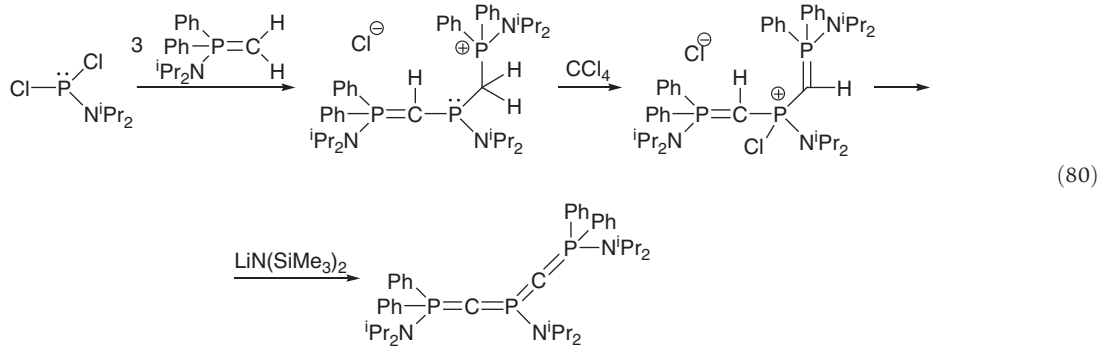
(78)

Phosphacumulene featuring three phosphorus–carbon 'double bonds' (compound D in equation 72) was readily prepared by treating the protonated form of the phosphine-substituted derivative of type C with a carbenoid ($Li[ClC(SiMe_3)_2]$), which was used both as a C_1 source and a base to eliminate HCl (equation 79).[208] Note that alkylation of the resulting cumulene with methyl trifluoromethanesulfonate gave rise to the first *C*-phosphonio-bis(methylene)phosphorane.



(79)

The longer cumulene E was obtained starting from (diisopropylamino)dichlorophosphine via treatment with $Ph_2(^iPr_2N)P{=}CH_2$ (three equivalents) followed by the addition of CCl_4 and dehydrohalogenation of the phosphonium salt obtained with lithium hexamethyldisilazide (equation 80).[208]

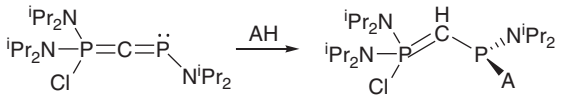


(80)

Due to their strongly nucleophilic nature, phosphacumulenes readily react with a variety of electrophilic substrates.[149a] This allowed for the development of two general approaches to convert cumulated phospharanes into 'more simple' phosphorus ylides: nucleophilic substitutions and cycloaddition reactions.

The first method involves the addition of an electrophile to the lone pair of oxo-, thioxo-, and imino-vinylidenephosphoranes followed by transformation of the resulting ketene phosphonium salt either into a new ylide by the addition of the external Nu^- to the central carbon atom or to 1,3-cyclobutanedione derivatives via [2+2] cycloaddition of the second molecule of the starting ylide. In this manner phosphacumulenes react with hydrogen chloride, alkyl halides, aromatic carboxylic acid chlorides, a range of OH-, NH-, SH-, and CH-acidic compounds, and Grignard reactants (which, on subsequent hydrolysis, provide acyl ylides).[1]

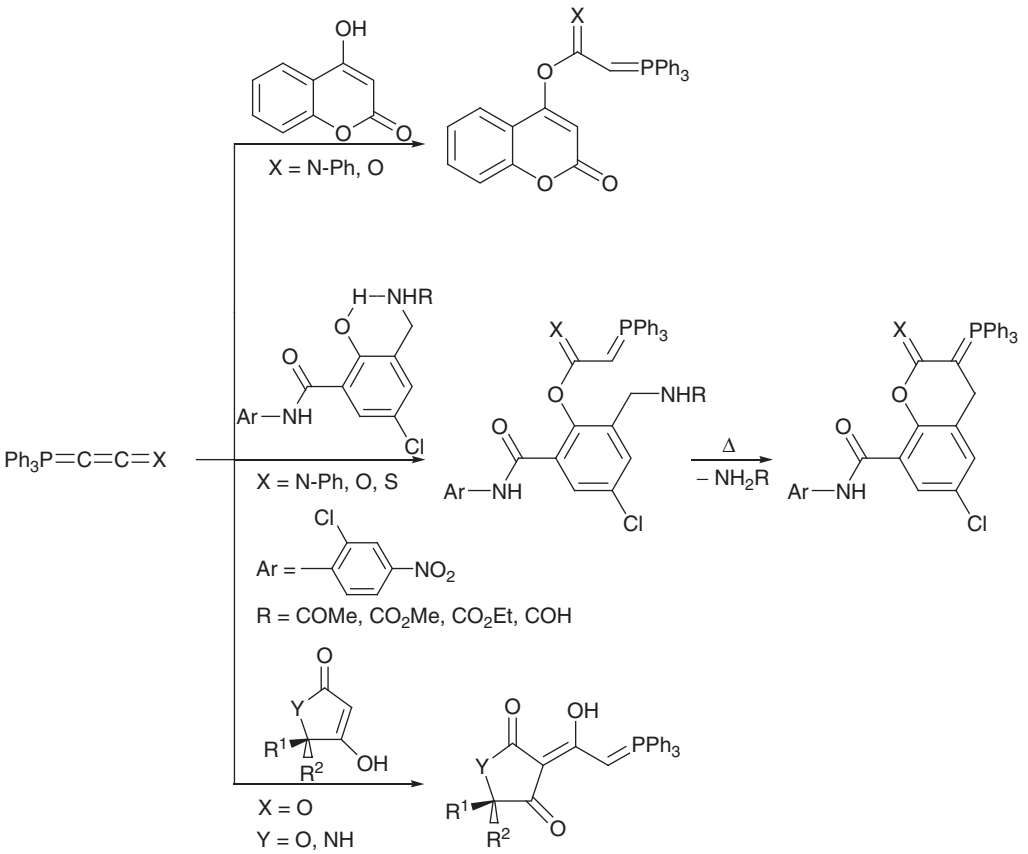
In recent years this route has found further application in the alkylation of phosphacumulenes with a PCP scaffold, as was described in equations 76 and 79,[203,208] Moreover, diphosphaallene of type C was shown to cleanly react with acidic compounds A–H (alcohols and thiols) to afford the phosphine-substituted P–Cl ylides (equation 81). This reaction readily proceeded even in the case of sterically crowded 2,6-di-*tert*-butyl-4-methylphenol.[209]



(81)

A = ^{t}BuS, 2,6-$Me_2C_6H_3S$, 2,6-$Me_2C_6H_4O$, 4-Me-2, 6-$^t Bu_2C_6H_2O$

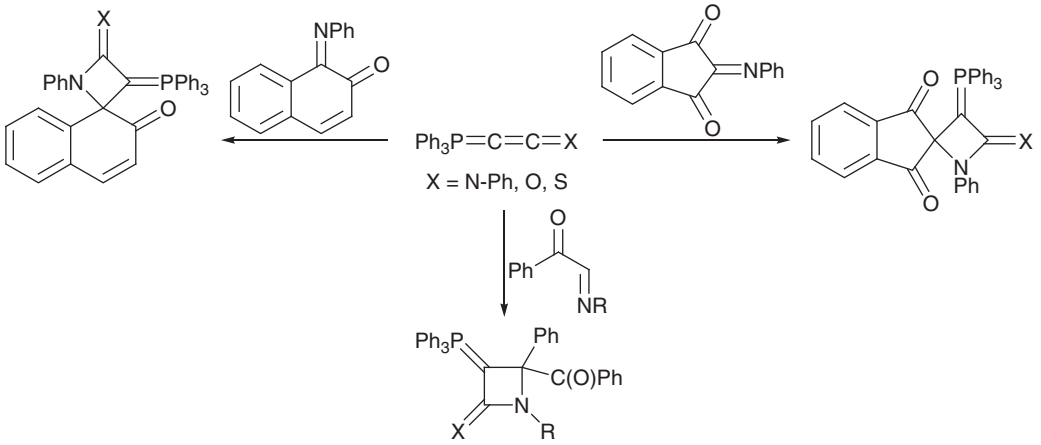
Furthermore, this method of phosphacumulene transformation (*see* Chapter 4.05) was also successfully adopted for the synthesis of linear and cyclic ylides functionalized with benzylidenebarbituric acid derivatives[139] and chromenone and pyranone moieties by the reaction with 4-hydroxy-2H-chromen-2-one[210] and niclosamide Mannich bases followed by cyclization,[138] as well as tetronic and tetramic acid residues[211] (equation 82).



(82)

The second approach – cycloaddition reactions affording various exocyclic alkylidenephosphoranes – was realized in the accounting period, for example, for diazomethylenephosphorane and $1\sigma^4,3\sigma^2$-diphosphaallene derivatives, as described in equations 70 and 76, respectively. In addition, the interaction of heterosubstituted phosphacumulenes $Ph_3P{=}C{=}C{=}X$

(X=NPh, O, S) with benzil, *o*-naphthoquinone, and triketone monoanils gave rise to phenylimino-, oxo-, and thioxoazetidinones (*see* Chapter 5.03) (equation 83), which constitute an important class of organic compounds with medicinal and biological importance.[140]



(83)

For related chapters in this Comprehensive, you can refer to – Chapters 1.15, 9.14, 9.10, 8.02, 8.03, 8.05, 9.11, 4.01, 1.17, 5.08, 2.04, 4.05, and 5.03.

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6.06 Synthesis of Fluorides

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Glossary

Deoxyfluorination A chemical transformation in which one or several C–O bonds in a molecule are replaced by *n*C–F bonds, where n is the sum of the bond order of all C–O bonds replaced.

Electrophilic fluorinating reagent A reagent that can perform an oxidative fluorination.

Nucleophilic fluorinating reagent A reagent that introduces fluorine into a molecule without oxidation or reduction of the molecule.

Oxidative fluorination The introduction of fluorine into a molecule with concomitant oxidation of the molecule, for organic molecules most commonly by two electrons.

Positron emission tomography (PET) A nuclear medical imaging method to obtain three-dimensional images indirectly resulting from positron-emission of positron-emitting nuclei.

6.06.1 Synthesis of Alkyl Fluorides

Carbon-fluorine bond formation has been known for more than a century[1] and is still of interest due to the beneficial properties fluorine can impart on pharmaceuticals,[2] agrochemicals,[3] and materials[4] as well as applications in positron emission tomography.[5] Nucleophilic fluorination for the synthesis of aliphatic fluorides has a thermodynamic driving force in forming the carbon–fluorine bond, the strongest carbon–heteroatom bond, but in many cases, high kinetic barriers make fluorination challenging[6]. Additionally, chemoselectivity can be difficult to obtain with nucleophilic fluorinating reagents due to other pathways that can lead to side products such as elimination byproducts. Basicity and nucleophilicity of fluoride need to be carefully

 doi:10.1016/B978-0-08-097742-3.00607-8

balanced to achieve high yields of the desired alkyl fluoride. Alkali metal fluoride salts are abundant, readily available and less expensive than electrophilic fluorinating reagents (not including fluorine gas).[7] Nucleophilicity of anhydrous fluoride salts can be increased through the use of crown ethers, which increase the solubility of metal fluoride salts through chelation of the metal cation.[8] The preferred solvents for nucleophilic fluorination are polar aprotic solvents[8b,9] such that hydrogen-bonding interactions would not diminish fluoride nucleophilicity; however, fluoride is basic in these solvents, which can lead to side reactions, including elimination. *tert*-Butanol[10] has been used as an additive or solvent to diminish fluoride basicity, thereby reducing byproduct formation, but empirically is observed to retain fluoride nucleophilicity.

Deoxyfluorination of carbon centers utilize specialized fluorinating reagents, which are used to both activate the oxy functional group as a leaving group and as the fluoride source for nucleophilic displacement. Aryl and aminosulfur trifluorides[11] derivatives as well as 2,2-difluoroimidazole-type reagents[12] can be used for fluorodeoxygenation reactions. Fluorodesulfurization can be accomplished with various hydrogen fluoride-based reagents[13] developed to assist sulfur displacement with fluoride.

6.06.1.1 Synthesis of Alkyl Fluorides

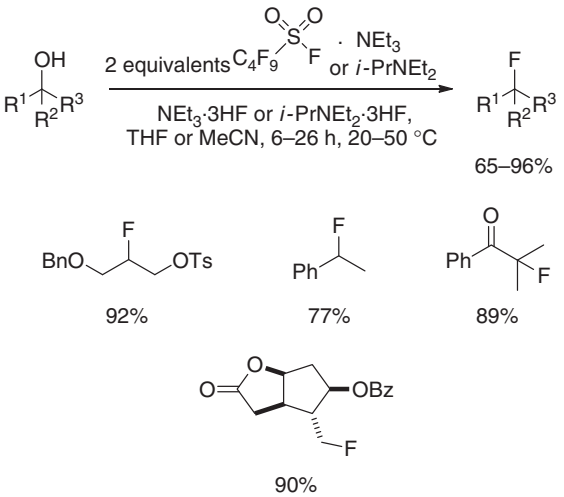
6.06.1.1.1 Via fluoride displacement of alkyl halides and sulfonates

The general approach for the synthesis of alkyl fluorides from alkyl halides and sulfonates involves S_N2 displacement of the halide or sulfonate leaving group with fluoride. Common fluoride sources employed include alkali metal fluorides such as KF and ammonium fluorides such as tetrabutylammonium fluoride (TBAF),[8a,14] but typically require heating to ≥80 °C to accomplish fluoride displacement of the alkyl electrophile. Ionic liquids can promote nucleophilic substitutions with fluoride and diminish the formation of byproducts.[9]

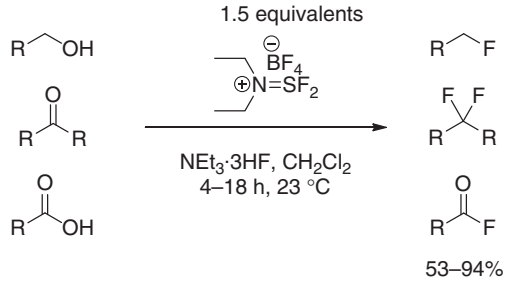
6.06.1.1.2 Deoxyfluorination and dethiofluorination approaches

Toxic and volatile sulfur tetrafluoride, reported to convert carbonyl groups to germinal difluoromethylene groups,[15] is undesirable to use and lead to the development of less volatile reagents such as aryl and aminosulfur trifluorides. Diethylaminosulfur trifluoride (DAST)[11i,16] is a moisture-sensitive, explosive (when heated) reagent[11e] that is most commonly used for deoxyfluorination of carbonyl and hydroxyl groups or fluorodesulfurization of thiocarbonyl or sulfide groups.[11c,17] The proposed mechanism involves hydroxyl group attack on DAST to form an alkoxyaminodifluorosulfane intermediate,[18] which can be displaced by fluoride via S_N2 attack. In some cases, an S_N1 pathway is observed.[17h]

Deoxyfluorination and dethiofluorination can be accomplished with several different fluoride sources beyond DAST: pyridinium poly(hydrogen fluoride) (Olah's reagent),[13a,b,13d] nitrosonium tetrafluoroborate/pyridinium poly(hydrogen fluoride),[13c] triethylamine tris(hydrogen fluoride) (TREAT•HF),[13e] perfluoro-1-butanesulfonyl fluoride (PBSF),[19] sulfonyl fluoride/TREAT•HF mixture (**Scheme 1**),[20] Yarovenko's reagent,[21] Ishikawa's reagent,[22] 1,1,2,2-tetrafluoroethyl-*N*,*N*-dimethylamine (TFEDMA),[23] *N*,*N*′-dimethyl-2,2,-difluoroimidazolidine,[12a] 4-morpholinosulfur trifluoride,[11d,24] Deoxo-Fluor®,[11f,25] and 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride.[26] Deoxo-Fluor® is a safer, more thermally stable alternative to DAST but exhibits moisture sensitivity and violent decomposition similar to DAST to generate toxic HF. TREAT•HF is mild enough to be used with borosilicate glassware and can be used as a less hazardous replacement for Olah's reagent. Crystalline, less moisture-sensitive deoxyfluorinating reagent XtalFluor-E® (diethylaminodifluorosulfinium tetrafluoroborate)[27] and related reagents[28] were later developed and afford less elimination side products (**Scheme 2**) and exhibits higher thermal stability than prior reagents albeit lower reactivity but often require additional fluoride for efficient reactivity.



Scheme 1 Deoxyfluorination of various alcohols with perfluorobutanesulfonyl fluoride-trialkylamine adduct and TREAT•HF. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



Scheme 2 Deoxyfluorination of alcohols, carbonyls, and carboxylic acids with XtalFluor-E®. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

Specialized reagents with tempered fluorinating reactivity must be used to achieve high deoxyfluorination regioselectivity. Selective monofluorination of diols can be accomplished with *N*,*N*-diethyl-*α*,*α*-difluoro(meta-methylbenzyl)amine (Figure 1)[29] whereas vicinal primary amino alcohols can undergo deoxyfluorination with *N*,*N*-diethyl-*α*,*α*-difluorobenzylamine (Figure 1).[30] Controlled, tempered reactivity of more recently developed fluorinating reagents allows for simple alkyl fluorides to be synthesized; however, functional-group tolerance and substrate scope is still limited.

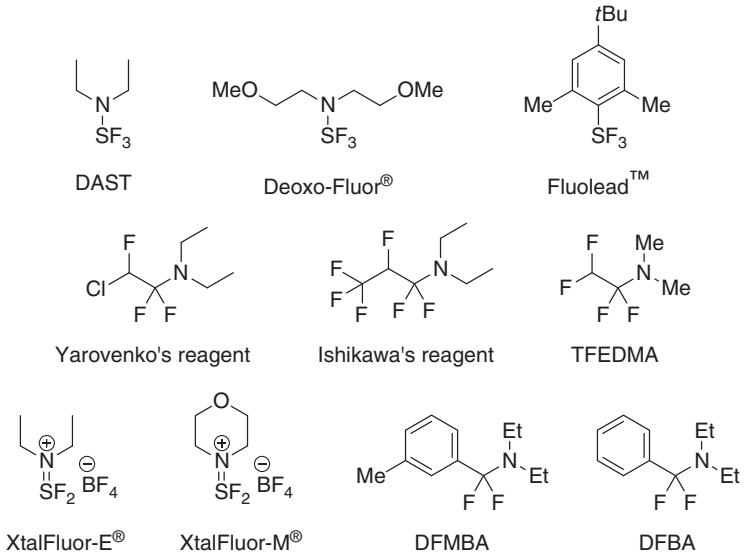


Figure 1 A selection of nucleophilic deoxofluorinating reagents. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

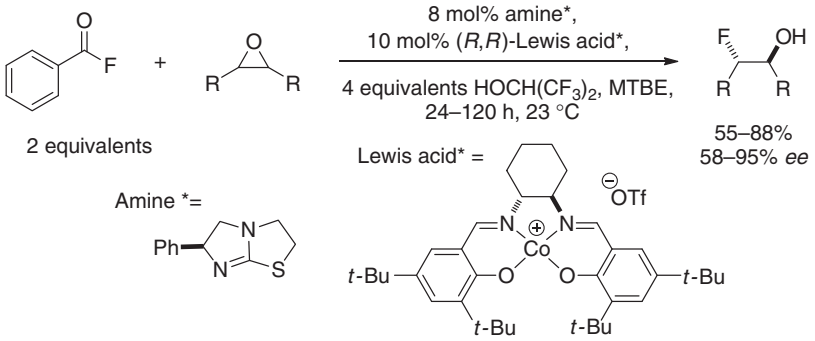
6.06.1.1.3 Addition reactions of fluoride to alkenes and epoxides

Alkenes can undergo halofluorination with *N*-iodosuccinimide and tetraalkylammonium hydrogen fluoride.[31] Fluoride reacts with epoxides[32] and aziridines[33] to afford vicinal fluoroalcohols and fluoroamines, respectively, which have been elaborated to multivicinal multifluoroalkanes.[32d,34]

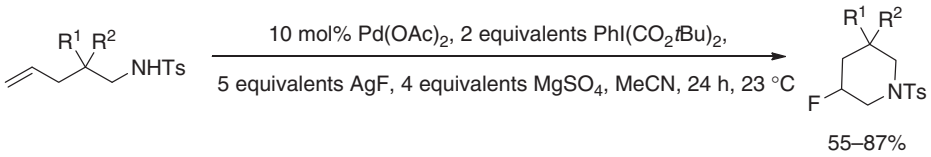
Enantiopure starting materials can be fluorinated to afford enantioenriched alkyl fluorides via nucleophilic S_N2 displacement of a leaving group. Another approach involves the asymmetric opening of *meso*-epoxides with fluoride and stoichiometric amounts of chiral Lewis acid complexes.[35] Co(III)-salen-catalyzed enantioselective ring opening of *meso*-epoxides by nucleophilic fluoride addition was subsequently reported (Scheme 3).[36] The reported method can afford ring-opening products with cyclic epoxides, whereas terminal epoxides undergo kinetic resolution to afford enantioenriched fluorohydrins. *In-situ* fluoride release from benzoyl fluoride instead of use of corrosive hydrogen fluoride reagents allows for this transformation to be accomplished under mild conditions.

6.06.1.1.4 Nucleophile addition-fluorination cascade reactions

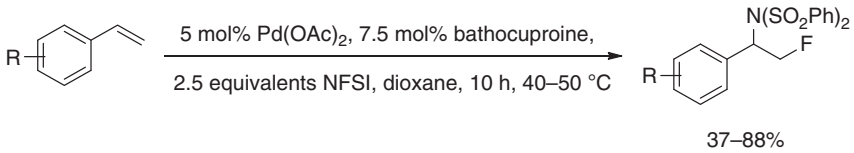
The intramolecular aminofluorination of unactivated alkenes (Scheme 4)[37] and intermolecular aminofluorination of styrenes (Scheme 5)[38] were both accomplished with palladium catalysis. Both cascade reactions accomplish aminofluorination but use two different approaches. The intramolecular variant with unactivated alkenes is proposed to arise from iodine(III)



Scheme 3 Co(III)-catalyzed asymmetric opening of *meso*-epoxides with fluoride. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



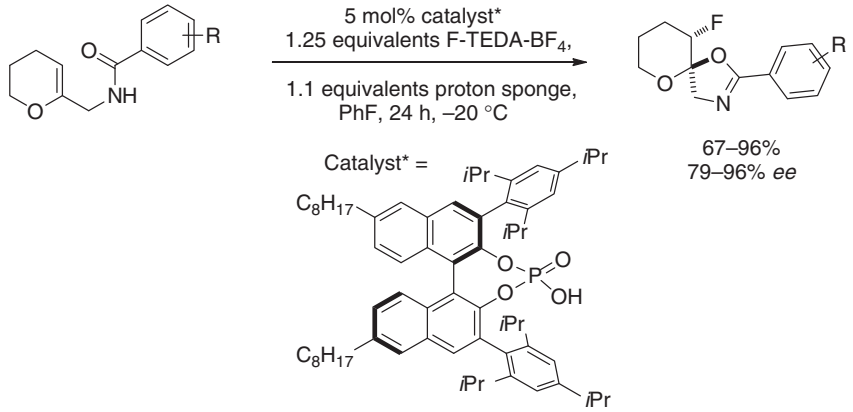
Scheme 4 Intramolecular Pd-catalyzed aminofluorocyclization of alkene sulfonamides. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



Scheme 5 Intermolecular aminofluorination of styrenes with NFSI. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

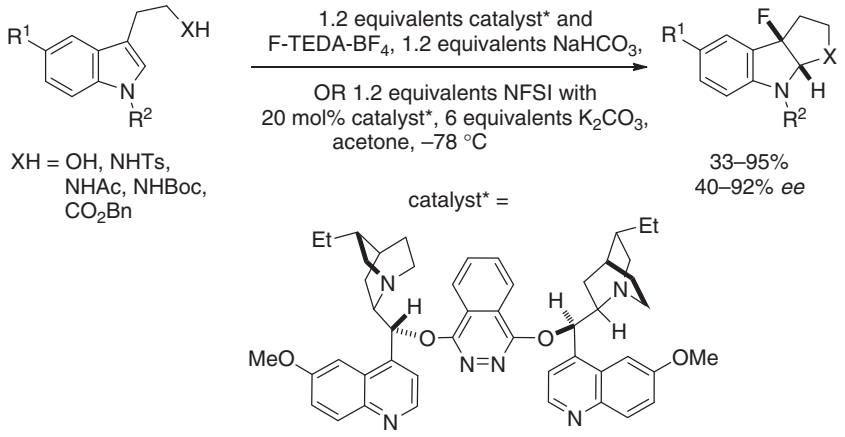
oxidant-coupled fluorination with silver fluoride after intramolecular aminopalladation of the alkene. In contrast, fluoropalladation with *N*-fluorobis(phenyl)sulfonimide (NFSI) of the double bond is hypothesized to occur with styrenyl substrates, followed by reductive elimination to form the carbon–nitrogen bond.

Enantioselective fluorospiro cyclization reactions have been accomplished via phase-transfer catalysis (PTC) with chiral phosphate anions in 79–96% *ee* (Scheme 6).[39] Enantioinduction is possible through chiral anion exchange with the tetrafluoroborate counterions of F-TEDA-BF_4 to generate a soluble chiral electrophilic fluorinating reagent. The enantioselective fluorocyclization of indoles can be mediated or catalyzed by cinchona alkaloids and an electrophilic fluorinating reagent



Scheme 6 Enantioselective spirocyclizations via chiral anionic PTC. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

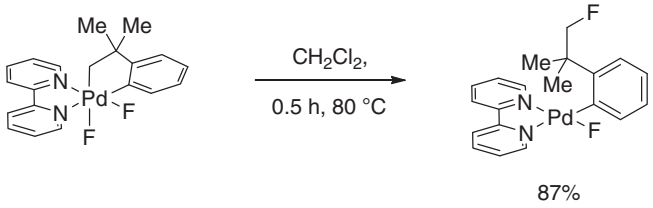
(Scheme 7).[40] Enantioinduction is proposed to arise from reaction of the indole substrates with a chiral fluorinating intermediate generated via *in-situ* fluorination of the alkaloid catalyst by NFSI or F-TEDA-BF_4.



Scheme 7 Enantioselective fluorocyclizations mediated and catalyzed by cinchona alkaloids. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

6.06.1.1.5 Transition metal-mediated synthesis of alkyl fluorides

High-valent transition metal complexes were investigated as a means to accomplish C–F reductive elimination at sp^3 carbon centers.[41] Stoichiometric alkyl Au(I) complexes can be oxidized with XeF_2 to Au(III) intermediates that undergo reductive elimination to afford the corresponding aliphatic fluorides.[41a] β-Hydride elimination from high-valent Au(III) is potentially problematic and thus β,β-disubstitution on the alkyl substituent was used to avoid byproduct formation. Additionally, Pd(IV) complexes can afford alkyl fluorides by reductive elimination (Scheme 8).[41c]



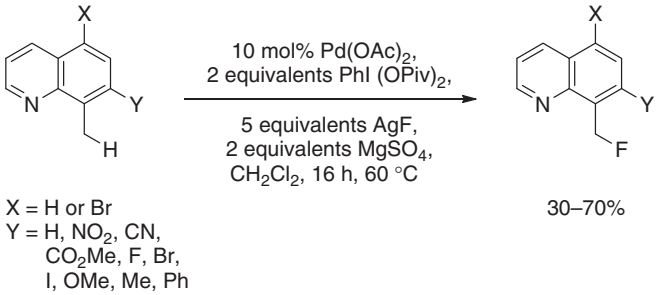
Scheme 8 Reductive elimination of C_{sp3}–F bond from a Pd(IV) alkyl fluoride complex. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

6.06.1.1.6 Transition metal-catalyzed oxidative fluorination of aliphatic C–H bonds with fluoride

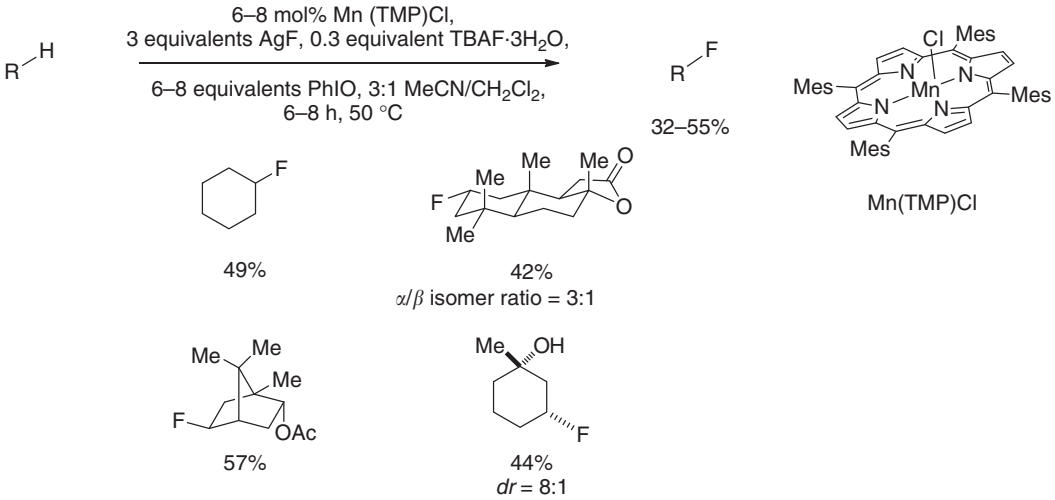
Transition metal-catalyzed oxidative fluorination of aliphatic C–H bonds using fluoride is rare and has at this time been reported twice.[42] Oxidative fluorination of functionalized 8-methyl quinolinyl substrates with $Pd(OAc)_2$ as the catalyst is postulated to occur through high-valent palladium fluoride intermediates via oxidation by $PhI(OPiv)_2$ in the presence of silver fluoride (Scheme 9).[42b] A manganese(III) porphyrin catalyst in the presence of silver fluoride and iodosylbenzene can accomplish oxidative C–H fluorination of aliphatic substrates (Scheme 10).[42a] This C–H functionalization is postulated to occur by radical C–H bond cleavage with the Mn(V) oxo intermediate resulting from Mn(III) catalyst oxidation with PhIO followed by radical recombination of the substrate with an *in-situ* generated Mn(IV) difluoride complex from AgF and an Mn(IV) complex.

6.06.1.1.7 Controlled radical and electrochemical fluorination

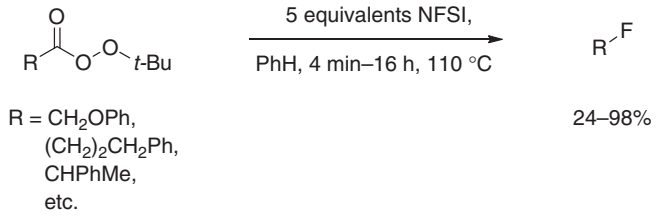
A variety of *tert*-butyl alkylperoxoates under either photolysis or thermolysis afford the corresponding alkyl fluorides upon treatment with NFSI (Scheme 11)[43] due to the low bond dissociation energies of N–F bonds in electrophilic fluorinating reagents (2.84 V for *N*-fluorosultam).[44]



Scheme 9 Pd-catalyzed *N*-directed oxidative fluorination of sp^3 C–H bonds with AgF and $PhI(OPiv)_2$. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



Scheme 10 Mn-catalyzed oxidative aliphatic fluorination with AgF/TBAF•$3H_2O$ and iodosylbenzene. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



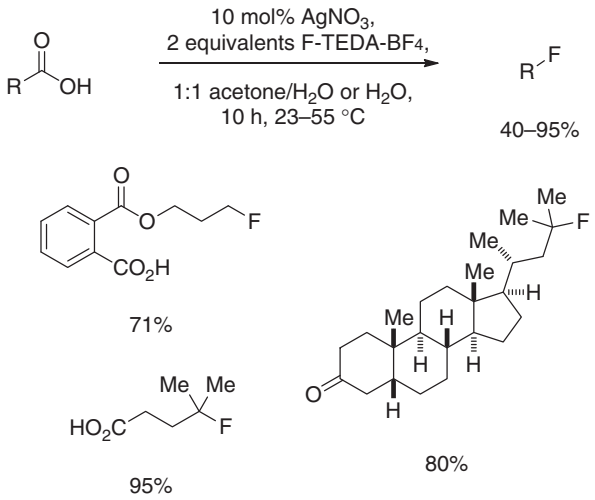
Scheme 11 Fluorination of *tert*-butyl alkylperoxoates with NSFI. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

Silver-catalyzed decarboxylative fluorination of secondary and tertiary aliphatic carboxylic acids with F-TEDA-BF_4 was reported by Li (Scheme 12).[45] This approach is complementary to traditional nucleophilic fluorination reactions with DAST-type reagents. Involvement of Ag-mediated decarboxylation to form an alkyl radical during the reaction was demonstrated, but the detailed mechanism for the key C–F bond formation is still indeterminate. Photodecarboxylative fluorination of α-aryloxyacetic acid with NaOH and F-TEDA-BF_4 can afford aryl fluoromethyl ethers.[46] Additionally, electrochemical fluorination with alkali metal fluorides has been explored as an approach for the synthesis of organofluorides.[47]

6.06.1.2 Synthesis of Propargyl and Allyl Fluorides

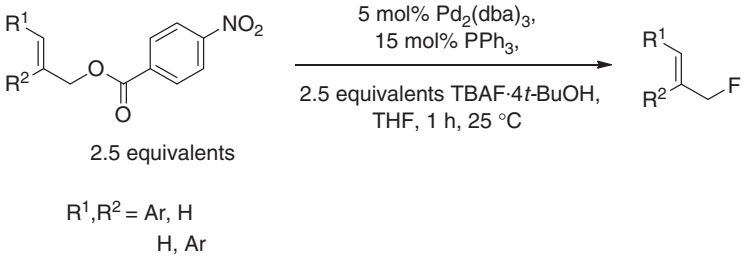
6.06.1.2.1 Via fluorodeoxygenation

Propargyl fluorides can be synthesized via deoxyfluorination of propargyl alcohols with DAST[48] and with SF_4,[49] dialkylaminosulfur trifluorides,[50] Yarovenko's reagent (Figure 1),[51] and Ghosez's reagent (*N*,*N*-diisopropyl-1-fluoro-2-methylpropenamine).[52] Propargyl mesylates or propargyl silyl ethers have also been used in lieu of propargyl alcohols.[49b,c,50,53]

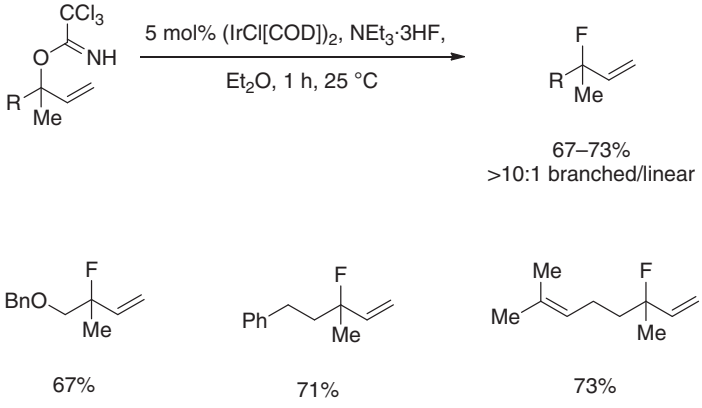


Scheme 12 Silver-catalyzed decarboxylative fluorination of aliphatic carboxylic acids with F-TEDA. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

Deoxyfluorination of allyl alcohols with DAST[48,54] affords allyl fluorides. Other fluoride sources (see **Figure 1**) can be employed for dehydroxyfluorination, including bis(dialkylamino)sulfur difluorides,[48,55] Yarovenko's reagent,[56] Ghosez's reagent,[57] and IF_5 in NEt_3•3HF,[58] and additionally other activated allyl substrates such as allyl halides have been used.[59] Rhenium[60] and iron[61] complexes were used with DAST to control the stereochemical outcome of allyl alcohol deoxyfluorination to give retention. Transition metal-catalyzed or -mediated allylic fluorination proceeds with double inversion. Allyl esters (**Scheme 13**)[62] as well as allyl trichloroacetimidates (**Scheme 14**)[63] can be transformed to terminal allyl fluorides and secondary and tertiary allyl fluorides via palladium and iridium catalysis, respectively, in less than 2 h at room temperature.



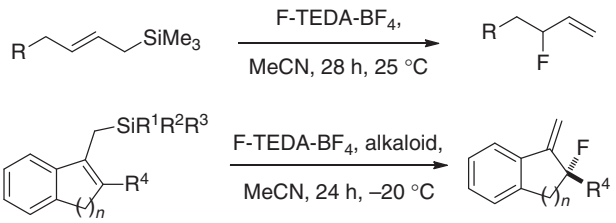
Scheme 13 Pd-catalyzed fluorination of allyl esters. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



Scheme 14 Ir-catalyzed fluorination of allyl trichloroacetimidates. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

6.06.1.2.2 Via electrophilic fluorination

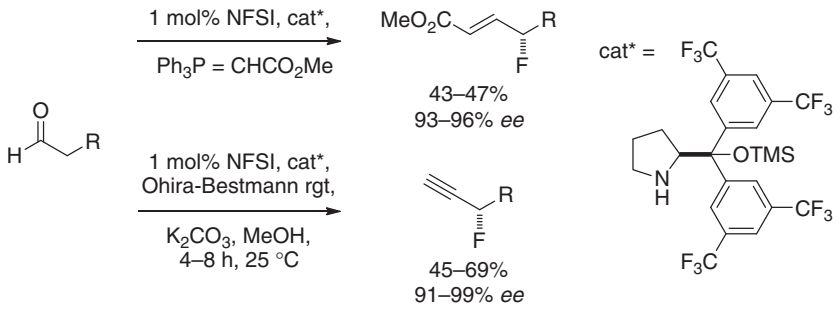
Hammond[64] and Gouverneur[65] have investigated electrophilic fluorination routes to propargyl fluorides. Allenyl and allylsilanes can undergo electrophilic fluorodesilylation to yield propargyl and allyl fluorides, respectively (Scheme 15).[65,66] Allylic C–H bond fluorination of α-methylstyrene can be accomplished with an *N*-fluoropyridinium salt and ytterbium catalyst.[67]



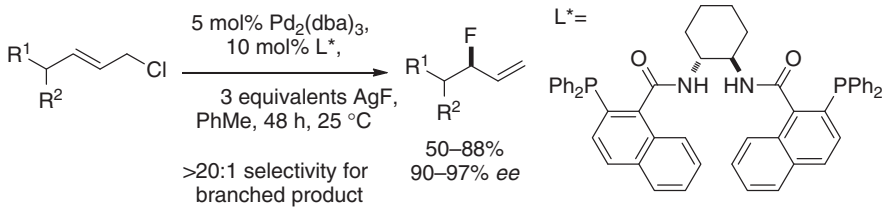
Scheme 15 Electrophilic fluorodesilyation for the synthesis of allyl fluorides. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

6.06.1.2.3 Enantioselective methods

Chiral propargyl alcohols can undergo an S_N2 displacement with fluoride after *in-situ* functionalization of the alcohol as a leaving group to yield enantioenriched propargyl fluorides.[68] An alternate S_N1 fluorination pathway is possible with some chiral propargyl alcohols after alcohol functionalization as a leaving group and results in enantiomeric excess eroded or racemized propargyl fluorides. Cinchona alkaloid-mediated electrophilic fluorodesilyation of allylsilanes can be used to prepare chiral tertiary allyl fluorides.[69] Organocatalysis has been used to synthesize enantioenriched allyl and propargyl fluorides from aldehydes with enantiomeric excesses of >90% *ee* (Scheme 16).[70] This one-pot process first involves α-fluorination of the aldehyde and subsequent olefination of the carbonyl. Cyclic[71] and acyclic (Scheme 17)[72] allyl chlorides can be fluorinated with three equivalents of silver fluoride in the presence of a chiral Pd catalyst and afford the branched products in >20:1 selectivity for acyclic allyl chlorides.



Scheme 16 Enantioselective synthesis of allyl and propargyl fluorides with organocatalysis. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

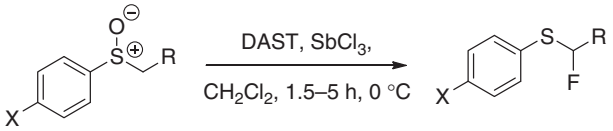


Scheme 17 Pd-catalyzed enantioselective synthesis of branched allyl fluorides. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

6.06.1.3 C–F Bond Formation to Afford Monofluoro-, Difluoro-, and Trifluoromethylated Compounds

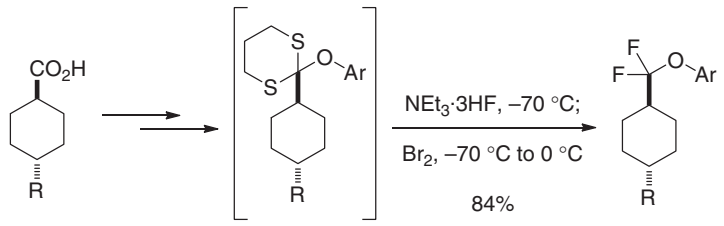
Chloromethyl ethers or thioethers can be used to synthesize α-fluoromethyl ethers[73] or sulfides, respectively,[74] through chloride displacement with KF. Fluoro-Pummerer rearrangements of sulfides and sulfoxides can be induced by nucleophilic fluorinating

reagents such as DAST (Scheme 18),[75] tetrabutylammonium dihydrogentrifluoride[76] and Deoxo-Fluor®[25c] to afford α-fluoromethylsulfides. With *O,S*-acetals[77] and α-carboxymethyl ethers,[78] electrophilic fluorination is used to synthesize α-fluoromethyl ethers. Similarly, the methyl C–H bond of aryl methyl thioethers can be oxidized with *N*-fluoropyridium triflate to afford aryl α-fluoromethyl thioethers.[79]



Scheme 18 Fluoro-Pummerer rearrangement of sulfoxides with DAST. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

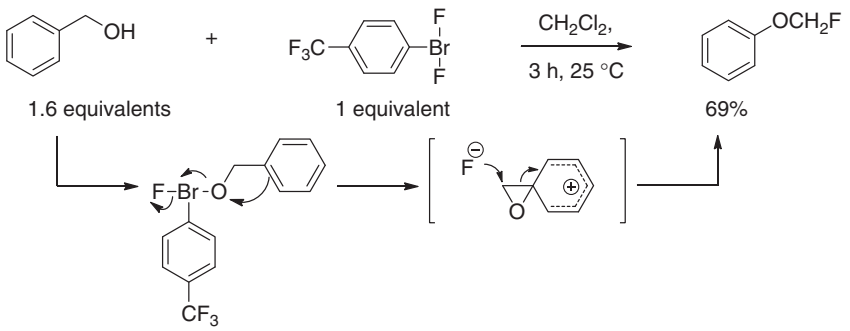
Alcohols and phenols functionalized as thionoesters,[25a,i] xanthates,[80] and formyl esters[81] are nucleophilically fluorinated to afford α,α-difluorinated ethers. Nucleophilic fluorination of ester thioacetal with triethylamine-hydrogen fluoride in the presence of bromine can also be used synthesize α,α-difluorinated ethers (Scheme 19).[82] When carbonates are treated with SF_4, bis(alkoxy) difluoromethane products are formed.[83]



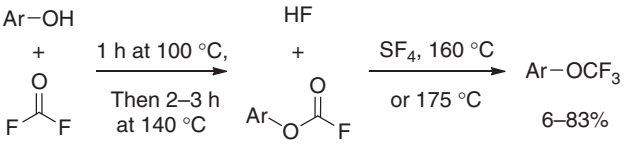
Scheme 19 Oxidative fluorination for the synthesis of difluoromethylene aryl ethers. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

Benzyl alcohols treated with XeF_2[84] or aryl difluoro-λ^3-bromane (Scheme 20)[85] undergo oxidative rearrangement through phenonium intermediates. Aldehydes, when treated with difluoroarylbromane, afford α,α-difluoroethers through an oxidative rearrangement.[86]

In 1913, Swarts reported nucleophilic fluoride substitution of trichloromethylbenzene for the synthesis of trifluoromethylbenzene,[1b] which was later derivatized to afford other trifluoromethylarenes.[87] SF_4 was used later to exhaustively fluorinate the carboxy group of benzoic acids to afford trifluoromethylated arenes.[88] Similarly, aryl trichloromethyl ethers have been fluorinated with hydrogen fluoride,[89] SbF_5,[90] SbF_3 in the presence of SbF_5,[91] and molybdenum hexafluoride,[92] with the trichloromethyl ether being synthesized *in situ*[89b] or before the reaction by chlorination of the aryl methyl ether.[91a,93] Aryl chlorothionoformates[91c,92a] can also be used as precursors to trifluoromethyl ethers. Nucleophilic fluorinating reagents SbF_3 and SF_4/HF can be used on phenol fluoroformates to synthesize trifluoromethoxyarenes (Scheme 21).[94] Additionally, oxidative fluorodesulfurization of aryl xanthates can be accomplished with HF/pyridine and dibrominated hydantoin (Scheme 22).[95]

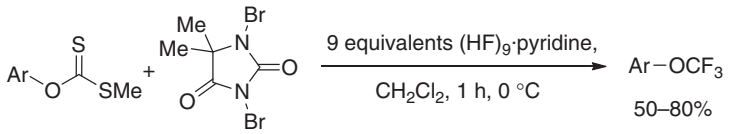


Scheme 20 Oxidative rearrangement of benzyl alcohol to monofluoromethyl phenol with aryl difluoro-λ^3-bromane. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



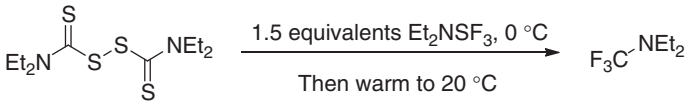
Where Ar = Ph, *o*-NO_2-Ph, 2,4-diBr-Ph, *m*-OH-Ph, *p*-Cl-Ph, etc.

Scheme 21 Synthesis of aryl trifluoromethyl ethers via fluoroformate intermediates. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

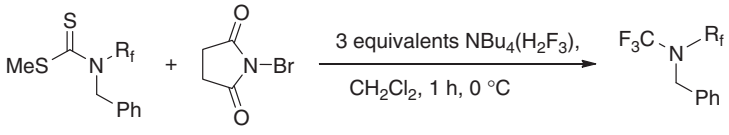


Scheme 22 Synthesis of aryl trifluoromethyl ethers by fluorodesulfurization of aryl xanthates. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

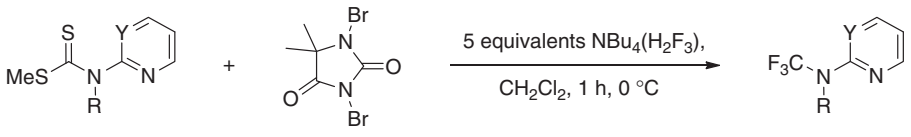
Trifluoromethylamines can likewise be synthesized via nucleophilic fluorination by prior derivatization to thiuramide sulfides (Scheme 23),[11c,96] *N*-alkyl dithiocarbamates (Scheme 24),[97] *N*-heteroaryl dithiocarbamates (Scheme 25),[98] or formamides[99] before being treated with nucleophilic fluoride sources. Use of the formamide precursor can afford trifluoromethylamine products in 90–94% yield but involves the use of toxic and volatile SF_4.



Scheme 23 Fluorodesulfurization of thiuramide sulfides. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



Scheme 24 Fluorodesulfurization of dithiocarbamates. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



Scheme 25 Fluorodesulfurization of *N*-heteroaryl dithiocarbamates. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

6.06.1.4 Synthesis of α-Fluorocarbonyl Compounds

6.06.1.4.1 General α-fluorination of carbonyl compounds

α-Fluorination of carbonyls, α′-ketocarbonyls, and related carbonyl derivatives was first accomplished with strongly oxidizing fluorinating reagents including gaseous fluorine,[100] hypofluorite,[101] perchloryl fluoride,[102] and fluoroxysulfate,[103] which are explosive if handled incorrectly, as well as with XeF_2,[104] Use of strongly oxidizing fluorinating reagents afforded undesired α,α-difluorinated products in addition to the α-monofluorinated products.[102d,104]

The development of crystalline, benchtop-stable fluorinating reagents (Figure 2) such as NFSI[105] and related analogs,[105,106] *N*-fluoropyridinium-based salts,[107] and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4)[108] allowed for the selective α-monofluorination of carbonyl and carbonyl derivatives without difluorinated side products.[107a,b,f,h,109] Although the N–F bond in *N*-fluoro reagents is polarized toward fluorine with partial negative charge on fluorine, reactions may occur via S_N2 displacement with nucleophilic attack of fluorine, formally reacting as fluoronium cation ('F^{+}'), because the σ_{*N-F} orbitals are sterically inaccessible on nitrogen for nucleophilic attack. The small orbital coefficient of the σ_{*N-F} on fluorine and the low energy level of the σ_{*N-F} orbital may contribute to other competitive mechanism pathways, such as single-electron transfer, which are often under discussion. The overall two-electron oxidative fluorination can proceed by two single-electron transfers or concerted two-electron transfer and have both been proposed.[109c,110] Investigations of asymmetric α-fluorination of carbonyl substrates were first accomplished with chiral electrophilic fluorinating reagents[106b,c,111] and later with chiral catalysts via chiral enolate intermediate generation.

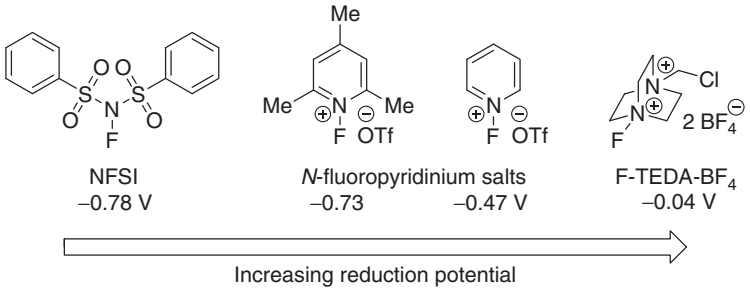
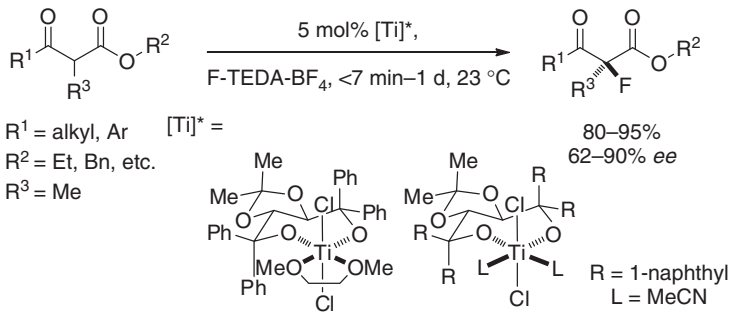


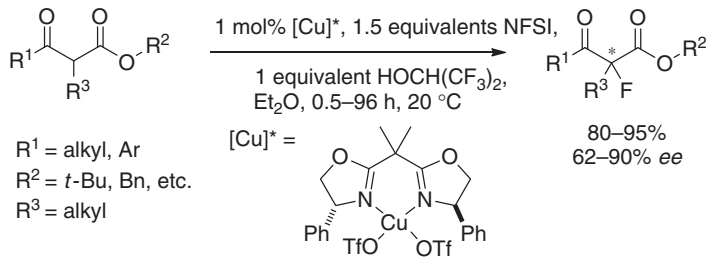
Figure 2 Comparison of the oxidation potential of crystalline, bench-top stable fluorinating reagents. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

6.06.1.4.2 Enantioselective α-fluorination

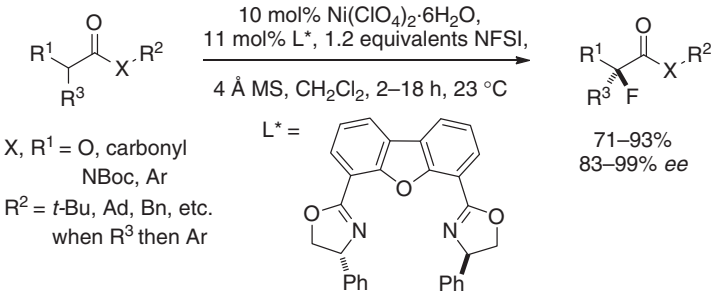
The development of methods for the asymmetric synthesis of enantioenriched fluorinated products is desirable and has been accomplished with many C–H acidic compounds catalyzed by chiral Lewis acids, organocatalysts, and phase-transfer catalysts. The fluorinating reagents of choice for these asymmetric methods are NFSI and F-TEDA-BF_4, which allow for the desired enantioselective pathway to occur with lower or in some cases no background reactivity with the substrate. Chiral Lewis acids utilize the two-point binding of dicarbonyl compounds to direct the subsequent enantioselective fluorination step to afford enantioenriched α-fluorodicarbonyl compounds. β-Ketoesters were asymmetrically fluorinated with titanium-TADDOLate-based catalysts (Scheme 26),[112,113] Cu(II)- (Scheme 27)[114] and Ni(II)-BOX complexes (Scheme 28),[115] chiral bis(imino)bis(phosphine)ruthenium(II) complexes (Scheme 29),[116] and scandium binapthylphosphate complexes.[117] The broadest substrate scope for α-fluorination of a variety of β-ketoesters and *N*-Boc-protected amides[115] can be accomplished under nickel catalysis, although the method requires 10 mol% catalyst loading. α-Substituted methyl *tert*-butyl malonate underwent enantioselective α-fluorination



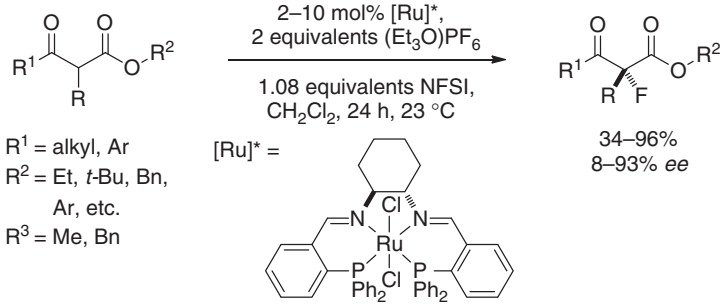
Scheme 26 Ti-catalyzed asymmetric α-fluorination of β-ketoesters. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



Scheme 27 Cu-catalyzed asymmetric α-fluorination of β-ketoesters. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



Scheme 28 Ni-catalyzed asymmetric α-fluorination of β-ketoesters. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



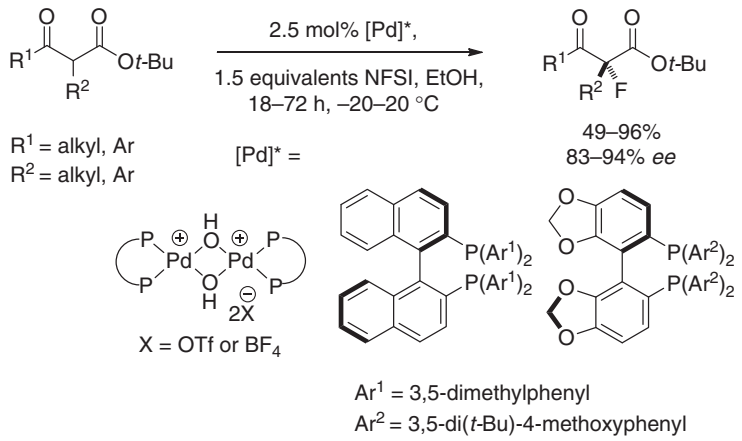
Scheme 29 Ru-catalyzed asymmetric α-fluorination of β-ketoesters. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

with Zn(II) acetate, (*R*,*R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) ligand, and NFSI.[118] These conditions were optimized for the prior-described malonate substrate for the enantioselective synthesis of fluorinated β-lactams and does not offer a general method for dicarbonyl substrates.

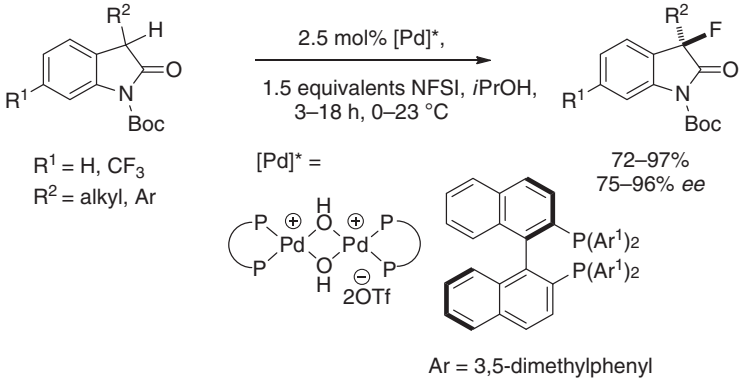
Chiral Pd-BINAP complexes can be used as catalysts for the enantioselective α-fluorination of α-ketoesters,[119] β-ketoesters (Scheme 30),[120] β-ketophosphonates,[121] oxindoles (Scheme 31),[122] and α-ester lactones/lactams.[123] α-Fluorination of acyclic α-ketoesters, cyclic and acyclic *tert*-butyl β-ketoester as well as oxindoles α-substituted with an electronically diverse range of aryl and alkyl groups can be accomplished with these chiral Pd-BINAP catalysts. Enantioinduction is proposed to arise from the presence of chiral palladium-bound enolates which induces enantioselectivity for the fluorination of the enolate.

Another approach for the enantioselective α-fluorination of C–H acidic compounds employs organocatalysts. The organocatalytic approach can be accomplished in two ways: (1) with chiral electrophilic fluorinating reagents derived from the fluorination of a chiral organocatalyst or (2) with chiral nucleophiles generated from reaction of the organocatalyst with the substrate. The chiral fluorinating reagent approach has been less successful than the fluorination of chiral nucleophile approach because of a faster background reaction between the nucleophile and the achiral fluorinating reagent than with the chiral fluorinating reagent.

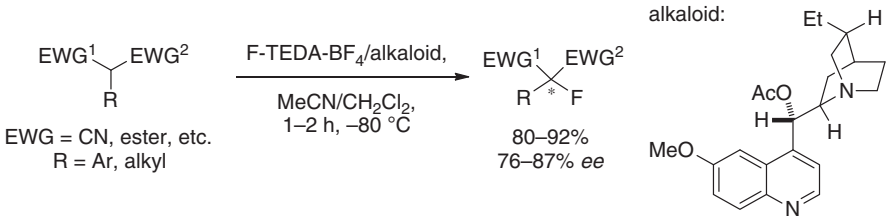
The enantioselective α-fluorination of substrates with two electron-withdrawing groups was accomplished with stoichiometric amounts of cinchona alkaloid acting as a chiral transfer agent of the fluorine atom between the achiral fluorinating reagent and the substrate (Scheme 32).[124] Cinchona alkaloids can also be used to afford enantioselectively α-fluorinated silyl enol ethers,



Scheme 30 Pd-catalyzed asymmetric α-fluorination of β-ketoesters. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



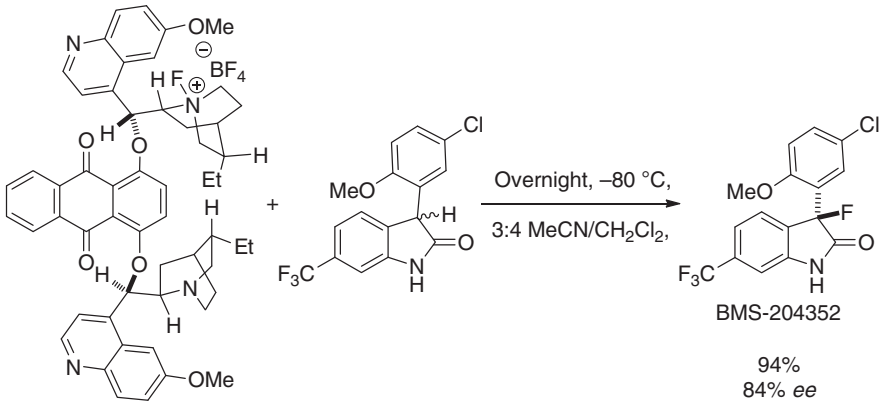
Scheme 31 Pd-catalyzed asymmetric α-fluorination of oxindoles. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



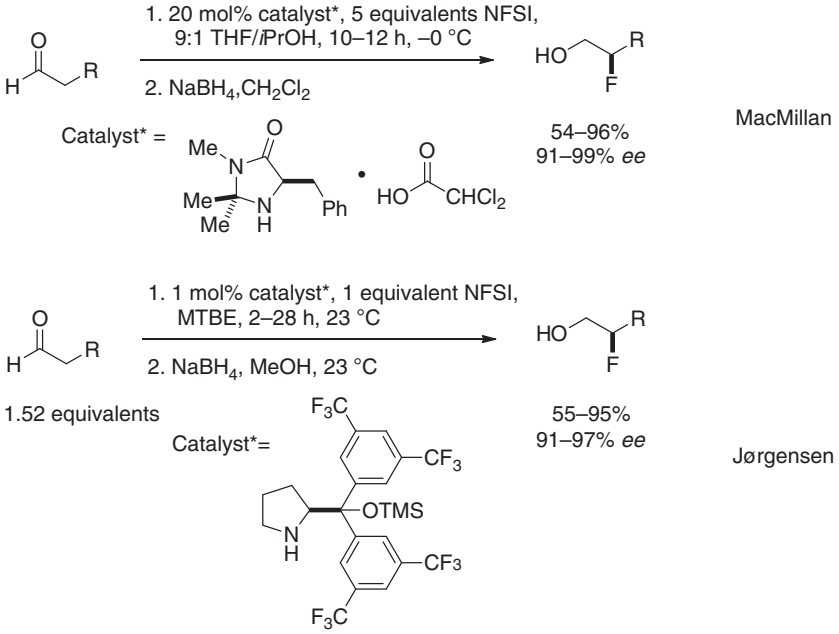
Scheme 32 Enantioselective cinchona-alkaloid–mediated fluorination of C–H acidic substrates. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

α,α-cyanoester C–H acids, β-ketoesters, and oxindoles[125] which was applied to the synthesis of BMS-204352 (Scheme 33).[126] β-Ketoesters are also substrates for enantioselective α-fluorination utilizing cinchona-alkaloid-derived thiourea catalysts.[127] Although the substrate scope for the Lewis acid-catalyzed fluorination of β-ketoesters and oxindoles is broader, cinchona alkaloids can be used for the enantioselective α-fluorination of silyl enol ethers, which is not possible with the Lewis acid-catalyzed two-point binding approach. As such, cinchona alkaloid-catalyzed α-fluorination of silyl enol ethers, allylsilanes, and oxindoles with NFSI[128] and acyl enol ethers with F-TEDA-BF_4 and sodium acetate[129] was established with NFSI affording products with higher enantiomeric excess than with F-TEDA-BF_4.

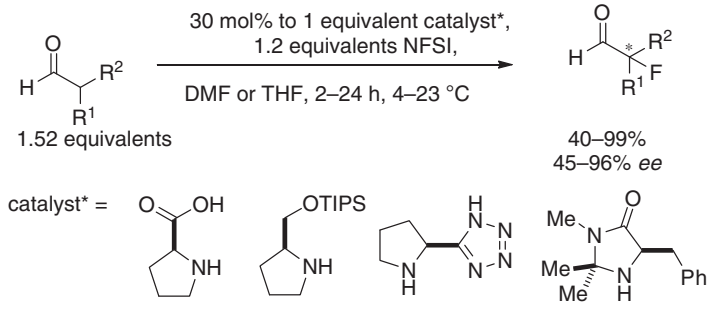
Aldehydes, ketones, and carboxylic acid derivatives can afford α-fluorination products with electrophilic fluorinating reagents through organocatalysis. Enders,[130] MacMillan (Scheme 34),[131] Jørgensen (Scheme 34),[132] and Barbas (Scheme 35)[133] reported the catalytic enantioselective α-fluorination of aldehydes with enamine catalysis, which was later used for the enantioselective



Scheme 33 Enantioselective α-fluorination of oxindoles mediated by *N*-fluoroammonium salts of cinchona alkaloids. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



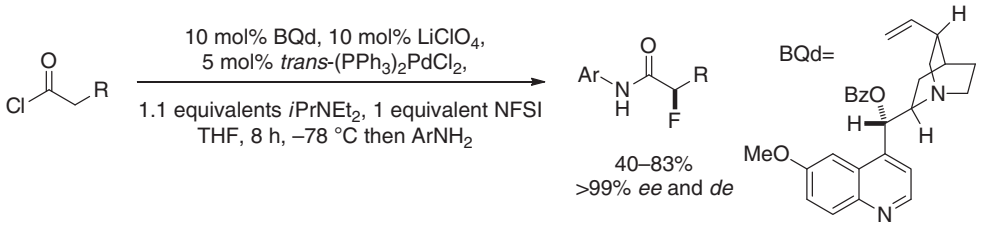
Scheme 34 Organocatalytic asymmetric α-fluorination of aldehydes. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



Scheme 35 Organocatalytic asymmetric α-fluorination of α-branched aldehydes. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

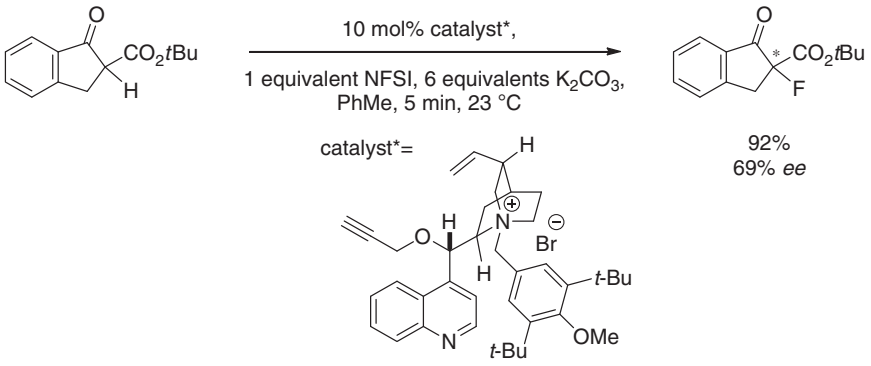
α-fluorination of ketones.[134] Though the MacMillan approach demonstrates the broadest substrate scope for non-α-branched aldehydes, enantioselective α-fluorination of branched aldehydes was described by Barbas in 98–99% yield and 45–66% *ee*. These α-fluoroaldehyde products can be converted to enantiopure β-fluoroamines by chiral sulfinyl imine condensation, chiral sulfinyl group-directed reduction, and deprotection of the sulfinamide to the free amine.[135]

A synergistic trifunctional catalytic system combining a palladium catalyst, a chiral nucleophile, and an alkali metal catalyst was used to accomplish the enantioselective α-fluorination of acid chlorides (Scheme 36).[136] The cinchona alkaloid-based nucleophile works cooperatively with the palladium catalyst to form a chiral zwitterion amide-enolate intermediate from the acid chloride for subsequent fluorination. The alkali metal catalyst is hypothesized to activate NFSI through cation chelation of the sulfonyl oxygens, activating NFSI for nucleophilic attack by the chiral enolate. Addition of an amine nucleophile after the fluorination step affords the α-fluoroamide product in >99% *ee* and *de*. Similarly, thiourea catalysts derived from cinchona alkaloids can act as synergistic bifunctional catalysts by utilizing the quinuclidine moiety as a base and thiourea moiety as a hydrogen-bond donor; the asymmetric α-fluorination of cyclic and acyclic β-ketoesters with NFSI can be accomplished with these cinchona alkaloid-thiourea catalysts through constructive hydrogen-bonding interactions.[127]



Scheme 36 Organocatalytic asymmetric α-fluorination of acid chlorides. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

PTC has been a useful approach for accomplishing asymmetric α-fluorination because it is operationally simple, utilizes mild organic catalysts, and can afford products in high enantiomeric excess. The choice of solvent is important to maintain a tight chiral ion pair, which is imperative for effective enantioinduction to occur. Chiral quaternary ammonium salts have been used as phase-transfer catalysts for enantioselective fluorination of β-ketoesters in up to 69% *ee* (Scheme 37).[137] Lower reported *ee* values most likely result from poor ion pairing between the chiral ammonium salt and the enolate or from fast α-fluorination background reaction. In contrast, chiral anionic PTC with chiral phosphate anions can be used to transfer F-TEDA into solution such that enamides can react with chiral F-TEDA-phosphate ion pair to afford α-fluoroimines (Scheme 38)[138] and additionally has been used to afford fluoroalkoxylation products of enamides.[139]

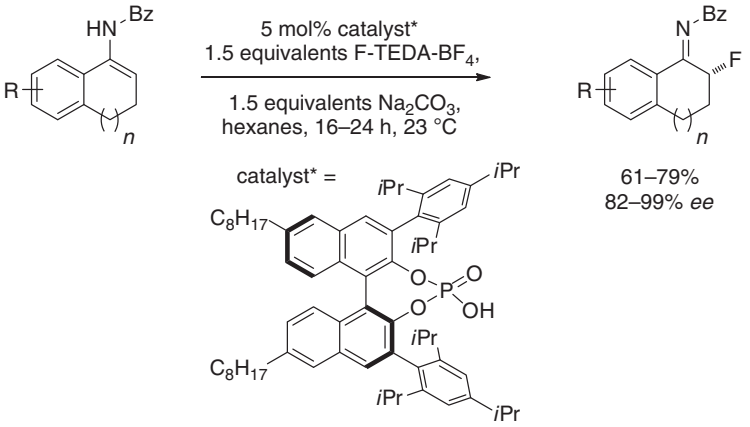


Scheme 37 Enantioselective α-fluorination of β-ketoesters with quaternary ammonium salts. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

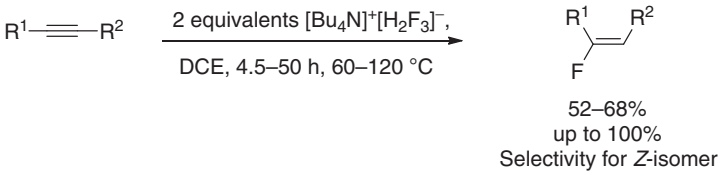
6.06.2 Synthesis of Alkenyl Fluorides

6.06.2.1 Without Transition Metal Catalysts

Monofluoroalkenes are accessible via *cis*-hydrofluorination of substituted alkynes with polymer-supported and tetra-butylammonium dihydrogen trifluoride (Scheme 39).[140] Likewise, *cis*-hydrofluorination of alkynyl iodonium salts[141] and

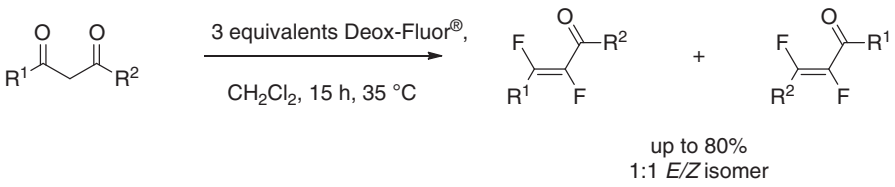


Scheme 38 Enantioselective α-fluorination of enamides with chiral anion PTC. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



Scheme 39 Hydrofluorination of alkynes with tetrabutylammonium hydrogen fluoride. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

alkynylsulfonamides[142] with various hydrogen fluoride reagents afforded *Z*-fluoroalkenyliodonium salts and *E*-α-fluoroenesulfonamides, respectively. When α-keto carbonyls are treated with Deoxo-Fluor® one of the carbonyls is deoxyfluorinated to yield α,β-difluoroenones (Scheme 40).[143]

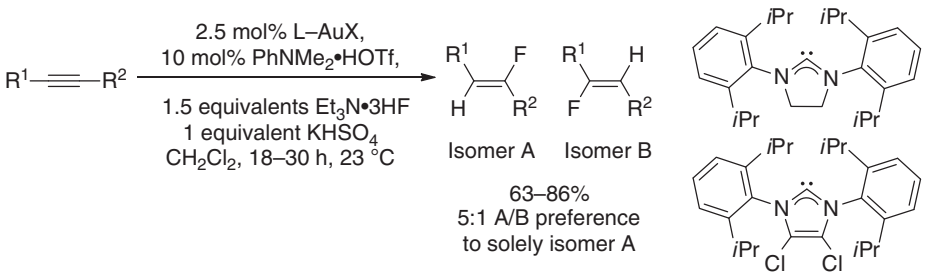


Scheme 40 Synthesis of α,β-difluoroenones via nucleophilic fluorination of Deoxo-Fluor®. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

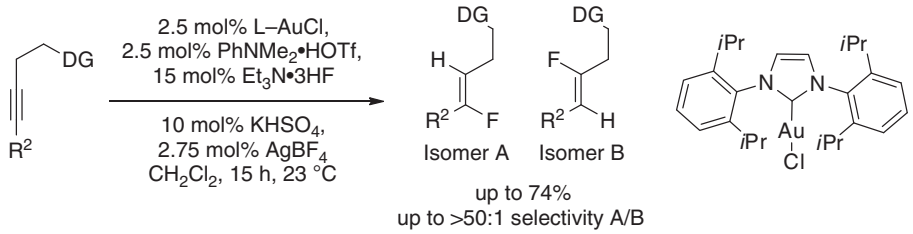
6.06.2.2 Via Transition Metal Catalysts

Hydrofluorination reactions with triethylamine-hydrogen fluoride of substituted alkynes can be mediated with electrophilic gold complexes to give reversible hydrofluorination (Scheme 41).[144] Hydrofluorination of disubstituted alkynes with >50:1 regioselectivity was subsequently established with gold catalysis when *N*-directing groups tethered to the alkyne were used (Scheme 42).[145] When ester groups are used as the directing group, regioselectivity drops to 1:1.5 in favor of isomer B (see Scheme 42).

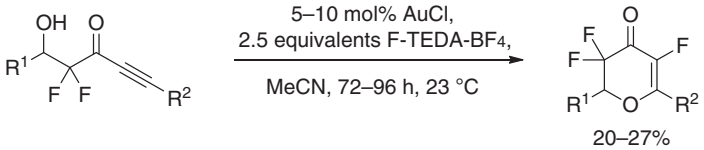
Electrophilic fluorination of the transient alkenyl gold intermediate resulting from gold-catalyzed cyclization of propargyl ketones affords cyclic α-fluoro vinylogous esters (Scheme 43).[146] Protodeauration is a major byproduct pathway that accounts for the rest of the starting material mass not transformed to the fluorinated product. Fluorocylization of enynes with palladium catalysts[147] as well as aminofluorocyclizations[148] with allenyl amines[148b] have been reported for the synthesis of alkenyl fluorides. Alkyl or phenyl proparyl acetates undergo rearrangements with gold-carbene catalysts and are fluorinated with F-TEDA-BF_4 after rearrangement to afford α-fluoroenones (Scheme 44).[149]



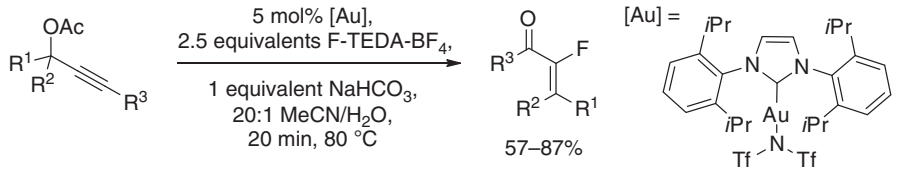
Scheme 41 Au-catalyzed hydrofluorination of alkynes. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



Scheme 42 Au-catalyzed ester-directed hydrofluorination of alkynes. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



Scheme 43 Au-catalyzed fluorocyclization of propargyl ketones. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



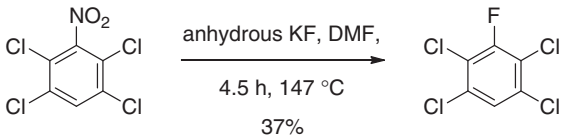
Scheme 44 Synthesis of α-fluoroenones via Au-catalyzed 1,3-acyloxy rearrangement of propargyl acetates. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

6.06.3 Synthesis of Aryl Fluorides

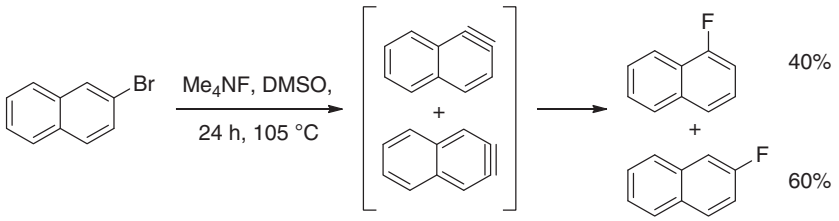
Direct fluorination of arenes via electrophilic aromatic substitution is more challenging than the corresponding iodination, bromination, and chlorination. Functional-group tolerant and regioselective fluorination instead has been most successfully accomplished with redox active transition metals, which proceeds through the intermediacy of high-valent organotransition metal fluorides. The transition metal–carbon bond can be formed via direct C–H metalation or transmetalation followed by oxidation of the metal center with an electrophilic fluorinating reagent, depending on the reaction conditions, to a monometallic high-valent intermediate[150] or a high-valent multimetallic complex.[151]

6.06.3.1 Traditional Methods

In 1927, Balz and Schiemann developed the thermal decomposition of aryl diazonium tetrafluoroborate salts for the nucleophilic fluorination of arenes.[152] Subsequently, the substitution of chloride in 1-chloro-2,4-dinitrobenzene with fluoride via S_NAr at 200 °C was established as an approach for the synthesis of aryl fluorides,[153] which was later more generally established for electron-deficient arenes with leaving groups such as chloride or nitro groups (Scheme 45).[154] More recent work in this area has allowed for the fluorination of electron-poor, chloro- or nitroarenes with anhydrous TBAF at room temperature in up to >95% yield.[155] Nucleophilic fluorodemetallation of toxic organothallium[156] and organomecury[157] substrates as well as diaryliodonium[158] substrates were investigated as well, but are less widely used. Aryl bromides, through fluoride trapping of aryne intermediates generated from hydrogen bromide elimination with anhydrous tetramethylammonium fluoride, were used to synthesize simple aryl fluorides (Scheme 46).[159] Some of the aforementioned methods are suitable to synthesize simple aryl fluorides on an industrial scale,[160] but none of these methods are tolerant toward a large variety of functional group or exhibit a broad substrate scope such that nucleophilic fluorination of complexly functionalized substrates could be accomplished.

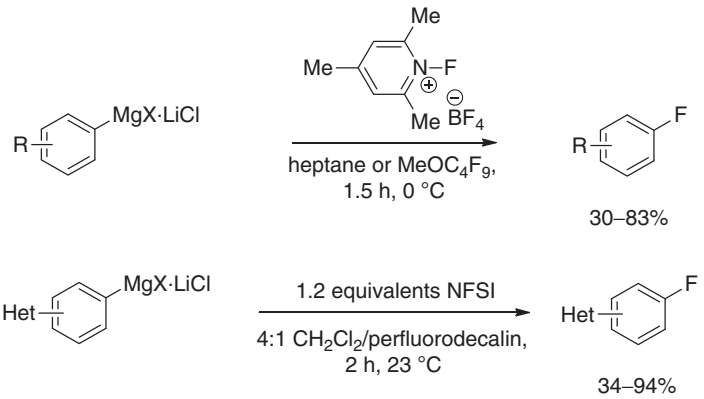


Scheme 45 Nucleophilic aromatic substitution with KF. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



Scheme 46 Fluorination of naphthyl bromide via aryne intermediates. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

Aryl fluorides can be synthesized via reaction of an aryl tin,[161] mercury,[161d,162] lead,[163] germanium,[161f] lithium,[164] magnesium (Scheme 47),[164a,165] silicon,[166] and boron[167] compounds with an electrophilic fluorinating reagent such as fluorine gas, xenon difluoride, acetyl hypofluorite, F-TEDA-BF_4, and NFSI. Tin, mercury, and lead aryl nucleophiles are toxic and less desirable to use than silyl- and boryl-based aryl nucleophiles; however, both silyl- and boryl-based aryl nucleophiles in most cases require the use of strong fluorinating reagents such as fluorine gas, XeF_2, and cesium fluoroxysulfate.[166a,b,e,f,167a,b] Aryl lithium or Grignard reagents can be fluorinated with less oxidizing fluorinating reagents such as NFSI and *N*-fluoropyridinium salts[164b,165a,168] but do

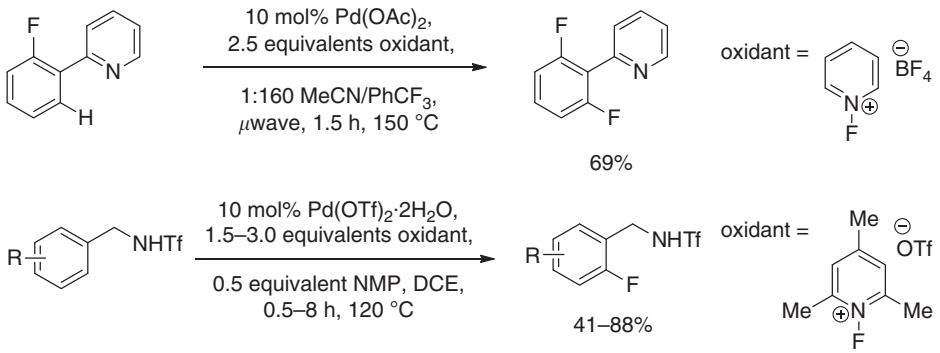


Scheme 47 Synthesis of aryl fluorides from aryl Grignard reagents. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

not tolerate protic and electrophilic functional groups. As with traditional nucleophilic fluorination methods, traditional electrophilic fluorination methods are not general but can afford simple aryl fluorides in up to >99% yield.

6.06.3.2 C–H Functionalization of Arenes with Fluorinating Reagents

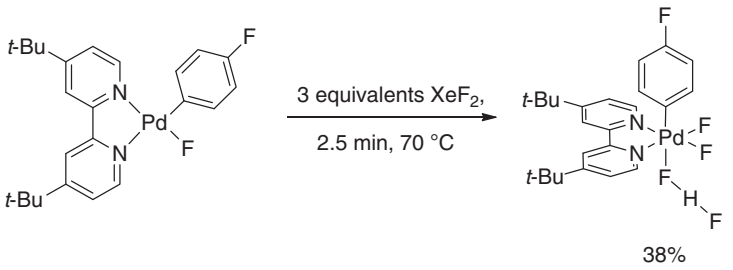
Direct, controlled fluorination of the C–H bonds of arenes is desirable because it would provide the most efficient approach to convert arenes to the corresponding fluorinated products. Copper(II)-mediated fluorination of benzene at >450 °C demonstrated that the C–H bond of benzene could be directly fluorinated[169] but has not been further developed. Palladium-catalyzed, *N*-directed electrophilic fluorination of arenes (Scheme 48) has been reported by Sanford[41b] and Yu.[170] The two *N*-directed fluorination reactions are proposed to undergo high-valent palladium cycles.



Scheme 48 *N*-directed Pd-catalyzed fluorination of arenes. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

6.06.3.3 Transition Metal-Mediated Fluorination

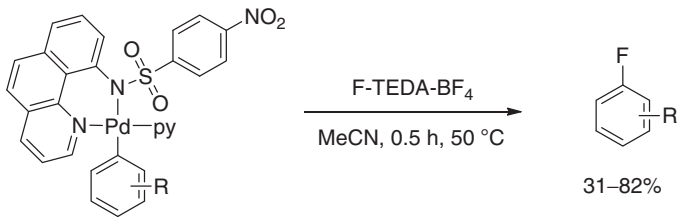
Studies of Pd(IV) aryl bipyridyl complexes demonstrated that reductive elimination from the bipyridyl Pd(IV) complexes affords aryl fluorides (Scheme 49).[171] Reductive elimination of aryl fluorides from Pt(IV) complexes have also been reported.[172]



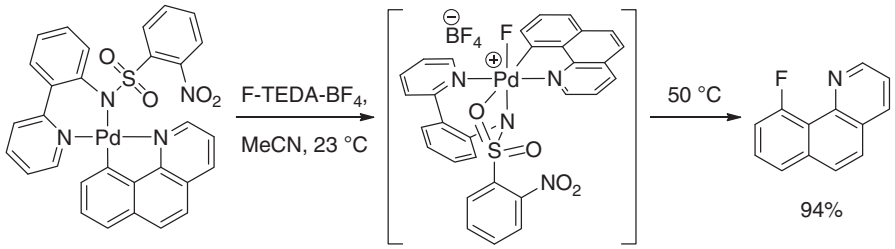
Scheme 49 Isolation of a Pd(IV) species involved in reductive elimation to afford aryl fluoride product. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

Stoichimetric Pd(II) aryl benzoquinoline-sulfonamide complexes synthesized from arylboronic acids were treated with F-TEDA-BF_4 to afford fluorinated functionalized arenes, tolerating functional groups such as aldehydes and phenols (Scheme 50).[173] Mechanistic studies with structurally related benzoquinoline phenylpyridinesulfonamide palladium(II) complex demonstrated the presence of a distinct intermediary Pd(IV) species directly involved in the formation of the aryl carbon–fluorine bond via reductive elimination (Scheme 51).[174]

Silver salts were used to mediate the fluorination of arylstannanes,[175] boronic acids,[176] and silanes.[177] Presence of a putative multimetallic, high-valent silver species is postulated to be the facilitating factor for aryl fluoride reductive elimination at room temperature. This silver salt-based fluorination method can accomplish the fluorination of nitrogenous heteroaryl and mesityl nucleophiles as well as nucleophiles containing electron-rich, electron-poor, electrophilic, and protic functional groups.



Scheme 50 Fluorination of Pd(II) benzoquinolyl sulfoamide complexes with F-TEDA-BF_4. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

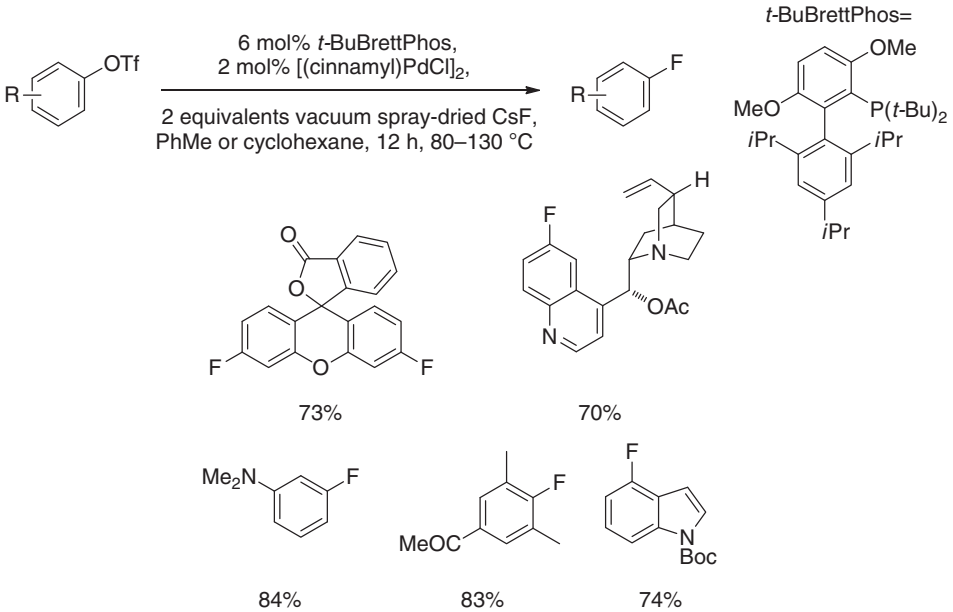


Scheme 51 Reductive elimination from Pd(IV) phenylpyridyl sulfonamide complexes. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

6.06.3.4 Cross-Coupling

6.06.3.4.1 With aryl electrophiles and fluoride sources

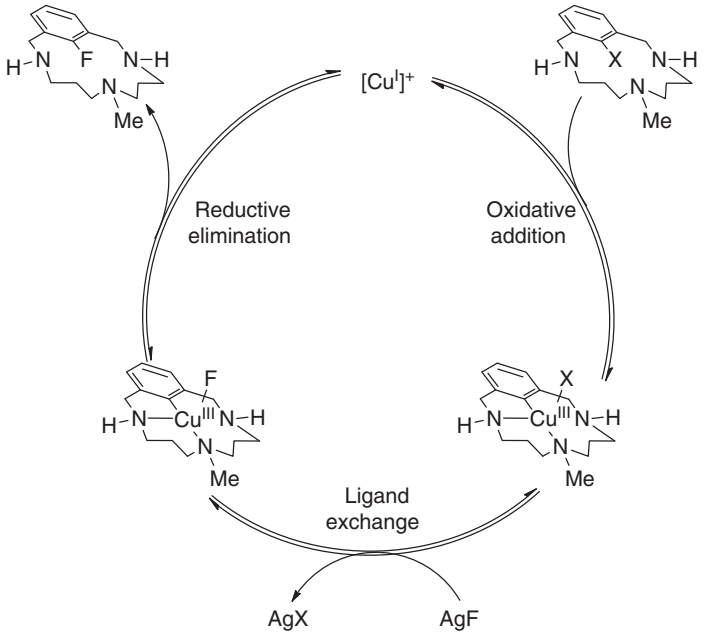
Late transition metals such as nickel, copper, ruthenium, rhodium, palladium, iridium, and platinum have been examined as the transition metals for cross-coupling with fluoride with aryl electrophiles such as aryl halides or sulfonates.[172,178] Cross-coupling of aryl triflates with cesium fluoride via palladium catalysis was successfully accomplished with sterically bulky monodentate phosphine *t*BuBrettPhos, which promoted reductive elimination of the aryl fluoride from a T-shaped aryl Pd(II) monophosphine fluoride complex (Scheme 52).[178f,179] A strong covalent, stable bond between the soft Pd(II) center and the hard fluoride as well as the tendency for monophosphine Pd(II) aryl complexes to form fluoride-bridged dimer complexes makes reductive elimination



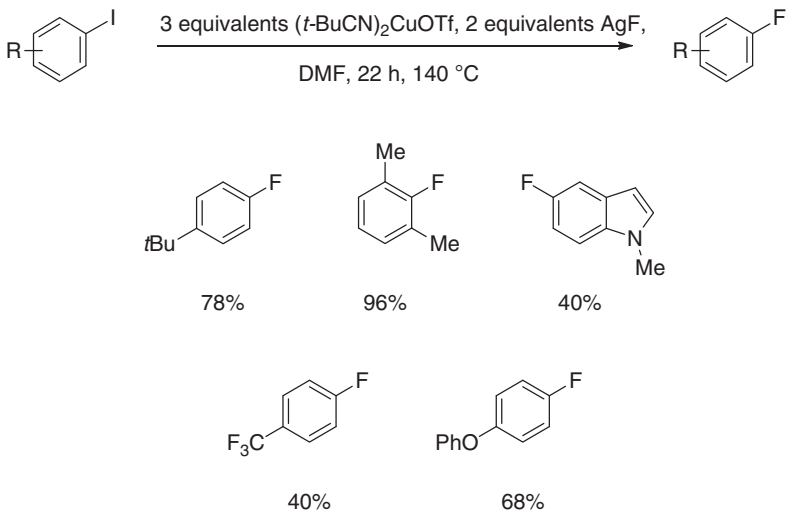
Scheme 52 Pd-catalyzed cross-coupling of aryl triflates with CsF. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

of aryl fluorides difficult. A broad range of substrates and functional groups such as dimethylamine are tolerated; however, protic functional groups are not tolerated under the reaction conditions and regioisomeric fluorination products form in some cases due to the use of basic anhydrous spray-dried cesium fluoride.

A copper(I)–copper(III) cycle was established for aryl halides using a contrived system in which the ligand was tethered to the arene, allowing for the isolation of intermediates (**Scheme 53**).[178e] Oxidative addition of copper(I) into the aryl halide supported by the tris(amine) ligand generates a copper(III) complex that undergoes ligand metathesis with silver fluoride. This copper(III) fluoride complex then undergoes reductive elimination to afford the aryl fluoride. Copper-mediated fluorination of electron-rich, -poor, and hindered aryl iodides was reported using three equivalents of copper(I) complex and AgF (**Scheme 54**).[180]



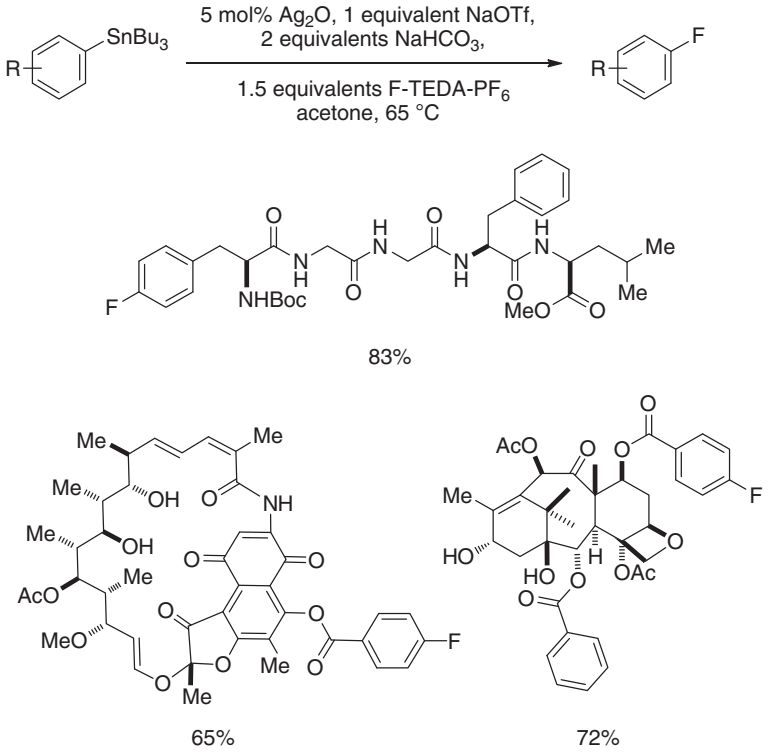
Scheme 53 Cu-catalyzed halide exchange on arenes with AgF. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



Scheme 54 Cu-mediation fluorination of aryl iodides with AgF. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

6.06.3.4.2 With aryl nucleophiles and electrophilic fluorinating reagents

Complex natural product-derived arylstannanes can undergo cross-coupling with F-TEDA-PF_6, which acts as an electrophilic source of fluorine, via silver catalysis (Scheme 55).[181] The silver-catalyzed fluorination is postulated to occur via multimetallic silver intermediates similar to the silver-mediated fluorination methods proposed for arylstannanes and boronic acids. Although toxic arylstannanes are used, this silver-catalyzed fluorination method displays a broad substrate scope for the synthesis of complex aryl fluorides.



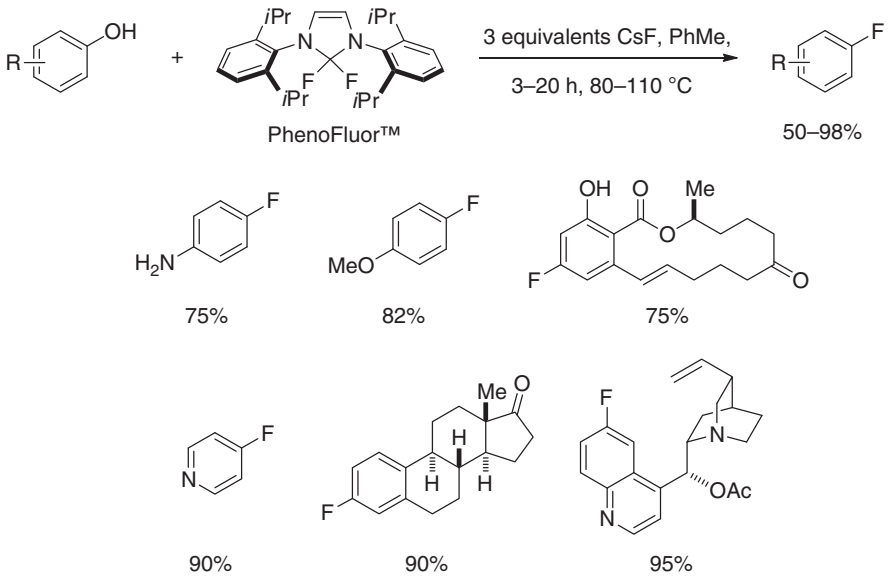
Scheme 55 Ag-catalyzed fluorination of complex arylstannanes. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

6.06.3.5 Phenol Deoxyfluorination

Late-stage deoxyfluorination of the hydroxy group in phenols with fluoride is advantageous for the expedient synthesis of complex fluorinated molecules and natural products. Catechol moieties can be monodeoxyfluorinated by oxidation of catechol to the *ortho*-quinone followed with fluorination with Deoxo-Fluor®, which gives an unselective mixture of fluorinated products.[182] Deoxyfluorination of *para*-nitrophenol with *N*,*N*′-dimethyl-2,2-difluoroimidazolidine[12a] led to the development of a general method for the *ipso*-deoxyfluorination of phenols with commercially available PhenoFluor™ and cesium fluoride (Scheme 56).[12b] Electron-poor, -neutral, and -rich phenols as well as hydroxypyridines can be transformed to the corresponding aryl fluorides.

6.06.4 Positron Emission Tomography with Fluorine-18

Positron emission tomography (PET)[5a–e,183] provides molecular imaging with radiotracers via positron decay detection as a clinical diagnostic tool for cancer[5c,d] as well as other potential clinical applications for patient care. Fluorine-18 is the radioactive isotope of fluorine-19, the naturally 100% abundant isotope, and has a half-life of 110 min. This radioactive decay limits incorporation of fluorine-18 into radiotracers to the late stage of the radiotracer synthesis. Simple ^{18}F-radiotracers can be synthesized via traditional methods; however, the lack of functional-group tolerance of traditional methods has limited the molecular complexity of radiotracers for medical applications. Ideally, the synthesis, purification, and formulation of radiotracers should take less than two half-life cycles and the method for introduction should be effective on the nanomolar scale with nonanhydrous ^{18}F-fluoride because desolvation to anhydrous ^{18}F-fluoride is difficult due to strong hydrogen-bonding interaction of fluoride with

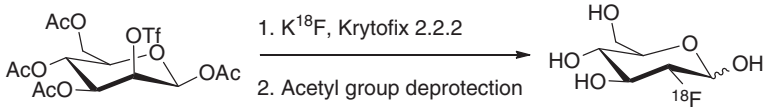


Scheme 56 Deoxyfluorination of phenols with difluoroimidazole-type reagents. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

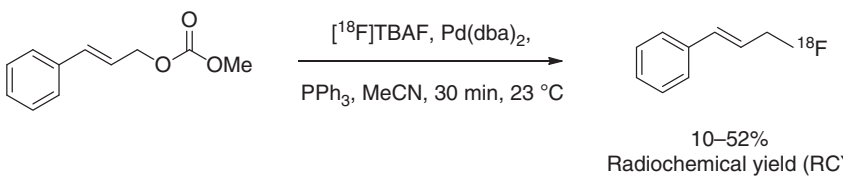
water.[6] Although ^{18}F-fluoride remains the most widely available, practical source of ^{18}F, ^{18}F-enriched fluorine gas is available but generally of lower specific activity with recent advances increasing the specific activity of [^{18}F]F_2.[184]

6.06.4.1 Nucleophilic Methods for the Incorporation of ^{18}F

Substitution reactions are most commonly used in nucleophilic radiofluorination reactions and accomplished with ^{18}F-fluoride with alkyl or aryl substrates. Nucleophilic substitution reactions often employ cryptands along with alkali salts to increase fluoride nucleophilicity.[5d] Polar aprotic reaction solvents such as DMF, DMSO, and acetonitrile that facilitate S_N2-type and S_NAr-type reactions are used for alkyl and aryl nucleophilic substitution reactions. Additionally, *tert*-butanol may be added as an additive to reduce fluoride basicity for aliphatic substitution reactions, reducing the formation of elimination byproducts.[10] Alkyl halides or sulfonates react through an S_N2 reaction with ^{18}F-fluoride to afford fluorinated radiotracers such as 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG), a commonly used radiotracer for tumor detection (Scheme 57).[185] The first palladium-catalyzed nucleophilic fluorination reaction with ^{18}F-fluoride was reported for the synthesis of ^{18}F-functionalized allyl fluorides (Scheme 58).[62]

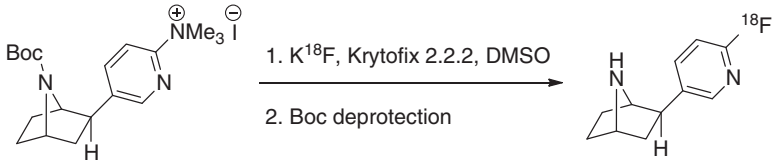


Scheme 57 Nucleophilic radiochemical fluorination with ^{18}F-fluoride to afford [^{18}F]FDG. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

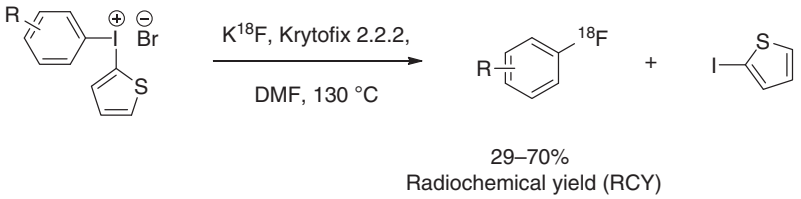


Scheme 58 Pd-catalyzed allylic fluorination with ^{18}F-fluoride. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

Nucleophilic aromatic substitution with ^{18}F-fluoride occurs with arenes functionalized with a leaving group such as nitro, trialkylammonium, halide, or sulfonate groups with at least one electron-withdrawing group *ortho* or *para* to the leaving group.[186] Heating or microwave heating in some instances facilitates the S_NAr reaction with ^{18}F-fluoride. An example in which nucleophilic aromatic substitution is used for the synthesis of radiotracers is with nicotinic acetylcholine receptor radioligands (**Scheme 59**).[187] Nucleophilic radiofluorination of diaryliodonium salts has also been reported for the synthesis of ^{18}F-labeled aryl fluorides (**Scheme 60**).[188] Selectivity of one arene over another on the diaryliodonium salt is for the more electron-poor or *ortho*-substituted arene, the latter being attributed to the *ortho*-effect.[189] The dummy ligand on iodine typically is 2-thiophene to encourage fluorination of the other arene of interest[188b] and the counterion of the iodonium salts is chosen to be dissociative and non-nucleophilic. The major drawback to this approach with diaryliodonium salts is that complex, natural product-like substrates are difficult to synthesize as diaryliodonium salts with the current methodologies that have limited functional group tolerance. The synthesis of aryl iodonium salts often employs oxidants such as *m*CPBA or peroxydisulfate salts and strong acids such as sulfuric acid and triflic acid.[190]



Scheme 59 Nucleophilic aromatic substitution with ^{18}F-fluoride. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



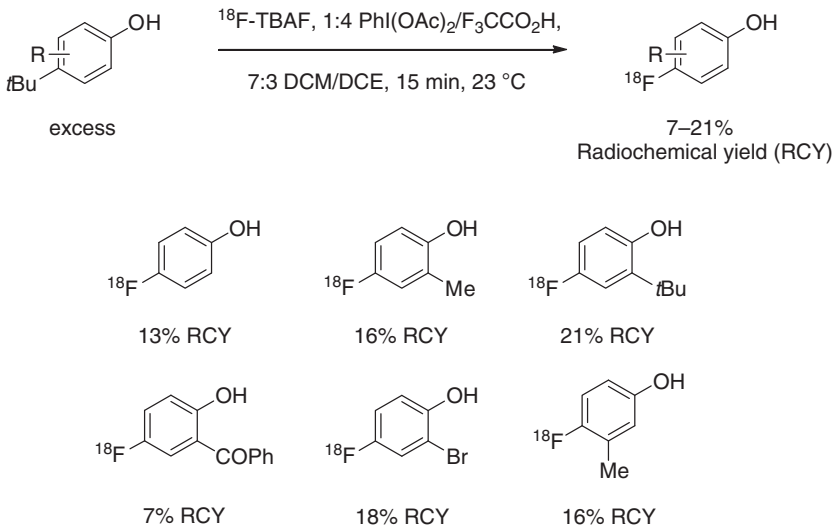
Scheme 60 Nucleophilic radiochemical fluorination of aryl(2-thienyl)iodonium bromides. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

6.06.4.2 Electrophilic Methods for the Incorporation of ^{18}F

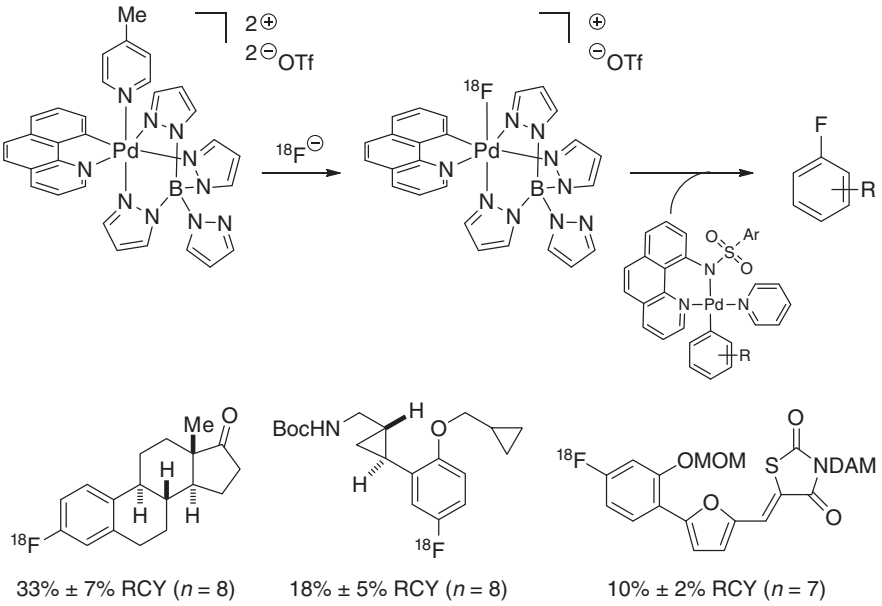
Several ^{18}F-electrophilic fluorinating reagents have been synthesized from ^{18}F-fluorine gas such as ^{18}F-acetyl hypofluorite,[191] ^{18}F-xenon difluoride,[191a,192] ^{18}F-*N*-fluorosulfonamide or imide reagents,[193] ^{18}F-*N*-fluoropyridinium salts,[194] and ^{18}F-TEDA salts.[184b] Electrophilic radiofluorination via direct, nonspecific fluorination of substrates such as alkenes[195] for the synthesis of [^{18}F]FDG and related sugars as well as with arenes[196] for the synthesis of [^{18}F]fluoro-3,4-dihydroxy phenylalanine ([^{18}F]F-DOPA) in many instances affords multiple fluorinated products and does not demonstrate functional-group tolerance when highly oxidizing ^{18}F-fluorinating reagents are employed. Radiochemical fluorodemetalation of aryl organometallic reagents,[193a] arylsilanes,[166c] and arylstannanes[161a,c,191b] often affords better selectivities than direct fluorination. Both direct radiofluorination and fluorodemetalation are hindered by the use of low specific activity fluorinating reagents.

para-tert-Butylphenols undergo efficient oxidative fluorination by formal substitution of the *tert*-butyl group with high specific activity ^{18}F-fluoride of the *para-tert*-butyl group via a proposed oxidative fluorination/dearomatization, followed by a rearomatization sequence (**Scheme 61**).[197] The approach enables fluorination via a substrate umpolung strategy. The method tolerates a wide range of electronically diverse *ortho*-substituents including halides, other *tert*-butyl groups, carbonyls, and olefins and afford isolated fluorination radiochemical yields of 7–21%.

^{18}F-Fluoride capture with Pd(IV) picoline complex shown in **Scheme 62**[198] can be used to radiochemically fluorinate benzoquinolylsulfonamide Pd(II) complexes to afford ^{18}F-labeled arenes. An advantage to this method is that ^{18}F-fluoride can be incorporated into arenes in high specific activity via an electrophilic radiochemical fluorination. Additionally, the Pd(IV)-[^{18}F] complex is not water sensitive and is also thermally stable. Direct S_N2 transfer and an electron-coupled fluoride transfer are both possible reaction pathways.



Scheme 61 Oxidative radiochemical fluorination of *para*-*tert*-butylphenols with ^{18}F-fluoride and iodobenzene diacetate. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.



Scheme 62 ^{18}F-Pd(IV) electrophilic fluorinating reagent from ^{18}F-fluoride for the synthesis of ^{18}F-labeled aryl fluorides. Reproduced from Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264, with permission from Wiley.

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6.07 Ritter-Type Reactions

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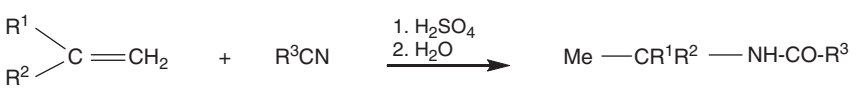
Glossary

The Ritter amide reaction A one-flask process in which a carbenium ion, usually formed under acidic conditions, reacts with a nitrile to produce a nitrilium ion. This species is transformed into an imidate intermediate that then undergoes hydrolysis to afford the final amide product.

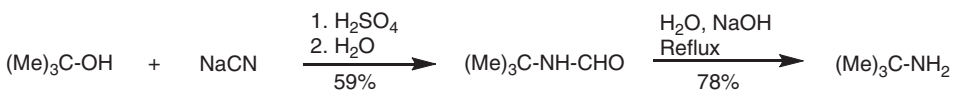
The Ritter heterocyclic reaction A one-flask process, closely related to the Ritter amide reaction, but in which a heterocyclic compound is produced. In the majority of cases, a carbenium ion and a nitrile undergo intermolecular reaction to form a nitrilium ion. The latter then undergoes cyclization. Less commonly, the cyclic nitrilium ion is formed intramolecularly and then the reaction is completed by nucleophilic addition. The heterocycle formed by either pathway always contains an imine part structure.

6.07.1 The Ritter Amide Reaction

John Ritter of New York University reported in 1948 that alkenes or tertiary alkanols reacted with nitriles in the presence of concentrated sulfuric acid to give amide products in good to excellent yields (equation 1).[1] This reaction provided an especially reliable means of linking a nitrogen atom with a tertiary carbon for synthetic work. Further, basic hydrolysis of *N-tert*-alkylformamide products (equation 2) provided an efficient route to the corresponding *N-tert*-alkylamines.[2] It soon became apparent that this new nitrile to amide reaction was applicable to many other functional group precursors and that it was a very general process. The scope of the reaction expanded enormously when Ritter and colleagues discovered, from 1952 onwards, that their reaction conditions could also yield a remarkable range of heterocyclic products (see Section 6.07.3).[3–5]



(1)

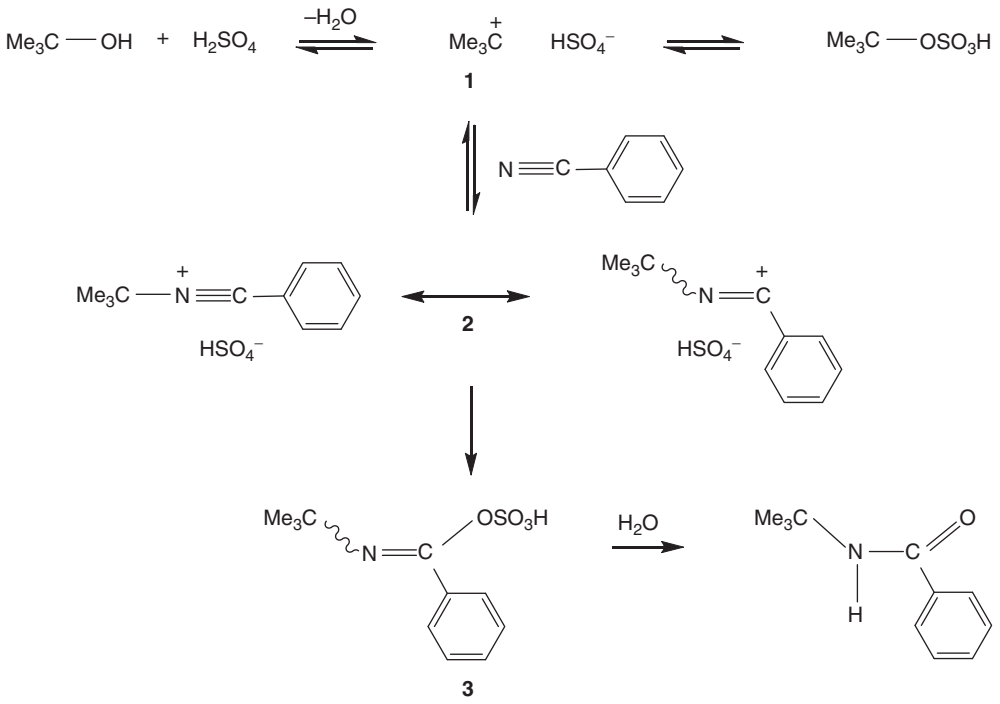


(2)

Today, the Ritter reaction is best considered as the one-flask reaction of a nitrile and a carbenium ion (or its equivalent), followed by subsequent chemical events. These are usually hydrolysis to an amide functional group or cyclization to form a heterocyclic molecule. The most comprehensive reviews available are those of Krimen and Cota,[6] and Bishop.[7] The former article provides a thorough description of the experimental scope, reaction conditions, and yields for all Ritter reactions reported up to 1966, while the latter article provides an historical, mechanistic, and synthetic overview of the many variants of the Ritter process. Both articles are available electronically. In addition, Meyers and Sircar have written an outstanding account of the heterocyclic systems accessible by means of intramolecular Ritter methods.[8] Much of the contemporary work centers on catalytic developments of the Ritter reaction. Guérinot, Reymond, and Cossy recently have published an excellent description of this important new research.[9] The aim of the present chapter is to provide a self-contained account that emphasizes new developments over the past 25 years.

6.07.1.1 Reaction Mechanism

Formation of an amide by the Ritter reaction is a process that involves three distinct intermediate species **1**–**3**. Its mechanism is illustrated in Scheme 1 for the example of *tert*-butanol and benzonitrile reacting with concentrated sulfuric acid and yielding *N*-*tert*-butylbenzamide. The alcohol reacts first under strongly acidic conditions to produce the carbenium ion **1**. Next, this combines with the nitrile reagent to generate the resonance-stabilized nitrilium ion **2**, which then produces the imidate **3**. The latter is hydrolyzed, on quenching the reaction with water, to give the amide product. All these events occur in a one-flask reaction, thereby making the Ritter reaction a particularly efficient procedure to carry out.

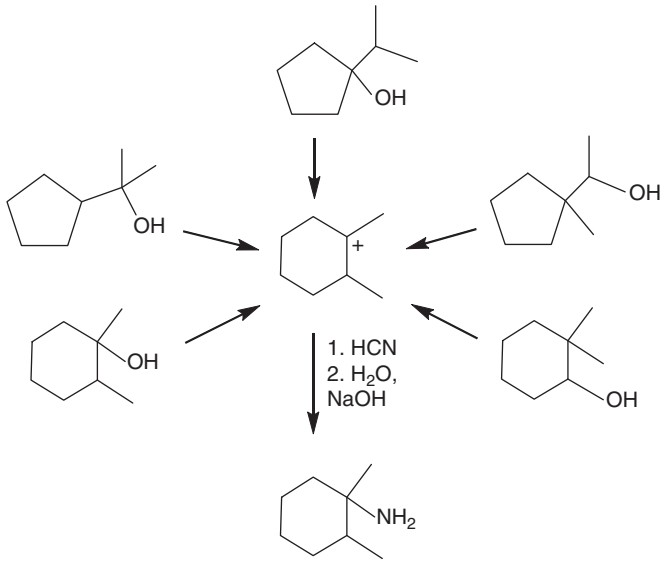


Scheme 1

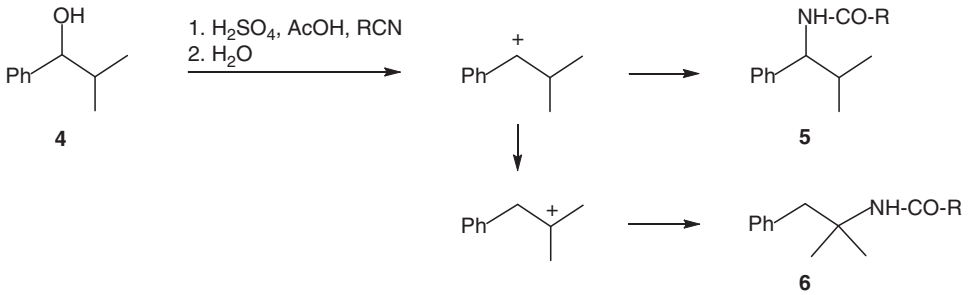
The considerable body of experimental evidence supporting this sequence has been reviewed,[7] but several aspects are worth repeating. The intermediacy of carbenium ions implies that Wagner–Meerwein rearrangements are likely to be encountered in some Ritter reactions. Indeed, formation of just one product from several alternative isomeric starting materials provides excellent supporting evidence for the mechanism (Scheme 2).[10]

Judicious control of the reaction conditions can also result in kinetic or thermodynamic control. For example, the alcohol **4** can yield either the kinetic product[11] **5** or the thermodynamic product[12] **6**, depending on the order of addition of the reagents (Scheme 3).[13] Conversely, in other cases, the deliberate use of forcing rearrangement conditions may be applied to achieve different and unexpected synthetic outcomes (see Section 6.07.5.1).

There is evidence that the carbenium ion **1** and its counterion exist as an ion pair, both components of which associate with the nitrile functional group in the reaction transition state **7**.[14] The efficiency of hydrogen sulfate ion in this role is believed to be a major factor in sulfuric acid often being the acidic reagent of choice for Ritter reactions. Nucleophilic attack of the nitrile on the carbenium ion can occur without difficulty, since nitrile samples are only about half-protonated under such strong acidic conditions.[15] Recently an intermediate nitrilium ion has been observed directly using ^{13}C CP/MAS nuclear magnetic resonance

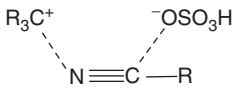


Scheme 2



Scheme 3

spectroscopy in a Ritter reaction carried out using zeolite H-ZSM-5.[16] The mechanistic subtleties of the Ritter process have led to its incorporation into several valuable teaching experiments.[17]



7

Ritter's early observation that heterocycles could arise in certain experiments[3–5] has since been developed into a remarkably wide range of valuable reactions (Section 6.07.3).[8] In these conversions, the acyclic nitrilium ion undergoes cyclization with a nucleophilic group within the same molecule or, alternatively, a cyclic nitrilium ion derivative is quenched by an external nucleophile. Both pathways result in the formation of a heterocyclic molecule containing an imine part structure.

Carbenium ions, nitrilium ions, and imidates can also be produced in processes that are very different from the original strong protic acid conditions. These methods, discussed in Section 6.07.2, provide alternative entry points into the Ritter reaction sequence. Since these three intermediates also feature in other well-known reaction mechanisms, there is therefore a close familial relationship between such processes and the Ritter reaction.[18]

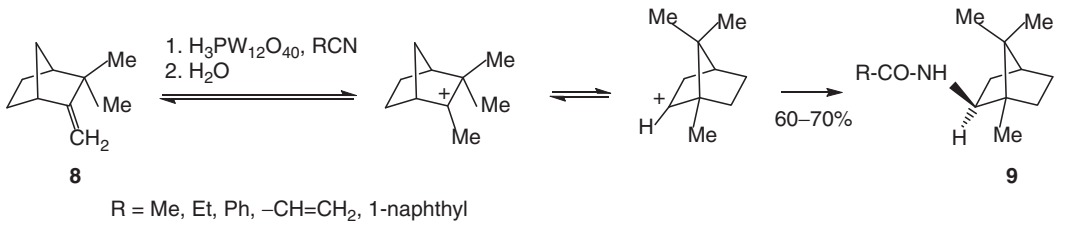
6.07.1.2 Reaction Conditions

A comprehensive listing of all Ritter reactions up to 1966 is presented by Krimen and Cota, along with full descriptions of typical experimental procedures.[6] The reaction efficiency, and sometimes even its outcome, depends on the precise method employed. Typical conditions are a reaction time of 1–24 h, temperature of 20–50 °C, and the use of 85–90% sulfuric acid, but superior yields can be obtained through a systematic variation of the reaction parameters. The presence of small amounts of water is usually

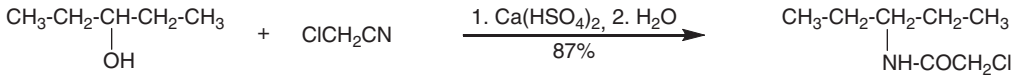
beneficial. Lower temperatures of 0–10 °C are necessary when hydrofluoric or hydrocyanic acids are used. The conditions chosen are also strongly influenced by the reactivity of the functional group chosen as the carbenium ion source. Many Ritter reactions simply use the acid and the nitrile as solvents. If a further solvent is required then it should preferably be polar, such as glacial acetic acid, acetic anhydride, cyclopentyl methyl ether, di-*n*-butyl ether, 1,2-dimethoxyethane, methyl isobutyl ketone, *N*-methylpyrrolidone, 2-methyltetrahydrofuran, nitrobenzene, or dioxane. These conditions enhance polarization of the nitrile group and improve its nucleophilicity. The reaction generally fails when methanol or ethanol is used as a solvent, and nonpolar solvents such as carbon tetrachloride or hexane give low yields. The most popular solvent is glacial acetic acid but this can lead to the formation of acetate side products.

The most commonly used protic acid is sulfuric and this was often found to be the most effective reagent when comparative trials have been conducted. However, many other familiar protic acids can used in its place: benzenesulfonic, fluoroboric, fluorosulfonic, formic, hydrofluoric, methanesulfonic (mesic), perchloric, phosphoric, polyphosphoric, sulfamic, *p*-toluenesulfonic, trifluoroacetic (TFA), and trifluoromethanesulfonic (triflic) acids. There is an increasing tendency to employ mesic, TFA, triflic, and various newer acids (see Sections 6.07.1.3 and 6.07.1.4).

Much of the current research is aimed at making the Ritter process greener by replacing the strong acid with alternative reagents. These acids include the heteropolyacids $H_3PW_{12}O_{40}$, $H_4SiW_{12}O_{40}$, and $H_7PMo_{12}O_{40}$ which are effective, for example, in the conversion of camphene **8** into the isobornylamides **9** via a carbocation rearrangement process (**Scheme 4**).[19] Dodecatungstophosphoric acid is also an efficient agent for Ritter reactions of *tert*-alkanols and their protected derivatives (methyl, trimethylsilyl, and tetrahydropyranyl). The resulting amide products are obtained in aqueous solution in excellent yields.[20] Heterogeneous reagents are also attracting increasing attention. These include the use of zeolites,[21,22] calcium hydrogen sulfate (equation 3),[23] acids immobilized on solid supports, and other substances. These reagents are discussed in detail in Section 6.07.4, which describes current catalytic developments.

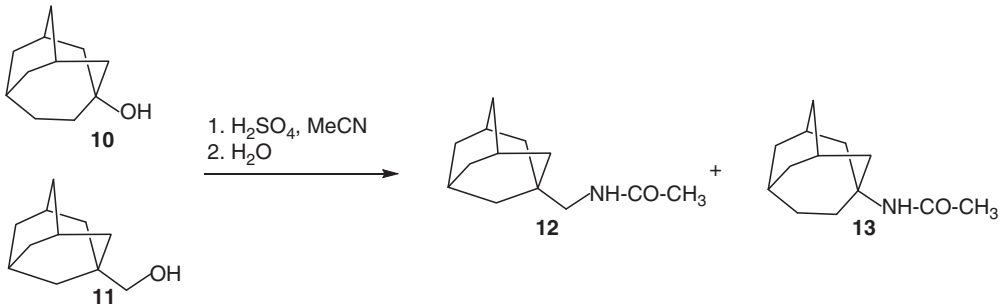


Scheme 4



(3)

The carbenium ion can also be generated through use of Lewis acids: aluminum(III) chloride, antimony(V) chloride, boron trifluoride, boron trifluoride acetic acid, boron trifluoride etherate, tin(IV) chloride, and others. This approach is advantageous for precursors that are labile to strong acids and it can allow greater control of product ratios in cases where mixtures are produced. This can be extended even further to using mixtures of protic and Lewis acids as demonstrated by Sasaki et al.[24] Both 3-homoadamantanol **10** and 1-hydroxymethyladamantane **11** produced mixtures of the isomeric acetamides **12** and **13** (**Scheme 5**), but in very different conversions and proportions dependent on the reaction conditions employed. Just using sulfuric acid, it was



Scheme 5

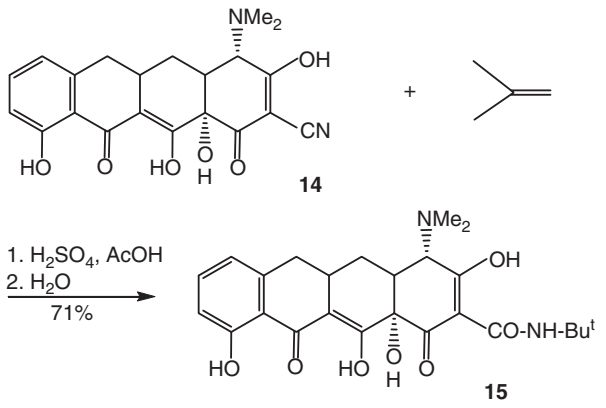
determined that the adamantane **12** was the thermodynamic product whereas homoadamantane **13** was the product of kinetic control. Protic and Lewis acid mixtures decreased the amide yields in both cases. However, the joint use of aluminum chloride increased the proportion of the kinetic product, whereas boron trifluoride etherate increased the proportion of the thermodynamic product, for an identical reaction time (Table 1).

Table 1 Reaction outcomes for the conversion of alcohols **10** and **11** into the acetamides **12** and **13**

Reagent(s)	*Time (h)*	*Temperature (°C)*	*Total yield of amides (%)*	*Relative yields (%)*	
				12	***13***
10	24	15	93	83.5	16.5
10	24	50	98	90	10
11	1	15	20	34	66
11	24	15	42	90	10
11	1	50	40	97.1	2.9
11	24	50	92	99.8	0.2
10, $AlCl_3$	24	15	72	69	31
10, $BF_3 \cdot Et_2O$	24	15	76	97	3
11, $AlCl_3$	24	15	23	8	92
11, $AlCl_3$	96	15	42	83	17

6.07.1.3 The Nitrile Component

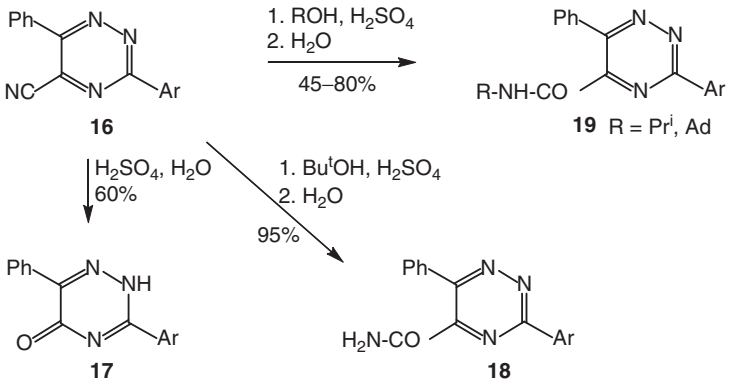
The majority of nitrile compounds (R–CN) react with carbenium ions, although the product yields can vary considerably. Ritter reported the successful use of NaCN, plus R=alkyl–, C_6H_5–, X–C_6H_4–, C_6H_5–alkyl–, H_2N–(cyanamide), H_2N–CO–alkyl–, H_2N–C(=NH)–NH– (dicyandiamide), $ClCH_2$–, $(CH_3)_2CCl$–, CH_2=CH–, CH_2=C(CH_3)–, alkyl–O–CO–alkyl–, alkyl–CO–O–alkyl–, Ph–CH=CH–, NC–alkyl–, and NC–CH=CH–, in the author's original amide-forming papers.[1,2] Conjugated alkenic, allenic, and alkynic nitriles also react without complications. Dinitriles yield bis(amides), or polyamides if aldehyde, diene, or glycol carbenium ion sources are employed.[7] Many nitrile compounds containing additional functional groups work very well. Arguably the most striking example is Ritter conversion of the tetracycline nitrile derivative **14** into its antibacterial derivative **15**, which occurs troublefree despite the many other functional groups in attendance (Scheme 6).[25]



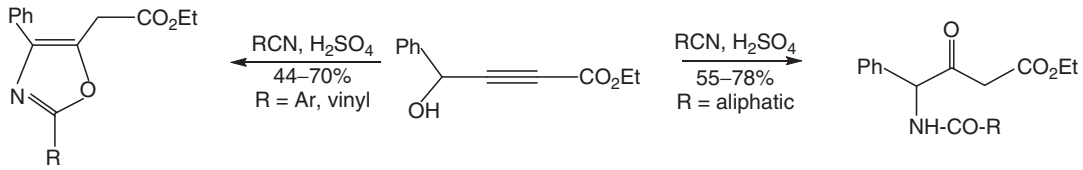
Scheme 6

However, more complex situations are possible. The triazine **16** is hydrolyzed by dilute sulfuric acid into **17**, but in the presence of *tert*-butanol it yields amide **18** instead (Scheme 7). However, if 2-propanol or 1-adamantanol are employed, then the Ritter reaction to produce **19** does occur.[26]

In rare cases, alternative types of products are obtained through the use of different nitrile classes (Scheme 8). It is proposed that, in all cases, the hydroxy group is converted into the nitrilium ion and thence to the amide. Hydrolysis then continues, either conventionally to give the β-keto ester, or through an intramolecular process to yield the oxazole product.[27]



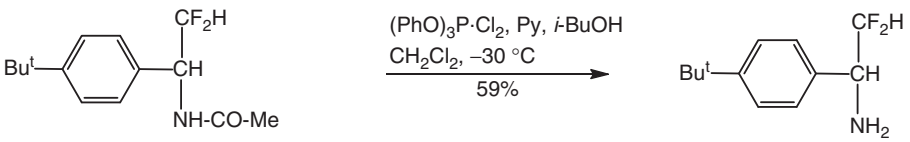
Scheme 7



Scheme 8

Hydrocyanic acid is usually generated *in situ* from the cyanide ion and acid during Ritter reactions, but its volatility and high toxicity require both extreme caution and low reaction temperatures. Nonetheless, HCN is a particularly important nitrile since it yields *N*-alkylformamide products that provide a route to *N-tert*-alkylamines. Although the usual Ritter procedure yields a primary amine, alkylation of the alkylformamide NH group before hydrolysis also affords a convenient route to secondary amines.[28] A limitation of the amine preparation is that acetamides (and many other amides) frequently require surprisingly savage basic hydrolysis conditions, whereas acidic hydrolysis often results in loss of the alkyl group. These conditions are contrasted here (Scheme 9) by the conversion of alkene **20** into *N-tert*-octylamine **21** using both the formamide **22** and acetamide **23** pathways. Although harsh conditions are required for both the cleavage reactions, the formamide route offers a lower temperature, shorter reaction time, and gives a higher yield. Acidic hydrolysis of either amide just regenerates the alkene **20**.[1,2]

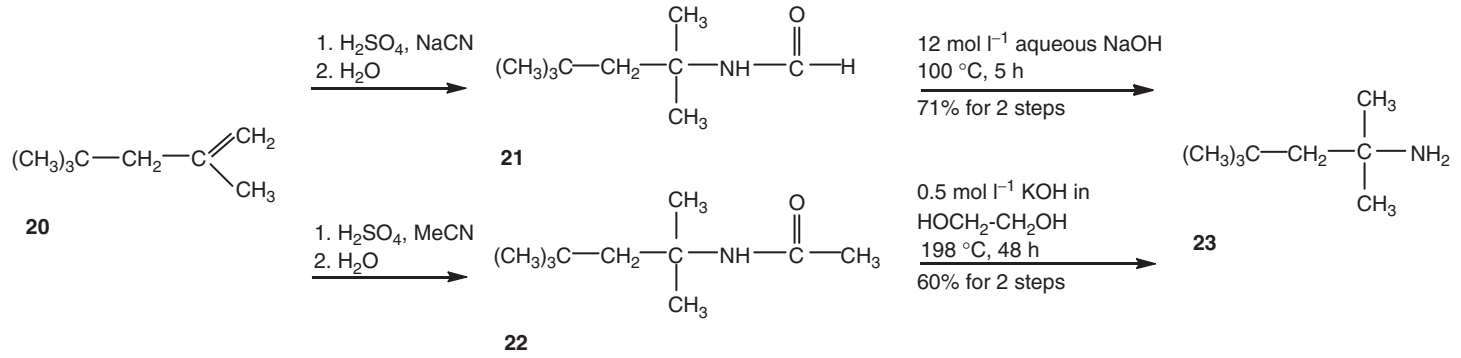
More satisfactory methods of obtaining the amine are desirable. An effective low-temperature acetamide hydrolysis method,[29] illustrated here using the work of Hu (equation 4),[30] has been introduced by Prati. This reagent may not be appropriate, however, if additional functional groups are present in the substrate.



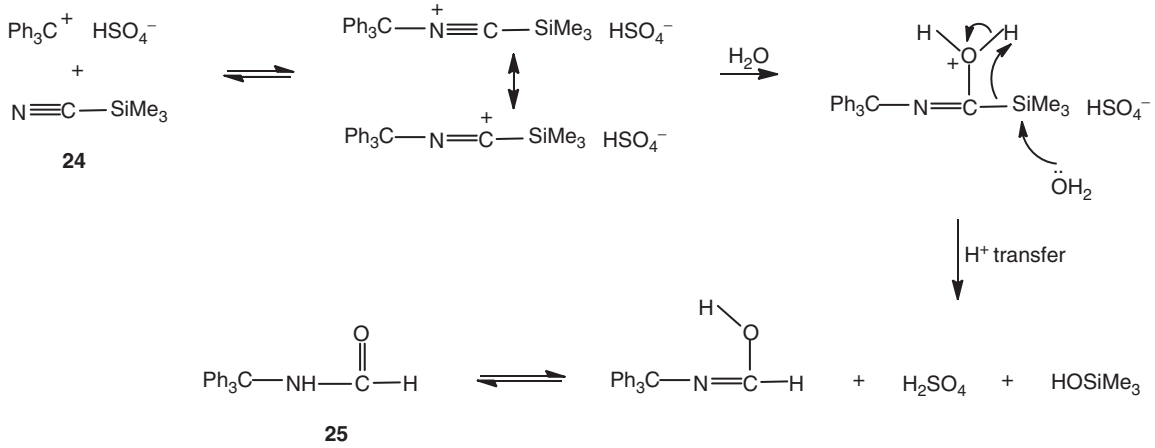
(4)

A significant improvement in formamide synthesis has been introduced by Goel,[31] in which the protic acid is retained, but NaCN is replaced by the liquid reagent trimethylsilyl cyanide (TMSCN). In this new procedure, the carbenium ion and Me_3SiCN **24** are reported to combine to produce a nitrilium ion in the normal way. The trimethylsilyl group is expelled later as $HOSiMe_3$ during the hydrolysis stage, thereby yielding the formamide product **25** by the process illustrated in Scheme 10. Later work, however, indicates that this conversion actually proceeds through *in situ* liberation of HCN from TMSCN under acidic reaction conditions.[32] So, although the TMSCN route is an attractive choice for producing formamides, appropriate safety conditions still must be employed.

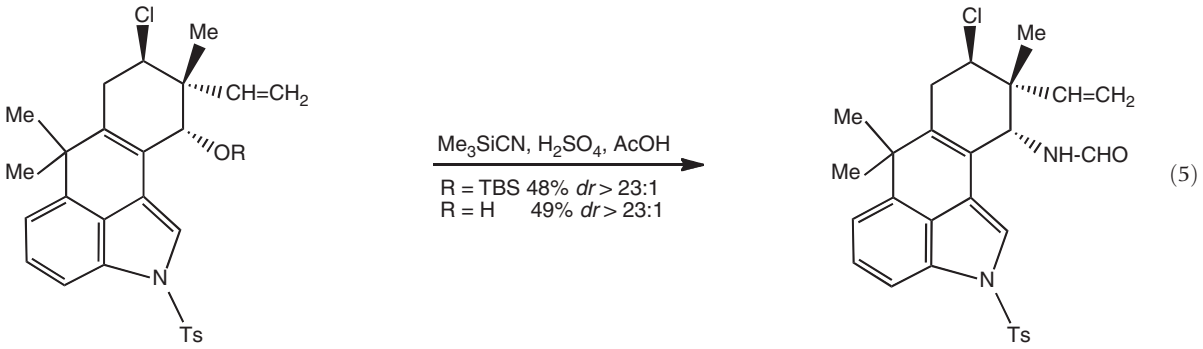
Yields using this new procedure are good and in some cases, considerably improved. Equation 5 illustrates its use as part of a hapalindole alkaloid synthesis. Either the free alcohol or its silylated derivative yielded the formamide product with high diastereoselectivity.[33]


1. H2SO4, NaCN
2. H2O
12 mol l−1 aqueous NaOH
100 °C, 5 h
71% for 2 steps
1. H2SO4, MeCN
2. H2O
0.5 mol l−1 KOH in
HOCH2-CH2OH
198 °C, 48 h
60% for 2 steps
20
21
22
23

Scheme 9

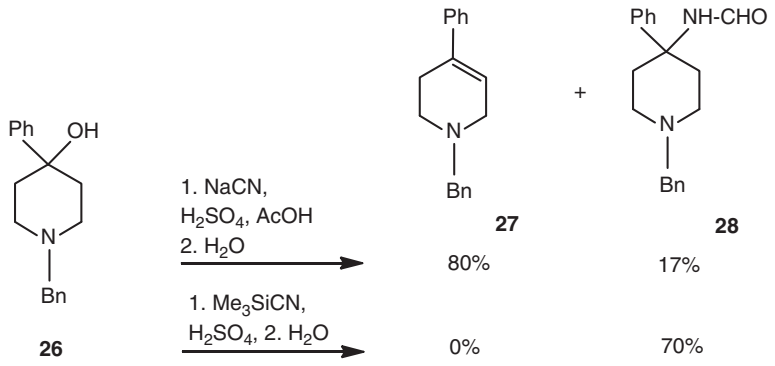


Scheme 10



(5)

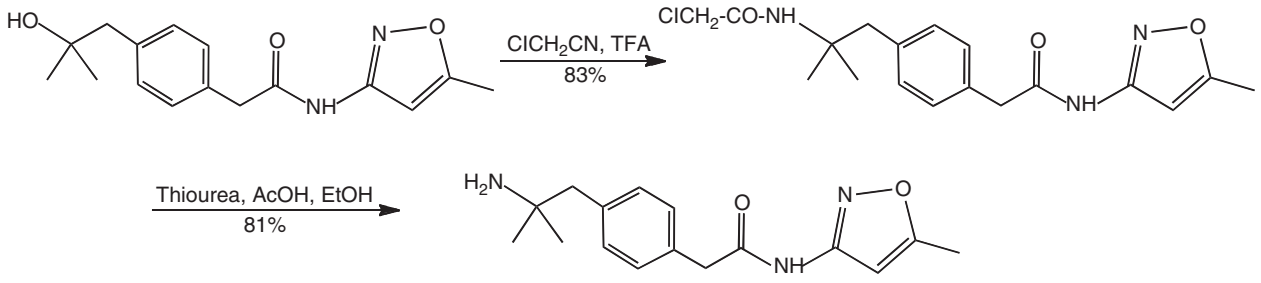
Another interesting case is the behavior of the piperidinol **26**, which proceeds exclusively to produce the formamide **28** without any of the dehydration product **27** that dominates under the classical reaction conditions (Scheme 11). This new TMSCN process failed for benzyl alcohol but succeeded for 1-trimethylsiloxyadamantane.[31]



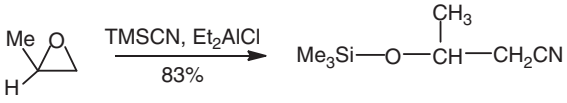
Scheme 11

If the amine product is required in synthetic work then, to avoid the toxicity and hydrolysis problems of the formamide pathway, the alternative Jirgensons procedure is usually now preferred.[34] This comprises the Ritter reaction with chloroacetonitrile to yield the chloroacetamide product, which is then hydrolyzed using thiourea and acetic acid in ethanol. A typical large-scale application of this method is illustrated in Scheme 12.[35]

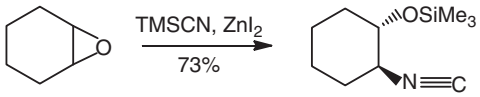
TMSCN **24** also reacts with oxiranes in the presence of aluminum-containing Lewis acids to generate nitrile products (equation 6).[36] Products such as this are, of course, potential Ritter reaction substrates. In marked contrast, however, the use of zinc-based Lewis acids yields isonitriles (equation 7).[37,38]



Scheme 12

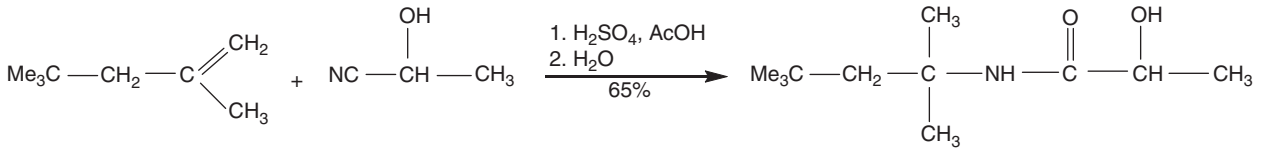


(6)

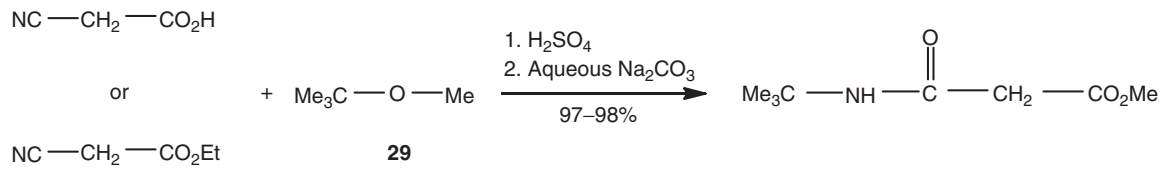


(7)

Of particular importance, the hydroxy group of cyanohydrins does not interfere with the Ritter reaction (equation 8),[39] but the corresponding acetoxy nitrile may give higher yields.[40] Cyano carboxylic acids and their esters are similarly unaffected by their additional functional groups. Dawar et al. have recently introduced a novel variant in which one-flask esterification and the Ritter reaction of these occur together (equation 9). Thus cyanoacetic acid in *tert*-butyl methyl ether (TBME) **29** yields a Ritter amide product with concomitant formation of a methyl ester group. Ethyl cyanoacetate forms the same product. Under acidic conditions, TBME is converted into *tert*-butyl cation and methanol. The carbenium ion reacts with the nitrile nitrogen atom in the normal manner, but methanol esterifies the carboxylic acid group (or transesterifies the ethyl ester) to yield the methyl ester product.[41]

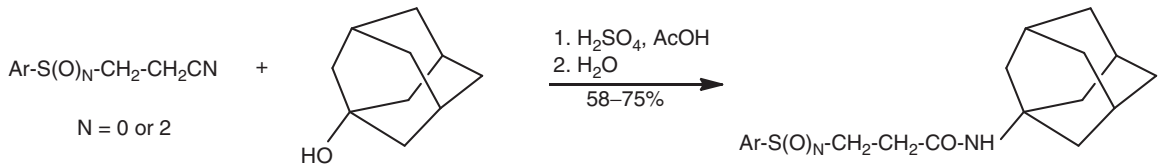


(8)



(9)

The Ritter reactions of arylsulfonylpropionitriles and arylthiopropionitriles likewise proceed smoothly with 1-adamantanol to produce the corresponding adamantyl amide derivatives (equation 10).[42]



(10)

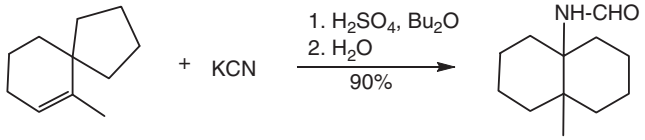
6.07.1.4 The Carbenium Ion Source

Any functional group that can react with a protic or Lewis acid to produce a carbenium ion is potentially able to undergo the Ritter amide-forming reaction. The majority of cases reported utilize alkene or alcohol precursors because of their ready access and ease of reaction. However, other functional groups are effective and many more can be made to work under stronger conditions. Further classes include aldehydes, alkanes, alkyl halides, carboxylic acids, dienes, epoxides (oxiranes), esters, glycols, ketones, *N*-hydroxymethylamides, oximes, and protected alcohols. Krimen and Cota present a comprehensive list of Ritter reactions reported up to 1966,[6] and representative examples are discussed here.

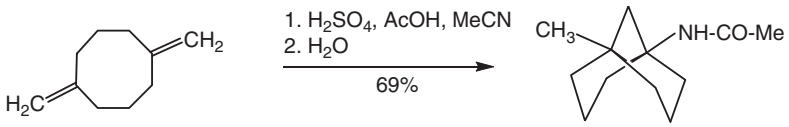
Standard alkene reactions are presented in equations 11 and 12.[1] Equation 13 combines the process with the Wagner–Meerwein rearrangement,[43] whereas equation 14 shows that transannular cyclization can be combined with the Ritter reaction in certain cases.[44]

$$Me_2C{=}CH_2 + PhCN \xrightarrow[90\%]{1.\ H_2SO_4,\ 2.\ H_2O} Ph\text{-}CO\text{-}NH\text{-}CMe_3 \quad (11)$$

$$Me_2C{=}CH\text{-}Me + Ph\text{-}CH{=}CHCN \xrightarrow[70\%]{1.\ H_2SO_4,\ 2.\ H_2O} Ph\text{-}CH{=}CH\text{-}CO\text{-}NH\text{-}C(Et)Me_2 \quad (12)$$



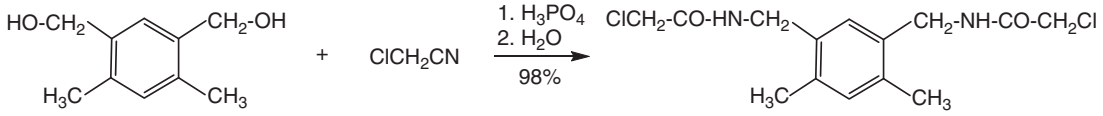
(13)



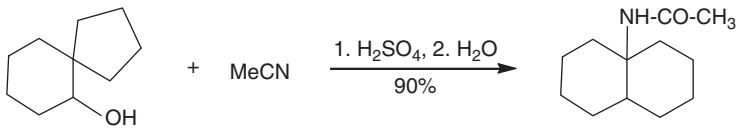
(14)

Tertiary (equation 15)[45] and benzylic alcohols (equation 16)[46] generally react efficiently, whereas secondary alcohols sometimes undergo rearrangement in conjunction with the Ritter reaction (equation 17).[47] Alternatively, mixtures of standard and rearranged amides can result (equation 18).[48] The Ritter reactivity of the acetylenic alcohol has recently been studied further in a flow-based synthesis. At 30 °C the standard Ritter product was obtained in 91% yield, but substantial formation of the by-product occurred above 40 °C.[49]

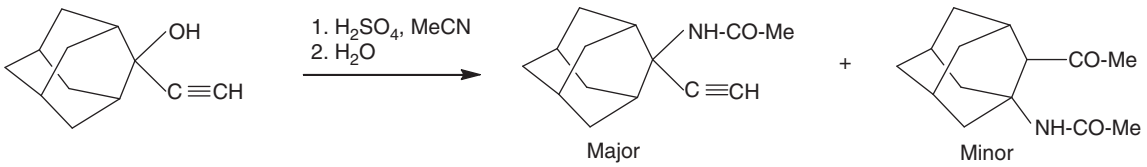
$$Me_3C\text{-}OH + NC\text{-}CH{=}CHCN \xrightarrow[88\%]{1.\ H_2SO_4,\ 2.\ H_2O} Me_3C\text{-}NH\text{-}CO\text{-}CH{=}CH\text{-}CO\text{-}NH\text{-}CMe_3 \quad (15)$$



(16)

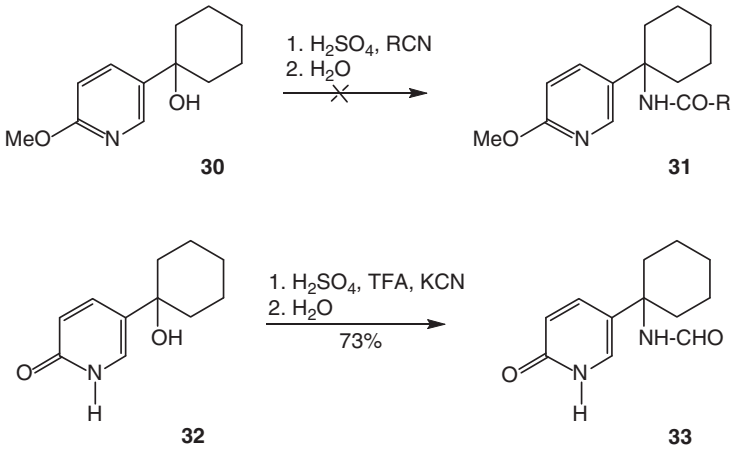


(17)



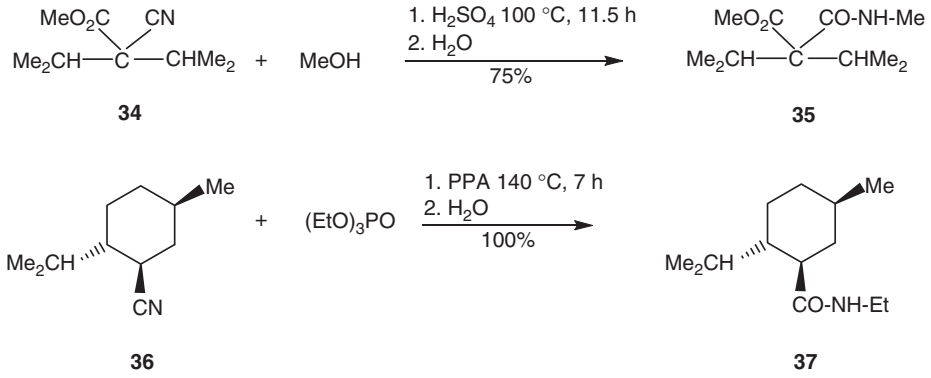
(18)

On rare occasions the Ritter reaction fails, such as the attempted conversion of alkoxypyridine **30** into amide **31** (an intended intermediate for an aminopyridinone synthesis). Rather than yielding a dicationic species, the protonated form of **30** preferred to undergo dehydration. However, the related pyridinone **32** did afford the Ritter product **33**, thereby allowing the synthesis to continue (Scheme 13).[50] It is always worth pursuing alternative procedures if synthetic difficulties are encountered.



Scheme 13

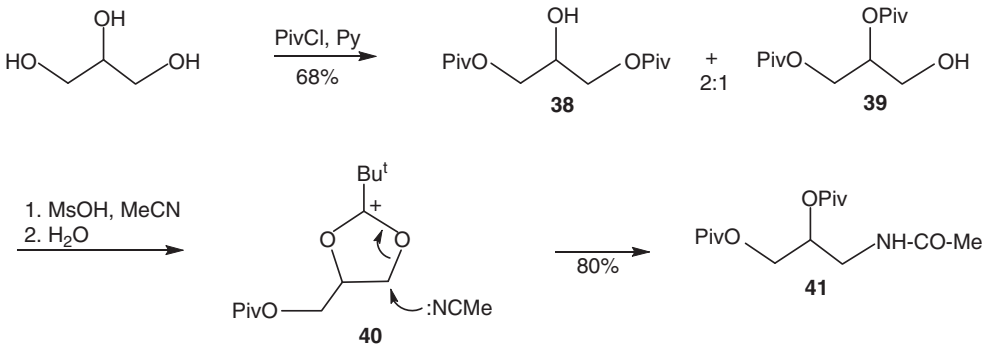
For many years it was believed that primary alcohols did not undergo Ritter reaction at all,[45] but this perceived wisdom now must be revised. Lebedev and Erman[51] (Scheme 14) have obtained good to high yields of amides using methanol, ethanol, or 1-butanol by using reaction temperatures of 100 °C or more, and higher molar ratios of alcohol and strong acids relative to the nitrile component. Thus nitrile **34** reacted with methanol to form amide **35** in 75% when sulfuric acid and methanol (4 equivalents each) and **34** (1 equivalent) were reacted at 100 °C for 11.5 h. Even better yields were obtained if the primary alcohol was replaced by an activated derivative such as dimethyl carbonate, dimethyl sulfite, trimethyl borate, tributyl phosphate, or triethyl phosphate. As an example, the nitrile **36** and triethyl phosphate afforded the amide **37** in quantitative yield using polyphosphoric acid. This Ritter-type process probably proceeds directly from these reagents to the imidate intermediate.



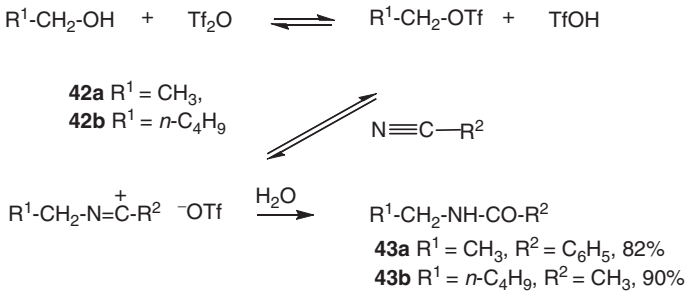
Scheme 14

Reaction of glycerol with 2 equivalents of pivaloyl chloride results in a 2:1 mixture of the alcohols **38** and **39**. On treatment with methanesulfonic acid these form the common 1,3-dioxonium cation **40**, which reacts with acetonitrile to produce the acetamide **41** in high yield. The site of the nitrile nucleophilic attack is largely determined by steric hindrance. This sequence provides a clever means of indirectly converting a primary alcohol group into its Ritter amide product (Scheme 15).[52]

Primary alcohols can be utilized effectively if they are treated with trifluromethanesulfonic anhydride (triflic anhydride, Tf_2O) instead of a strong acid (Scheme 16).[53] For example, the primary alcohols **42** are converted in excellent yield into the amides **43**. These conversions do not require the vigorous conditions of the previous method and occur at room temperature in 5 h. Some tertiary alcohols give lower yields if their highly reactive triflate intermediate can undergo elimination. If this is not structurally possible then the yields can be excellent, such as 98% for the conversion of 1-adamantanol into its acetamide derivative.

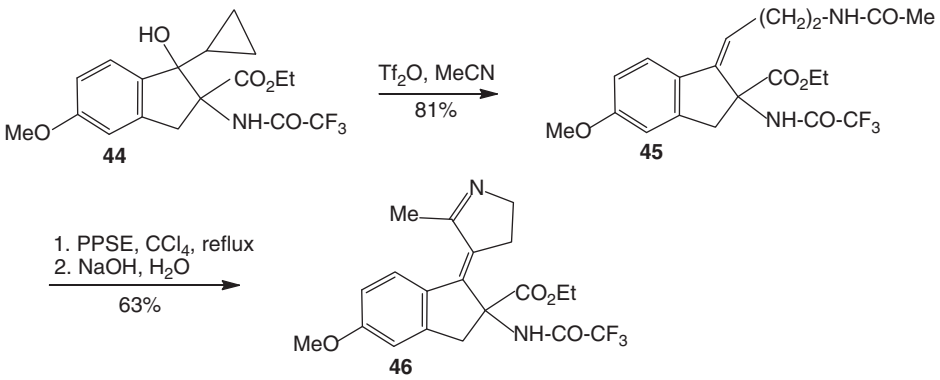


Scheme 15



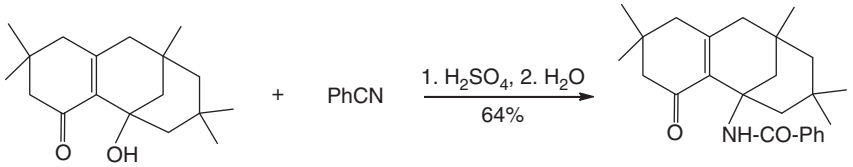
Scheme 16

A recent example of the triflic anhydride method in synthesis is shown in Scheme 17.[54] Here the cyclopropyl alcohol **44** underwent an efficient Ritter reaction and ring opening to form the unsaturated amide **45**. Further reaction with trimethylsilyl polyphosphate produced the cyclic imine **46**.

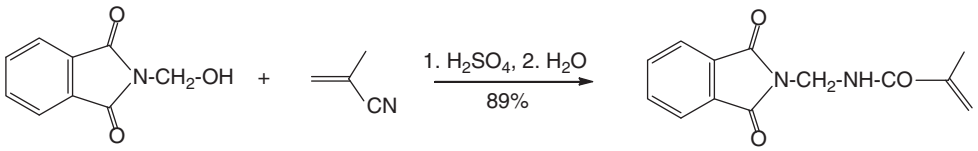


Scheme 17

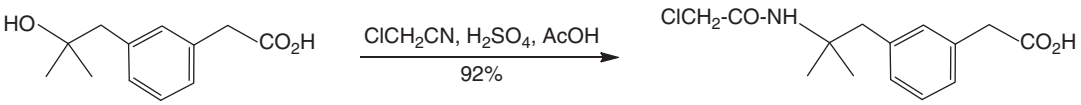
It is generally the hydroxy group that undergoes Ritter reaction in molecules where multiple functional groups are present, or where the hydroxy group comprises part of a more complex functional group. Equations 19–23 illustrate representative examples.[55–59]



(19)



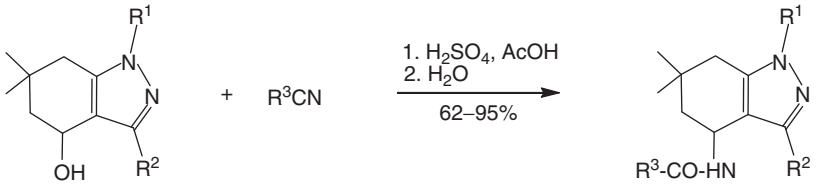
(20)



(21)

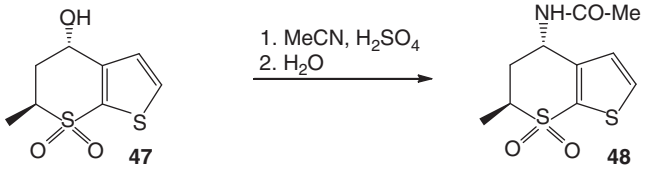


(22)



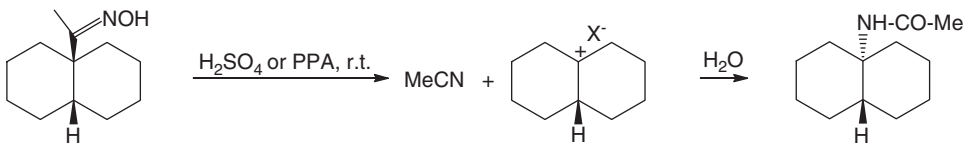
(23)

The *trans*-substrate **47** was found to undergo Ritter amidation to **48** with unexpected retention of configuration (equation 24), whereas the *cis*-isomer yielded the anticipated diastereomeric mixture. This process comprises a double inversion sequence involving transannular participation by the sulfone group.[60] Stereocontrol utilizing a proximal functional group is an extremely useful facet of the Ritter process in synthesis (see Section 6.07.5.5).

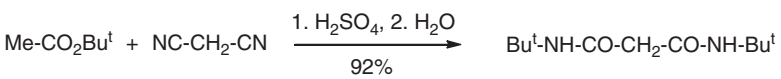


(24)

Substituted oximes undergo Ritter reaction initiated by protonation of their hydroxy group (equation 25).[61] Esters of *tert*-alcohols (equation 26) are equivalent to masked carbenium ions under Ritter conditions.[14] Therefore, examples such as triphenylmethyl formate[62] or *tert*-butyl acetate[63] can be employed in place of the corresponding alcohols or alkenes to obtain the controllable reaction conditions necessary for large-scale preparations.[64] The reactions can be conducted as a flow system by using microfluidic devices to control the various reaction parameters,[65] and the exothermic nature of the reaction can also be mitigated by (1) adding the components in small quantities over time and (2) maintaining a high and constant ratio of acid to the reactants mixture by means of separate addition ports.[66]

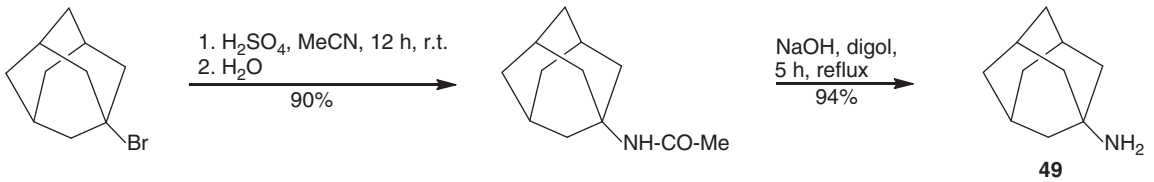


(25)



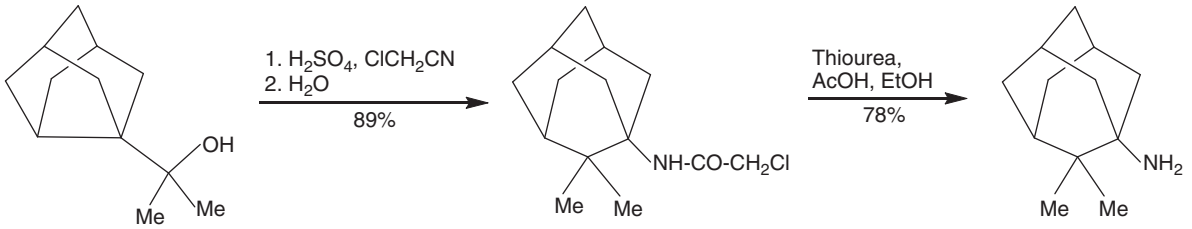
(26)

The use of alkyl halide substrates can be highly efficient in cases where a tertiary bridgehead carbenium ion is obtained, such as in the conversion of 1-bromoadamantane into its acetamide derivative by Stetter.[67] Hydrolysis provides a convenient synthesis of the drug 1-aminoadamantane (amantadine) **49** that alleviates symptoms of Parkinsonism and is effective against influenza A by blocking the M2 ion channel (equation 27). Many other polycyclic bridgehead amines exhibit related biological properties and the Ritter approach has been widely exploited in their synthesis. Equation 28 shows one recent example using more modern methods. Ritter reaction of the noradamantyl diol **50** is combined with rearrangement to the adamantyl product **51**. Hydrolysis employing the Jirgensons method[32] then affords the free amine.[68] Polycyclic lactones are also capable of undergoing the Ritter amide-forming reaction (equation 29).[69]



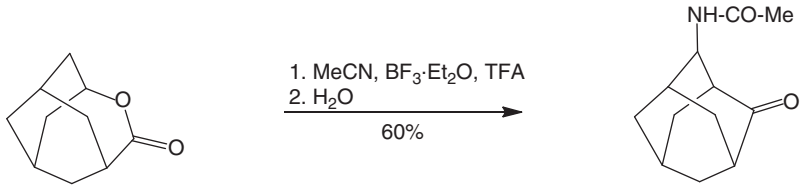
(27)

49



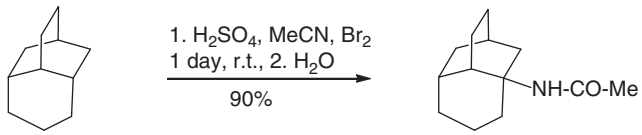
(28)

50 **51**



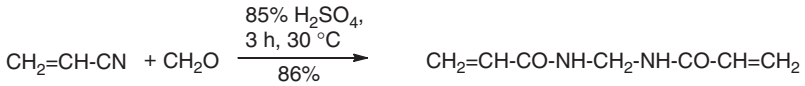
(29)

Polycyclic hydrocarbons can also be employed as substrates provided that an appropriate hydride acceptor reagent is supplied.[70] Alternatively, a one-flask tandem halogenation and the Ritter reaction can lead efficiently and directly to the amide product (equation 30).[71]

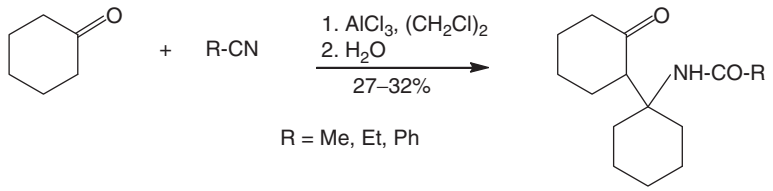


(30)

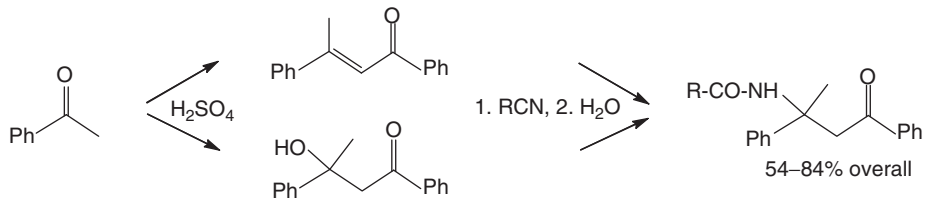
Nitriles react with aldehyde reagents to yield bis(amide) products (equation 31) by means of sequential steps that equate to two Ritter reactions.[72] A few ketones (camphor, cyclopentanone, and cyclohexanone) can behave similarly, but this is not general. More frequently, ketones and nitriles condense to form β-amido ketone products in modest yield (equation 32).[73] This reaction proceeds via the α,β-unsaturated ketone or β-hydroxy ketone aldol condensation compounds, as shown in **Scheme 18** for the example of acetophenone.[74] Ritter reactions of α,β-unsaturated ketones usually give the 1,4-addition product in only modest yield.



(31)

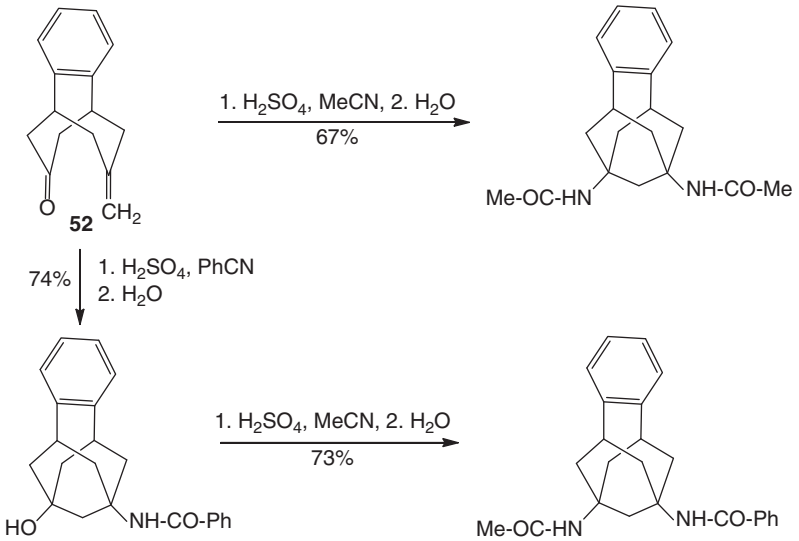


(32)



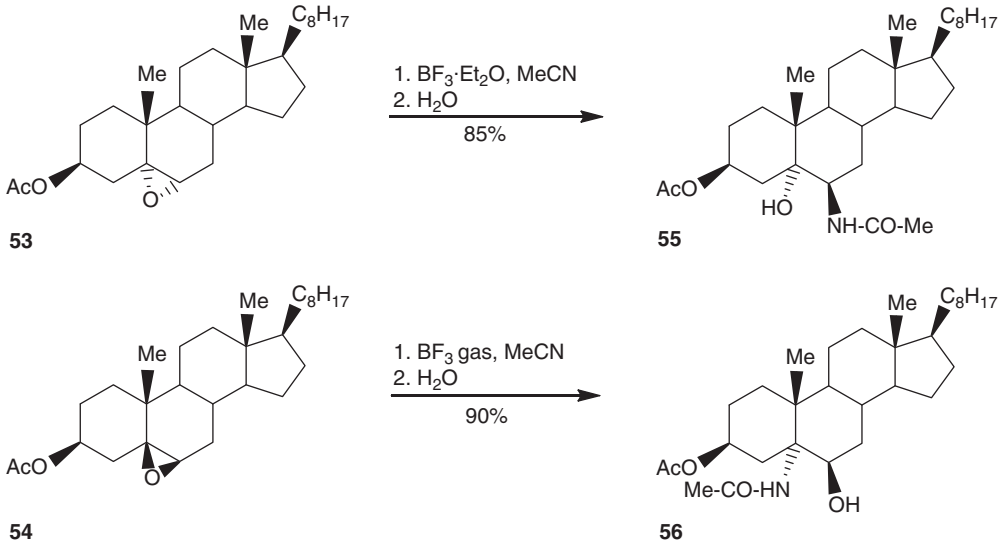
Scheme 18

Efficient transannular cyclizations can occur if the carbonyl group is proximal to an alkene functional group. Thus, protonation of the ketone **52** can produce the cyclized hydroxy amide, or either of two bis(amide) products, depending on the reaction conditions selected (Scheme 19).[44]



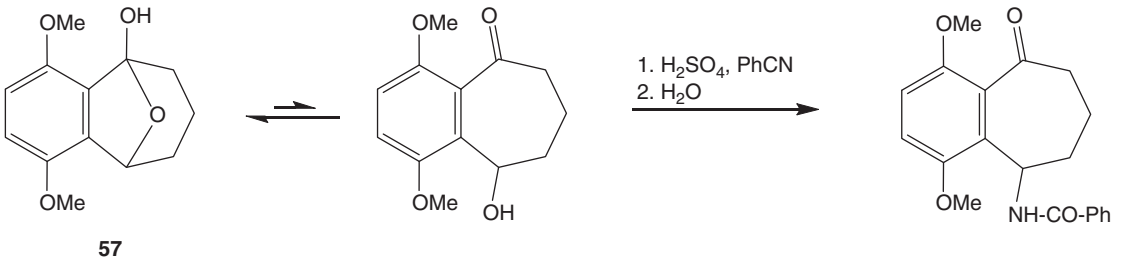
Scheme 19

Epoxides undergo efficient Ritter reaction using either protic or Lewis acids and the stereochemical outcomes of their ring opening are well understood. Thus the diastereomeric epoxides **53** or **54** yielded the *trans*-diaxial isomers **55** or **56**, respectively (Scheme 20).[75] The majority of functional group types can be induced to react with nitriles under strongly acidic conditions.



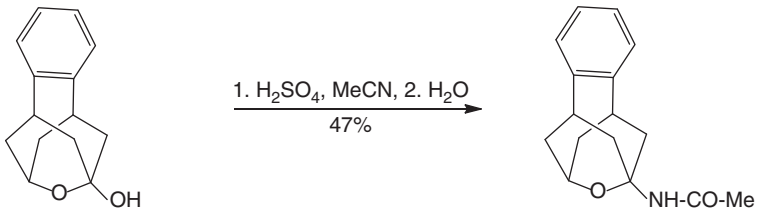
Scheme 20

For example, the bridged hemiacetal **57**[76] reacts through its ketol tautomer (Scheme 21), whereas its cousin **58**[77] reacts directly as the cyclic tautomer (equation 33).



57

Scheme 21



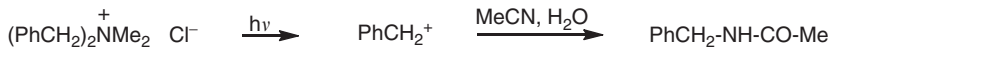
58 (33)

6.07.2 Extensions of the Original Process

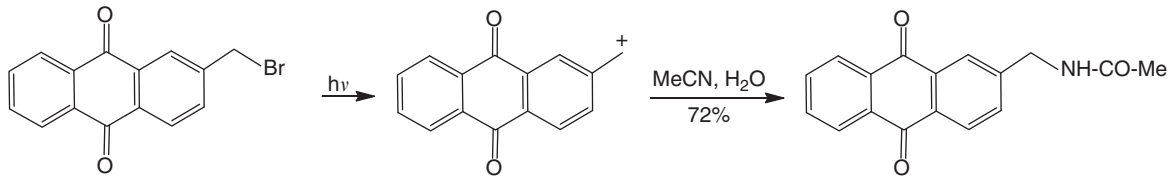
The use of strongly acidic conditions is by no means the only method of producing a cationic intermediate, and therefore the classical Ritter reaction can be expanded to incorporate these alternative techniques. In doing so, acidic conditions can be avoided and different types of substrates can be employed. The scope of the original Ritter process is considerably extended as a consequence.

6.07.2.1 Cleavage of Single bonds

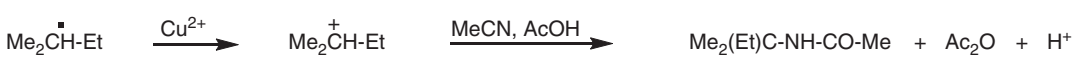
Carbenium ions can sometimes be generated directly by photolysis and then trapped as amide products (equations 34 and 35).[78,79] Gas-phase radiolysis also permits the Ritter amide formation.[80] Free radicals generated using various methods also may be oxidized to the carbenium ion, and then converted into the Ritter product (equation 36).[81] Some of these methods give low yields or mixtures, but the series of aryl bromides represented by equation 35 is synthetically significant.[79] Consistently high yields are obtained when organotrifluoroborate salts undergo Ritter reaction in the presence of copper(II) acetate (equation 37).[82]



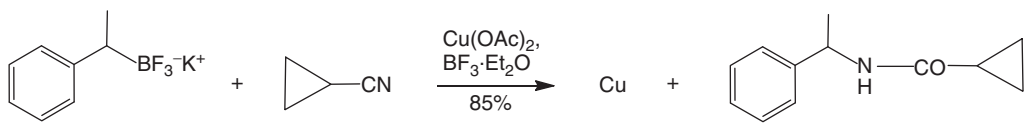
(34)



(35)

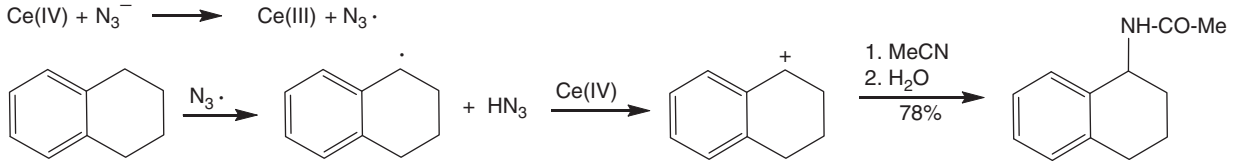


(36)



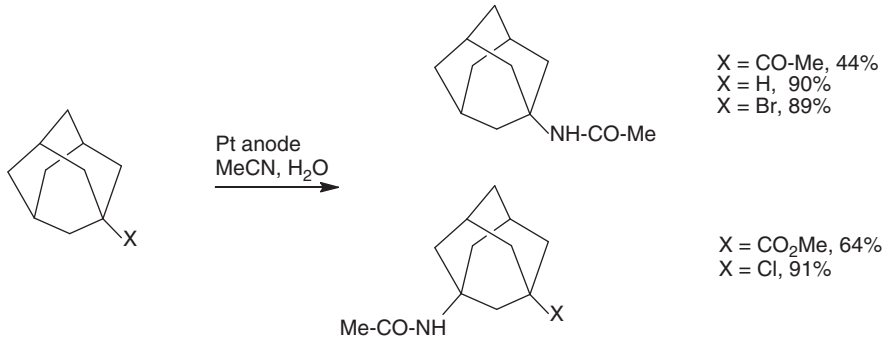
(37)

Nair has reported the novel radical formation–oxidation sequence, using sodium azide and cerium(IV) ammonium nitrate (CAN), shown in equation 38.[83] Related reactions also occur using CAN in conjunction with *N*-hydroxyphthalimide.[84]



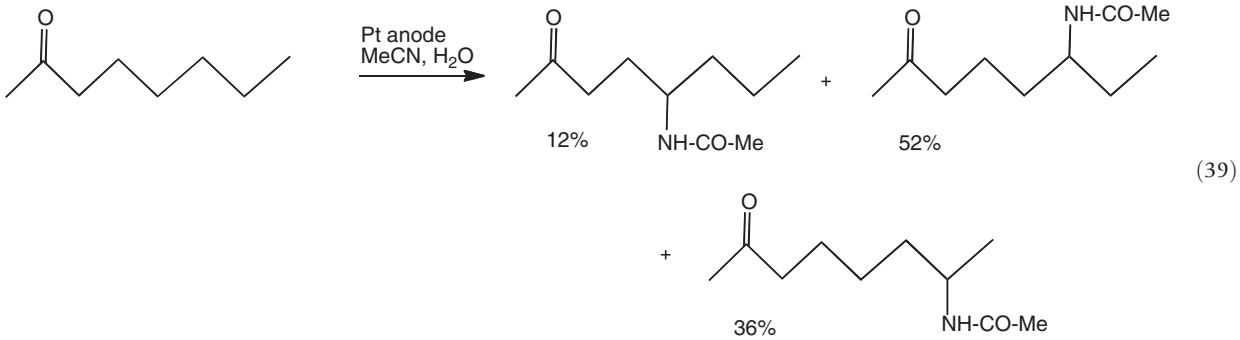
(38)

Reliability increases markedly when electrochemical variants of the Ritter reaction are employed. The review by Eberson and Nyberg provides a highly informative account of research in this area.[85] Electrochemistry has the advantage that aromatic hydrogens and nonactivated alkane hydrogens now can be easily functionalized. This process, $C–H \rightarrow C^+ + H^+ + 2e^-$, involves anodic oxidation of a C–H bond to produce a carbenium ion which then reacts with the nitrile in the normal manner. Anodic acetamidation has been performed on hydrocarbon, alkyl halide, ester, ketone, and other substrates, and the yields are comparable to conventional Ritter reactions (**Scheme 22**).[86] The procedure is limited, however, to nitriles with reasonable water solubility.

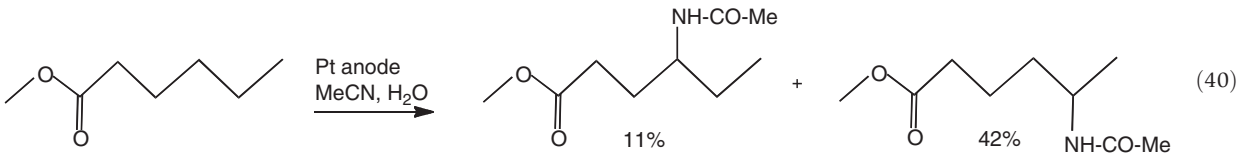


Scheme 22

As shown earlier, α-branched ketones undergo α-cleavage followed by amide formation. However, unbranched (or remotely branched) ketones produce mixtures through reaction at the remote γ, δ, and ε positions (equation 39).[87] Acyclic esters are more discriminating and the (ω-1)-substituted product is preferred (equation 40).[88]

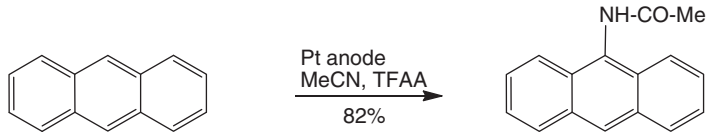


(39)

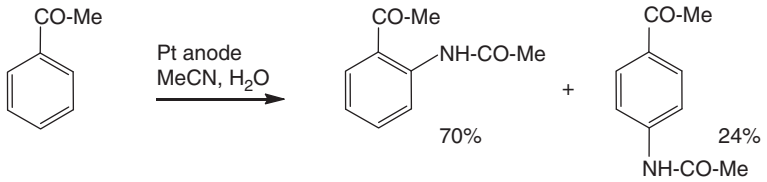


(40)

Aromatic compounds undergo direct acetamidation, with anthracene being converted into just one positional isomer (equation 41).[89] In contrast, acetophenone yields a mixture of the *o*- and *p*-acetamides (equation 42).[90] It should be noted that conventional electrophilic aromatic substitution of this substrate favors *m*-substitution, and that it is almost unknown for an *o*-isomer to be the major product of any aromatic electrophilic substitution reaction.

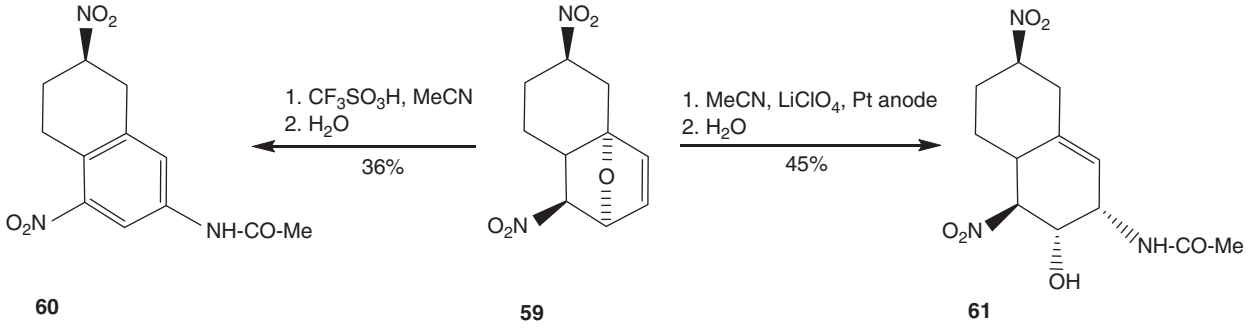


(41)



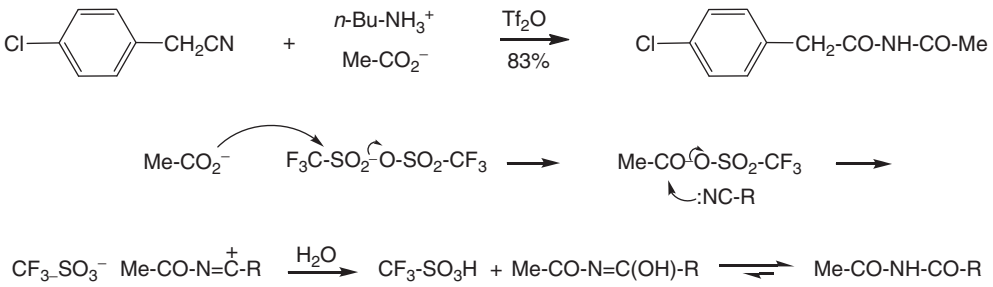
(42)

The electrochemical Ritter reaction therefore can provide a novel alternative in organic synthesis. Acarbose is a pseudotetrasaccharide α-glucosidase inhibitor that is clinically useful for the treatment of type-II diabetes. Its structure comprises a trisaccharide chain bonded to a carbocyclic unit named valienamine. Analogs of valienamine have been synthesized during a search for new glycosidase inhibitors, and one such approach introduced the putative amine functional group by means of a Ritter reaction on the tricyclic intermediate **59**. The standard acidic process yielded amide **60** with undesired aromatization, but the milder electrochemical method afforded amide **61** with appropriate substitution and stereochemistry for its subsequent conversion into a valienamide analog (Scheme 23).[91]



Scheme 23

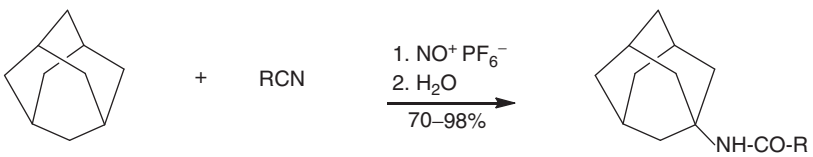
The reaction of a nitrile with triflic anhydride in an ionic liquid medium can provide a convenient means of obtaining unsymmetrical imides (equation 43). This novel Ritter-type reaction probably proceeds as described in Scheme 24.[92]



(43)

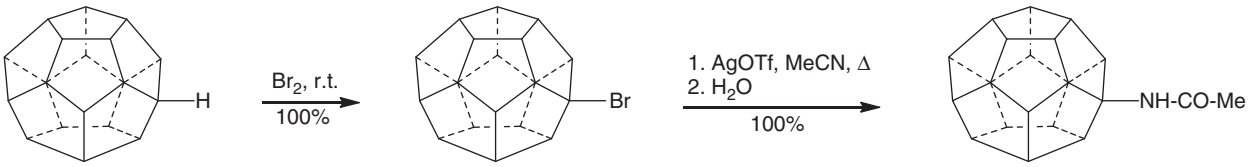
Scheme 24

Conversion of a hydrocarbon directly to a carbenium ion[70] can be performed more efficiently using reagents such as nitrosonium hexafluorophosphate, as illustrated here for the case of adamantane (equation 44).[93]

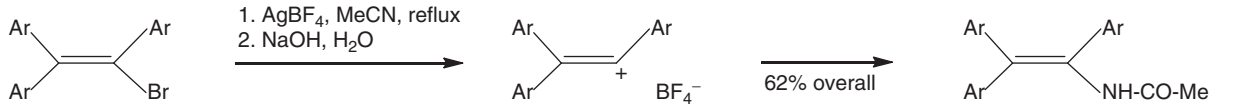


(44)

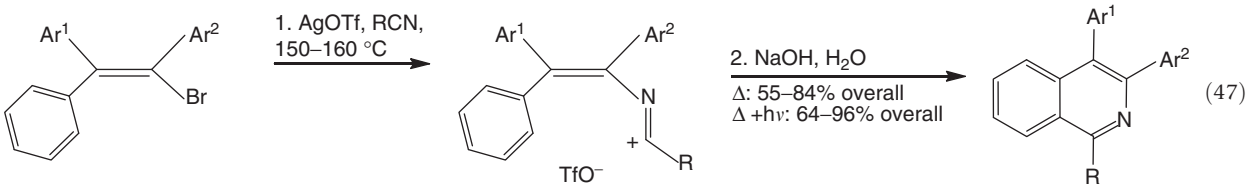
It has long been known that the treatment of alkyl halides with Ag^+ favors reaction through the S_N1 mechanism. This can be applied to bridgehead halides, a particularly striking example allowing the conversion of dodecahedrane into its Ritter product (equation 45).[94] Vinyl cations can also be generated using this approach and then being trapped as amide products (equation 46).[95] Less reactive triarylvinyl bromides require higher reaction temperatures. This results in cyclization of the nitrilium ion intermediate and formation of isoquinoline derivatives (equation 47).[96]



(45)

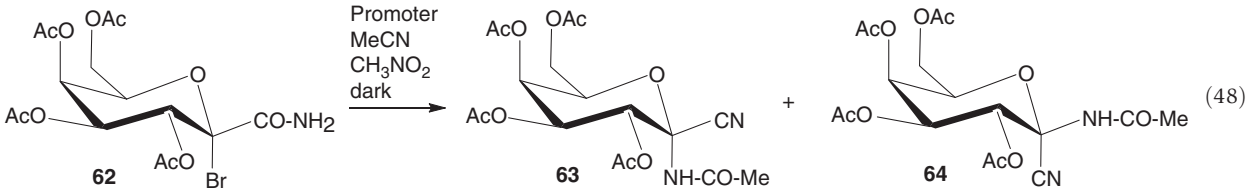


(46)



(47)

Somsak has recently described novel Ritter reactions carried out on the vicinal bromo amido sugar **62** (equation 48). The epimeric cyano amide derivatives **63** and **64** were formed in differing proportions in the presence of metal salt promoters, with Ag_2CO_3, AgOTf, and HgO yielding **63** exclusively.[97]

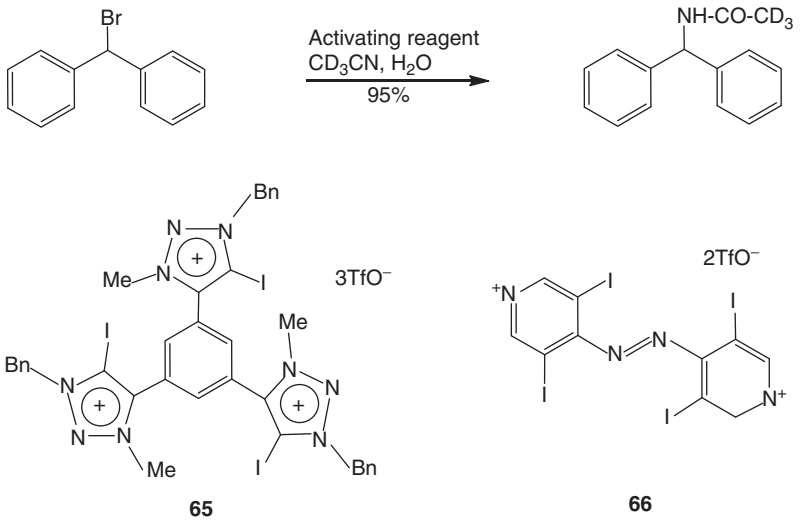


(48)

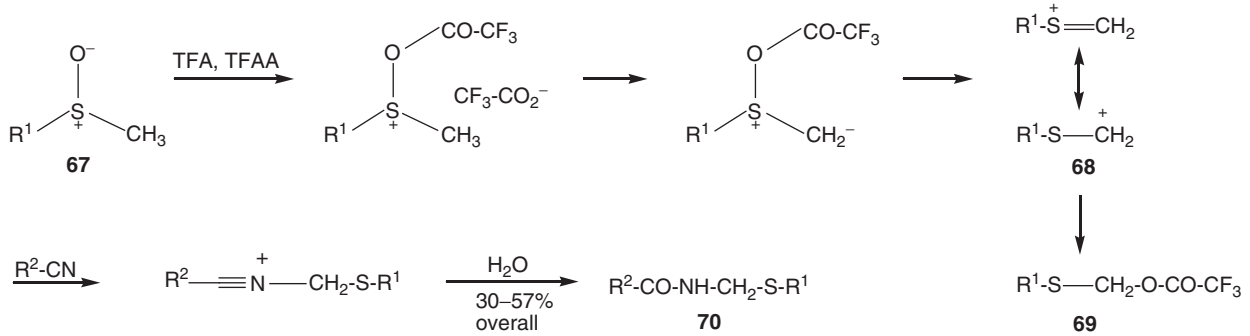
A family of new polycationic activating agents has been developed to facilitate the removal of bromide ion and stimulate the Ritter reaction. Thus bromodiphenylmethane normally gave less than 5% of the acetamide product, but a yield of over 95% when either of the activating reagents **65** or **66** was added (**Scheme 25**). These novel Lewis acids are specifically designed to make full advantage of the halogen bond supramolecular attraction.[98]

The Pummerer reaction describes the conversion of a sulfoxide **67** into an acyloxythioether **69** by means of attack by an acid anhydride. If the Pummerer intermediate **68** can undergo competitive quenching by a nitrile reagent instead of the customary anion then this alternative reaction produces an iminium ion, which ultimately affords the novel Ritter product **70** (**Scheme 26**).[99]

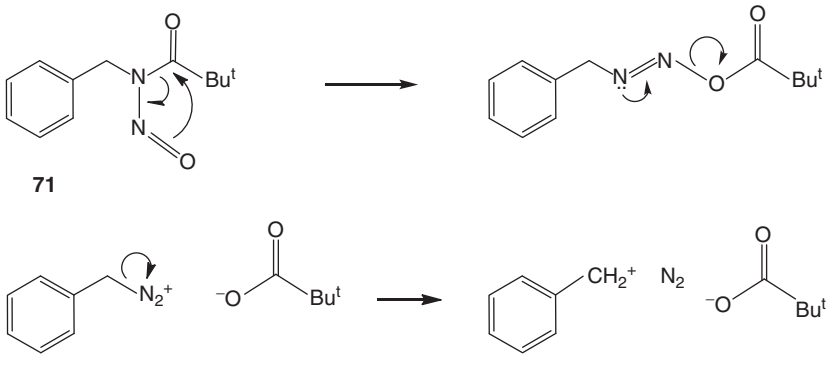
Thermal decomposition of *N*-benzyl-*N*-nitrosopivalamide **71** results in the formation of benzyl carbenium ion, dinitrogen, and pivalate ion (**Scheme 27**). If this process is conducted in a molten 4-substituted benzonitrile medium, then the nitrogen-separated ion pair undergoes an unusual sequence of events named the Darbeau–White–Gribble reaction.[100–102] The benzyl ion and the benzonitrile first combine to give a nitrilium ion, which is next scavenged by the pivalate ion to form the (*Z*)-ethanimidic anhydride **72**. Inversion to the (*E*)-isomer **73** is followed by rearrangement to the *N*-benzoyl-*N*-pivaloylbenzylamine product **74** (**Scheme 28**). This novel one-flask variant of the Ritter amide reaction differs from it in three respects: (1) no acid is used, (2) the nitrilium intermediate is quenched by its counterion rather than water, and (3) an acylamide product is formed instead of an amide.



Scheme 25



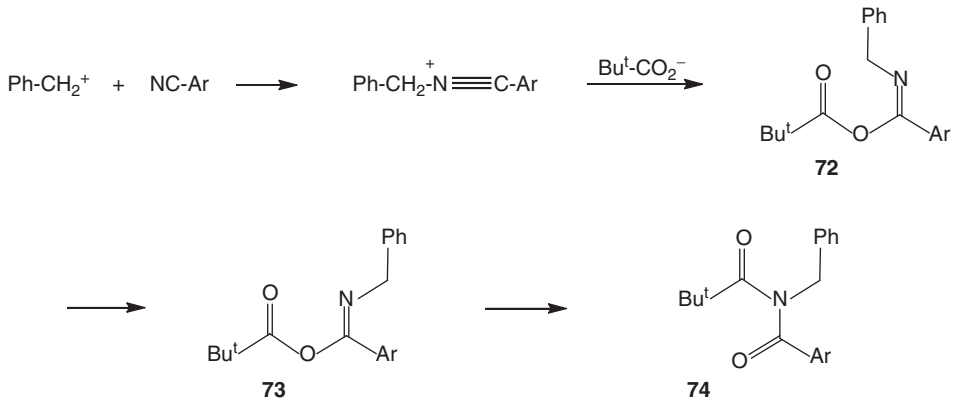
Scheme 26



Scheme 27

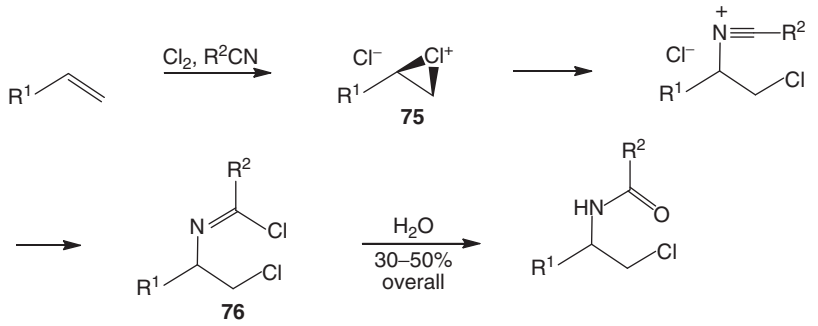
6.07.2.2 Addition to Double Bonds

Addition of electrophilic reagents to alkene or aryl substrates produces cations while avoiding strongly acidic conditions. These varied species can be attacked by nitriles, often very efficiently, to yield iminium ions and hence, Ritter products. Reactions involving bridged onium ions are subject to the usual stereo- and regioselectivity expected for S_N2 ring-opening processes.

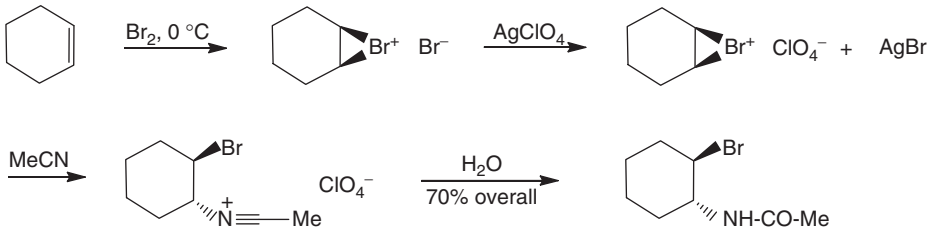


Scheme 28

Reaction of an alkene with a mixture of chlorine and a nitrile provides a simple route to *N*-(2-chloroalkyl)amides (Scheme 29), since the nitrile can compete with chloride in opening the ionic chloronium intermediate **75**. For the case where the nitrile substituent R^2 had no α-hydrogen atoms, then the intermediate imidoyl chloride **76** could be separated from the vicinal dichloride side product R^1–CHCl–CH_2Cl by distillation. Immediate hydrolysis to the amide was preferable for the alternative case.[103] Higher yields are achieved in the presence of the silver ion (Scheme 30) since the halide ion is removed as the insoluble silver halide, thereby suppressing formation of the vicinal dihalide.[104] Halohydrins also react via the bromonium intermediate in a stereospecific manner.[105]



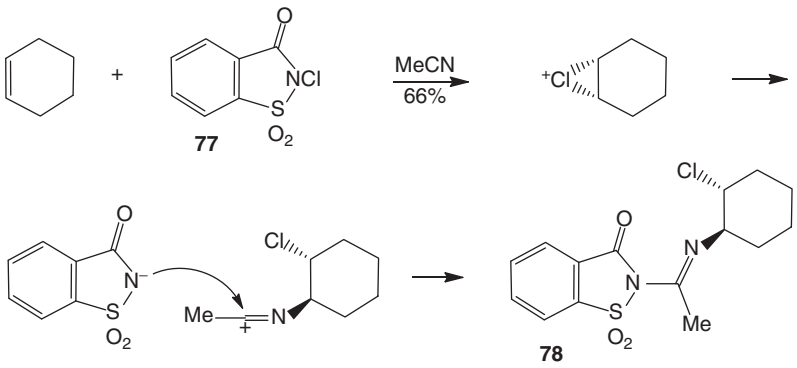
Scheme 29



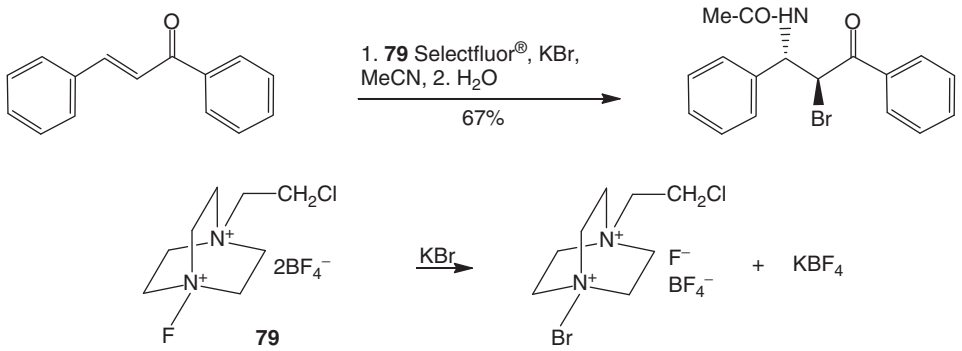
Scheme 30

N-Chlorosaccharin **77** is a convenient source of electrophilic chlorine. Its reaction with cyclohexene in acetonitrile gave a 66% yield of the unexpected material **78**, formed through the reaction sequence shown in Scheme 31.[106] Although the Ritter protocol yields cyclic imine structures in its heterocyclic variant (see Section 6.07.3), it is unusual for an acyclic imine to be produced. However, this reaction is general here for alkene precursors. Compound **78** and its analogs can be cyclized into imidazolines and/or aziridines, making this a valuable synthetic discovery.

If a mixture of Selectfluor® **79**, KF, and acetonitrile is reacted with chalcone (Scheme 32) then a vicinal bromo amide is produced.[107] The insolubility of KBF_4 switches the original electrophilic fluorine source to a new electrophilic bromine source which initiates this reaction sequence.

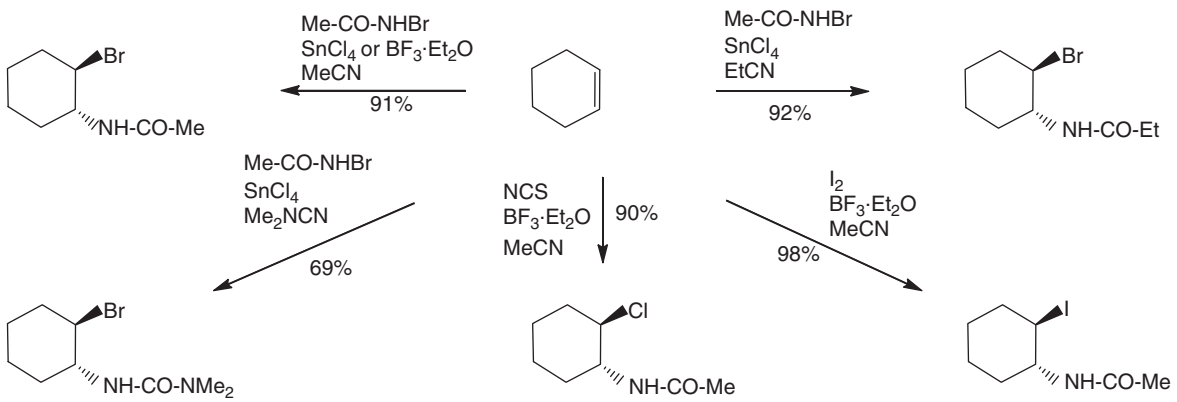


Scheme 31



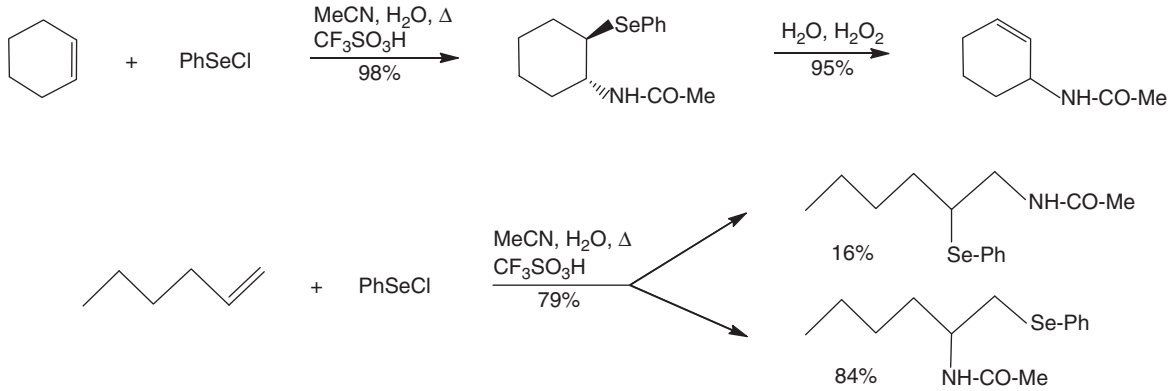
Scheme 32

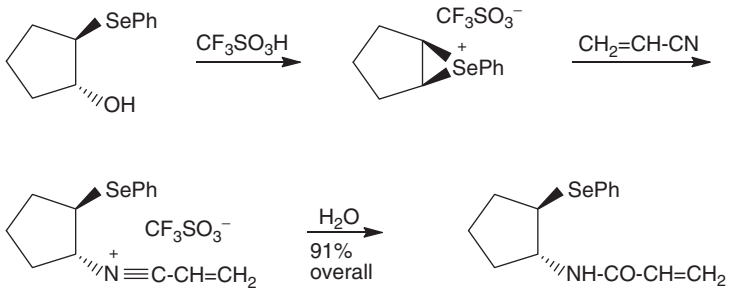
Corey[108] has investigated haloamidation reactions in greater detail through systematic variation of the halogen source, nitrile, and Lewis acid. The example of cyclohexene is summarized in Scheme 33. *N*-Chlorosuccinimide, *N*-bromoacetamide, and molecular iodine were employed as the electrophilic halogen progenitors.



Scheme 33

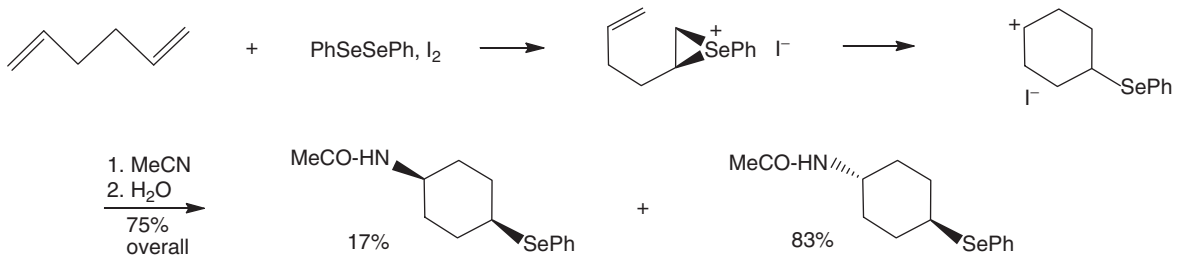
Phenylselenyl chloride and nitriles react with alkenes to produce β-amido phenylselenides in near quantitative yield. Oxidative elimination of the selenium moiety gives the allylic amide (equation 49). Nonsymmetrical alkenes exhibit high regioselectivity in forming these β-amido phenylselenides (equation 50).[109,110] Alternatively, the easily accessible β-hydroxy phenylselenides undergo Ritter reaction with retention of configuration via an episelenonium ion intermediate (Scheme 34).[111]





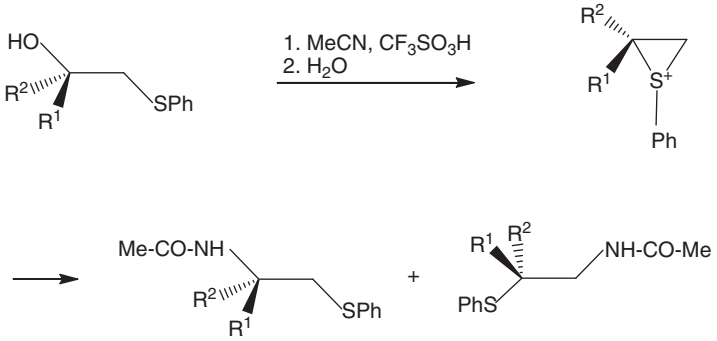
Scheme 34

Acyclic 1,5-dienes react with diphenyl diselenide and iodine in the presence of a nitrile reagent to produce carbocyclic amido phenylselenides as shown in Scheme 35.[112]



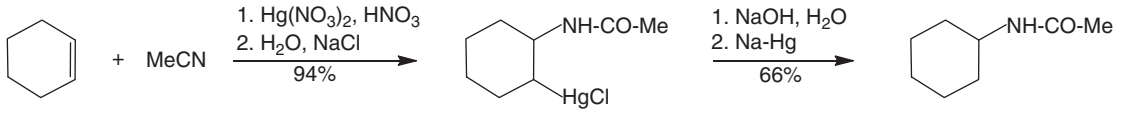
Scheme 35

Episulfonium ions also yield amide products under Ritter conditions, and Toshimitsu has carried out extensive analyses of the stereospecificity encountered for the chiral substrates shown in Scheme 36.[113]

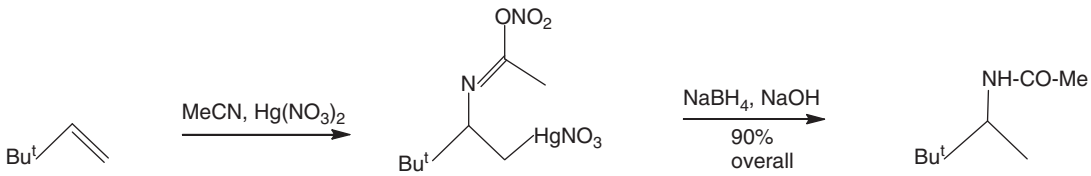


Scheme 36

In 1970, Brown introduced a new method of obtaining alcohols by Markovnikov addition of water to an alkene. This two-step conversion involves addition of mercury(II) acetate followed by reduction. The intermediacy of a bridged mercurinium ion precludes the Wagner–Meerwein rearrangements of carbenium ions that occur in the traditional acid-catalyzed hydrations.[114] Related processes permit the alkene to amide conversions. The early conditions used[115] (equation 51) have since been superseded by improved methods[116,117] (equation 52). A serious limitation is that crowded alkenes fail to react with these bulky Hg(II) reagents.

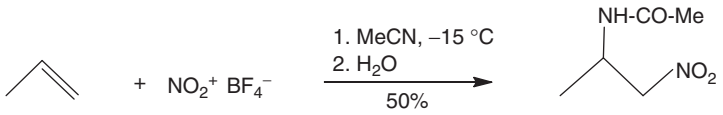


(51)



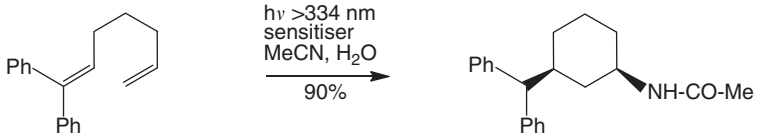
(52)

An alternative approach is to modify the reactivity of the carbenium ion intermediate participating in the Ritter reaction. Thus, nitronium fluoroborate reacts with propene to afford a nitrated amide product (equation 53).[118] Entirely different types of materials are formed if nitrosonium fluoroborate (NO^+ BF_4^-) is used.



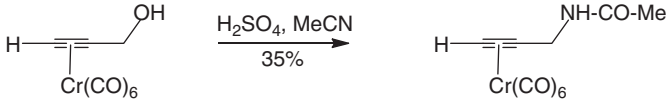
(53)

Hirano and Niwa have described the unusual photo-Ritter reaction in equation 54. This proceeds with notably high diastereoselectivity and yield.[119]

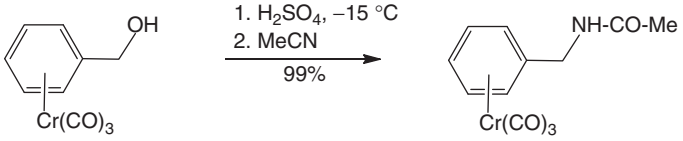


(54)

The use of an organometallic complex is a clever means of controlling cation reactivity. Thus a propargyl alcohol complex underwent Ritter reaction without the usual acid-catalyzed rearrangement difficulties (equation 55). Benzyl alcohol normally forms *N*-benzylacetamide in only 48% yield,[46] but the use of its tricarbonylchromium complex afforded 99% of the Ritter product (equation 56).[120,121] Further, nitriles such as *o*-MeC_6H_4CN and $ClCH_2CN$ that react inefficiently in the standard reaction now gave excellent yields (83% and 98%) with the stabilized benzyl cation. Stabilized tertiary benzyl ions no longer underwent the Ritter reaction, although the behavior of secondary benzylic ions was dependent on the specific case (**Scheme 37**).

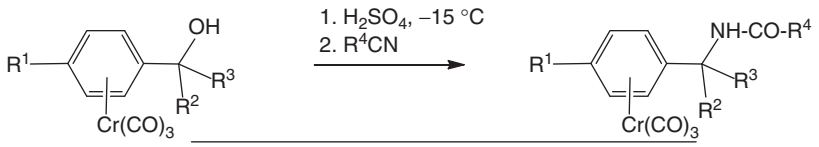


(55)



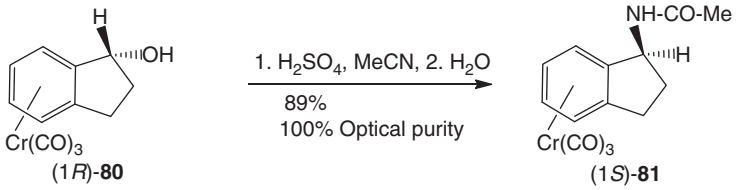
(56)

Some of these amidation reactions proceed with excellent stereospecificity. Thus the indanol complex (1*R*)-**80** underwent the Ritter reaction to yield (1*S*)-**81** with complete inversion of configuration (equation 57). In contrast, amidation of the complex (*S*)-(+)-**83** took place with almost complete retention to (*S*)-(−)-**84** (**Scheme 38**). Explanations of these novel stereochemical outcomes are provided.[121,122] This significant procedure provides a valuable method of converting a racemic precursor **82** into either enantiomer of its chiral Ritter amide product **85**.

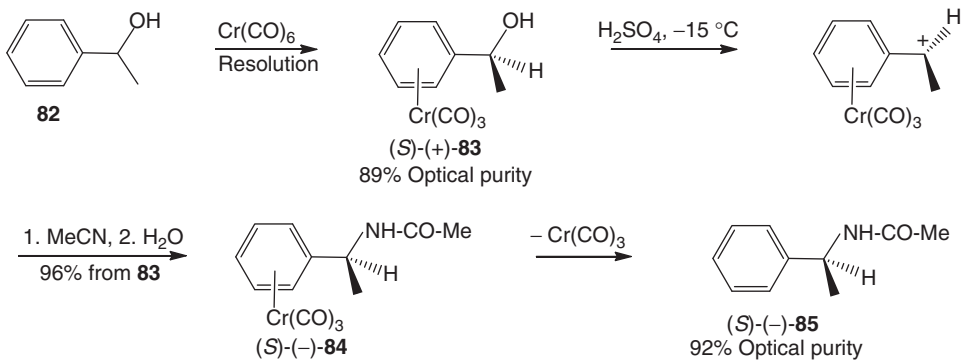


R^1	R^2	R^3	R^4 = Me	R^4 = Ph
p-MeO	Me	H	99%	84%
H	Ph	H	82%	0%
H	Me	Me	0%	0%

Scheme 37



(57)



Scheme 38

6.07.3 The Ritter Heterocyclic Reaction

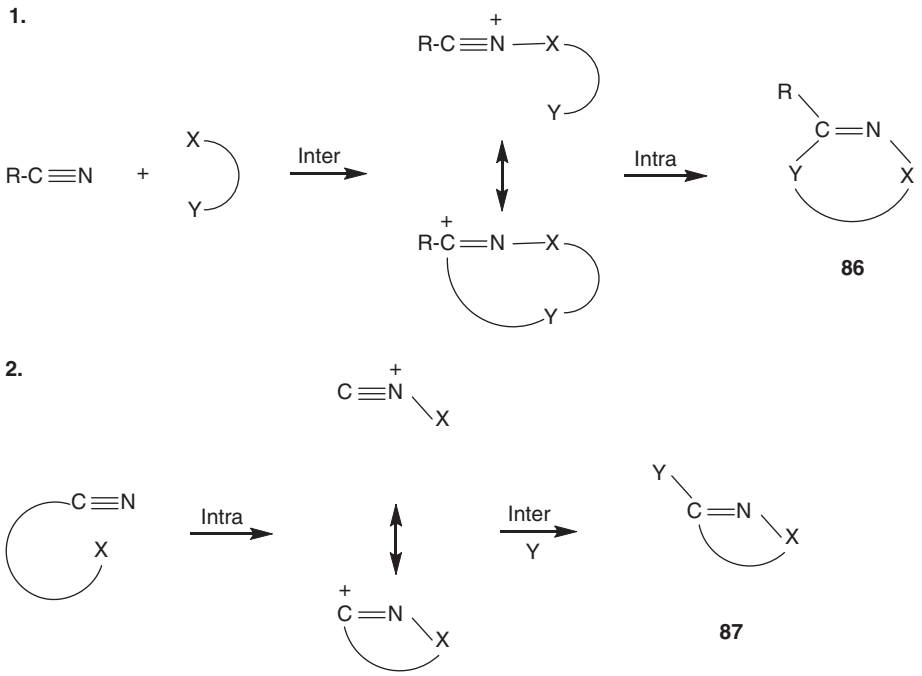
The original amide-forming Ritter reaction conditions can also yield a wide range of heterocyclic products.[8] These intramolecular versions of the process can be divided into two distinct classes according to the sequence of their mechanistic steps.

1. In the more common type, a nitrile and carbenium ion (or its equivalent) first combine to produce a nitrilium ion by an intermolecular process. A nucleophilic group (Y) within this species then reacts intramolecularly to yield the heterocycle **86** (Scheme 39).
2. The less common reaction class commences with intramolecular formation of a nitrilium ion, which is then followed by intermolecular nucleophilic attack to produce the heterocycle **87** (Scheme 39).

Both the processes involve intramolecular ring formation and therefore are subject to constraints in the ring sizes, predominantly 5- and 6-membered, generated through these cyclizations. It should be also noted that both the pathways produce heterocycles containing a C=N imine structure, although its chemical properties may be seriously modified by the presence of additional functional groups.

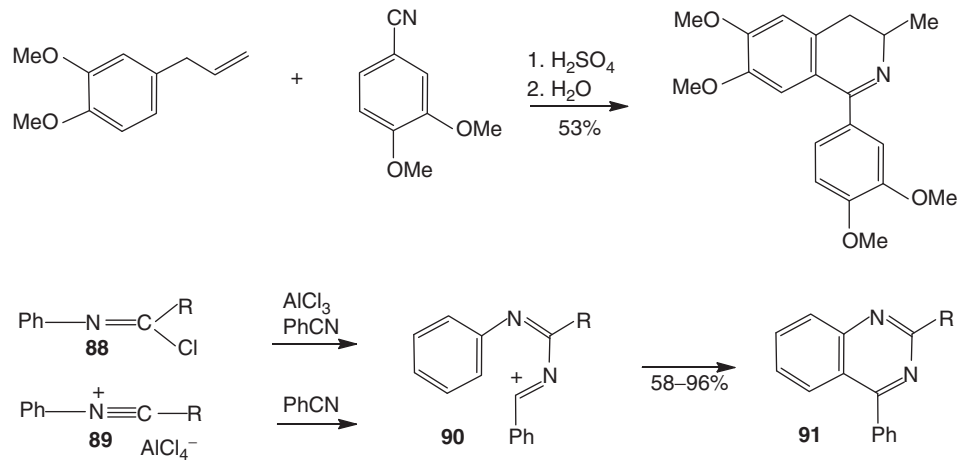
6.07.3.1 Intermolecular Initial Step

Ritter and Murphy reported the first example of this process in 1952 when they reacted methyleugenol with veratronitrile, thereby obtaining a dihydroisoquinoline product (equation 58).[3] The internal nucleophile in this reaction is a highly electron-rich aryl ring. This type of process was greatly developed by Meerwein (Scheme 40).[123] Aryl imidoyl chlorides **88** or aryl nitrilium ions **89**, under Lewis acid conditions, both yield the carbocation intermediate **90**. This then undergoes a Friedel–Crafts reaction to produce the quinazoline derivatives **91**. Formation and cyclization of nitrilium species under Friedel–Crafts conditions have been widely employed in heterocyclic synthesis.[124,125] Recent work has shown that this cyclization is more complex than initially thought.

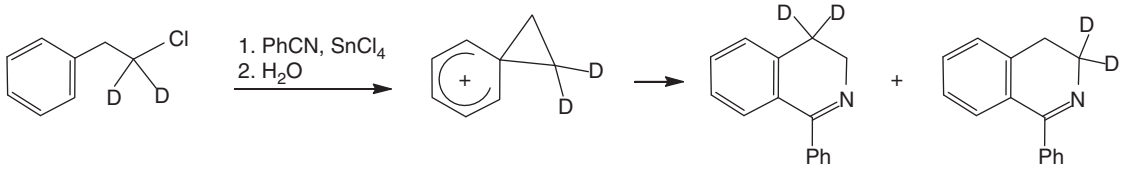


Scheme 39

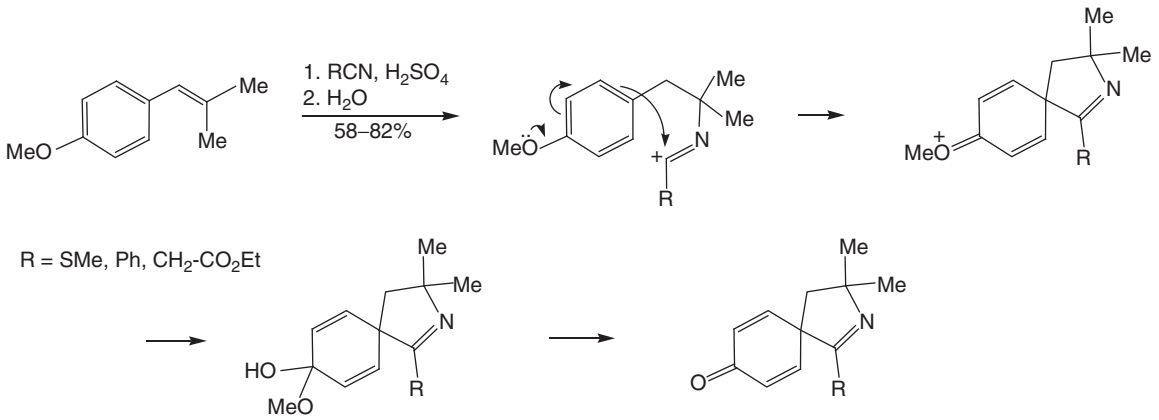
Ho has demonstrated that phenylethyl chloride initially forms a phenonium ion before producing the nitrilium intermediate (equation 59),[126] and this sequence may well occur more often. Glushkov et al. have further shown that alternative spiro pyrrolidine products can result (Scheme 41).[127] The halonium ion approach (Scheme 42) permits the synthesis of the less accessible 3,3-disubstituted isoquinoline derivatives. Reduction of these products yields aziridine derivatives.[128]



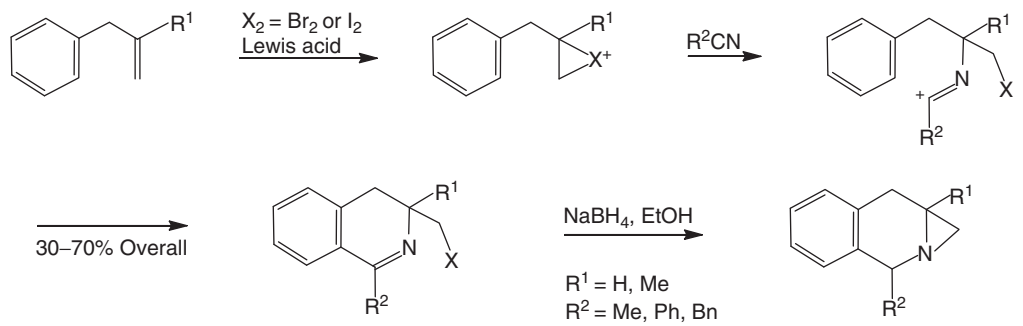
Scheme 40



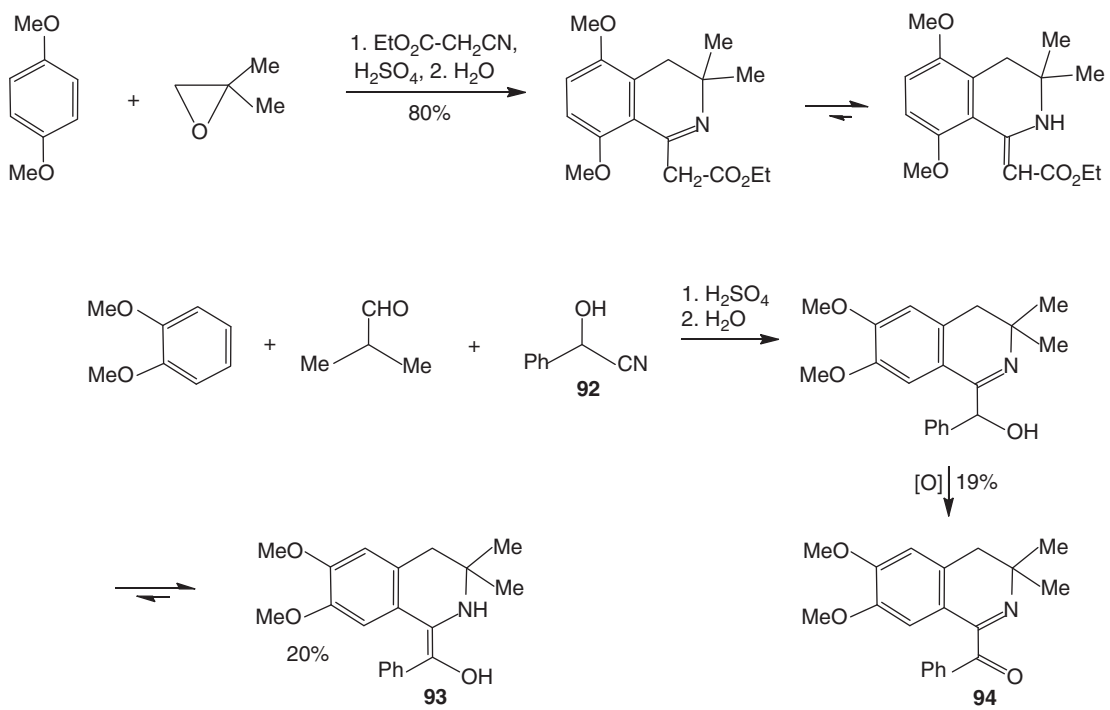
Tandem reaction syntheses have also been developed for the 3,4-dihydroisoquinoline derivatives by Shklyaev. In the first of these methods, the electron-rich aromatic was reacted with both an oxirane and a nitrile (equation 60).[129,130] Alternatively, the electron-rich arene substrate, 2-methylpropanal, and mandelonitrile **92**, are combined under Ritter conditions. Modest equimolar yields of the derivatives **93** and **94** were obtained (Scheme 43).[131]



Scheme 41



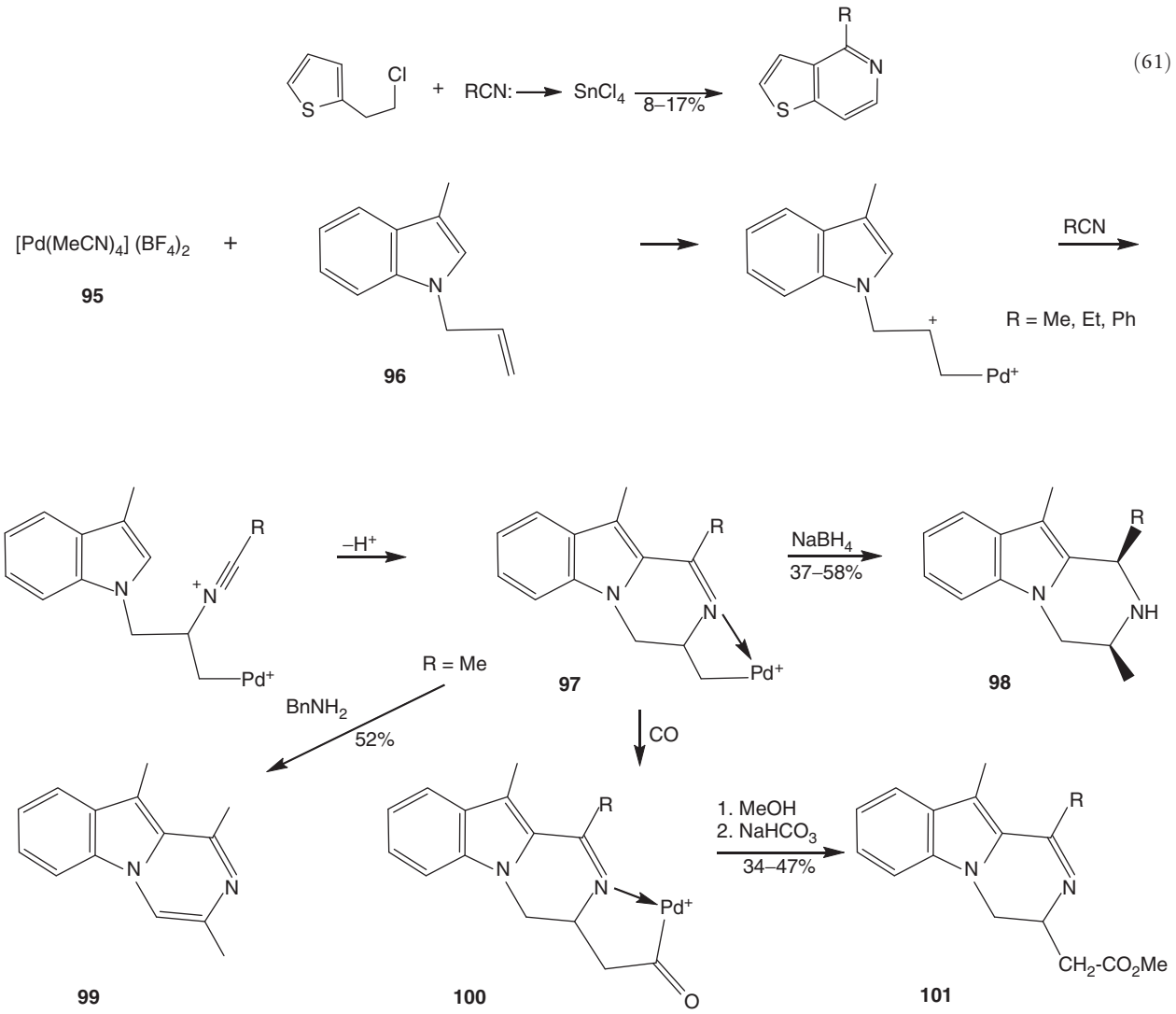
Scheme 42



(60)

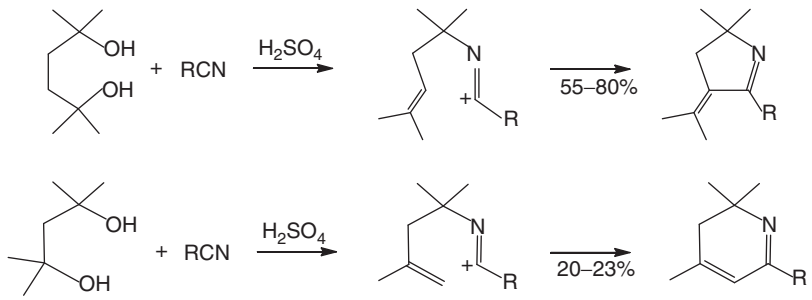
Scheme 43

It is also possible to employ heteroaromatic nucleophiles such as thiophene derivatives (equation 61).[132] Aromatic systems undergo direct metalation with many palladium salts. The strongly electrophilic complex **95**, however, interacts with alkenes by reactions that involve incipient carbenium ions. Thus its reaction with *N*-allylskatole **96** in a nitrile solvent induces cyclization that involves the indole moiety as a nucleophile. The initial σ-alkylpalladium(II) complex **97**, a most versatile synthetic substance, is stabilized through chelation. A stereospecific reduction to the *syn*-1,2,3,4-tetrahydropyrazino[1.2-*a*]indole **98** occurs with sodium borohydride. An alternative reaction work-up using benzylamine produces the pyrazinoindole **99**, while carbon monoxide undergoes insertion to afford the acylpalladium complex **100**. This may be demetallated to yield the heterocyclic ester **101** (Scheme 44).[133]



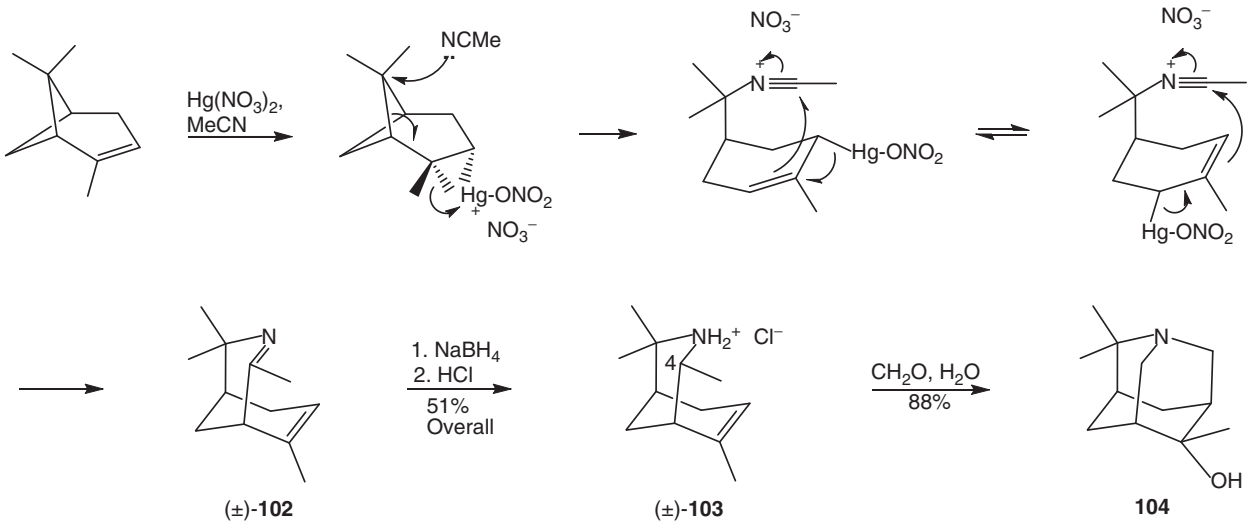
Scheme 44

Meyers and Ritter obtained either 1-pyyroline or 5,6-dihydropyridine products when the internal nucleophile was an alkene functional group (Scheme 45).[5] These reactions were subsequently extended into synthetic routes for a variety of fused heterocyclic systems.[134,135]



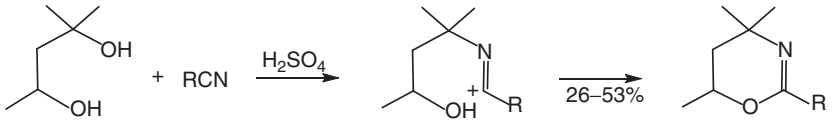
Scheme 45

A complex sequence of reactions ensued when the mercury(II) nitrate addition (see equation 52) was applied to (−)-α-pinene and acetonitrile. Good yields of either racemic **102** or **103** were obtained depending on the reaction work-up used. These azabicyclo[3.3.1]nonene derivatives arose from skeletal rearrangement and subsequent alkene nucleophilic attack on the nitrilium ion (Scheme 46). The unusual formation of azaadamantanol **104** from **103** involved loss of C4 and the attached methyl group of the latter as acetaldehyde. Replacement of the water by alternative nucleophiles provided simple access to a range of substituted azaadamantane derivatives.[136]



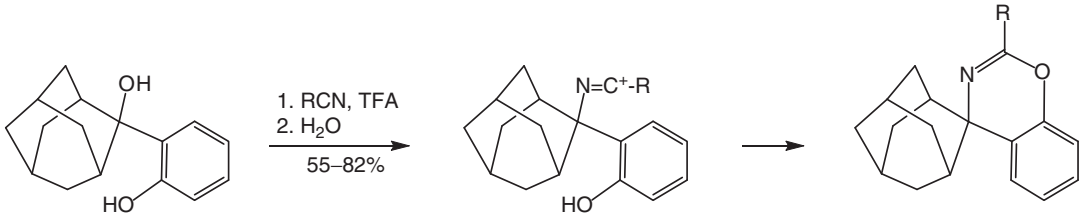
Scheme 46

Oxygen, sulfur, and nitrogen atoms have all been utilized as internal nucleophiles in the intramolecular Ritter reaction. Tillmanns and Ritter found that the 1,3-diol **105** could be converted into the dihydro-1,3-oxazine system instead of forming dihydropyridine or bis(amide) products (equation 62). Here, only the tertiary alcohol group forms a carbenium ion. The secondary hydroxy group does not dehydrate and later acts as the nucleophile that attacks the nitrilium ion intermediate.[4] Exploitation of differing hydroxy group reactivity will be revisited in Section 6.07.5.5. Controlled reduction of a dihydro-1,3-oxazine, followed by hydrolysis, provides a convenient preparation of the aldehyde functional group. Meyers greatly extended this concept, now known as the Meyers aldehyde synthesis, to afford acyclic, alicyclic, α,β-unsaturated, γ-hydroxy, and γ-oxo aldehyde derivatives.[137]



105 (62)

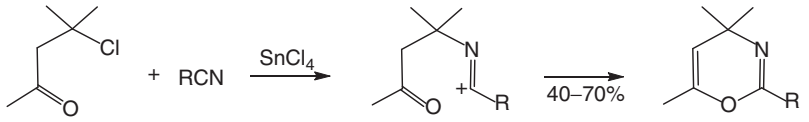
In a manner similar to **105**, the adamantyl 1,3-diol in equation 63 was transformed into dihydro 1,3-oxazine derivatives using seven nitriles under Ritter conditions. The one exception was acetonitrile, which underwent conventional acyclic amide formation.[138]



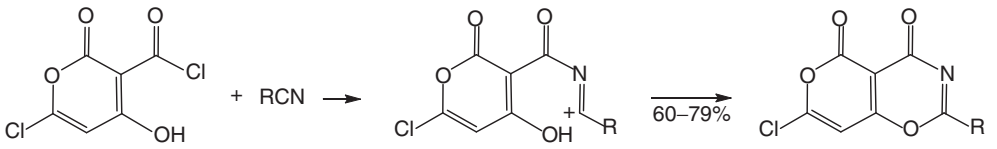
(63)

1,3-Oxazine products are also obtained by reactions of β-chloroketones under Lewis acid conditions (equation 64), and from the direct reaction of malonyl chloride derivatives with nitriles (equation 65).[139,140] Oxetanes **106** can also afford dihydro-1,3-oxazines in excellent yield (equation 66).[141] However, the epimeric oxetane compounds undergo cleavage and Wagner–Meerwein

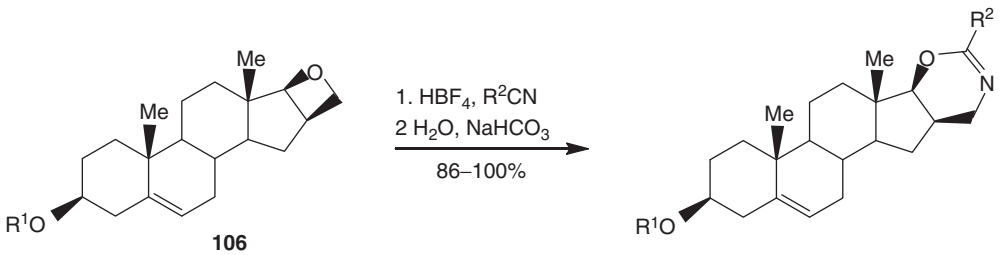
rearrangement (without Ritter reaction) under identical reaction conditions. The palladation process (see Scheme 44) can also be employed to synthesize dihydro-1,3-oxazine derivatives (equation 67).[113]



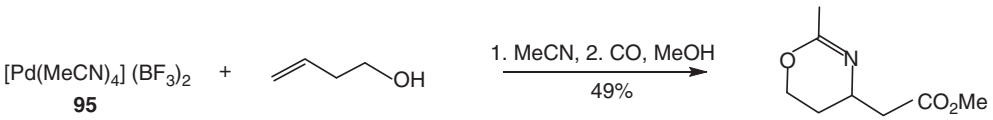
(64)



(65)

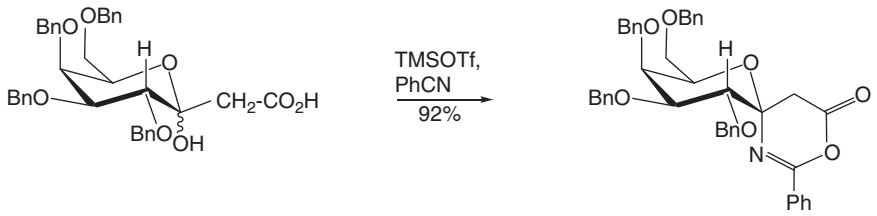


(66)



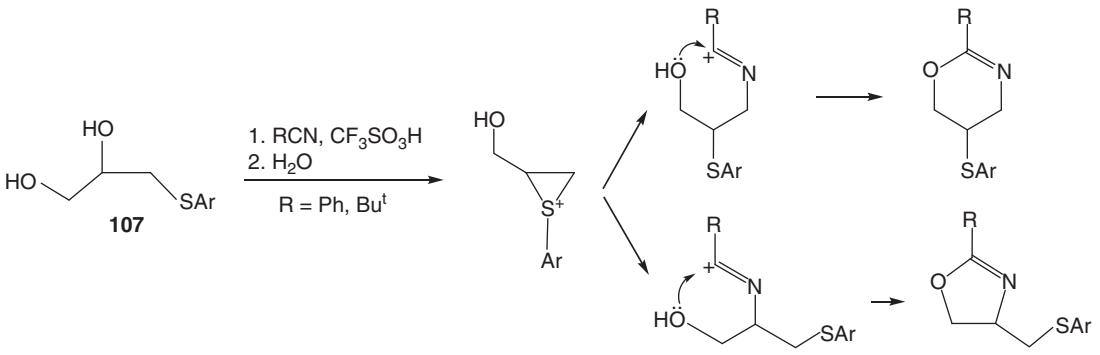
(67)

The hemiacetal group of glycosyl derivatives can also undergo the Ritter reaction in high yield to produce a spiro dihydro oxazinone derivative (equation 68).[142] Oxazoline derivatives are also produced using sugar derivatives, and Rota has recently reported elegant synthetic applications of the Ritter protocol in the synthesis of important neuraminic acid derivatives.[143]



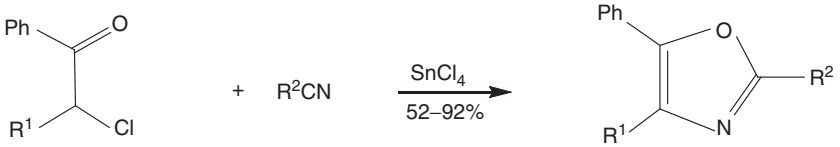
(68)

Episulfonium ions were seen in Scheme 36 to yield acyclic Ritter amides. In contrast, the sulfur-substituted 1,2-diols **107** undergo the Ritter heterocyclic process to yield mixtures of dihydro oxazine and oxazoline products (Scheme 47).[113]

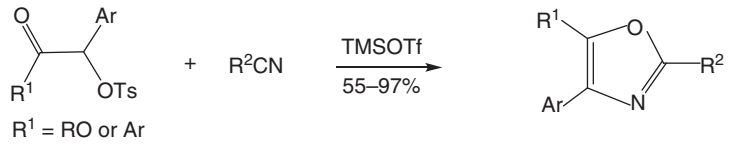


Scheme 47

The smaller oxazole ring system is obtained from a diverse range of Ritter-type reactions, for example, using a Lewis acid reagent but switching the substrate from β- to α-chloroketone (equation 69).[144] This approach has led to the development of a widely applicable procedure using the related α-oxo tosylates as the substrate and promoters such as TMSOTf or Lewis acids (equation 70).[145]

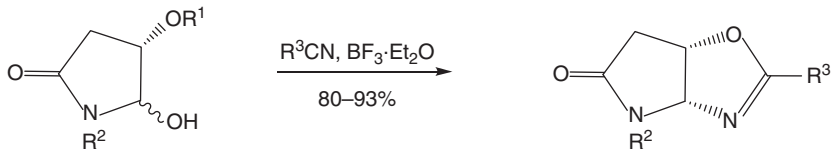


(69)



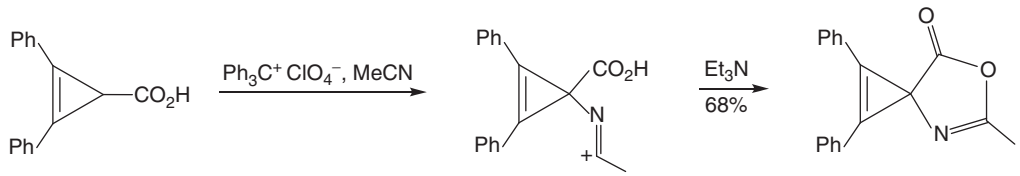
(70)

Pyrrolo- and pyrido-oxazole derivatives can be obtained with high diastereoselectivity through the process shown in equation 71.[146]

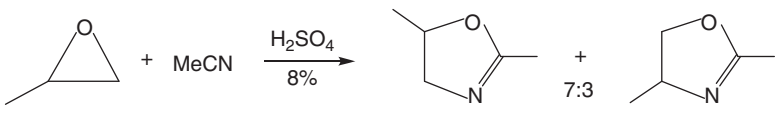


(71)

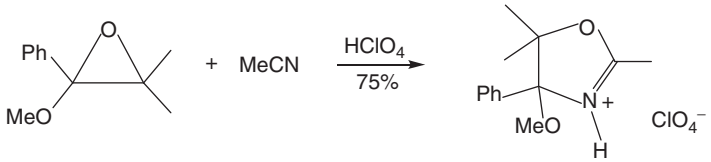
A novel Ritter example is shown in **Scheme 48**, whereby acetonitrile attacks a cyclopropenium ion to yield the nitrilium ion intermediate. A carboxylic acid hydroxy group then acts as the internal nucleophile and forms a novel spirocyclic product.[147] The Ritter reaction of epoxides yields oxazolines but in poor yields and often as isomeric mixtures,[148] but the use of epoxy ethers circumvents these difficulties (equations 72 and 73).[149] This approach has been extended to monosaccharide derivatives by Danishefsky.[150] Epoxy esters are also effective, and equation 74 illustrates their use to synthesize the paclitaxel side chain.[151]



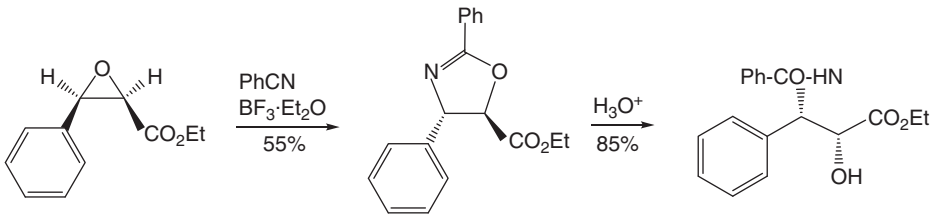
Scheme 48



(72)

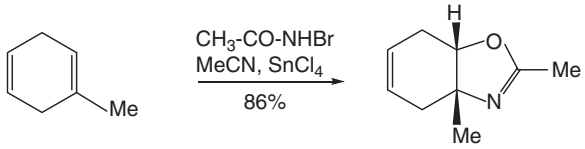


(73)



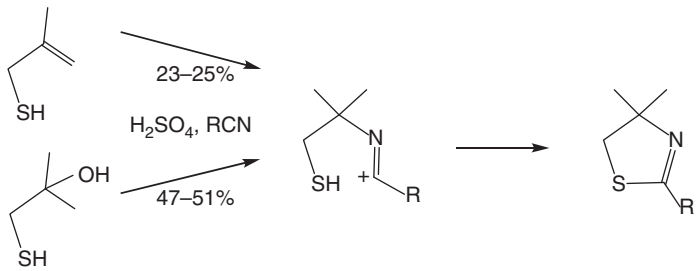
(74)

The Ritter haloamidation process using bromoacetamide was discussed in Section 6.07.2. A number of alkene substrates instead form oxazoline products under these reaction conditions (equation 75).[108]



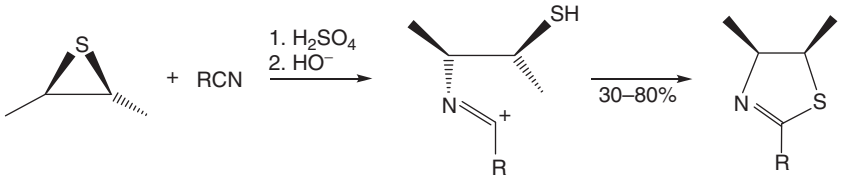
(75)

By analogy with their oxygen analogs, thiazoline and thiazine products result when a sulfur species is used as the internal nucleophile. 2-Thiazolines are formed in modest yield when methallyl mercaptan is subjected to these reaction conditions,[5] but the corresponding alcohol reagent produces double the amount of product via the common intermediate ion[152] (equation 76). This example is a timely reminder that the optimum Ritter conditions generally must be determined through rigorous experimentation.

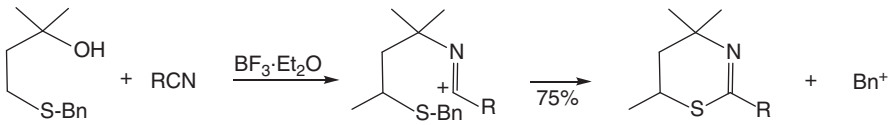


(76)

Episulfides generally undergo cleaner reactions than epoxides and typically are converted by means of stereospecific ring expansion into thiazoline products in good yields (equation 77).[153,154] Six-membered thiazines are produced (equation 78) through the sulfur analog of the equation 62 reaction using either protic or Lewis acid reagents.[155]

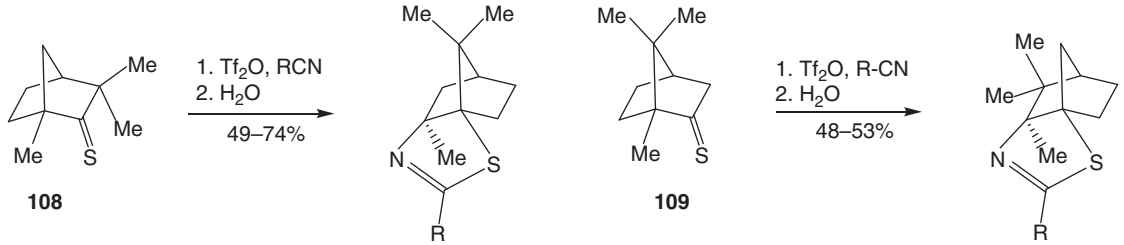


(77)



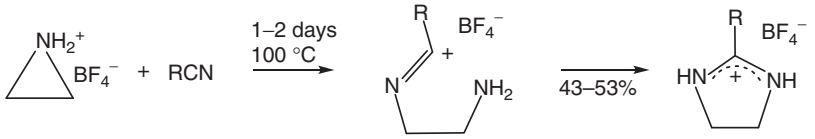
(78)

Reactions of (1*R*)-(−)-thiofenchone **108** and (1*R*)-(−)-thiocamphor **109** with triflic anhydride result in stereoselective conversions into the multicyclic thiazolines shown in **Scheme 49**.[156]

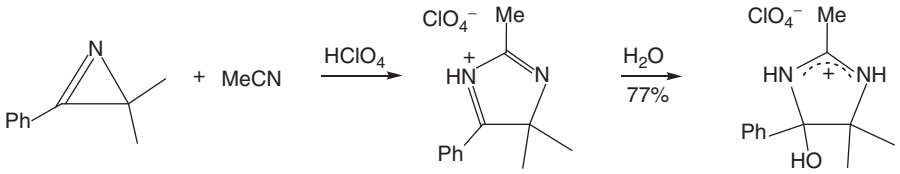


Scheme 49

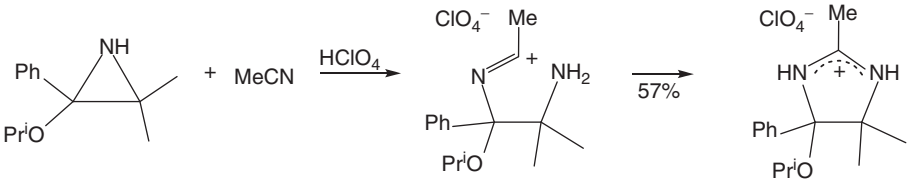
Nitrogen nucleophiles are also effective as nitrilium ion traps in heterocycle formation. Aziridinium salts and nitriles readily react to yield imidazoline salts (equation 79),[157,158] and both azirenes (equation 80)[149] and alkoxyaziridines (equation 81)[149] form similar products under Ritter reaction conditions.



(79)

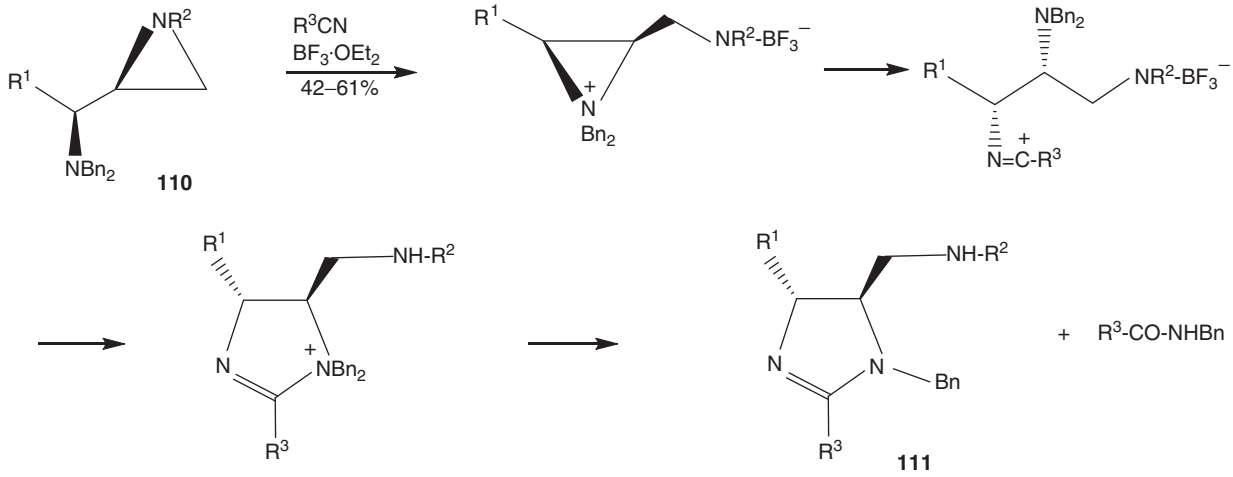


(80)



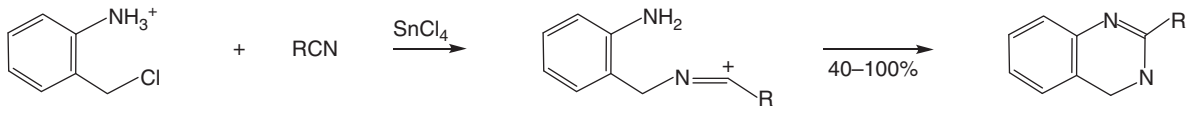
(81)

The enantiopure amino aziridine **110** undergoes the complex sequence of steps shown in Scheme 50 to yield the heterocyclic product **111** with very high stereospecificity.[159]



Scheme 50

Once again, six-membered systems can also be synthesized, a notable example being the 3,4-dihydroquinazoline derivatives prepared by Lora–Tamayo using the Lewis acid reagent $SnCl_4$ (equation 82).[160]

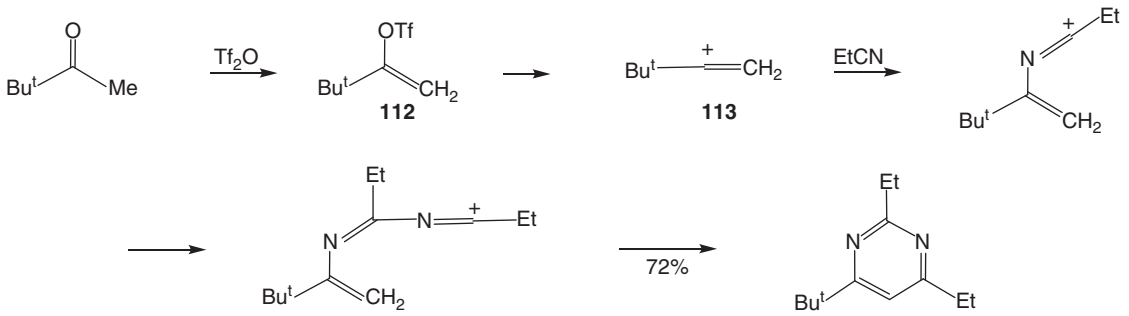


(82)

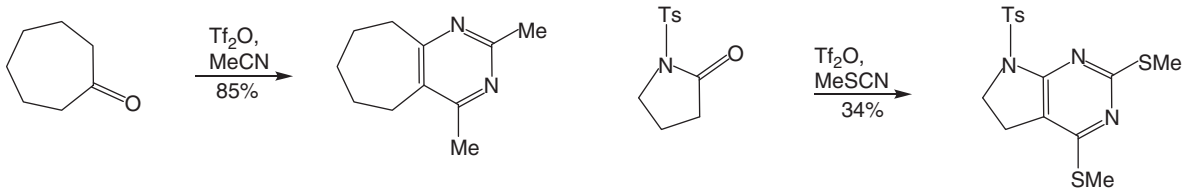
Pyrimidines may be prepared from ketones via their triflate derivatives **112**. Loss of triflic acid first gives the vinyl cation **113**, which then reacts sequentially with 2 equivalents of the nitrile reagent before undergoing cyclization (Scheme 51).[161] This approach has been extended to the syntheses of fused carbocyclic and heterocyclic pyrimidines (Scheme 52).[162,163]

6.07.3.2 Intramolecular Initial Step

Cyclization, usually to a six- or seven-membered ring, may occur through an intramolecular reaction of carbenium ion and nitrile functionalities. The nitrilium ion generated in this comparatively uncommon process is then quenched by an intermolecular nucleophilic attack to yield the Ritter-type product. The most common carbenium ion precursors are alkene, ketone, oxime, or a

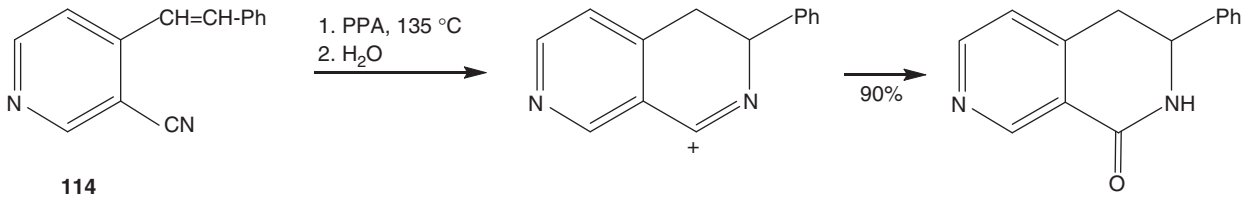


Scheme 51

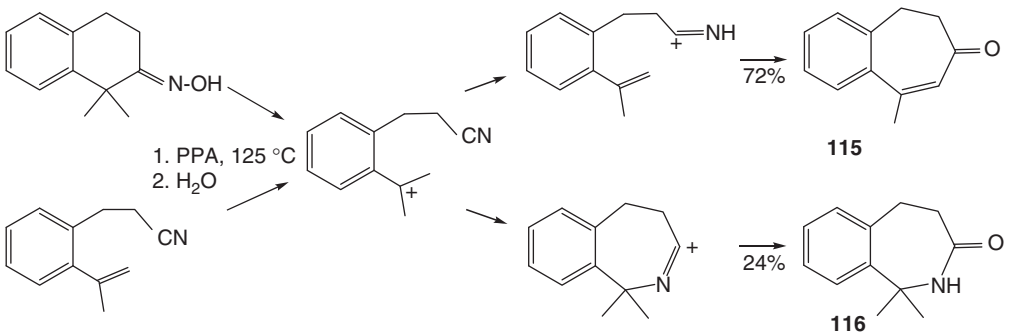


Scheme 52

second nitrile. 3-Cyano-4-stilbazole **114** utilizes an alkene functional group in this step and produces an excellent yield of a tetrahydrocopyrine derivative (equation 83).[164] This efficiency is atypical, however, as illustrated in Scheme 53. Here, a common carbenium ion intermediate is produced from either an oxime or an alkene precursor. Competitive cyclizations then occur, the favored one leading to the Hoesch product **115** and the minor one affording the Ritter product **116**.[165]



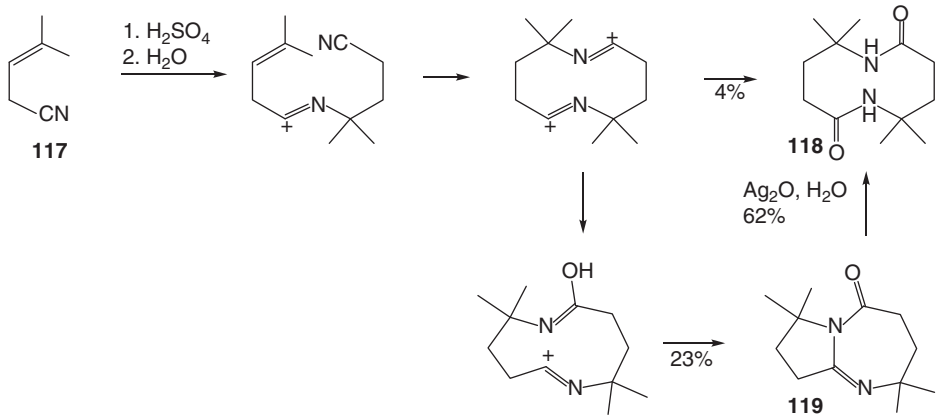
(83)



Scheme 53

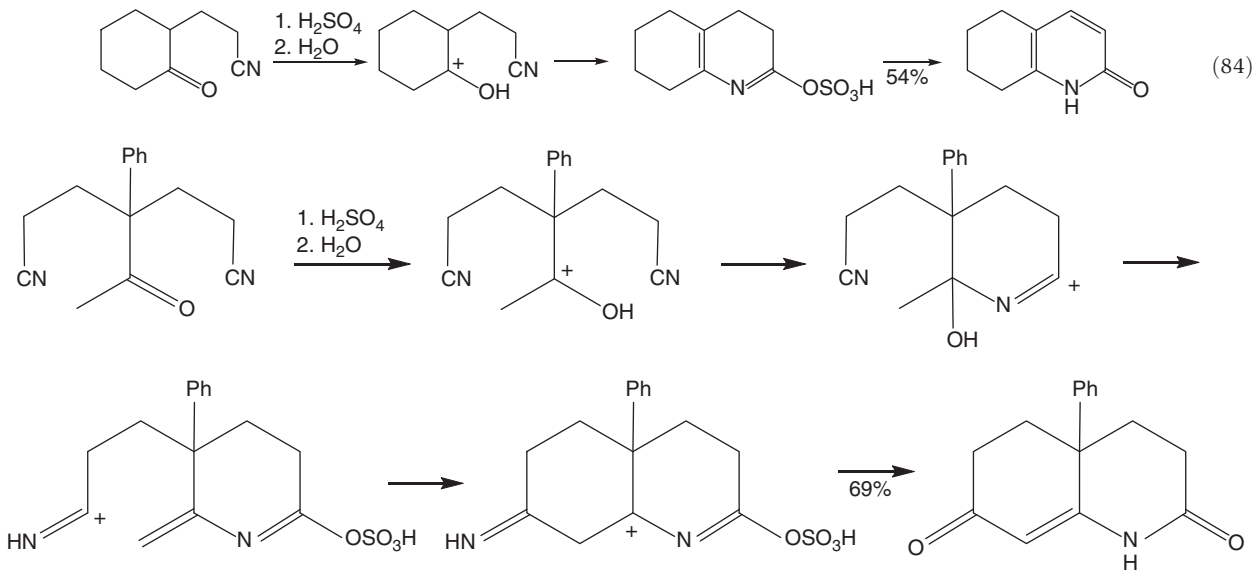
4-Methyl-3-pentenonitrile **117** undergoes the novel reaction sequence outlined in Scheme 54, during which the reagent first dimerizes and then undergoes cyclization. The resulting ionic intermediate undergoes quenching to yield a minor monocyclic product **118**, and competing transannular reaction (followed by nucleophilic attack) thereby giving a bicyclic structure **119**. Silver oxide ring opens the latter to the former.[166]

δ-Ketonitriles are well known to form 2-pyridone products under acidic conditions,[8] and in some cases (equation 84), this conversion is combined with spontaneous oxidation to afford the aromatized product.[167] A novel δ-ketonitrile reaction is an



Scheme 54

acetylpimelonitrile derivative (Scheme 55) which affords a bicyclic 2-pyridone in a one-pot process after sequential Ritter and Hoesch steps.[168] The cyclization of further $\alpha\omega$-dinitriles has been reviewed by Johnson and Madronero.[124]



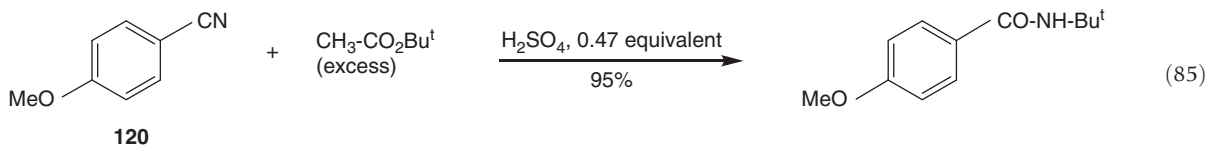
Scheme 55

6.07.4 Catalytic Developments

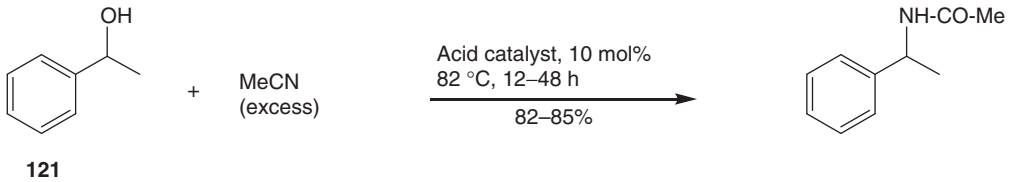
6.07.4.1 Protic (Brønsted) Acid Reagents

The original Ritter reaction employed sulfuric acid to generate the carbenium ion but extensions of the procedure using other strong Brønsted acids, or Lewis acid reagents, were soon introduced. These various methods used at least equimolar amounts of the acid despite, in principle, both methods requiring only catalytic quantities. Considerable effort has been made recently to develop effective catalytic methods and also to introduce environmentally benign acidic reagents.

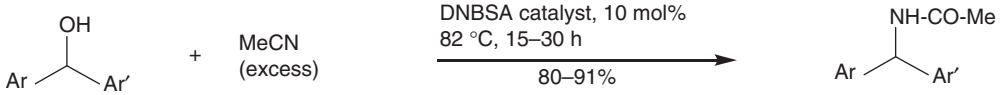
Esters of *tert*-alcohols act as masked *tert*-carbenium ions and are well known to give excellent yields of *N*-*tert*-alkylamides when excess quantities are heated with nitriles and sulfuric acid.[63] Substoichiometric molar ratios of acid to nitrile (0.94:1.00) can be used, but only the electron-rich 4-methoxybenzonitrile **120** permitted use of a significantly lower ratio (0.47:1.00) while retaining the short reaction time (equation 85).[169]



Sanz et al. demonstrated that 1-arylethanol **121** and benzhydrol **122** derivatives (equations 86 and 87) react efficiently with catalytic amounts (10 mol%) of 2,4-dinitrobenzenesulfonic (DNBSA), *p*-toluenesulfonic, sulfuric, or triflic acids in refluxing acetonitrile.[170] Interestingly, the former group of substrates were initially converted into their bis(1-arylethyl) ether before formation of the ultimate amide product. DNBSA was a particularly efficacious catalyst, giving both high yields and being easy to handle. Nonetheless, the use of only 5 mol% doubled the reaction time for a reduced yield. Secondary benzylic alcohol substrates all gave good yields of the acetamides using 10 mol% DNBSA, but the corresponding tertiary alcohols produced dimeric hydrocarbons instead.

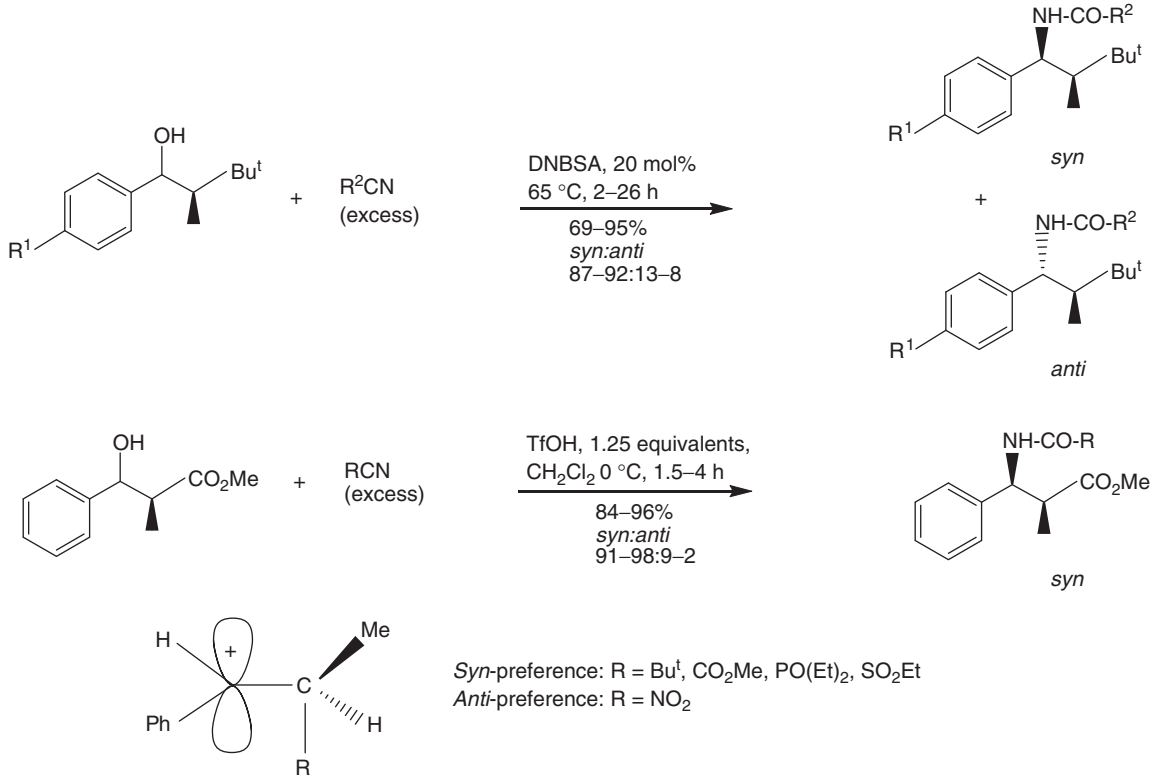


121 (86)



122 (87)

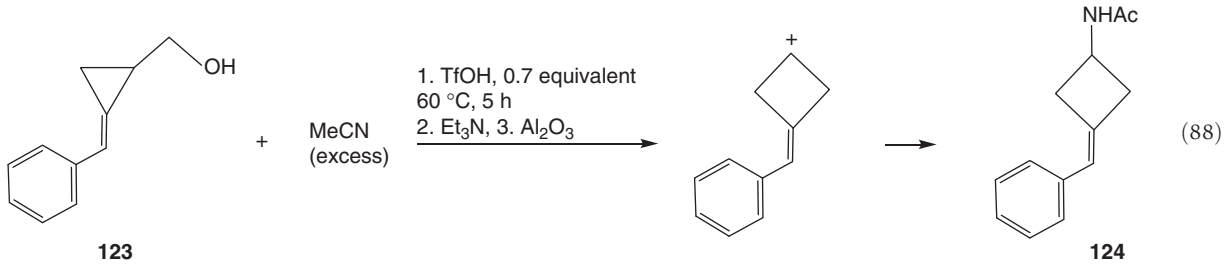
When chiral secondary benzylic alcohols were reacted with excess nitrile and 20 mol% DNBSA, it was found that the highly diastereoselective Ritter reaction occurred efficiently (**Scheme 56**). Similar reactions were effected by triflic acid, except that 1.25 equivalents of acid were required. However, solid nitrile reagents could now be used in CH_2Cl_2 solution. Rubenbauer and Bach proposed that the diastereoselectivity resulted from the conformation abutting the carbenium ion, in which one face was shielded by the methyl group and the other by the *tert*-butyl or ester group. Since the latter groups are bigger, the *syn*-reaction dominates. This suggestion is in accord with further observations where the smaller NO_2 group resulted in the predominantly *anti*-product.[171]



Scheme 56

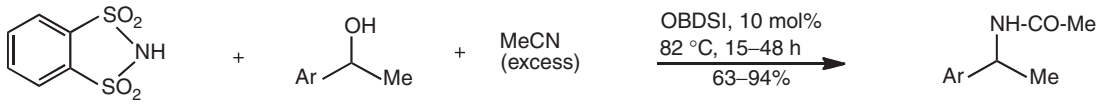
As seen earlier,[170] triflic acid can be used in substoichiometric amounts in some circumstances. Another interesting example is the Ritter rearrangement reaction of 2-(arylmethylene)cyclopropylcarbinols **123** to produce cyclobutylamides **124** (equation 88).[172]

Reaction of the phenyl alcohol was performed at 60 °C using TfOH over the range of 1.2–0.12 equivalents. The maximum yield of 76% was obtained for 0.7 equivalent of acid. Sulfuric acid only gave a 20% yield under these conditions, whereas methanesulfonic acid and trifluoroacetic acid were completely ineffective. A total of 10 aryl-substituted compounds were tested under these optimum conditions and acetamide yields of 32–76% resulted. Primary alcohols generally do not undergo Ritter reaction unless they are adjacent to an activating group, such as an aromatic substituent or, as here, a highly strained ring. Loss of water, ring expansion, and trapping of the nitrile leads to the observed product.

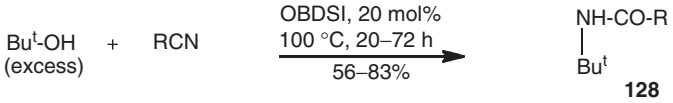


123 **124** (88)

The use of less common Brønsted acids has also been explored, one of these being *o*-benzenedisulfonimide **125** (OBDSI) which has a pK_a value of −4.1 at 20 °C.[173] Several 1-arylethanol derivatives **126** underwent the Ritter reaction in high yield to produce **127** on using 10 mol% of **125**, but the 4-MeO- and 4-NO_2 alcohols failed to react (equation 89). Benzyl alcohols required more OBDSI and the yields were lower. Reactions of *tert*-butanol to produce *tert*-butylamides **128** were also catalyzed by OBDSI, although the more crowded 2-methoxybenzonitrile failed to react (equation 90).

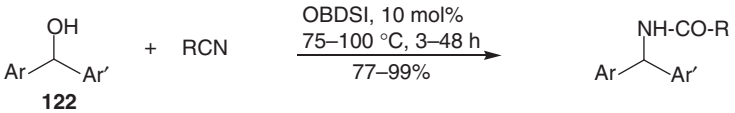


125 = OBDSI **126** **127** (89)



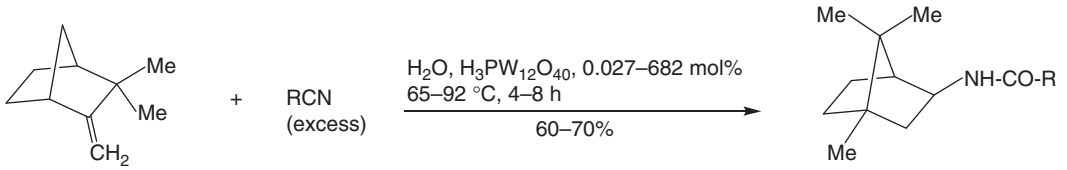
128 (90)

By far the best outcomes were obtained for the OBDSI-catalyzed (10 mol%) reactions of benzhydrols **122** with nitriles, from which amide yields of 77–99% were obtained across a very wide range of substrates (equation 91). Both electron-donating and electron-withdrawing groups were accommodated (except when two electron-withdrawing groups were present in the benzhydrol structure). The only other restriction was reduced yields in the case of crowded reagents. It was possible to recover most of the catalyst and use it twice more, and stoichiometric amounts of the nitrile could be employed without deleterious effects.[173]

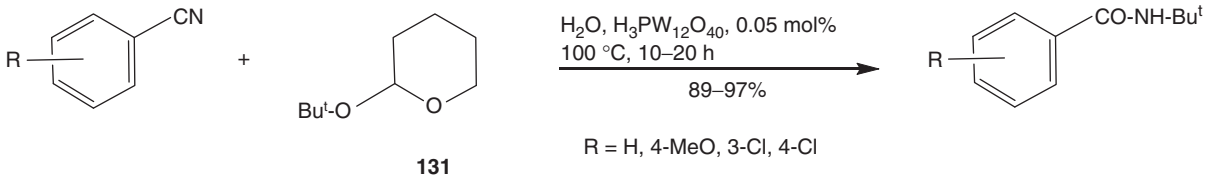


122 (91)

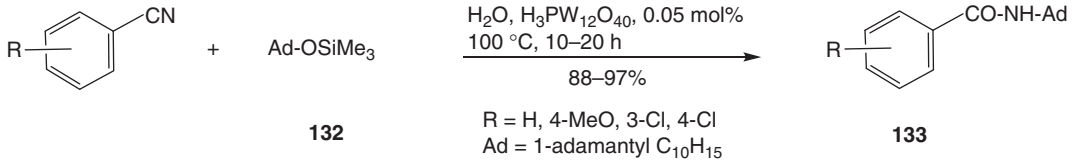
Heteropolyacids such as $H_7PMo_{12}O_{42}$, $H_3PW_{12}O_{40}$, and $H_4SiW_{12}O_{40}$ are also effective Ritter reaction catalysts, with dodecatungstophosphoric acid generally being the most versatile. Thus, camphene **129** was converted by Kartashov et al. into a series of five amides **130** in good yields by using catalytic amounts of $H_3PW_{12}O_{40}$ (equation 92).[19,174] Firouzabadi and Iranpoor have developed this reagent into a potent catalyst for amide preparation in aqueous solution.[20] Alcohols and their protected derivatives (silyl ether, THP – tetrahydropyranyl ether, and *tert*-butyl methyl ether) underwent Ritter reaction in excellent yields. For example, benzonitriles reacted with *tert*-butyl THP ether **131** to produce *tert*-butylamides in yields of 89–97% (equation 93). Similarly, 1-trimethylsilyloxyadamantane **132** was efficiently converted into the series of adamantylamides **133** (equation 94). A small quantity of sodium dodecyl sulfate should be added when reacting solid nitriles using this method.



129 **130** (92)

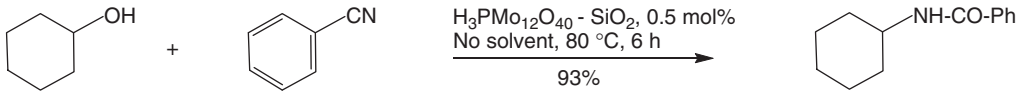


131 (93)



132 **133** (94)

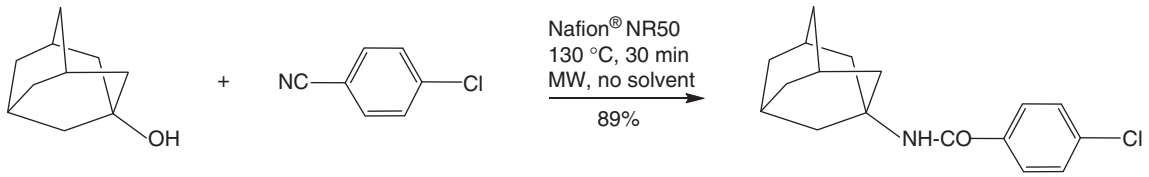
Heterogeneous catalysts have also attracted considerable interest. Phosphomolybdic acid $H_3PMo_{12}O_{40}$ on silica (0.5 mol%) effects Ritter reactions of benzylic alcohols, tertiary alcohols, and cyclohexanol **134** at 80 °C under solvent-free conditions (equation 95). The catalyst can be recovered by filtration and used for three cycles. This reagent gives higher yields than the alternative solid acids Amberlyst-15, montmorillonite KSF, or zeolite H-ZSM-5.[175]



134 (95)

Phosphorus(V) oxide on alumina or silica also catalyzes Ritter reactions. A comparative study of the acetonitrile and benzyl alcohol reaction demonstrated that P_2O_5–SiO_2 (60 wt%, 100 °C, 3 h) gave a 93% yield, superior to the use of 15 other acids or different P_2O_5–SiO_2 conditions. Comparable yields were obtained using the same quantity of catalyst, but using microwave irradiation (475 W, 120 s) instead of thermal heating.[176]

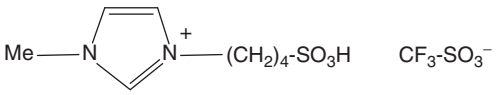
It was demonstrated by Olah and Prakash in 1987 that the perfluorinated resinsulfonic acid Nafion-H®-catalyzed Ritter reactions, which were carried out in sealed pyrex tubes at 145 °C for 18–48 h. The catalyst was recovered by filtration and retained its catalytic activity.[177] Such processes can be performed more efficiently at 130 °C using solid-supported Nafion® NR50, only 1.1 equivalents of the nitrile, and microwave radiation (200 W, 30 min). The catalyst beads were recovered mechanically and could be used at least six times (equation 96).[178]



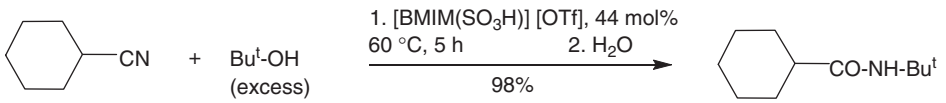
(96)

Recently, Laali has introduced the imidazolium ionic liquid [BMIM(SO_3H)] [OTf] **135** as an acid catalyst for carrying out Ritter reactions (**Scheme 57**). This material has also been employed in concert with the reagent $NOPF_6$.[179]

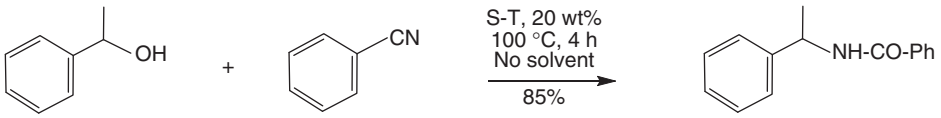
Sulfated tungstate (S–T: sodium tungstate plus chlorosulfonic acid) (20 wt%) under solvent-free conditions can be recycled four times (equation 97).[180]



135 [BMIM(SO_3H)] [OTf]

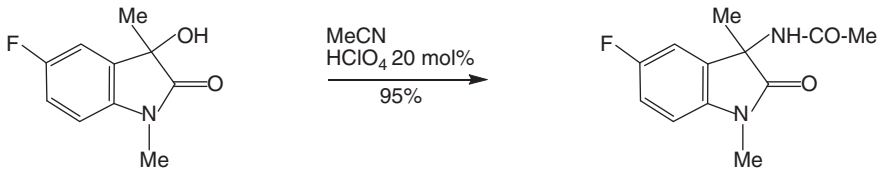


Scheme 57

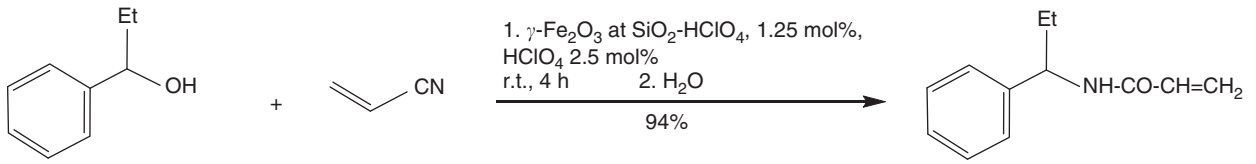


(97)

Catalytic amounts of perchloric acid have been found effective in converting 3-hydroxyindole amides into their corresponding acetamide derivatives (equation 98).[181] Perchloric acid-functionalized silica-coated nanoparticles γ-Fe_2O_3 at SiO_2–$HClO_4$ have been synthesized by Heydari and shown to act as a recyclable catalyst for Ritter reactions (equation 99).[182] Following completion, the catalyst can be removed using an external magnetic device and recycled. Only low amounts of catalyst and $HClO_4$ are required and the yields reported were consistently over 90%.

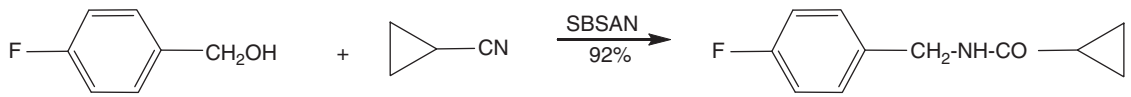


(98)

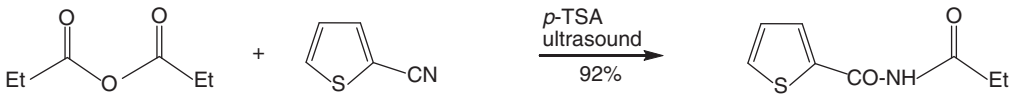


(99)

More recently, silica boron chlorosulfonic acid nanoparticles have been used over eight catalytic runs (equation 100).[183] Catalytic quantities of *p*-toluenesulfonic acid permit the conversion of symmetrical acyclic carboxylic anhydrides into their corresponding unsymmetrical imides. Typically, 30 mol% of acid was employed for liquid nitriles and 50 mol% for solid nitriles. Reaction times were shorter, and yields higher, if ultrasound was used in addition to heating (equation 101).[184]



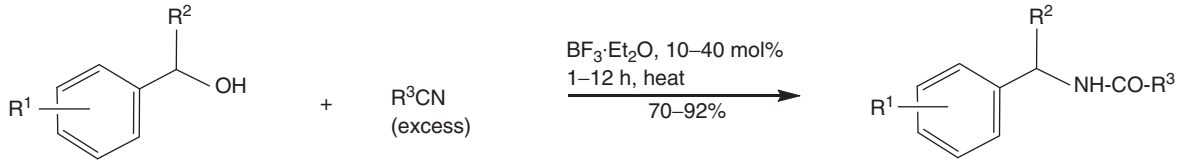
(100)



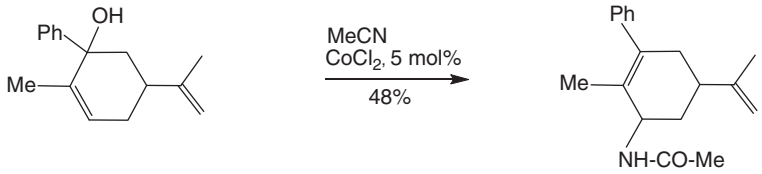
(101)

6.07.4.2 Lewis Acid and Metallic Reagents

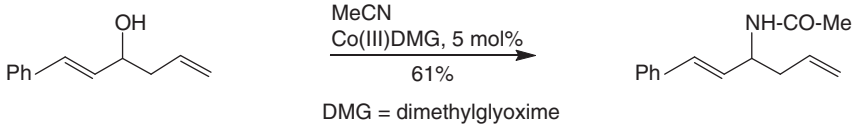
Boron trifluoride etherate catalysis of the amidation of benzylic alcohols was reported in 1994 by Firouzabadi et al. (equation 102),[185] and this was quickly followed by Iqbal's account of effective Co(II) (equation 103)[186] and Co(III) (equation 104)[187] catalytic Ritter processes.



(102)



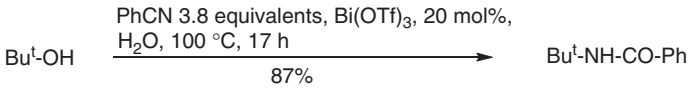
(103)



DMG = dimethylglyoxime

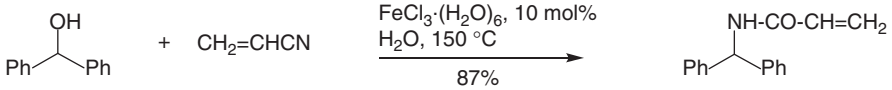
(104)

Barrett[188] found that catalytic use of various metal triflates could effect Ritter reactions, and this approach provides a new and widely applicable method with excellent yields of 75–96% when 20 mol% of $Bi(OTf)_3$ is employed (equation 105).

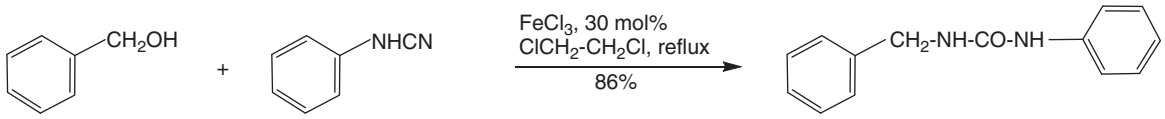


(105)

In 2009, Reymond and Cossy[189] reported that the inexpensive and green reagent $FeCl_3.(H_2O)_6$ catalyzed the Ritter reaction of benzylic alcohols in excellent yields (equation 106). Their new protocol was also efficient for the catalytic preparation of *N-tert*-butylamides using *tert*-butyl acetate.[63] Fe(III) catalysis is also effective in the synthesis of unsymmetrical urea derivatives from cyanamides (equation 107),[190] whereas $ZnCl_2$–SiO_2 provides an alternative catalytic route to *N-tert*-butylamides.[191] Further useful heterogeneous catalysts include BF_3 supported on polyvinylpolypyrrolidone,[192] montmorillonite KSF,[193] and Fe^{3+}-montmorillonite K10.[194]

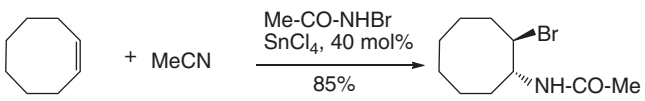


(106)



(107)

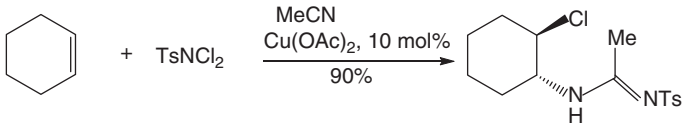
Catalytic amounts of bismuth(III) bromide (10–20 mol%) are effective in the conversion of epoxides into *trans*-1,2-hydroxy amides.[195] For example, the steroidal epoxides **53** and **54** gave product yields comparable to the earlier uncatalyzed BF_3 methods (see **Scheme 21**). The bromoamidation reactions described in **Scheme 33** can be performed under catalytic conditions using boron trifluoride etherate or tin(IV) halides (equation 108).[108]



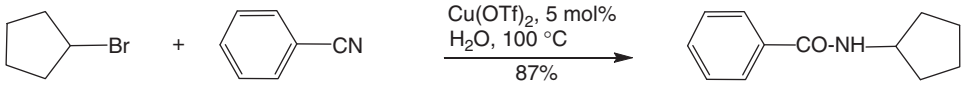
(108)

Dichloramine-T, $TsNCl_2$, undergoes reaction with both an alkene and nitrile in a Ritter-type reaction catalyzed by copper(II) acetate (equation 109). In this process, the nitrilium ion intermediate is trapped by the amine reagent. The resulting amidine product can be readily cyclized to yield the corresponding imidazole.[196] It has been recently demonstrated that copper(II) triflate efficiently catalyzes the Ritter reaction between nitriles and halogenated hydrocarbons in water at 100 °C (equation 110).[197] 1-Bromoadamantane undergoes Ritter reaction in high yield with a variety of manganese catalysts (3 mol%) and nitrile reagents

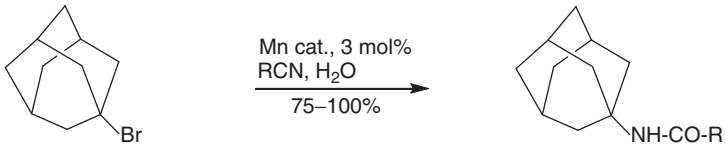
(equation 111). The most effective catalysts were found to be $Mn(acac)_3$ and $Mn_2(CO)_{10}$.[198] These conversions should be compared with the earlier work in Scheme 22 and equation 44.



(109)

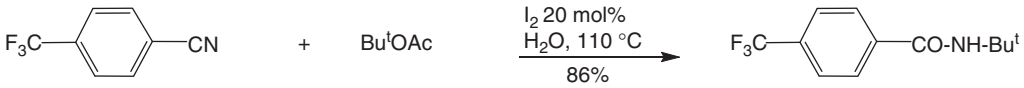


(110)

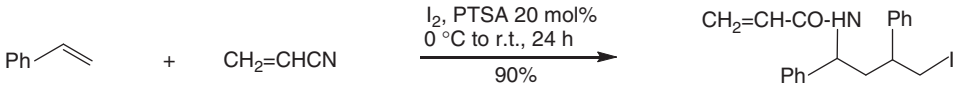


(111)

Although molecular iodine has been used in haloamidation reactions,[198] Lalitha has found that small amounts catalyze standard Ritter reactions rather efficiently in the presence of water at high temperatures (equation 112).[199] If equimolar amounts of I_2 are used in the presence of catalytic amounts of a protic acid, then vinyl arenes undergo the novel dimeric variant of the Ritter process illustrated in equation 113.[200]



(112)



(113)

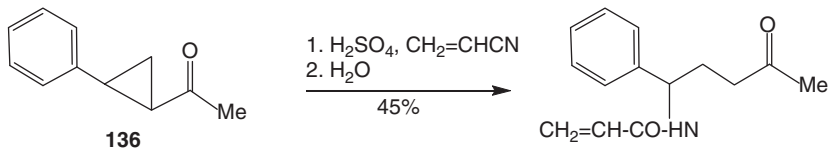
6.07.5 Selected Topics

Both the Ritter amide-forming and Ritter heterocycle-forming reactions have found wide applications in organic synthesis. A selection of these applications is presented here.

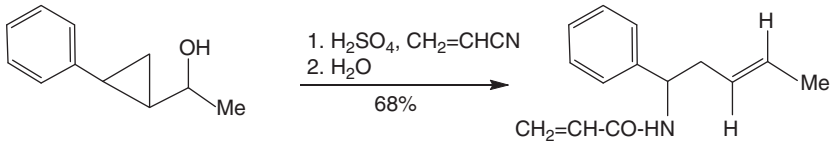
6.07.5.1 Wagner–Meerwein Rearrangements

The original Ritter reactions use strong protic acid to generate a carbenium ion. It is well understood that these often undergo Wagner–Meerwein rearrangement to give an isomeric ion of lower energy (see Scheme 2) and that this new carbon framework will be the one present in the amide product. Variation of the reaction conditions may also lead to formation of a kinetic product under mild conditions, or a thermodynamic product employing more vigorous techniques (see Scheme 3). Hence the outcome of a given Ritter process can very much depend on the precise experimental procedure chosen, and skeletal rearrangement can be incorporated deliberately into the synthetic design.

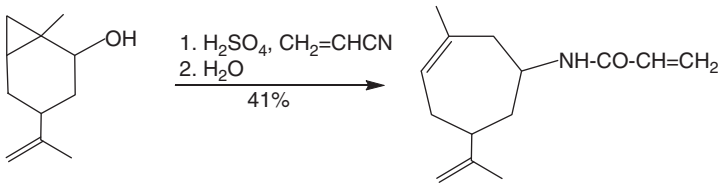
For example, cyclopropyl derivatives are prone to ring opening during the Ritter process. Ketones such as **136** give a γ-ketoamide product (equation 114), whereas the corresponding alcohols produce homoallylic amides (equation 115). Remarkable variations occur, however, when bifunctionalized norcarane derivatives are employed. The alcohol functional group of **137** reacts in preference to its alkene group, and in concert with ring cleavage expansion, to yield the product **138** (equation 116). In marked contrast, the corresponding ketone **139** reacts through its more reactive alkene functional group to give **140** without the cyclopropane ring cleavage occurring (equation 117).[201]



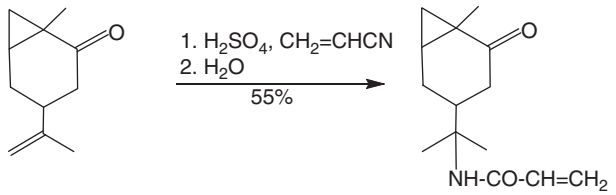
136 (114)



(115)

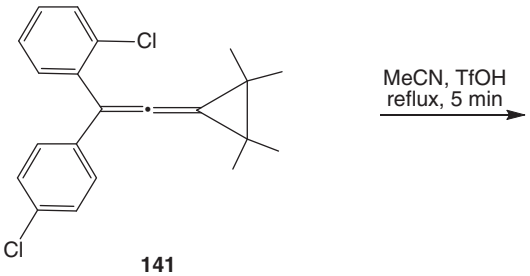


137 **138** (116)

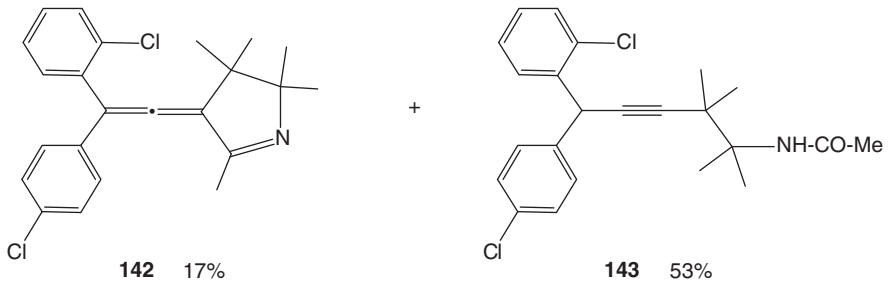


139 **140** (117)

Allenic cyclopropane derivatives similar to **141** normally undergo exclusive [3+2] cycloaddition with acetonitrile in the presence of triflic acid. For **141** itself, however, the expected substance **142** was only obtained in low yield. A competing Ritter reaction instead afforded the acetylenic derivative **143** as the major product (**Scheme 58**). The formation pathway for the latter is outlined in equation 118.[202]

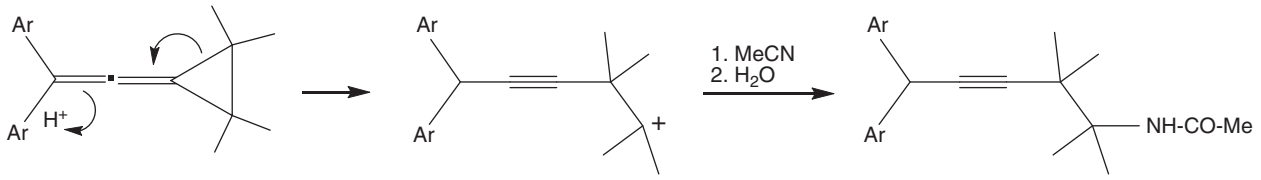


141



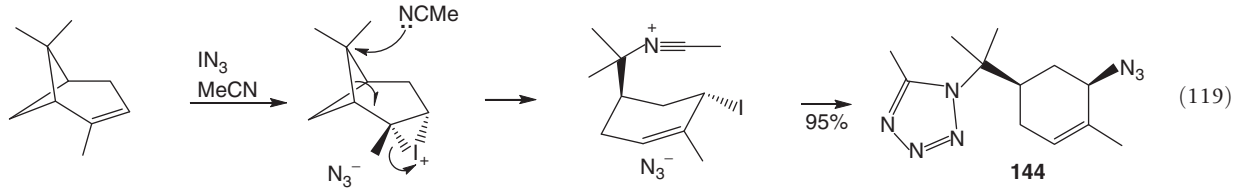
142 17% **143** 53%

Scheme 58



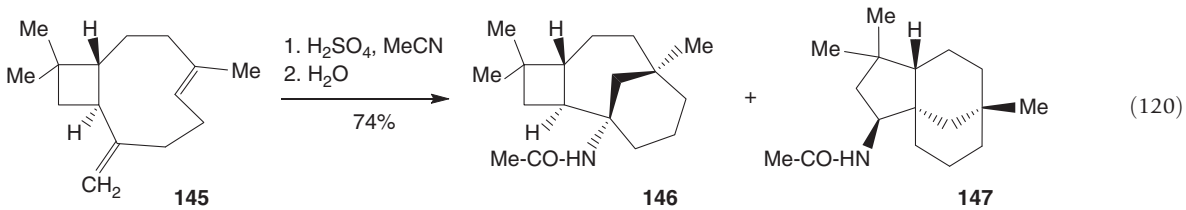
(118)

The pinene monoterpenes are other strained molecules that readily undergo rearrangement under Ritter conditions. Alkenes generally react with iodine azide to give a bridged iodonium ion that is then opened by an azide. In the case of (−)-*α*-pinene, however, acetonitrile is effective as a competing nucleophile (equation 119). Azide ion then intercepts the nitrilium intermediate by means of a click reaction. Formation of the stereospecific tetrazole product **144** is termed a Hassner–Ritter reaction.[203]

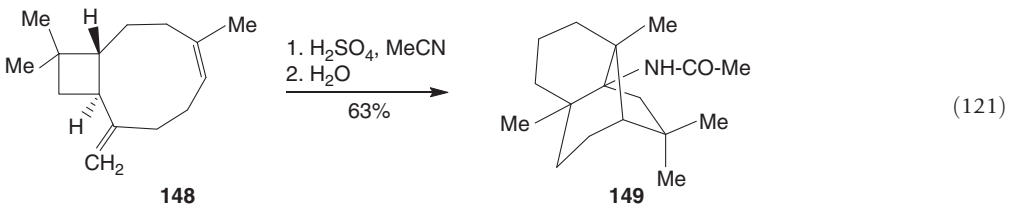


(119)

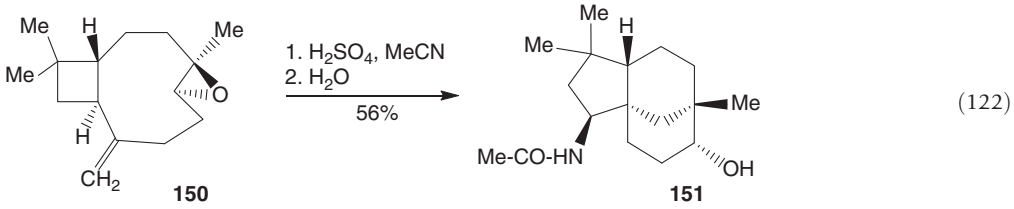
The sesquiterpene caryophyllene **145** undergoes rearrangement under Ritter reaction conditions to produce a mixture of the caryolane **146** and clovane **147** derivatives in a 3:1 ratio (equation 120). In contrast, its *cis*-isomer isocaryophyllene **148** yields **149** (equation 121), almost certainly formed via the intermediacy of neoclovene. Caryophyllene epoxide **150** and isocaryophyllene epoxide **152** afford the epimeric alcohol derivatives **151** and **153**, respectively (equations 122 and 123). It should be noted that these terpenoid reagents are all enantiomerically pure substances and that their reactions proceed stereospecifically. Mechanistic pathways for these elegant rearrangements are provided.[204]



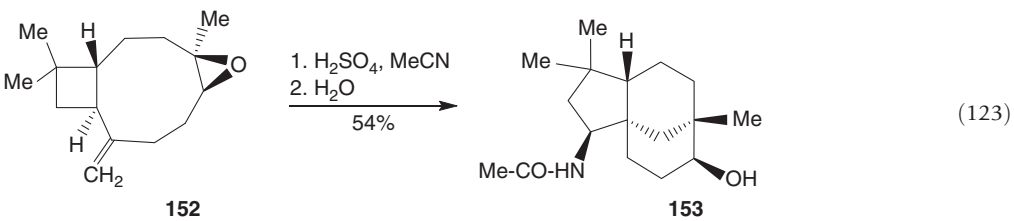
(120)



(121)

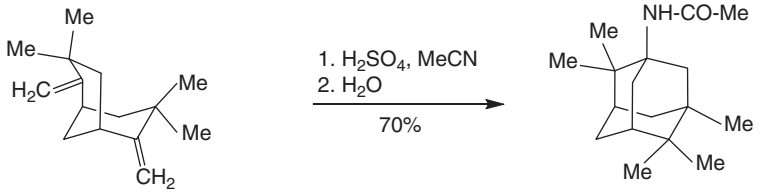


(122)



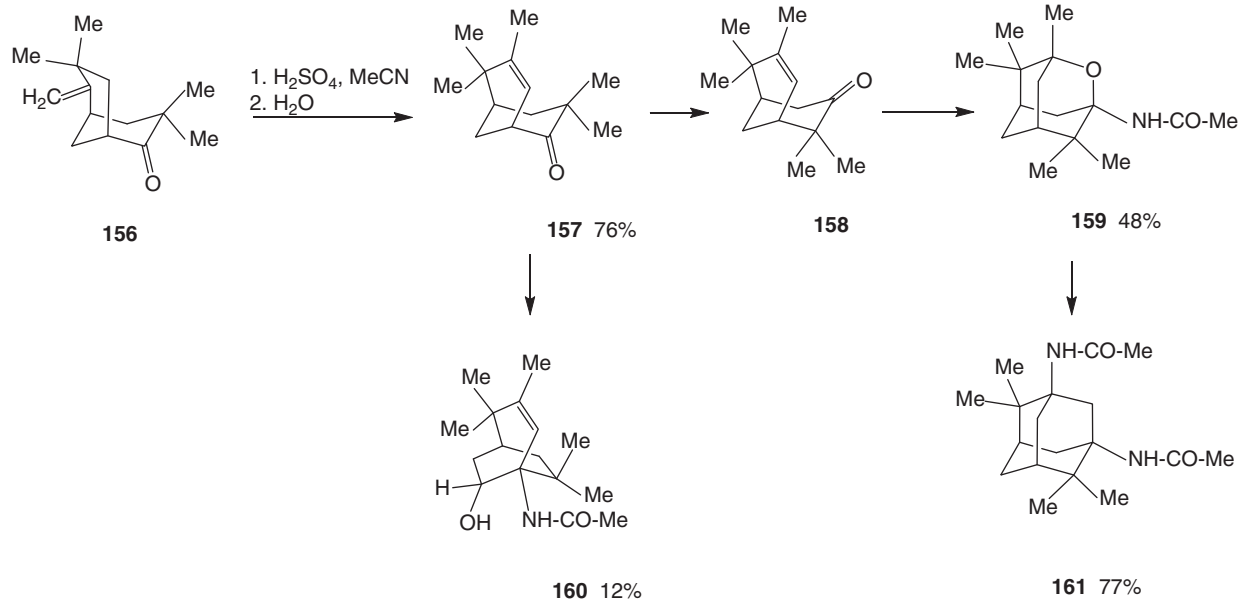
(123)

It can be seen from these examples that complex and deep-seated Wagner–Meerwein rearrangements can occur in conjunction with the Ritter reaction. If deliberately forcing reaction conditions are chosen, then unusual and unexpected products can be obtained. Some of these are compounds that would be laborious to prepare using more logical synthetic methods. For example, reaction of the diene **154** affords a 70% yield of the adamantyl amide **155** (equation 124).[205]



154 **155** (124)

A more striking example is the unsaturated ketone **156**, from which the five products **157–161** were identified under Ritter conditions (Scheme 59). A series of reactions were conducted using varied parameters and from these runs the indicated optimum yields were obtained. Mechanistic explanations were provided for the formation of these diverse compounds.[206]



156 **157** 76% **158** **159** 48%

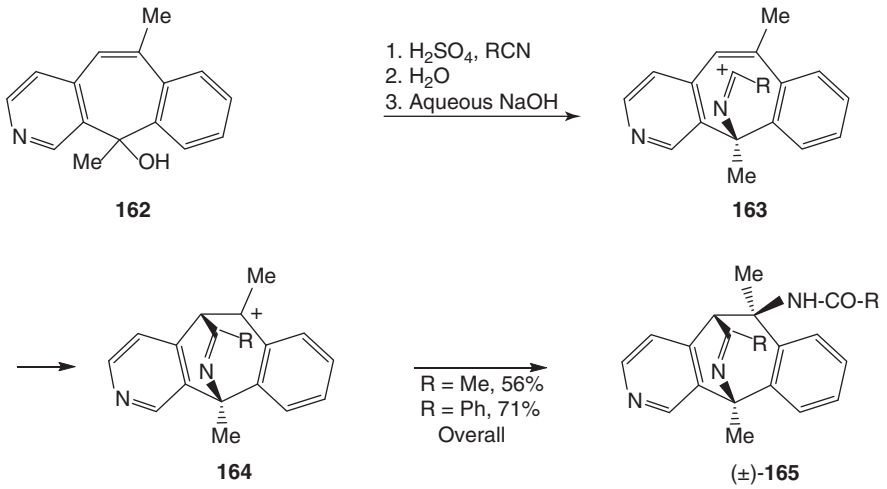
160 12% **161** 77%

Scheme 59

6.07.5.2 Bridged Imine Formation and Reactivity

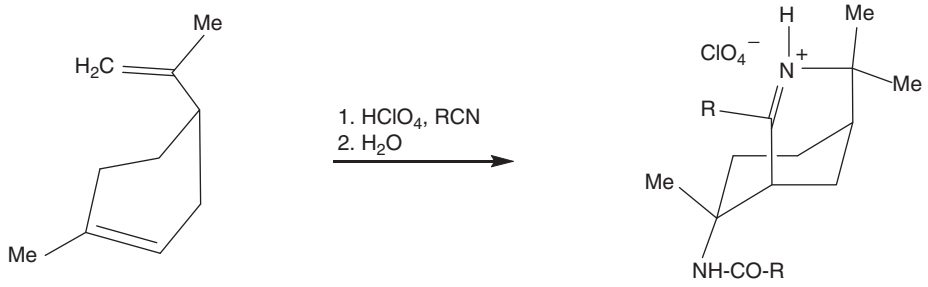
The versatile Ritter heterocyclic reaction generally affords monocyclic or fused bicyclic products (see Section 6.07.3). There are, however, a smaller number of cases where a bridged bicyclic structure results. In these bridging cyclizations, the nitrile reagent essentially clips across a preexisting ring by utilizing two suitably separated functional groups. A multicyclic product is thereby produced that contains a 1-azacyclohexene part structure. An early example of this process is shown in Scheme 60. The hydroxy group of the diaryl suberenol **162** is converted into the carbenium ion and thence the nitrilium ion **163**. The latter undergoes an intramolecular nucleophilic attack by the alkene group to produce the bridged skeleton. Finally, the new carbenium ion **164** undergoes the Ritter amide reaction to yield the bridged imine **165**. The bridging process can occur on either the top or bottom face of the first (achiral) carbenium ion. Therefore racemic **165** results, even though each individual conversion **162–165** is stereospecific.[207]

If the first carbenium ion is part of a chiral molecule then a stereospecific conversion can be carried out. Thus (*R*)-(+)-limonene **166** yields (−)-(**168**) and (1*S*)-(−)-*β*-pinene **167** produces the enantiomer (+)-**169**, respectively (equations 125 and 126).[208] Similar bridged-Ritter processes also occur using a variety of other terpenoid substrates.[208,209] The iminium salts initially formed are remarkably stable to hydrolysis under acidic and neutral conditions. Deliberate treatment with a base is necessary to obtain the free base products.[210,211]



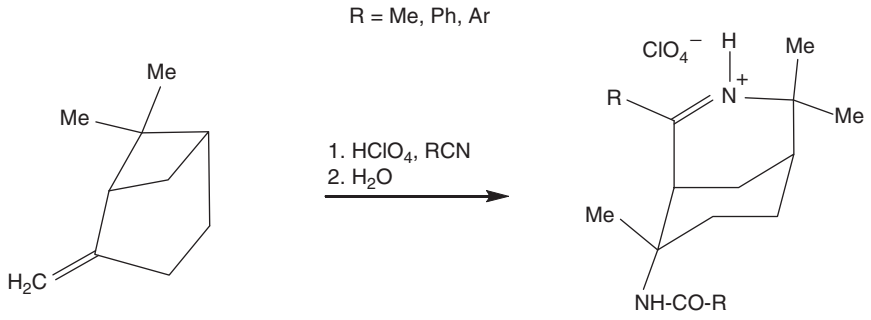
162 **163** **164** (±)-**165**

Scheme 60



(125)

(+)-(**166**) (–)-(**168**)

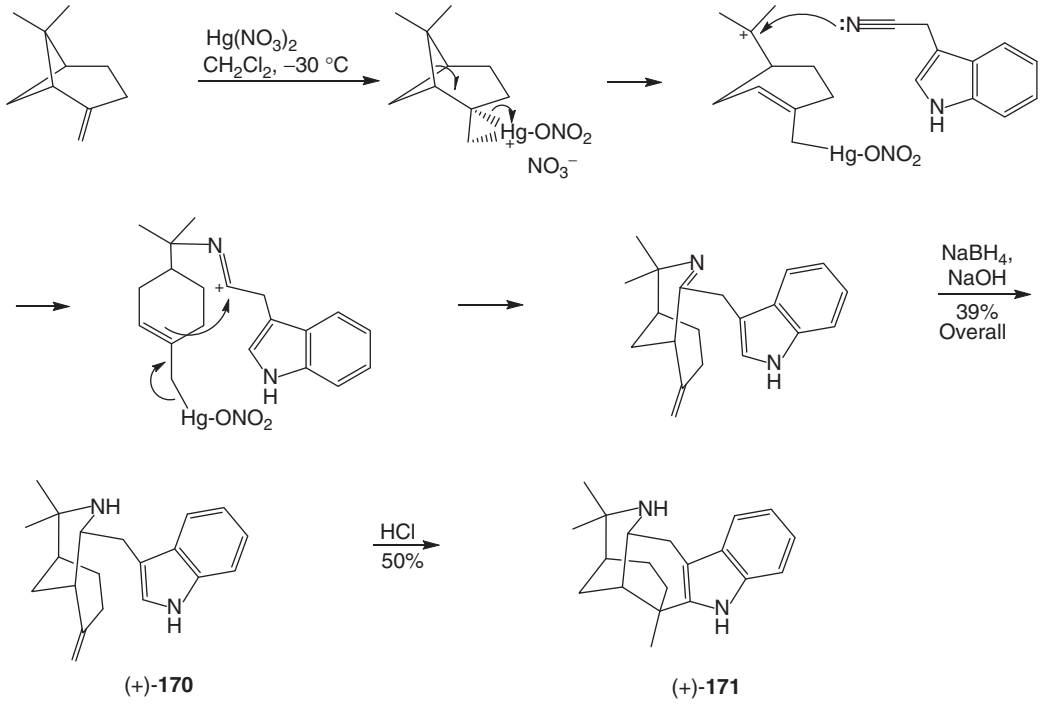


(126)

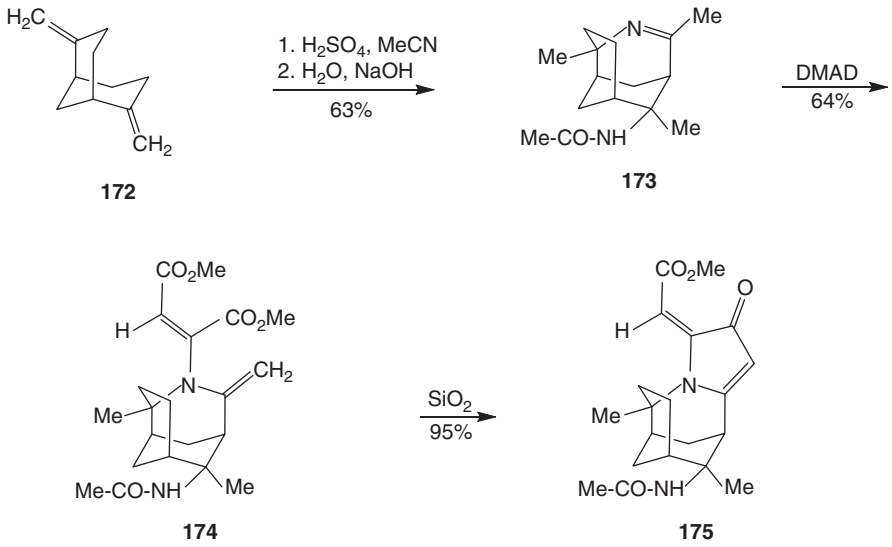
(–)-(**167**) (+)-(**169**)

These bridged-Ritter compounds contain a reactive imine group, the chemistry of which can be exploited in further synthesis. Delpech and Khong-Huu converted (−)-*α*-pinene into the racemic bridged imine **102** using mercury(II) nitrate method. This was reduced to the amine **103** and thus to the azaadamantane derivative **104** in excellent yield (see Scheme 46).[136] The stereochemistry is retained, however, in the related reactions of (−)-*β*-pinene and this important property has been harnessed by several groups for efficient syntheses of *Aristotelia* alkaloids.[212–214] The Stevens and Kenney[213] approach to (+)-makomakine **170** and (+)-aristoteline **171** in only two and three steps, respectively, is shown in Scheme 61. A similar reaction using (+)-*a*-pinene afforded a third alkaloid (±) hobartine. The loss of stereospecificity in this case is due to the mechanistic racemization process described earlier in Scheme 46. Further development of this Ritter method allowed Stoermer and Heathcock to synthesize (+)-alloaristoteline, (−)-serratoline, and (+)-aristotelone.[214]

The reactivity of these bridged imine Ritter products has also been used for the construction of artificial alkaloid-like structures. Dimethyl acetylenedicarboxylate (DMAD) is well known to exhibit a remarkably diverse range of reactivity,[215] which is compounded here by the nitrogen functional group being able to react in solution as either its imine or enamine tautomer. Complex molecules of unpredictable structure are thus obtained very simply. For example, the diene **172** affords the Ritter heterocyclic product **173**[216] and with DMAD this readily gives **174** and **175** in high yields (Scheme 62).[217,218]



Scheme 61

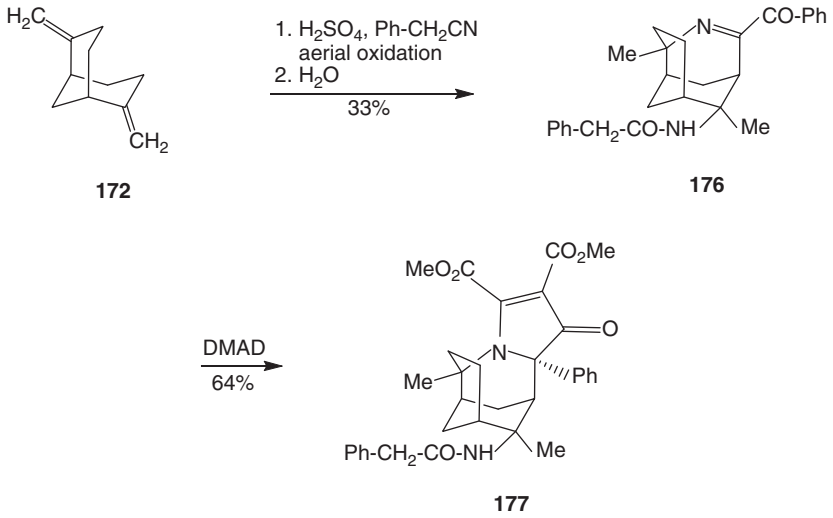


Scheme 62

In contrast, the same diene **172** undergoes the Ritter reaction with benzyl nitrile to produce the bridged imine **176** where spontaneous aerial autoxidation of the side chain has also taken place. Its reaction with DMAD results in the entirely different multicyclic structure **177** (Scheme 63).[218]

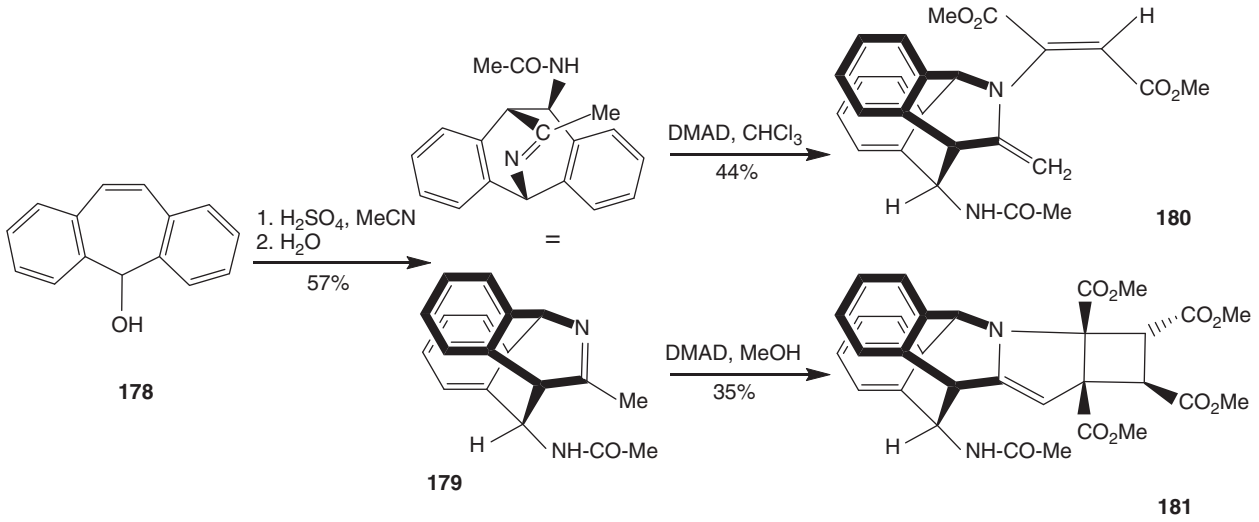
Dibenzosuberenol **178** undergoes Ritter heterocyclic reaction to afford the bridged imine **179**, shown in Scheme 64 from two differing perspectives. Reaction of **179** with DMAD yields the alternative and disparate compounds **180** or **181**, merely by employing alternative solvents.[219]

Formation of the unusual DMAD products presented in Schemes 62–64 is a thoroughly unpredictable process. Each bicyclic imine reacted quite differently, and the outcome was highly dependent on the choice of solvent and reaction conditions. However, relatively complex structures were obtained in just one- or two steps and their synthesis by more conventional methods would not be easy. Further, these substances may be regarded as nonnatural cousins of the plant alkaloids with good potential for biological activity. Indeed, a close relative of **179** has recently been shown to be an effective inhibitor of acetylcholinesterase.[220]



172 **176** **177**

Scheme 63

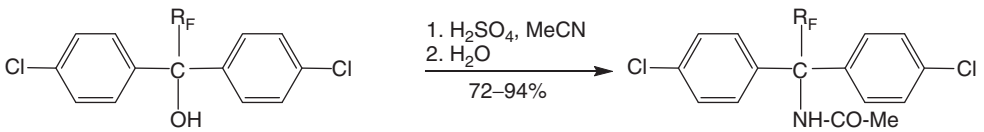


178 **179** **180** **181**

Scheme 64

6.07.5.3 Fluorinated Derivatives

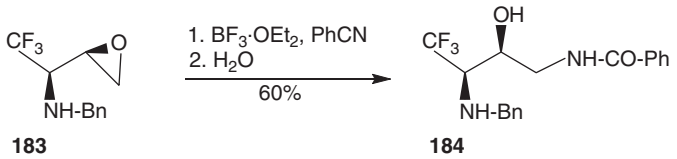
Currently, there is a considerable interest in the synthesis of potential fluorinated drugs since this atom is only slightly bigger than hydrogen yet it confers very different physical properties. Approximately 20% of currently marketed pharmaceuticals contain fluorine. The presence of fluorine atoms in Ritter carbenium ion precursors causes no difficulties, as shown by the standard behavior of tertiary alcohol **182** in equation 127.[221] Ring opening of epoxide **183** provides high regioselectivity in forming the product **184** which is the central unit of a protease inhibitor (equation 128).[222] Trifluoromethyl groups can also be introduced in a two-step process (e.g., **185**–**186**) whereby a ketone is reacted with (trifluoromethyl)trimethylsilane and then the silylated product subjected to Ritter conditions (equation 129).[223] Yields of the amide are good for diaryl ketones and moderate for the dialkyl cases. The behavior of cyclohexenone in forming **187** (equation 130) is particularly noteworthy. Difluoromethyl amides (equation 131) and monofluoromethyl (equation 132) benzylamides are produced in excellent yields in the usual manner.[30] It should be noted, however, that whereas the benzyl fluoride **188** underwent the Ritter reaction with tin(IV) chloride (equation 133), its difluoro analogs were completely inert.[224]



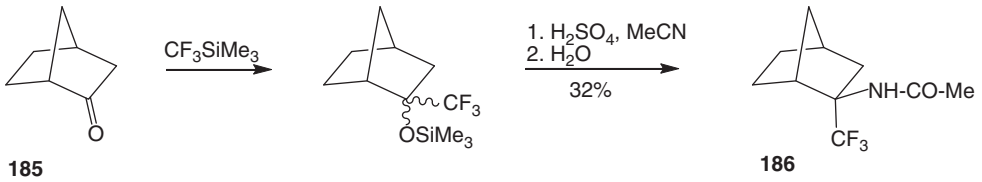
$R_F = CF_3$, C_2F_5 or C_3F_7

182

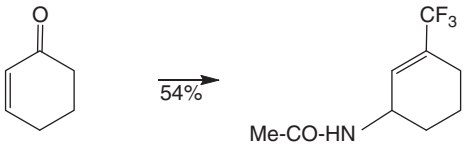
(127)



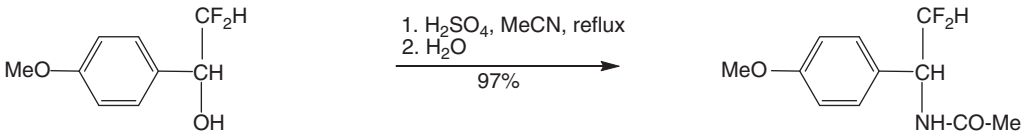
183 **184** (128)



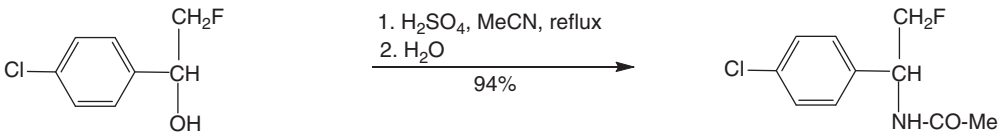
185 **186** (129)



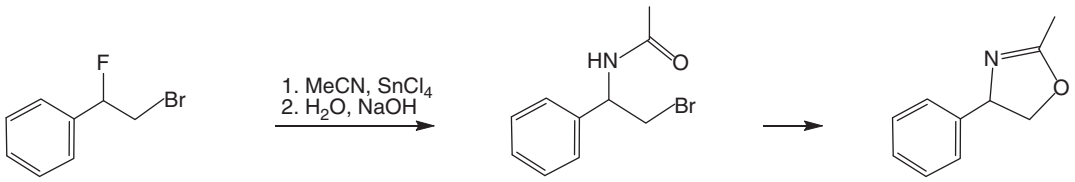
187 (130)



(131)



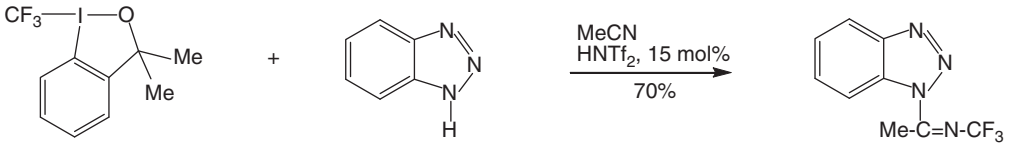
(132)



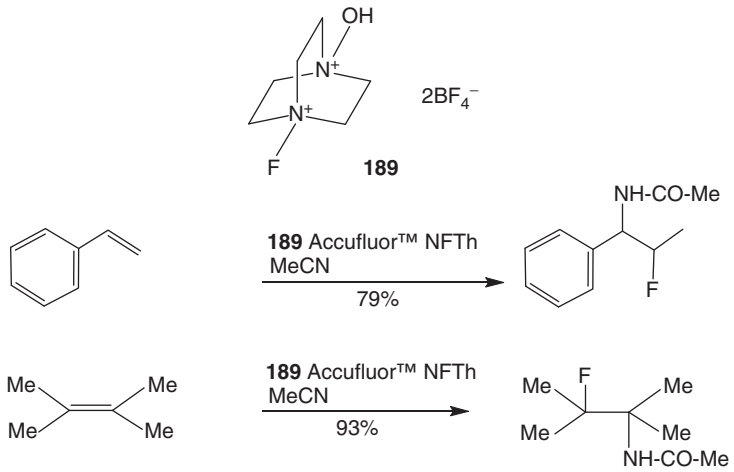
188 (133)

An exciting procedure has been introduced by Stavber whereby alkene derivatives undergo concomitant introduction of fluorine and amide functional group in high yields through use of the electrophilic fluorinating agent **189** (Scheme 65).[225] These conversions proceed with good regioselectivity but poor diastereoselectivity. Related reactions conducted in a continuous-flow microreactor using Selectfluor® **79** generally give higher yields (Scheme 66).[226]

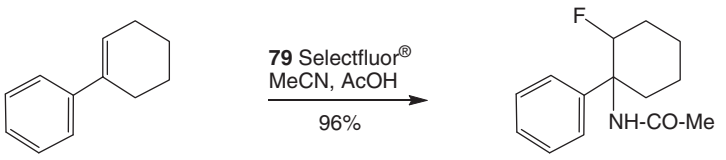
Direct addition of a trifluoromethyl group to triazoles and azoles occurs using hypervalent iodine reagents such as **190**. The *N*-trifluoroimidoyl derivative **191** is produced in high yield in the presence of catalytic amounts of a protic acid such as $HNTf_2$ (equation 134).[227]



190 **191** (134)



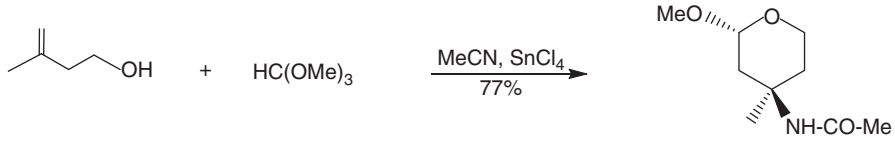
Scheme 65



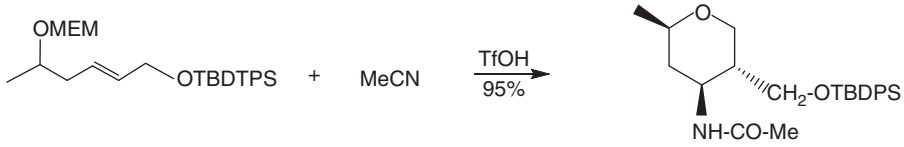
Scheme 66

6.07.5.4 Multicomponent Reactions

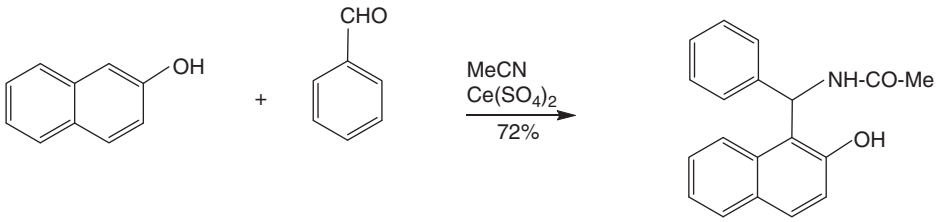
The Prins reaction describes the combination of an alkene and an aldehyde (or its structural equivalent) under acidic conditions. In 1987, Perron and Albizati reported a number of pyranoside preparations using mixtures of homoallylic alcohol, orthoester, and nitrile reagents in the presence of a Lewis acid (equation 135). This process is a one-flask tandem Prins–Ritter reaction.[228] Later, Willis and coworkers reported the intramolecular Prins–Ritter conversion in equation 136. This reaction was notable for both its excellent yield and high diastereoselectivity. Both the *cis*- and *trans*-alkenes yielded the same all-equatorial tetrahydropyran product.[229] Three-component phenol/aldehyde/nitrile one-flask reactions, such as that in equation 137, were also effective synthetic methods.[230] These reports have led to considerable interest in multicomponent tandem transformations that terminate with a Ritter reaction. Much of this work has sought to employ catalytic quantities of the acid.



(135)

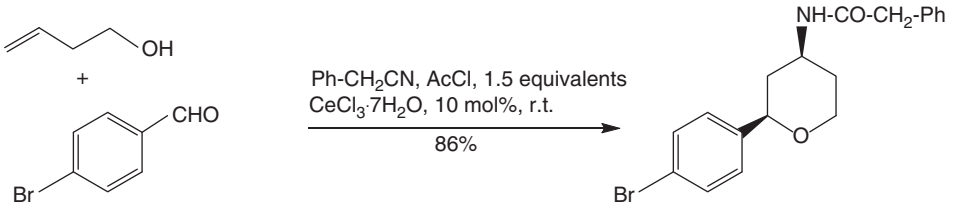


(136)

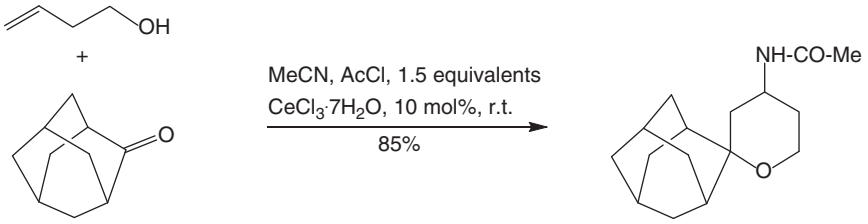


(137)

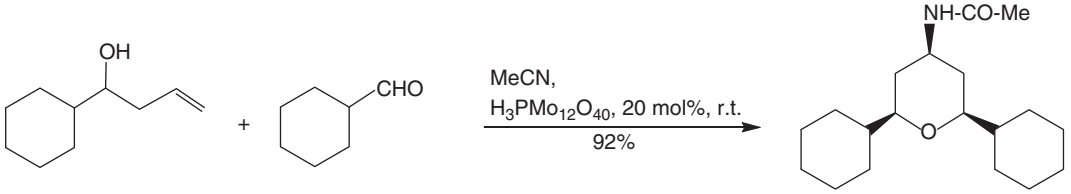
Yadav has carried out extensive studies on the Prins–Ritter formation of 4-amido tetrahydropyran derivatives. Mixtures of homoallylic alcohol, aromatic aldehyde, and nitrile reagents gave excellent yields at r.t. employing catalytic amounts of cerium(III) chloride hydrate and addition of 1.5 equivalents of acetyl chloride (equation 138). These conditions allowed extension of the process to include alicyclic ketone reagents, whereby spirocyclic tetrahydropyrans were generated (equation 139).[231] The use of bismuth(III) triflate (10 mol%) provides an effective alternative method that can also be applied to nonaromatic aldehyde reagents.[232] This is also the case using phosphomolybdic acid as a protic catalyst (equation 140).[233] This synthetic concept has recently been extended into an aza–Prins–Ritter sequence by utilizing an amine reagent and thereby providing a one-flask synthesis of 4-amidopiperidine derivatives (equation 141).[234]



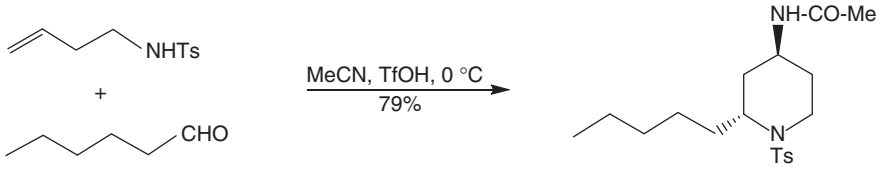
(138)



(139)

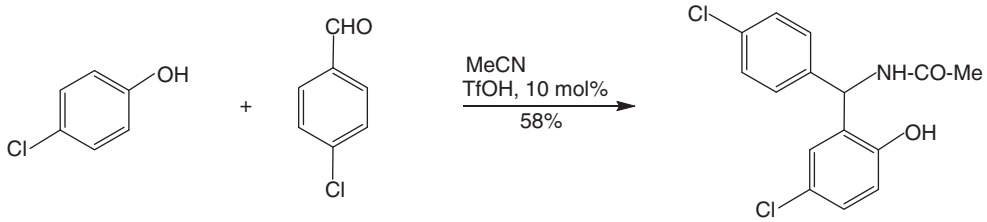


(140)

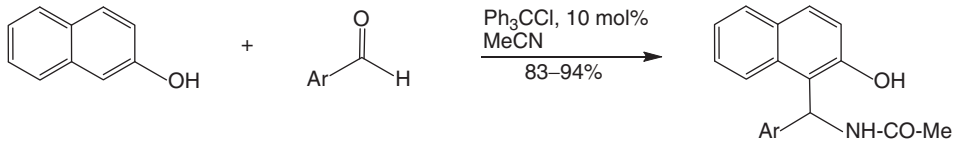


(141)

The tandem Friedel–Crafts–Ritter sequence illustrated in equation 137 is also effective when $FeCl_3$ on silica,[235] triflic acid (10 mol%: equation 142),[236] or $HClO_4$ on silica (6 mol%),[237] are used. Khazaei and Zolfigol have recently introduced a novel version that is catalyzed by trityl chloride (equation 143).[238]

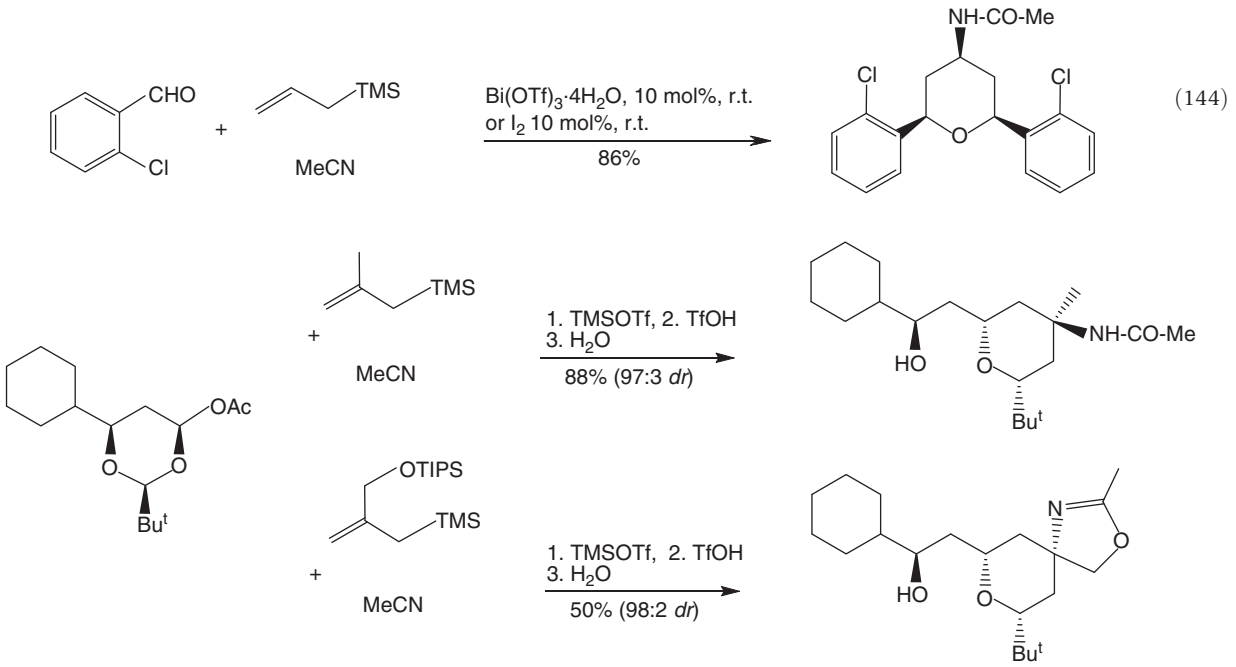


(142)



(143)

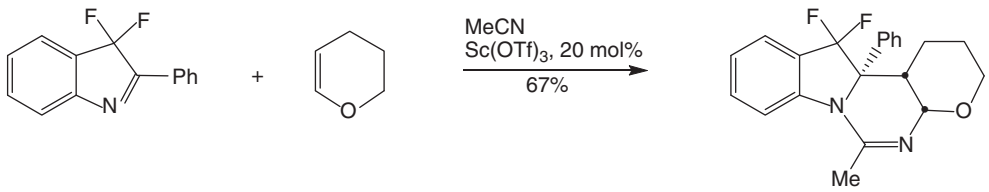
Sakurai reaction occurs when an allylic silane and a carbon electrophile react under Lewis acid conditions. The silane group is expelled with concomitant regiospecific transposition of the alkene functional group. Three-component tandem Sakurai–Prins–Ritter conversions provide an alternative efficient route to 4-amido tetrahydropyrans. For example, the conversion in equation 144 may be carried out using excess $BF_3{\cdot}Et_2O$,[239] or catalytic amounts of either bismuth triflate[240] or molecular iodine.[241] Use of a 1,3-dioxane derivative as an aldehyde equivalent permits the incorporation of significant stereochemistry, thereby leading to excellent product diastereoselectivity (Scheme 67). The method is applicable to a wide range of nitriles, including functionalized examples. Intramolecular trapping of the nitrilium ion intermediate by a proximal protected hydroxy group yields the spiro oxazoline product with strict stereocontrol.[242]



(144)

Scheme 67

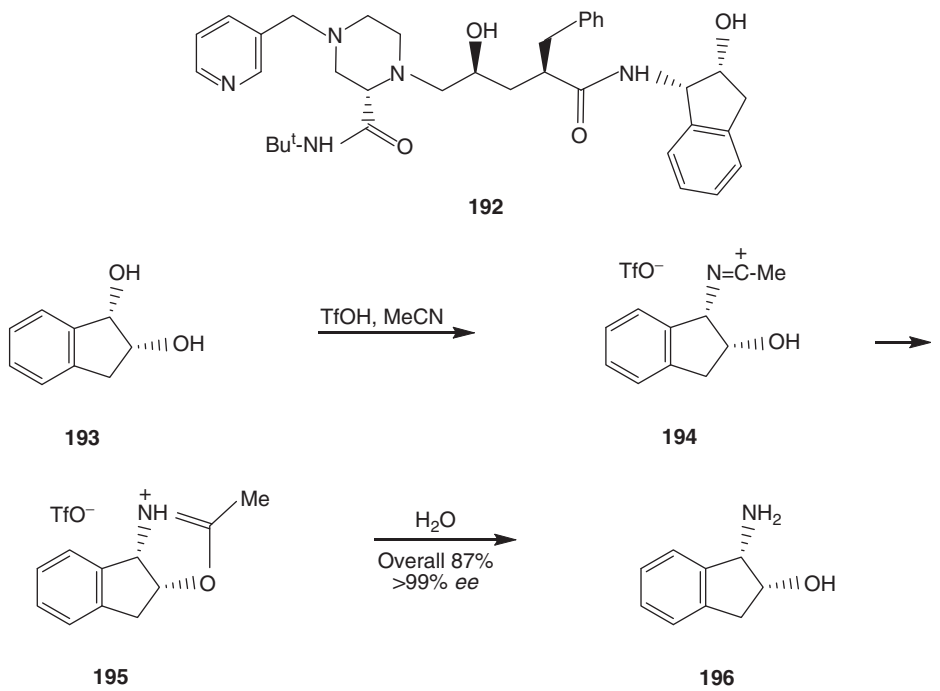
The conversion shown in equation 145 is an example of multicomponent Mannich–Ritter reaction. First, the cyclic imine reacts with dihydropyran under scandium triflate catalysis in a Mannich process. Ritter reaction then produces a nitrilium ion, and this becomes trapped by the aniline nitrogen to yield the final amidine product. This one-flask process is applicable to a wide range of different imine, nitrile, and activated alkene reagents.[243]



(145)

6.07.5.5 *cis*-Stereocontrol

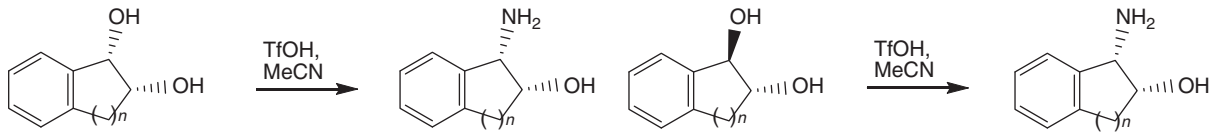
The anti-HIV drug Indinavir **192** (marketed as its H_2SO_4 salt, Crixivan) is prepared commercially in large quantities. A key synthetic intermediate is the *cis*-aminoindanol **196**, one route which utilizes the one-flask intramolecular Ritter sequence **193**–**196** (Scheme 68).[244,245] There are several subtleties involved in this remarkably efficient process. First, the benzylic hydroxy group of **193** is considerably more reactive than the secondary group and so generation of the benzylic carbenium ion determines the



Scheme 68

regioselectivity. Formation of the nitrilium ion is reversible, but only the configuration present in structure **194** can lead to the low-energy *cis*-fused heterocylic ring of the iminium salt **195**. Thus, the previously unreactive secondary hydroxy group actually controls the stereochemistry of this reaction. The enantiopure indane diol **193** is obtained by the microbial reaction.[246] It also reacts with dinitriles to produce bis(oxazoline) tweezer-like ligands.[247]

The yield and *cis*-selectivity hold up well for the benzocyclohexanediol homolog, but fall off somewhat for the benzocycloheptane case (equation 146).[245]

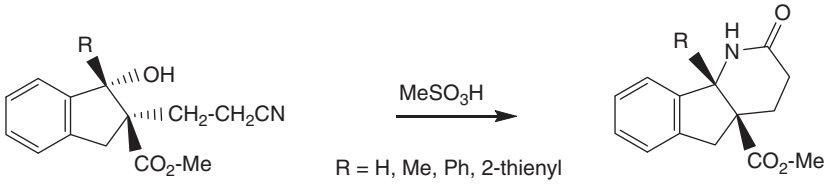


n = 2: 80% yield, 99% *cis*-selectivity
n = 3: 63% yield, 86% *cis*-selectivity

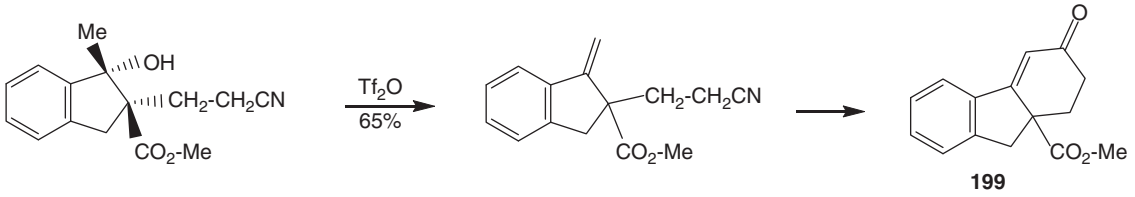
n = 2: 71% yield, 95% *cis*-selectivity
n = 3: 62% yield, 85% *cis*-selectivity

(146)

The intramolecular Ritter cyclizations of **197** are likewise subject to *cis*-stereocontrol, producing compounds **198** that are constrained analogs of NK_1-antagonists (equation 147).[248,249] If stronger reaction conditions are used with **197** (R=Me), then dehydration is followed by cyclization to produce the unsaturated ketone **199** (equation 148).[250]

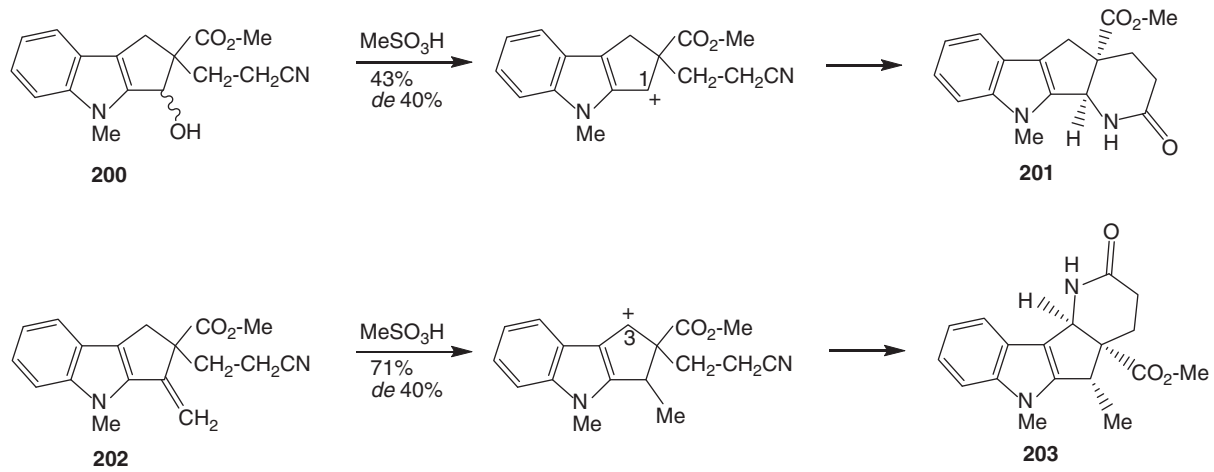


(147)



199 (148)

Related reactions occur when the benzo group of **197** is replaced by an indole functional group. However, these processes are less predictable. Thus, compound **200** reacted through the C1 cation to yield **201**, whereas the cation produced from **202** rearranged to C3 and thence afforded the product **203** (Scheme 69).[251]



Scheme 69

6.07.5.6 Conclusion

It is now more than 65 years since Ritter, Minieri, and Kalish published their two short articles on the amidation reaction.[1,2] Since this modest beginning, Ritter and related reactions have expanded into a wide range of quite different chemical subareas. Catalytic and green processes, efficient stereocontrol for organic synthesis, and the development of multicomponent reactions, are current hot spots. The versatility of the Ritter reaction lies in its complex, but highly efficient, one-flask sequence; and also in its mechanistic interconnections with so many other reaction types. No doubt its future evolution will continue to surprise chemists.

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6.08 Acylation-Type Reactions: Synthesis of Esters via Acyl Transfer

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6.08.1 Introduction

Although esterifications were part of daily life over millennia, Carl Wilhelm Scheele in 1782 apparently was the first chemist reporting the acid-catalyzed esterification of organic acids with alcohols.[1,2] In the nineteenth century chemists such as Meyer,[3,4] Berthelot, and Fischer[5] explored the fundamentals of this type of reaction. Today, esterification reactions are some of the most common chemical transformations in nature, in the chemical laboratory, and even in industry (e.g., synthesis of polyesters). Having an increasing demand for enantiomerically pure substrates (e.g., for use as pharmaceuticals, as flavors, as aroma, or agricultural chemicals), efficient ways of synthesizing enantiopure products in high yields are required. Optically pure substrates can be obtained by utilizing chromatographic methods, crystallization processes or selective transformations such as kinetic resolution of racemic substrates by acyl transfer; additionally, enantiopure molecules can be prepared by desymmetrization of prochiral molecules. Nature uses enzymes for the selective transfer of acyl groups onto a large variety of substrates. The isolation of specific enzymes led to their application as catalysts for enantioselective acyl transfer reactions.

This chapter introduces catalysts that are highly effective in the selective acylation of alcohols. Esterification reactions are widely used in this field because acylation agents such as anhydrides are commercially available and because acyl transfer proceeds under mild reaction conditions utilizing a large variety of catalysts (enzymes, small molecules, metal complexes).

Classic Brønsted acid catalysis is one of the oldest and most popular methods for the esterification of alcohols and therefore will not be discussed in this chapter. This chapter focuses on new and, in particular, on asymmetric, nonenzymatic approaches for acyl transfer onto alcohols.

Depending on the starting material, two principally different acyl transfer processes can occur. The first is to start from a racemic substrate whereby one enantiomer is much more rapidly acylated by a chiral catalyst than the other. Under optimal conditions 50% of enantiopure ester and 50% of enantiopure starting alcohol can be isolated at 50% conversion (kinetic resolution, KR).[6,7] One obvious drawback of this approach is the limitation of the product yield to 50%. The efficiency of a KR can be expressed utilizing Kagan's equation.[8] This method is applicable for reaction following first-order kinetics in the absence of nonlinear effects. The selectivity (*S*-value) can be determined using the following approximations:

$$C = \frac{ee}{(ee + ee')}\,100$$

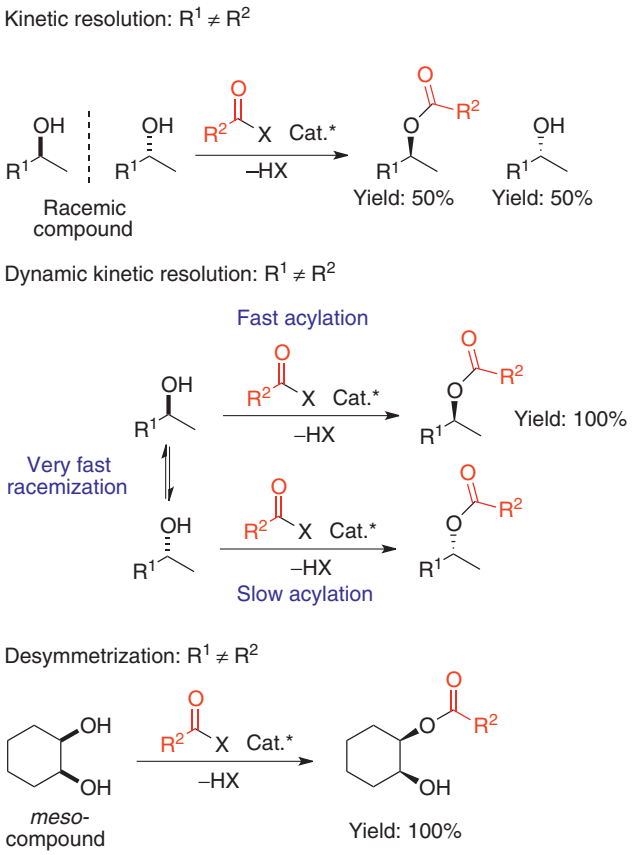
$S = k_{fast}/k_{slow}$, ee = enantiomeric excess predicted for the starting material, ee' = enantiomeric excess predicted for the product, C = conversion.

$$S = \frac{\ln[1-C(1+ee')]}{\ln[1-C(1-ee')]}$$

$$S = \frac{\ln[(1-C)(1-ee)]}{\ln[(1-C)(1+ee)]}$$

S-values >20 guarantee high enantiomeric excesses for the product as well as the starting material and a conversion close to 50%. *S*-values <10 are usually not practically useful in organic syntheses because of incomplete enantiomer separation.

A more efficient way to separate enantiomers is the dynamic version of KR (DKR) as the desired product can then theoretically be isolated in quantitative yield and high *ee*s. DKR is possible when the starting material racemizes, whereas the acylated enantiopure product is configurationally stable (**Scheme 1**). There are many examples for DKR (e.g., Jacobsen's hydrolytic DKR of epoxides[9] and Bäckvall's DKR via acyl transfer onto alcohols[10]) that have been developed in the past 20 years.[11–14]



Scheme 1

The desymmetrization of prochiral substrates or *meso*-compounds has become a powerful method in asymmetric synthesis because in this theory 100% yield can be obtained (**Scheme 1**).[15]

6.08.1.1 Synthesis of Esters via Acyl Transfer onto Alcohols

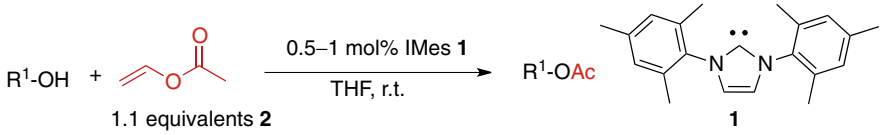
6.08.1.1.1 Organocatalytic synthesis of esters

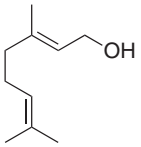
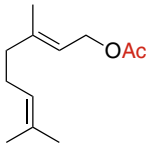
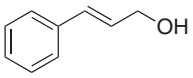
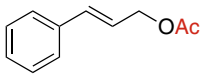
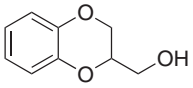
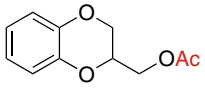
6.08.1.1.1.1 N-Heterocyclic carbenes as catalysts for acyl transfer onto alcohols

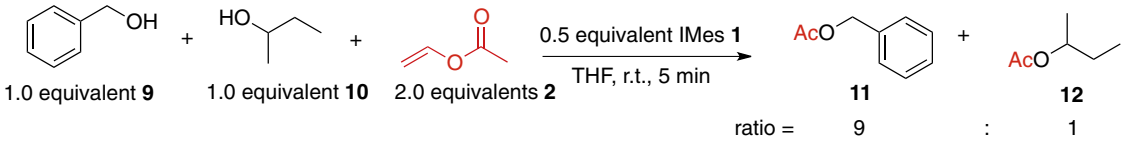
The nonstereoselective synthesis of esters traditionally proceeds via Lewis/Brønsted base or Lewis/Brønsted acid catalysis.[16] A problem of these approaches is the potential cleavage of acid sensitive functional groups such as commonly employed epoxides and acetals. Furthermore, Lewis acid (e.g., $Sc(OTf)_3$, TMSCl, $La(O^iPr)_3$) as well as base catalysts (e.g., phosphines) show low selectivity between primary and secondary alcohols. In 2003 Nolan[17] as well as Hedrick[18] reported almost simultaneously their transesterification approaches utilizing *N*-heterocyclic carbene (NHC) as catalysts. Nolan and coworkers introduced a catalytic method for synthesizing various esters by using NHC's or their precursor salts and base as catalysts. First they applied their NHC

catalyst in the esterification of primary alcohols with vinyl acetate as the acyl source. Almost quantitative yields were obtained even with unsaturated alcohols or alcohols bearing acid sensitive groups (Table 1).[17] In the presence of primary and secondary alcohols in the reaction mixture, acylation of the primary alcohol is clearly favored (equation 1).

Table 1 Acylation of primary alcohols with IMes **1** as catalyst



Entry	Alcohol	Product (Ester)	Time (min)	Yield (%)
1		**3**  **4**	60	99
2		**5**  **6**	15	96
3		**7**  **8**	15	100



(1)

Under slightly modified conditions the transesterification of methyl esters with alcohols is possible (Table 2). Secondary alcohols can be acylated, but the reaction requires higher catalyst loadings (3.5 mol%) because of their lower reactivity. NHCs are air and moisture sensitive and therefore Nolan and coworkers tested the *in situ* generation of the free carbene from a precursor salt by adding base to the reaction mixture. The obtained yields were excellent (up to 100%) even at short reaction times (30 min). The precursor salts for the *in situ* generation of the carbene are commercially available.

An advantage of the NHC-catalyzed esterification reactions is that these catalysts display broad functional group tolerance. Esterification of substrates bearing amine, olefin, nitro, ether, or thioether functions are feasible. The esterification reactions mediated by NHCs require short reaction times, and excellent yields can be obtained.

6.08.1.1.1.2 Asymmetric acyl transfer

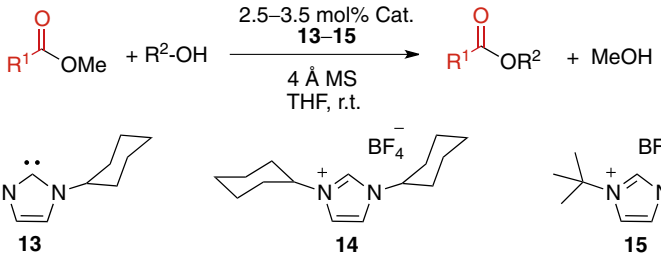
As mentioned in Section 6.08.1, acyl transfer is the most common group transfer reaction in organic synthesis. Traditionally, the generation of enantiopure products from racemic alcohols utilizing enzymes was accomplished via selective acyl transfer (esterification) or selective hydrolysis of esters (ester hydrolysis) (Scheme 2).

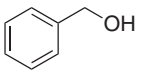
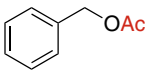
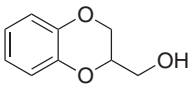
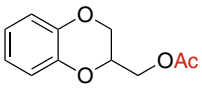
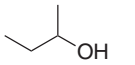
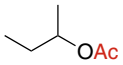
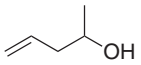
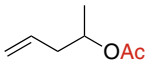
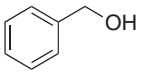
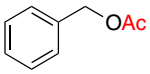
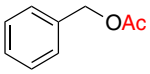
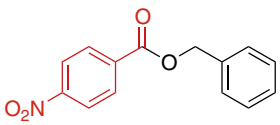
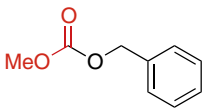
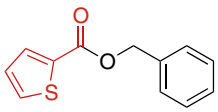
Although enzymes were successfully applied in the enantioselective esterification of various substrate classes and although they give high *S*-values, they do not present the optimal catalysts form a chemist's point of view. One drawback is the accessibility of one enantiomeric form of the enzyme and only one enantiomer of the substrate can be selectively acylated. Furthermore, enzymes cannot be modified easily. Small chiral organic molecules however can readily be synthesized in both enantiomeric forms, and therefore are capable of resolving both enantiomers in a given reaction. Such organocatalysts are structurally more variable and can be further optimized to improve their selectivity. The first part of the present chapter introduces various types of small organic molecules utilized for stereoselective acyl transfer. The availability of the catalysts, the reaction conditions, the substrate scope, and the selectivities will be discussed and compared to other approaches. Some selected steps in natural product syntheses are presented to demonstrate the practicality of these methods.

6.08.1.1.1.2.1 Enantioselective acyl transfer using DMAP-derivatives

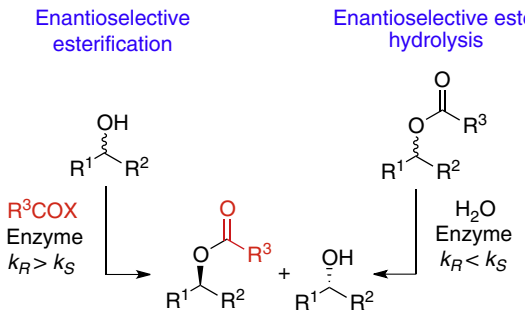
The first achiral acyl transfer onto alcohols utilizing 4-dimethylaminopyridine (DMAP) as catalyst and acetic anhydride as acyl source was reported in the late 1960s by Steglich and Höfle.[19] Independently, Litvinenko and Kirichenko found a rate acceleration for the benzoylation of *m*-choloroaniline by adding DMAP instead of pyridine as catalyst.[20] It took nearly 30 years until the first

Table 2 Transesterification of methyl esters with primary and secondary alcohols mediated by *N*-heterocyclic carbene (NHC) catalysts **13–15**[a]



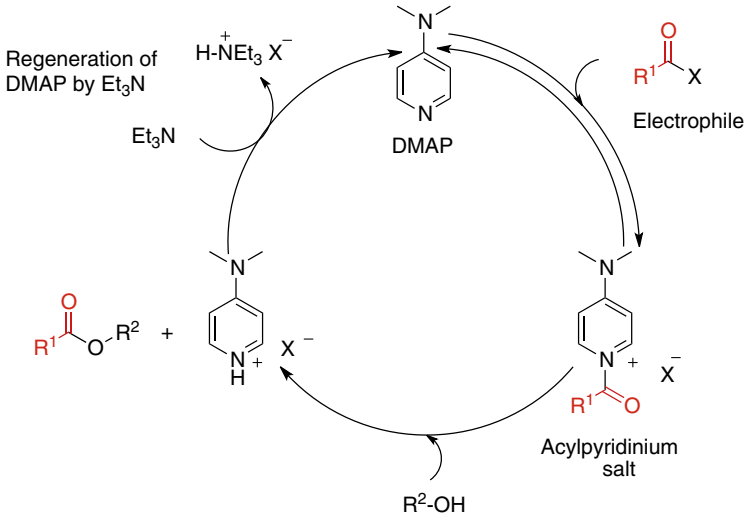
Entry	*Alcohol*		*Product (Ester)*		*Catalyst (mol%)*	*Time (min)*	*Yield (%)*
1		**9**		**11**	**13** (2.5)	60	95
2		**7**		**8**	**13** (2.5)	30	90
3		**10**		**12**	**13** (3.5)	60	92
4		**16**		**17**	**13** (3.5)	60	96
5[d]		**9**		**11**	**14** (3.0)	30	93
6[d]		**9**		**11**	**15** (3.0)	30	100
7[b]		**9**		**18**	**13** (2.5)	15	96
8[c]		**9**		**19**	**13** (2.5)	30	93
9[b]		**9**		**20**	**13** (2.5)	15	96

[a]Reaction conditions: 1 mmol alcohol, 1 ml of methyl acetate, 0.5 g 4 Å MS, r.t.
[b]1.5 mmol alcohol, 1 mmol methyl ester, 1 ml THF, 0.5 g 4 Å MS.
[c]1 mmol alcohol, 1 mmol dimethyl carbonate, 1 ml THF.
[d]1 mmol benzyl alcohol, 1 ml methyl acetate, 3 mol% imidazolium salt, 2.5 mol% KO*t*Bu, 0.5 g 4 Å MS, r.t., 30 min.



Scheme 2

asymmetric approach was introduced by Vedejs et al. in 1996.[21] Experimental[22–24] and theoretical[25,26] studies support a nucleophilic mechanism for the DMAP-catalyzed acylation of alcohols. In the first step the nucleophilic nitrogen of the pyridine ring attacks the electrophile (e.g., anhydride or acid halide) and forms an acylpyridinium salt. The reactive intermediate transfers the acyl group onto the alcohol (Scheme 3). Additional base is needed to neutralize the acid that is produced during the acylation process. In some rare examples, additional base is not required, because of the weakness of the generated acid (e.g., acetic acid).[27] Yet, the role of the base is not fully understood, because even in the latter case a rate acceleration is often observed, maybe because of assisting by the proton abstraction from the alcohol.[28] Additionally, the rate of the acylation is highly affected by the character of the anion and the solvent.[29,30]



Scheme 3

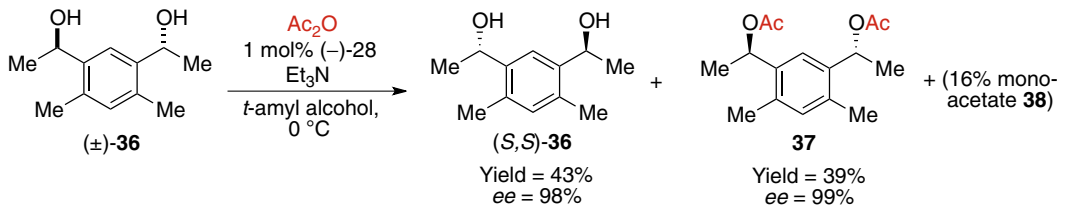
The first enantioselective approach of Vedejs et al. required 1 equivalent of catalyst and two equivalents of a Lewis acid in the presence of base. The KR of aryl alkyl alcohols could be achieved with $S \leq 45$.

In 1996 Fu introduced the new planar chiral ferrocenyl-DMAP derivative **28** as a catalyst for the KR of aryl alkyl carbinols. In addition to **28** the same group also synthesized an analogous 4-pyrrolidino pyridine (PPY)-based catalyst **29**.[31] Both **28** and **29** are commercially available or can be synthesized in eight steps from readily available starting materials (Scheme 4).[32] These planar-chiral DMAP derivatives are discussed in connection with organocatalytic acyl transfer catalysts, because the nitrogen atom of the DMAP moiety is key. The iron ion of the complex only functions as structure-forming element and supposedly does not influence the activity of the catalyst.

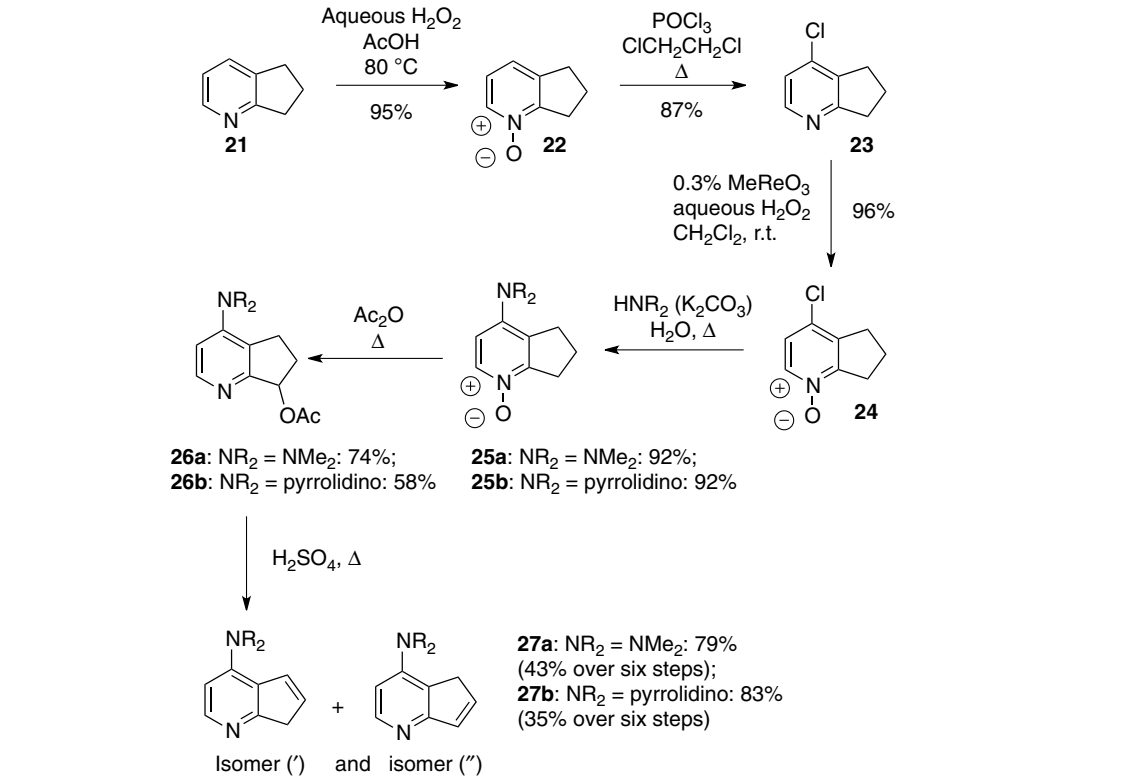
Catalyst (–)-**28** was successfully applied in the KR of aryl alkyl carbinols (Table 3).[33–35] The *ee*s and *S*-values (32–95) are excellent even at low catalyst loadings of 1 mol% in *tert*-amyl alcohol as solvent. In contrast, in Et_2O the selectivities ranged from 12 to 52 even at a catalyst loading of 2 mol% at room temperature. The *ee*s provided by catalyst **28** strongly depend on the solvent. The selectivity increased as the steric demand of the alkyl moiety increases. A big advantage of this method is the possible recovery of catalyst (–)-**28**, the low sensitivity of the catalyst toward moisture and oxygen and the absence of chemical byproducts. The *S*-values obtained by catalyst **29** were lower and will not be discussed further.

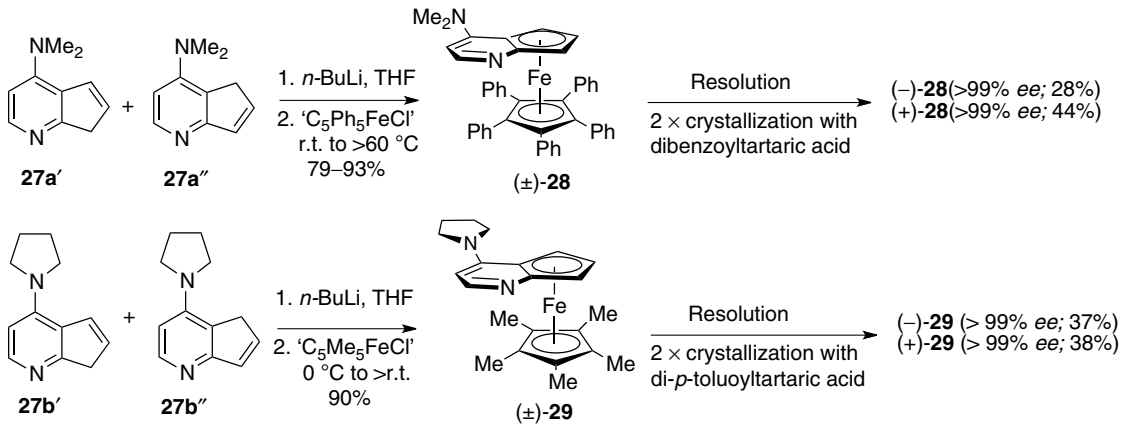
Fu also applied catalyst (–)-**28** in the KR of racemic 1,5-diols as well as in the desymmetrization of *meso*-1,5-diols. In both cases high selectivities could be achieved utilizing the same reaction conditions as for aryl alky alcohols (equations 2 and 3).[33–35]

Kinetic resolution of racemic 1,5-diol **36**



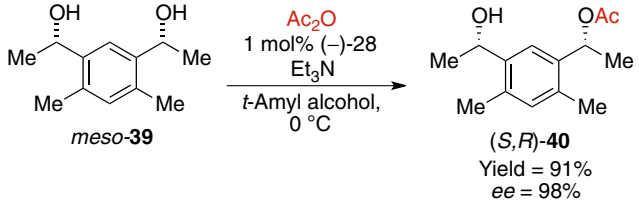
(2)





Scheme 4

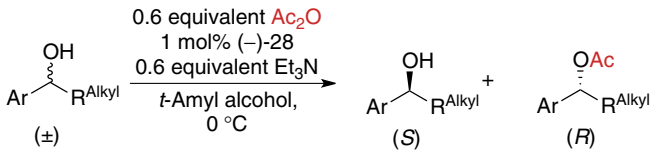
Desymmetrization of *meso*-1,5-diol **39**

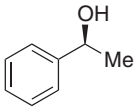
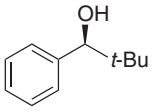
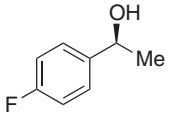
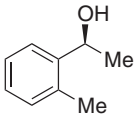
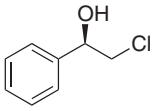
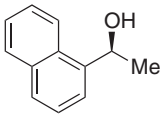


(3)

In addition to Birman's amidine catalyst **130** ($S \leq 32$, Scheme 9 and Table 17), only catalyst (–)-**28** is capable of resolving propargylic alcohols.[36,37] The selectivities are in a range between 3.8 and 20 and therefore synthetically useful. In contrast to aryl alkyl alcohols no additional base was employed, because the acylation of propargylic alcohols occurred under basic conditions in

Table 3 Efficiency of catalyst (–)-**28** in the kinetic resolution (KR) of aryl alkyl carbinols[35]

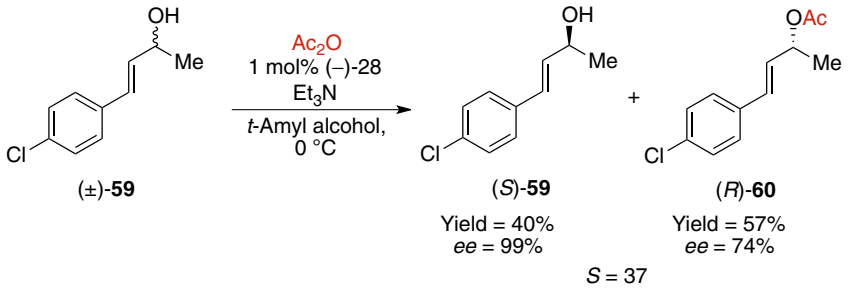


Entry	*Unreacted alcohol*		*Conversion (%)*	ee *(%) of unreacted alcohol*	S-*value*
1		**30**	55	99	43
2		**31**	51	96	95
3		**32**	54	99	68
4		**33**	53	99	71
5		**34**	56	98	32
6		**35**	52	95	65

the absence of catalyst. The selectivity for the KR decreases as the steric demand for the alkyl group of the substrate increases (Table 4).[33,34,36]

Catalyst (+)-**28** was successfully applied the KR of allylic alcohols. A large variety of substrates can be resolved with good to excellent enantioselectivities (Table 5).[33,34,38]

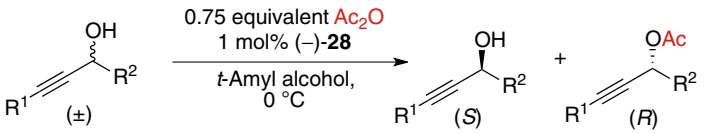
To illustrate the utility of this selective acyl transfer onto allylic alcohols, Fu applied catalyst (–)-**28** to the KR of allylic alcohols, which serve as key intermediates in natural product syntheses. The KR of a racemic allylic alcohol **59** was achieved with good selectivities ((–)-**59**: *ee* = 99.4%; (+)-**60**: *ee* = 74%) and high yields ((–)-**59**: Yield = 40%; (+)-**60**: Yield = 57%). Allylic alcohol (*S*)-(–)-**59** served as a key intermediate in Brenna's total synthesis of (–)-baclofen (equation 4).[34,38,39]

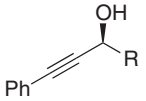
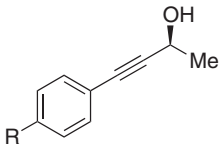
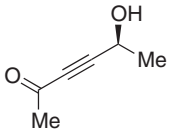
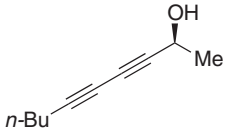
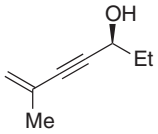


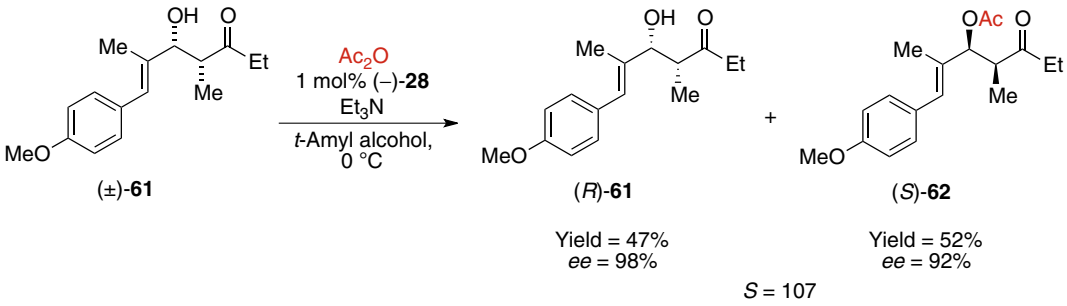
(4)

A second example is the KR of **61** mediated by (–)-**28**. The selectivity realized with Fu's catalyst is higher than that of an aldolase antibody (*ee* = 96%; *S* = 17) utilized by Sinha and Lerner in their total synthesis of epothilone (equation 5).[34,40] Examples of a small molecule catalyst being superior to an enzymatic approach are rare.

Table 4 KR of propargylic alcohols by catalyst (–)-**28**



Entry	Unreacted alcohol	R		Conversion (%)	ee (%) of unreacted alcohol	S-value
1		Me	**41**	58	96	20
2		Et	**42**	58	94	18
3		^{i}Pr	**43**	63	93	11
4		^{t}Bu	**44**	86	95	3.8
5		OMe	**45**	60	94	14
6		CF_3	**46**	71	99	10
7		F	**47**	65	97	13
8		–	**48**	64	95	12
9		–	**49**	66	95	10
10		–	**50**	69	94	7.9



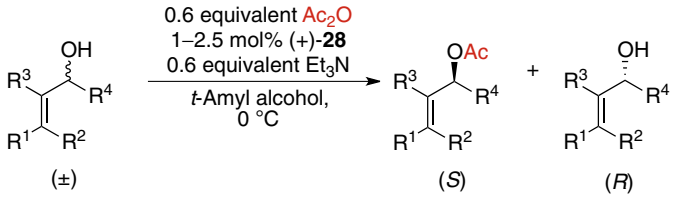
(5)

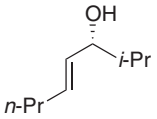
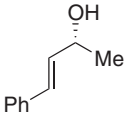
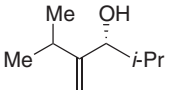
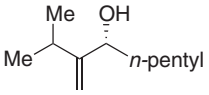
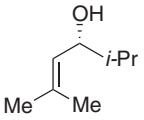
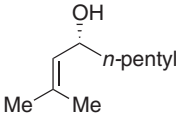
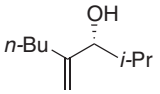
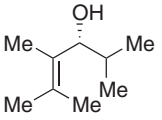
In addition to Fu's planar-chiral DMAP derivative various chiral DMAP and PPY catalysts have been developed by other research groups and have been applied in KRs of various substrates. In 1999, Spivey et al. employed a chiral DMAP derivative in the KR of a variety of substrates.[33,41,42] Catalyst **63** can be synthesized in seven steps from commercially available 4-pyridone. The selectivities for the KR of secondary alcohols are moderate to good but cannot compete with the selectivities achieved by Fu's catalyst (Table 6).

Spivey et al. tested a range of substrates (e.g., monosubstituted cyclic diols, a cyclic *meso*-diol, and 2-bromo- and 2-phenylcyclohexanol) under optimized conditions. The best selectivities were observed for monobenzoylated cyclic 1,2-diols (Table 7).[43]

In 1996 Fuji and Kawabata introduced a 4-PPY-derived chiral catalyst **73**.[33,34,44] On the basis of NMR studies, Fuji and coworkers proposed an 'induced fit' mechanism for the acylation of secondary alcohols. They examined **73** and the acylium ion adduct **74** in $CDCl_3$ by ^{1}H-NMR (arrows in Scheme 5 denote the observed NOEs). Catalyst **73** seems to adopt an 'open conformation' in which the naphthalene ring and the pyridine ring are separated from each other. In contrast, the naphthalene ring and pyridine ring of **74** are interacting (π–π-stacking) and the catalyst adopts a 'closed conformation' (Scheme 5).

Table 5 Efficiency of (+)-**28** in the KR of allylic alcohols



Entry	*Unreacted alcohol*		*Conversion (%)*	ee *(%) of alcohol*	S-*value*
1		**51**	75	92	5.4
2		**52**	54	99	64
3		**53**	63	92	10
4		**54**	77	90	4.7
5		**55**	60	97	18
6		**56**	66	97	12
7		**57**	55	94	25
8		**58**	59	99	29

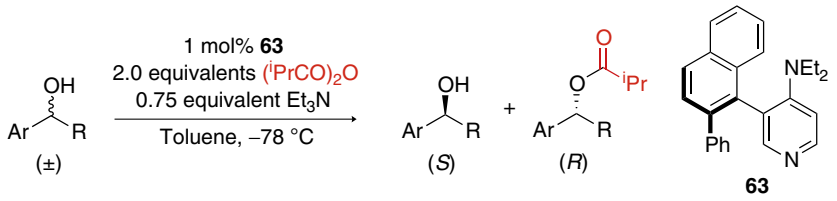
Fuji applied catalyst **73** in the KR of cyclic monobenzoylated 1,2-diols[44] and monobenzoylated 2-aminoalcohols (Table 8).[45] In general, the selectivities for the mono-benzoylated 2-amino alcohols are higher (10–17) than those obtained for the mono-benzoylated 1,2-diols (5.8–10.1). The *S*-value for entry 6 can be increased to 54 by running the reaction at −40 °C.

In the late 1990s, Yamada and Katsumata reported a new acylating catalyst **83**, which undergoes a conformational switch during the acylating step of the catalyst.[33,34,46] They proposed a reaction model that could be confirmed by ^{1}H-NMR measurements, X-ray analysis, and DFT computations.[47] It has been suggested that the selectivities in the KRs of secondary alcohols are because of self-complexation of the acylated catalyst. After the acyl transfer onto the substrate the catalyst adopts its 'open conformation' again (Scheme 6).

Catalyst **83** can readily be prepared from 4-aminonicotinic acid and an auxiliary. Yamada utilized **83** in the KR of secondary alcohols with selectivities ranging from 2.2 to 9.6 (Table 9). High *S*-values were achieved for aryl alkyl alcohols, whereas secondary aryl–alkyl alcohols were resolved with much lower selectivities.[48,49]

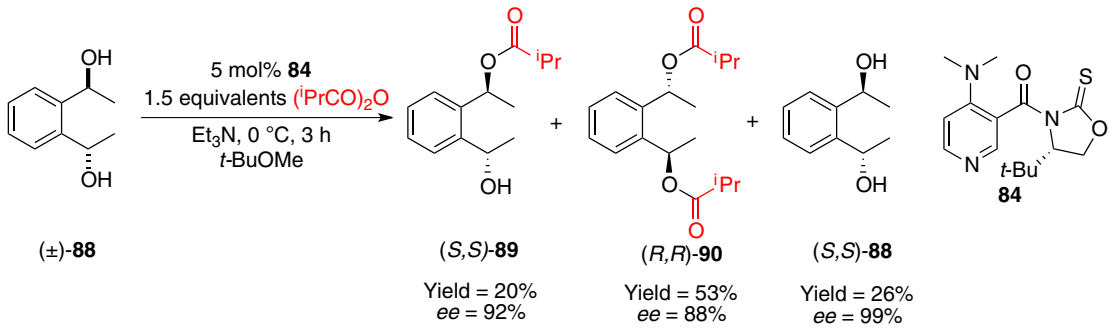
Diols are important building block in organic synthesis and therefore methods for their enantioselective preparation are highly desirable. Catalyst **84** was successfully applied in the KR of racemic 1,4-diol (**88**). Although substrates such as aryl alkyl alcohols and cyclic *meso* as well as cyclic racemic 1,2- and 1,3-diols are often used as test substrates for desymmetrizations and KRs mediated by various catalysts and successfully resolved, catalysts for KRs of racemic 1,4-diols are rare (equation 6).

Table 6 KR of aryl alkyl alcohols mediated by catalyst **63**



Entry	*Ar*	*R*		*Conversion (%)*	ee *(%) of alcohol*	ee *(%) of ester*	S*-value*
1	1-Nap	Me	**35**	17	19	89	21
2[a]	1-Nap	Me	**35**	22	26	91	29
3	Ph	Me	**30**	39	50	78	13
4	2-Tol	Me	**33**	41	61	86	25
5	Ph	*t*-Bu	**31**	18	19	89	20

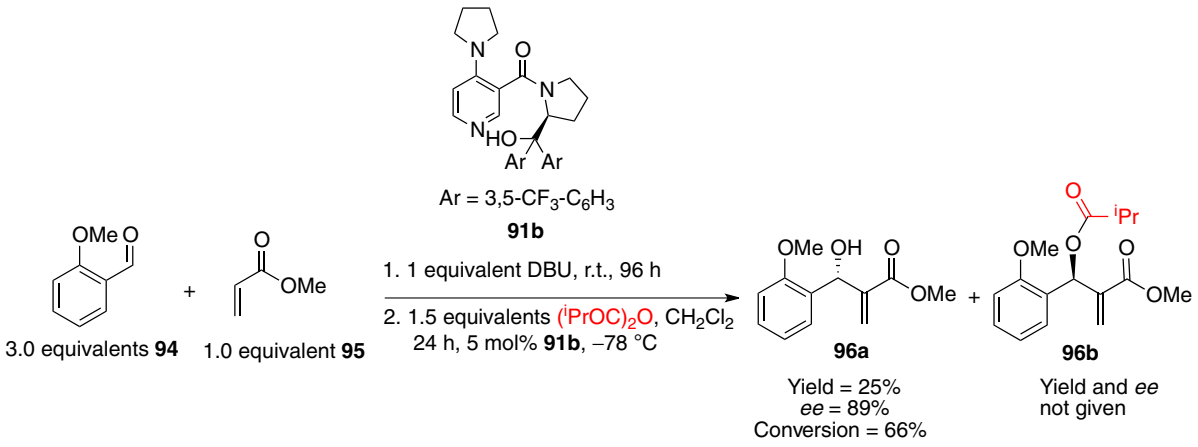
[a]Reaction conditions: 1.0 equivalent $(^{i}PrCO)_2O$.



(6)

In 2005 Connon and coworkers reported a PPY-derived catalyst **91** that can be easily synthesized in three steps from 3-carboxy-4-chloropyridine without the need for a resolution step.[33,50] The catalyst design was inspired by the 'induced fit' concept of Fuji's catalyst **73** and Connon and coworkers tested catalyst **91** in the KR of various secondary alcohols (Table 10).[51] The selectivities were moderate to good and ranged from 2.3 to 30.0. Good selectivities were achieved for aryl alkyl alcohols and 2-phenylcyclohexanol, whereas *N*-substituted amino alcohols were poorly resolved. The conversions were low for all examples in Table 10 except of entry 6 because the reactions were stopped after 6 h.

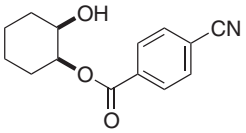
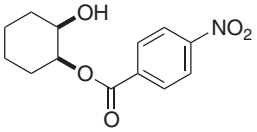
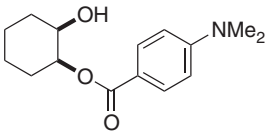
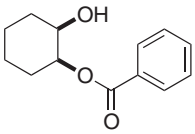
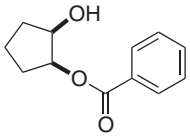
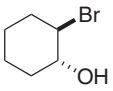
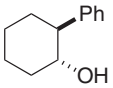
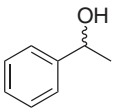
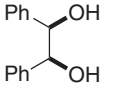
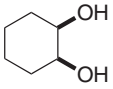
In 2007 Connon and coworkers also applied the slightly modified catalyst **91b** in a one-pot-Baylis–Hillman reaction following an acylative KR.[52] In this process DBU acts as the catalyst for the Baylis–Hillman reaction but does not promote acyl transfer. The enantioselective acylation is mediated by catalyst **91b** (equation 7).



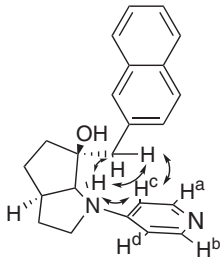
(7)

In 2003 Campbell and coworkers reported readily accessible PPY-derived catalyst **97**.[53] The first step of the synthesis is the nucleophilic substitution of 4-chloropyridine with α-methylproline. The carboxylic acid group of the proline can be functionalized

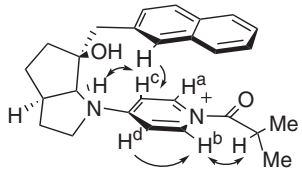
Table 7 Efficiency of catalyst **63** in the KR of various secondary alcohols[43]

Entry	*Substrate*		*Conversion (%)*	ee *(%) of alcohol*	ee *(%) of ester*	S-*value*	*Product/enantiomer*
1		**64**	11	8	67	6	(–)/1*R*,2*S*
2		**65**	96	85	39	6	(–)/1*R*,2*S*
3		**66**	18	18	86	16	(–)/1*R*,2*S*
4		**67**	64	98	65	20	(–)/1*R*,2*S*
5		**68**	51	75	73	14	(–)/1*R*,2*S*
6		**69**	54	61	53	6	(–)/1*R*,2*S*
7		**70**	16	14	78	9	(–)/1*R*,2*S*
8		**30**	34	37	71	8	(+)/*R*
9		**71**	26	–	45	–	(+)/1*S*,2*R*
10		**72**	20	–	78	–	(–)/1*R*,2*S*

Reaction conditions: 2.0 mmol $(^{i}PrCO)_2O$; 0.75 Et_3N; 1 mol% (–)-**63**; –78 °C, 9 h.



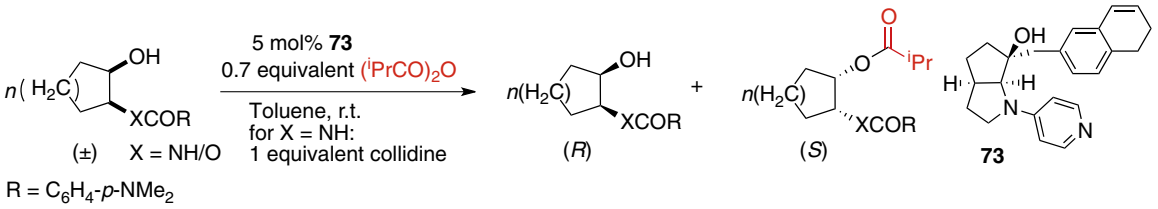
73 (Open conformation)

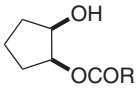
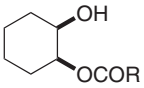
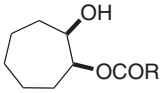
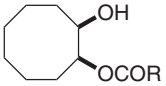
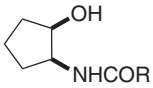
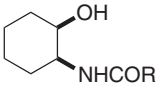
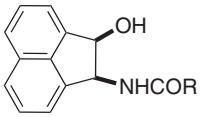
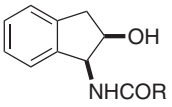
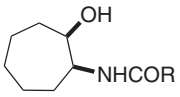


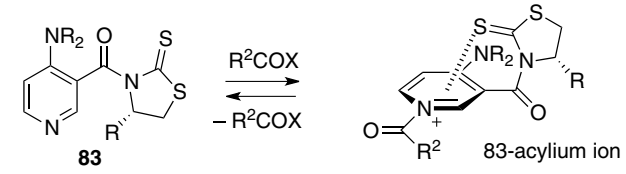
74 (Closed conformation)

Scheme 5

Table 8 KR of monobenzoylated 1,2-diols and monobenzoylated 2-aminoalcohols mediated by catalyst **73**



Entry	Substrate		Time (h)	Conversion (%)	ee (%) of alcohol	ee (%) of ester	S-value
1		**75**	4	71	97	–	8.3
2		**66**	3	72	99	–	10
3		**76**	4	70	92	–	7
4		**77**	5	73	92	–	6
5		**78**	9	69	99	44	>12
6		**79**	9	58	93	68	17
7		**80**	24	68	99	46	>13
8		**81**	3	64	99	56	17
9		**82**	9	69	97	46	10

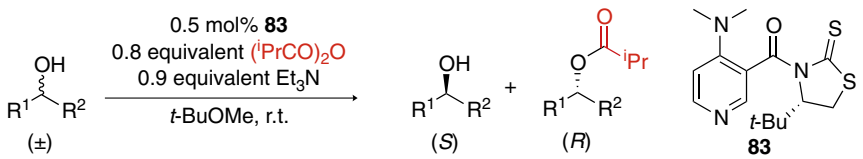


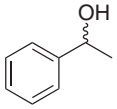
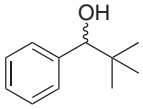
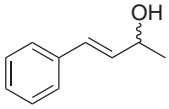
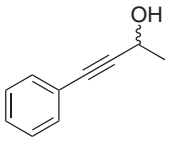
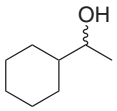
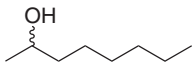
Scheme 6

by various amines by standard peptide coupling agents (e.g., HATU). Catalyst **97** was utilized for KRs of secondary alcohols. The selectivities are poor for aryl alkyl alcohols and 2-phenyl cyclohexanol but are good for *N*-substituted amino alcohols (Table 11).

In conclusion, all chiral DMAP- or PPY-derived catalysts are capable of selective acyl transfer. The best results for the KR of aryl alkyl alcohols were obtained by Fu's catalyst **28** with *S*-values in the range of 32–95. The other catalysts resolve aryl alkyl alcohols with selectivities of 13–29 (Spivey **63**), 9.6 (Yamada **83**), 13.5 (Connon **91**), and 1.4 (Campbell **97**). KRs of allylic alcohols,

Table 9 KR of secondary alcohols with catalyst **83**



Entry	Substrate		Conversion (%)	ee (%) of unreacted alcohol	S-value
1		**30**	65	89	7.6
2		**31**	62	88[a]	9.6
3		**85**	65	94[b]	9.8
4		**41**	61	78[b]	6.6
5		**86**	52	31	2.3
6		**87**	48	25	2.2

[a]Reaction time 72 h.
[b]Temperature −30 °C, 48 h.

propargylic alcohols, racemic 1,5-diols, and the desymmetrization of *meso*-1,5-diols were achieved with catalyst **28** with good to excellent selectivities.

Spivey's catalyst **63** catalyzes KRs of monobenzoylated 1,2-diols with high selectivities under mild conditions. The same substrates can be resolved by Connon's catalyst **91** with excellent selectivities. Catalyst **91** was the first catalyst utilized in a 'one-pot' Baylis–Hillman reaction followed by a KR. The selective acyl transfer onto 2-phenyl cyclohexanol mediated by **91** produced high enantiomeric excesses. Good selectivities for the KR of *N*-functionalized 1,2-aminoalcohols were reported for catalysts **73** (Fuji) and catalyst **97** (Campbell). Yamada's catalyst **83** is, to the best of our knowledge, the only chiral DMAP or PPY-derived catalyst capable of transferring an acyl moiety selectively onto racemic cyclic 1,4-diols.

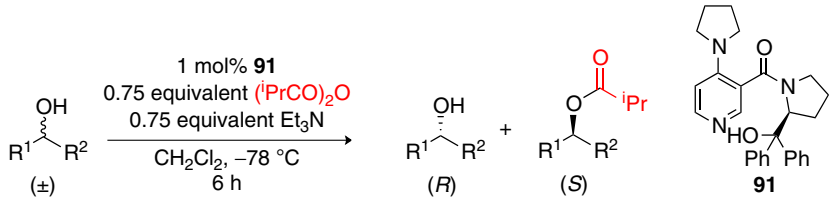
6.08.1.1.1.2.2 Phosphines and phosphinites-mediated enantioselective acyl transfer

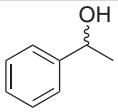
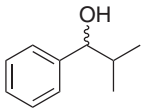
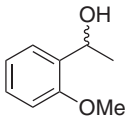
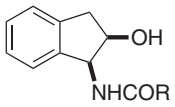
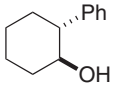
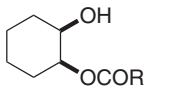
Vedejs and Diver reported in 1993 the first acylation reaction mediated by tributylphosphines.[54] They compared the catalytic efficiency of DMAP and tributylphosphine in the acylation reaction of alcohols and both catalyst product similar results. The first chiral phosphines were published in 1996 but the selectivities were only moderate.[21] In 1999 Vedejs introduced catalysts **100a-c**, which were successfully employed in the KR of racemic secondary alcohols (Table 12).[33,34,55]

Many other phosphine catalysts were employed in the KR of racemic secondary alcohols, but to date **100a** is the most efficient catalyst for enantioselective acyl transfer in the field of phosphine catalysts. In addition to catalysts **105a–c**, **100a–c** were also capable of transferring acyl moieties onto *meso*-**71**. Phosphine **100b** showed the highest enantiomeric excesses and conversions. The ratio of **106** to *meso*-**107** is 2.6:1, whereas catalyst **105c** gave 87% *ee* and a ratio of 20:1 at 20% conversion (Table 13). The high catalyst loading of 35–41 mol% required, and the low activity of phosphines **105a–c** makes catalyst **100b** preparatively more feasible.[56]

In 2003 Fujimoto and his group used a different approach to design a catalyst with a trivalent phosphorus center.[57] They modified a cinchona alkaloid and synthesized an efficient bifunctional acylation catalyst, which combines a tertiary amino group with a trivalent phosphorus center. The postulated reaction mechanism involves the activation of acyl chloride by the phosphinite

Table 10 Efficiency of catalyst **91** in the KR of various secondary alcohols



Entry	*Substrate*		*Conversion (%)*	ee *(%) of unreacted alcohol*	S-*value*
1		**30**	28	25	6
2		**92**	19	19	14
3		**93**	18	18	11
4	 R = *p*-Me_2N-C_6H_4	**81**	23	11	2
5		**70**	19	22	30
6[a]	 R = *p*-Me_2N-C_6H_4	**66**	77	>99	20

[a]The reaction was stopped after 24 h. The phenyl groups of catalyst **91** were replaced by 3,5-CF_3-C_6H_3 groups.

moiety, whereas the nitrogen atom of the quinuclidine abstracts a proton of the OH-group. Catalyst **108** was successfully applied in the desymmetrization of *meso*-1,2-, *meso*-1,3- and *meso*-1,4-diols (Table 14).[33,57,58]

The yields and enantiomeric excesses for all examples were very good. Catalyst **108** can be synthesized readily from cinchonidine in one step. The broad substrate scope for the desymmetrization of diols by **108** and fast access to the catalyst makes **108** preparatively very useful. A drawback might be the high susceptibility of the phosphinite moiety to oxidation and therefore the catalyst needs to be freshly prepared. To solve this problem, Fujimoto et al. published an aminophosphinite catalyst in early 2012. Catalyst **117** can be synthesized in two steps with high yield from commercially available aminoindanols (Scheme 7).[59]

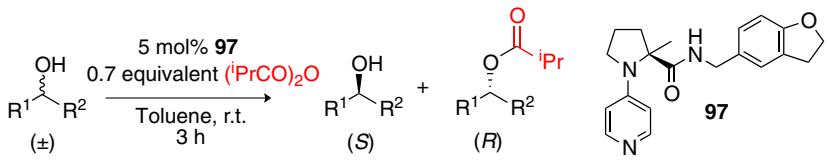
This catalyst can be isolated and stored under argon in a refrigerator for several months. The selectivities for the desymmetrization of *meso*-1,2-diols (Table 14, entry 1, 2, 5, 8) are comparable to those with catalyst **108**. Consequently, Fujimoto et al. applied catalyst **118** (i.e., catalyst **108** bearing a methoxy group) in the KR of chiral 1,2-diols (Table 15).

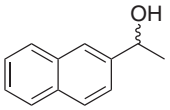
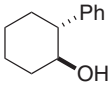
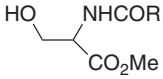
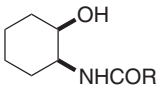
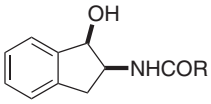
The best selectivities utilizing **108** or **118** were obtained for racemic hydrobenzoin derivatives (*S*-values up to 525), for cyloalkyl-1,2-diols the enantiomeric excesses were good to moderate, whereas for cyclohexane-1,2-diol the conversion was low. Hence, **118** would be the catalyst of choice for the KR of chiral hydrobenzoin derivatives, whereas Schreiner's catalyst **238** (see Section 6.08.1.1.1.2.4) is more efficient in the KR of cycloalkane-1,2-diols.

6.08.1.1.1.2.3 Amidines and vicinal diamines as catalysts for enantioselective acyl transfer

In 2004 Birman reported the first KR of secondary allylic alcohols utilizing 2,3-dihydroimidazo[1,2-a]pyridines as catalysts.[33,34,60] This structural motif has been known since 1936, but has not been used as a catalytic moiety for acylation reactions. The acyl transfer was proposed[61] to proceed via a nucleophilic mechanism, because Birman obtained the X-ray crystal structure of the *N*-acylated CF_3-PIP hexafluoroantimonate. Catalyst **127a** can be easily synthesized from substituted amino alcohols in two steps and therefore various modifications of **127a** are possible (Scheme 8).[62]

Table 11 KR of various secondary alcohols mediated by catalyst **97**



Entry	*Substrate*		*Conversion (%)*	ee *(%) of recovered alcohol*	S-*value*
1		**98**	74	22	1.4
2		**70**	65	11	1.2
3		**99**	69	99	12.0
4		**79**	59	96	18.8
5		**81**	74	98	8

R = *p*-Me_2N-C_6H_4.

Electron-withdrawing groups in the pyridine ring increase the selectivities and the best *S*-values were achieved by catalyst **127d**. Since the introduction of **127a-d** in 2004, Birman and coworkers tested and optimized various amidine catalysts.[60] The replacement of the pyridine moiety by a quinoline moiety (see **127**→**128** or **129**→**130**) improved the performance of the catalysts in the KR of secondary alcohols. Birman et al. proposed additional π–π-interactions as the reason of this observation. Theoretical studies by Houk and coworkers[61] confirmed the importance of the additional aromatic ring for the selectivity of the acyl transfer (Scheme 9).

Catalyst **130** showed the best results in the KR of secondary aryl alkyl alcohols; the selectivities for all substrates are very high. Even substrates with two bulky moieties (entry 2) could be resolved with high *S*-values ($S = 166$). One exception was mesityl methyl carbinol (Table 16, entry 4). In this case poor selectivity of only 2.5 was observed. In contrast, catalyst **127d** is capable of transferring an acyl moiety with a selectivity of $S = 20$ onto mesityl methyl carbinol. The highest *S*-value for this special substrate was obtained with Vedejs' catalyst **100** ($S = 369$).

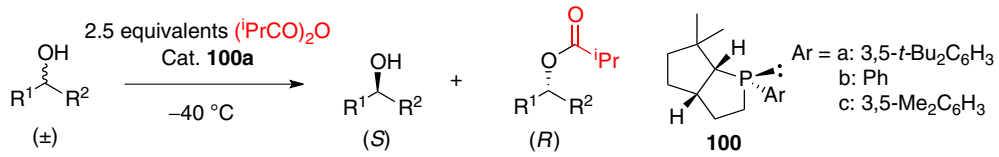
Although there are many nonenzymatic catalysts for the KRs of benzylic or allylic alcohols, the KR of propargylic alcohols was just recently achieved by Fu's planar chiral DMAP-derivative catalyst **28** with selectivities up to 20. Birman and his group applied their catalyst **130** in the KR of various propargylic alcohols as well;[60,63] the selectivities ranged from 5.4 to 32. Although the *S*-values were not as high as in the KR of aryl alkyl alcohols, they are the highest observed by a nonenzymatic catalyst for this substrate class to date. In addition to aryl and alkenyl moieties, amidine catalyst **130** is capable of selective acyl transfer onto alkynyl group bearing substrates (Table 17).

Superficially, it may seem as if new catalysts were synthesized to achieve the best possible selectivities in a particular test reaction, but the real motivation often is the synthesis of a catalysts for industrial applications. Hence, test reactions are needed to determine the efficiency of a new catalyst system for asymmetric transformations (e.g., enantioselective acyl transfer). Test reactions offer the possibility to compare selectivities of various catalysts. An example of the utilization of a catalyst in total syntheses of a natural product is shown in Scheme 10. Catalyst **130** was successfully applied in the desymmetrization of lobelanidine. The desymmetrization step proceeds with high conversion and selectivity.[64]

In 2008 Birman and Li extended the substrate scope by using aryl cycloalkanols in the KR mediated by catalyst **131**.[65] Good enantioselectivities were achieved for substrates with aromatic moieties, whereas the *S*-values decreased for substrates containing an $-N_3$ or –OBz group in the 2-position of the alkyl ring (Table 18).[65]

In 2007 Shiina and Nakata reported the KR of secondary benzylic alcohols mediated by catalyst **130**.[66] In contrast to Birman's approach, where anhydrides were used as acyl source, Shiina used carboxylic acids as the acylation agents. The reaction requires benzoic anhydride (PMBA, **145**), which forms a mixed anhydride with the carboxylic acid catalyzed by **130** (Table 19). In fact, the mixed anhydride presents the acyl source (similar to Scheme 11).

Table 12 KR of racemic secondary alcohols by phosphine catalyst **100a**



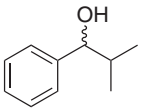
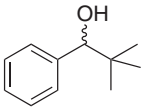
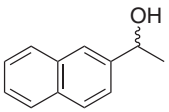
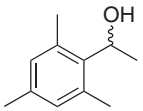
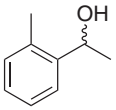
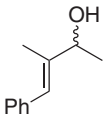
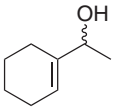
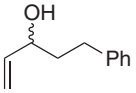
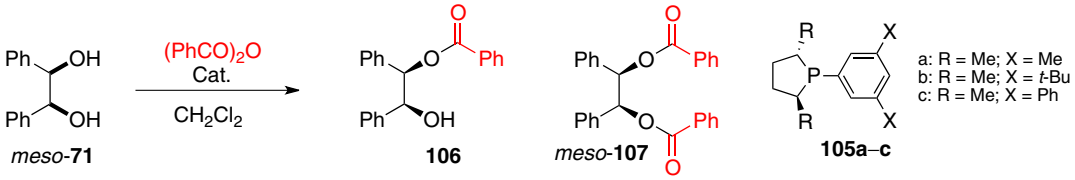
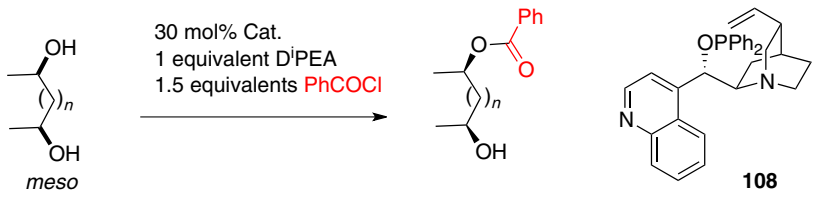
Entry	Substrate		Catalyst (mol%)	Solvent	ee (%) alcohol	ee (%) ester	Conversion (%)	S-value
1		**92**	2.8	Heptane	84	95	47	100
2		**31**	4.9	Heptane	79	93	46	67
3		**98**	3.9	Heptane	41	97	30	99
4		**101**	12.1	Heptane	79	99	44	369
5		**33**	3.5	Heptane	95	95	50	145
6		**102**	5.0	Toluene	67	82	45	21
7		**103**	5.0	Toluene	90	88	50	49
8		**104**	5.0	Toluene	42	45	48	4

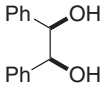
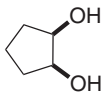
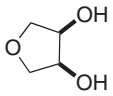
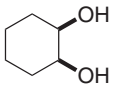
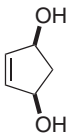
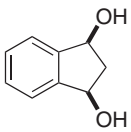
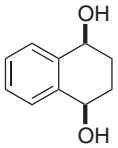
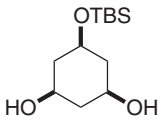
Table 13 Desymmetrization of *meso*-**71** by phosphine catalysts **105a–c** and **100a–b**

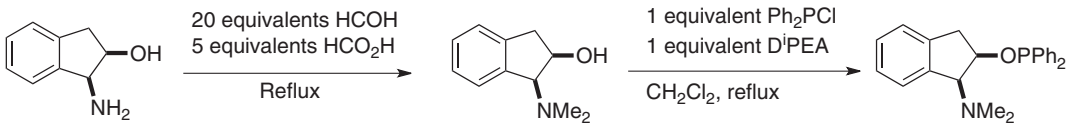


Entry	Catalyst	Mol%	Time	Temperature (°C)	Conversion (%)	**106/107**	ee (%) **106**
1	**105a**	38	4 h	r.t.	20	>20:1	78
2	**105b**	41	1.5 h	r.t.	20	>20:1	87
3	**105c**	35	17 h	r.t.	32	>20:1	87
4	**100a**	4.1	5 min	r.t.	64	5:1	61
5	**100b**	10	22 h	−30	97	2.6:1	94

Table 14 Desymmetrization of *meso*-1,2-, *meso*-1,3-, and *meso*-1,4-diols with catalyst **108**

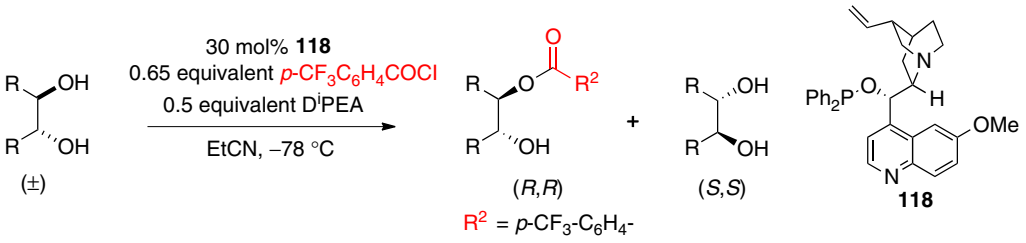


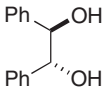
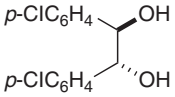
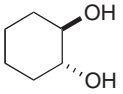
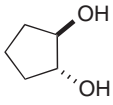
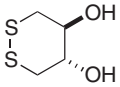
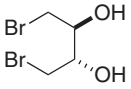
Entry	*Substrate*		*Time (h)*	*Temperature (°C)*	*Solvent*	*Yield (%)*	ee *(%)*
1		**109**	4.0	–78	EtCN	99	86
2		**71**	1.5	–78	EtCN	98	91
3		**110**	3.5	–78	EtCN	80	93
4		**111**	4.5	–78	EtCN	80	76
5		**72**	6.0	–78	EtCN	85	94
6		**112**	4.0	0	CH_2Cl_2	82	81
7		**113**	2.5	0	CH_2Cl_2	71	97
8		**88**	4.0	0	CH_2Cl_2	55	82
9		**114**	6.0	0	CH_2Cl_2	73	70

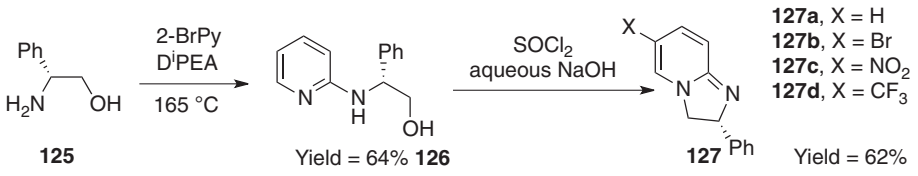


Scheme 7

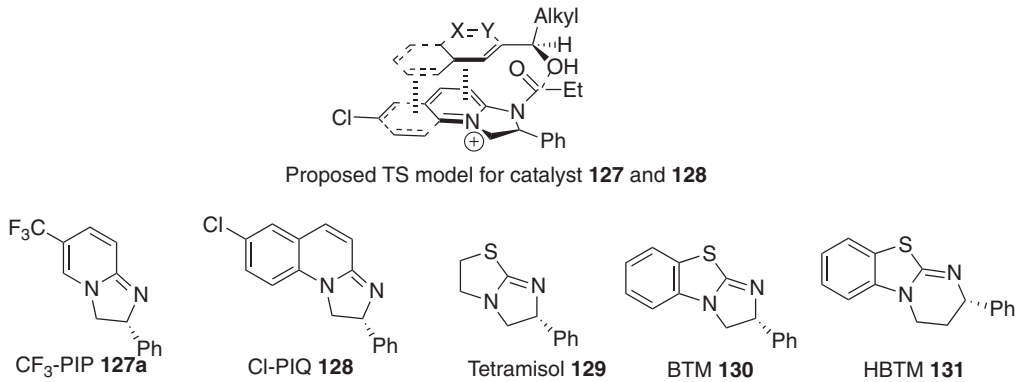
Table 15 KR of chiral 1,2-diols with bifunctional catalyst **118**



Entry	*Substrate*		*Conversion (%)*	ee *(%) alcohol*	ee *(%) ester*	S-*value*
1		**119**	50	99	98	525
2		**120**	51	90	85	38
3		**121**	14	15	89	20
4		**122**	44	63	81	18
5		**123**	41	52	74	11
6		**124**	50	69	68	11

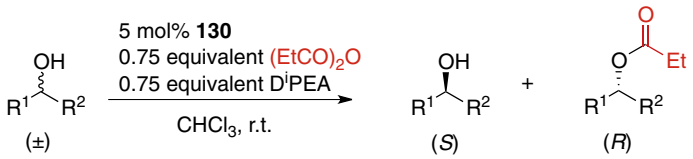


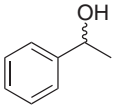
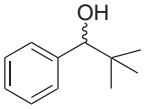
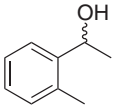
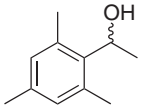
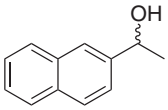
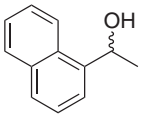
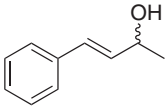
Scheme 8



Scheme 9

Table 16 Efficiency of catalyst **130** in the KR of aryl alkyl alcohols



Entry	*Substrate*		*Time (h)*	*Conversion (%)*	S-*value*
1		**30**	33	49	80
2		**31**	48	51	166
3		**33**	33	50	209
4		**101**	24	20	3
5		**88**	10.5	50	108
6		**35**	8.5	49	128
7		**85**	32	36	23

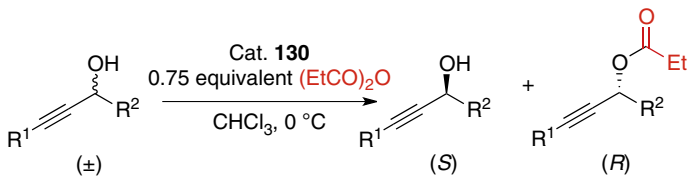
The KR of 2-hydroxyalkanoates can be achieved by using the same mixed anhydride technique. In this case pivalic anhydride is utilized to generate the mixed anhydride catalyzed by (*R*)-benzotetramisol (BTM) **130**. Shiina and his group proposed following catalytic reaction mechanism: pivalic anhydride reacts with BTM and forms acylated species **A**. The carboxylic acid attacks **A** and forms mixed anhydride **B**. BTM activates mixed anhydride **B** and generates a second intermediate **C**, which transfers the acyl moiety (the former carboxylic acid) enantioselectively onto the racemic 2-hydroxyalkanoate (Scheme 11). Schreiner and co-workers reported a similar concept by generating the anhydride *in situ* from carboxylic acids by using substituted carbodiimides as coupling agents. This led to the first enantioselective Steglich esterification.[67] Approaches in which carboxylic acids are directly used as acyl source, are rare because of the need for water removal.

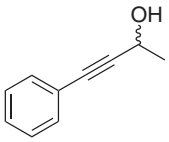
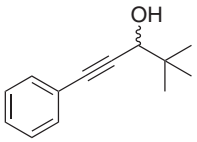
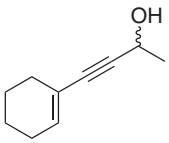
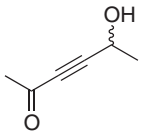
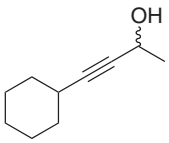
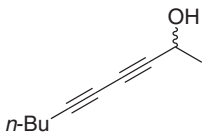
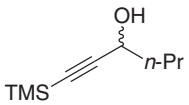
Shiina et al. applied their method to various 2-hydroxyalkanoates and excellent selectivities were observed with catalyst **130** (Table 20). The KR of 2-acyloxyalkanoates with other catalysts is not known and this approach is the first practical method to prepare enantiopure 2-hydroxyalkanoates and 2-acyloxyalkanoates.[68]

Consequently, Shiina et al. applied the mixed anhydride method to the KR of chiral carboxylic acids with achiral alcohols.[69] The reaction conditions were similar to those used for the KR of chiral alcohols with achiral acids.[66] The best results were obtained by utilizing bis(α-naphthyl)methanol, catalyst **157**, and pivalic anhydride for the KR of various 2-arylpropanoic acids (Table 21).[70]

In summary, amidine-based catalysts (e.g., **130**, **131**, and **157**) are excellent catalyst for enantioselective acyl transfer reactions. The synthesis of the catalysts can be achieved in a few steps from commercially available starting materials. Various substrates such as aryl alkyl alcohols, propargylic alcohols, and aryl cycloalkanols can be selectively acylated by **130** and **131**. Shiina employed a mixed anhydride method and extended the substrate scope to 2-hydroxyalkanoates and (chiral) carboxylic acids. A big advantage of Shiina's and Schreiner's[67] methods is the possibility to use carboxylic acids as acyl equivalents.

Table 17 Efficiency of catalyst **130** in the KR of various propargylic alcohols



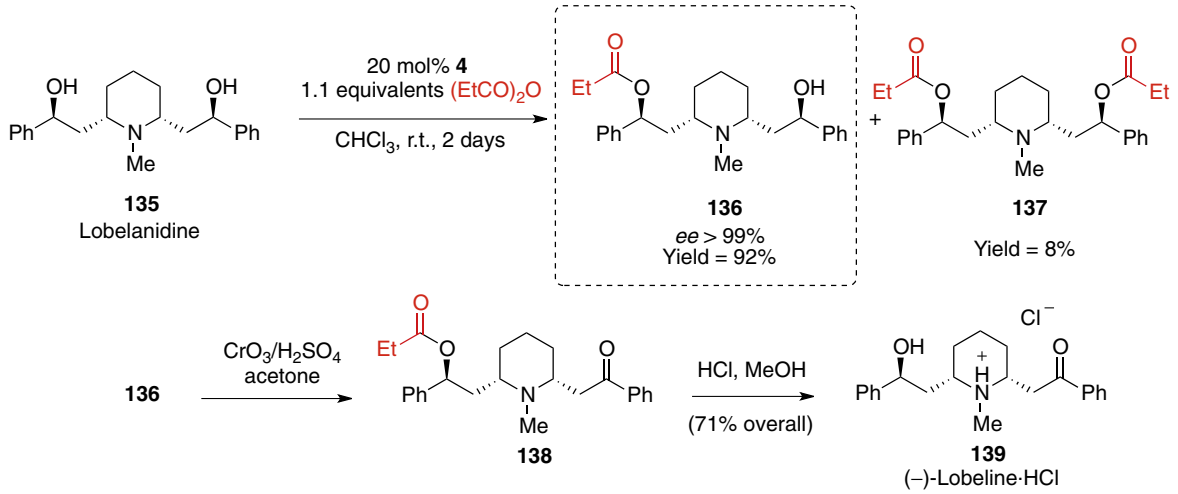
Entry	*Substrate*		*Time (h)*	*Conversion (%)*	*S-value*
1[a]		**41**	10.5	59	31
2[a]		**44**	10.5	43	10
3[b]		**132**	18	62	27
4[a]		**48**	1.5	55	32
5[c]		**133**	23	60	11
6[a]		**49**	2	52	32
7[c]		**134**	2.5	57	5

[a]Catalyst loading: 4 mol% **130**.
[b]10 mol% **130**, 1.5 equivalents $(EtCO)_2O$.
[c]10 mol% **130**.

In 1998 Oriyama reported the desymmetrization of *meso*-alcohols with amine-based catalyst **167** and **168**.[34,71] The proline derived-catalysts **167** and **168** showed similar selectivities at low catalyst loadings (0.5 mol%) with acyl chlorides as the acyl source (Table 22). KRs of secondary alcohols with catalyst **167** were also tested and produced *S*-values up to 160 for 2-phenylcyclohexanol at − 78 °C.

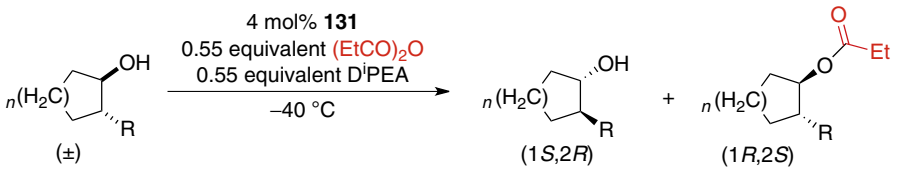
In 2010 Kawamata and Oriyama accomplished the first nonenzymatic KR of racemic cyclic *β*-hydroxy sulfides. Catalyst **167** catalyzed the acyl transfer with good to excellent selectivities (Table 23).[34,72]

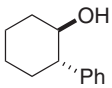
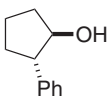
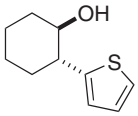
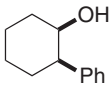
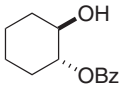
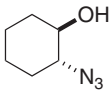
Nonenzymatic approaches for the KR of primary alcohols are rare. Oriyama achieved the first KR of a primary alcohol with good selectivities.[73] Primary alcohols are challenging substrates for desymmetrizations or KRs mediated by a small molecule catalyst owing to the fact that no functional group, which is usually required to achieve recognition by a catalyst, is close to the hydroxyl group. Even enzyme-mediated enantioselective acyl transfer onto primary alcohols is rather rare and the selectivities are much lower than those for secondary alcohols. The KR of (±)-**182** with catalyst **168** under optimized conditions is shown in equation 8.[73]

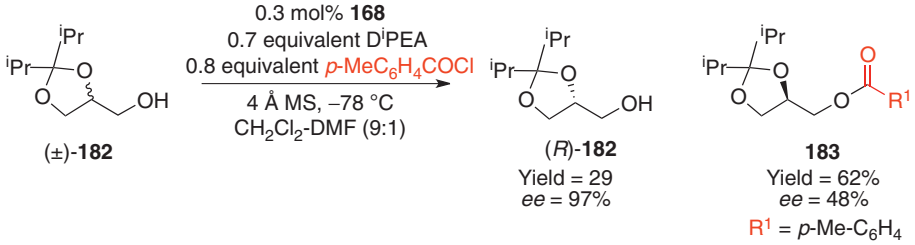


Scheme 10

Table 18 KR of aryl cycloalkanols by catalyst **131**

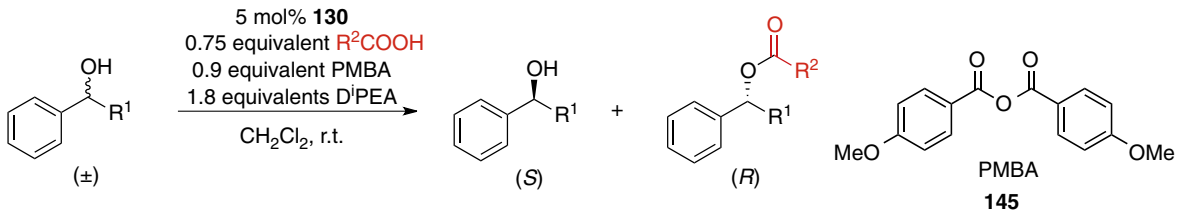


Entry	*Substrate*		*Time (h)*	*Conversion (%)*	S-*value*
1		**70**	10	51	107
2		**140**	7	51	66
3		**141**	10	44	44
4		**142**	12	46	28
5		**143**	10	28	5.6
6		**144**	10	26	10

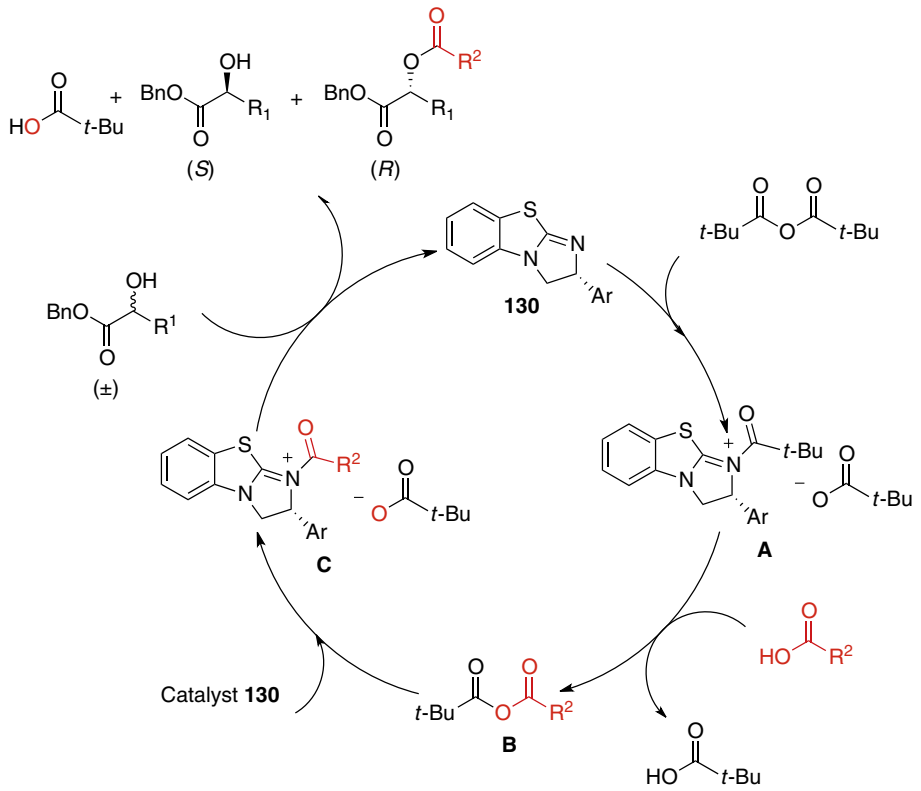


(8)

Table 19 KR of secondary benzylic alcohols with carboxylic acids catalyzed by **130**



Entry	R^1		R^2	ee *(%) alcohol*	*Yield (%) alcohol*	ee *(%) ester*	*Yield (%) ester*	S-*value*
1	Et	**146**	Et	76	40	89	40	39
2	Et	**146**	$Ph(CH_2)_2$	75	46	90	41	43
3	Et	**146**	$Ph(CH_2)_3$	69	45	90	39	39
4	Et	**146**	$Me_2CH(CH_2)_2$	71	38	83	43	23
5	Et	**146**	$CH_2{=}CH{-}(CH_2)_2$	91	38	86	47	42
6	Et	**146**	$MeOCH_2$	38	51	82	32	15
7	Et	**146**	Cy	51	40	76	53	12
8	^{i}Pr	**92**	Et	81	43	90	39	47
9	^{i}Pr	**92**	$Ph(CH_2)_2$	64	53	92	38	46
10	^{t}Bu	**31**	Et	44	67	93	32	42
11	^{t}Bu	**31**	$Ph(CH_2)_2$	58	54	96	36	88



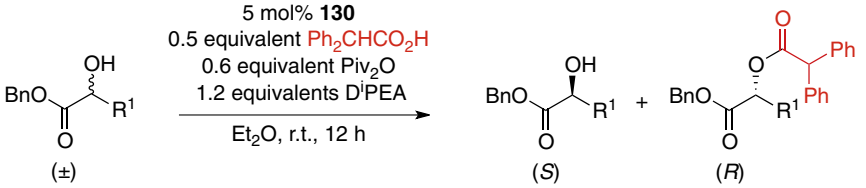
Scheme 11

In 2004 Kündig et al. reported the desymmetrization of a *meso*-Cr^0-complex utilizing chiral diamine catalysts **190** and **191**.[34,74] The synthesis of catalysts **190** and **191** can be achieved in four steps starting with quinine or quinidine (Scheme 12).[75]

The selectivities for the desymmetrization of the *meso*-Cr^0-complex are very good. Beside the chiral diamines **190** and **191**, Kündig et al. also tested Oriyama's catalyst **168** under similar reaction conditions' (Table 24).[76]

Consequently, Kündig et al. tested catalyst **191** in the desymmetrization of *meso*-1,2-diols.[75] Oriyama et al. had already successfully applied catalyst **168** to the desymmetrization of the same substrates. Kündig et al. used slightly modified conditions

Table 20 KR of 2-hydroxyalkanoates utilizing the mixed anhydride method and diphenylacetic acid as the acyl source



Entry	*R*[1]		ee *(%) alcohol*	*Yield (%) alcohol*	ee *(%) ester*	*Yield (%) ester*	S-*value*
1	Me	**147**	82	55	97	44	146
2	Et	**148**	94	43	95	46	126
3	*n*-Pr	**149**	97	48	95	50	171
4	*i*-Pr	**150**	73	50	92	46	53
5	*n*-Bu	**151**	88	51	96	47	128
6	*i*-Bu	**152**	97	55	94	45	140
7	Cy	**153**	75	53	91	43	47
8	$Ph(CH_2)_2$	**154**	95	47	96	48	202
9	$TBSOCH_2$	**155**	87	50	93	47	80
10	$TBSO(CH_2)_2$	**156**	87	52	96	45	146

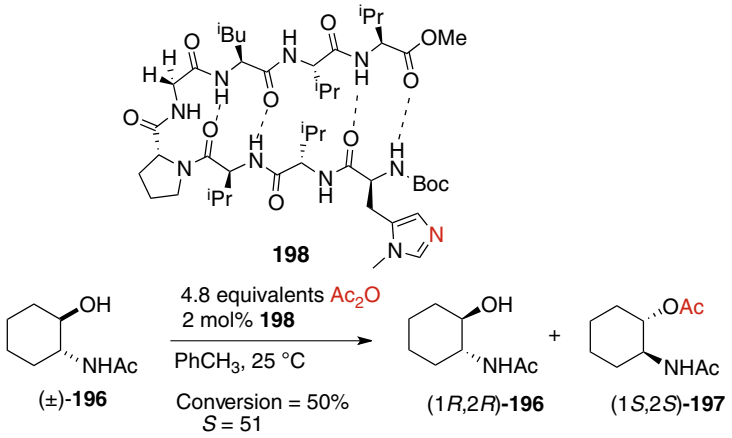
(2 mol% of catalyst **191** instead of 0.5 mol% of **168**; EtOAc as solvent) for his approach. The selectivities achieved by catalyst **191** are comparable to those reported for **168**. Catalyst **191** showed better results for substrate **72**, whereas catalyst **168** performed better in the desymmetrization of substrates **71** and **169** (Table 25).

In conclusion, chiral diamines such as **167**, **168**, **190**, and **191** are capable catalysts for enantioselective acyl transfer. In particular, *meso*-1,2-diols can be resolved with high selectivities and good yields. Catalyst **168** was also successfully utilized in the KR of *β*-hydroxy sulfides and a glycerol-derivative bearing a primary alcohol moiety.

6.08.1.1.1.2.4 Enantioselective acyl transfer via *N*-alkylimidazoles

As outlined in the 'Introduction,' enantioselective acylation reactions are widely used in nature. Enzymes are capable of transferring acyl moieties in a highly efficient and chemoselective way. Although enzymes are used as catalysts in enantioselective acylation reactions, scientists were interested in the design of small organocatalysts with comparable properties but advantages such as ease of handling, availability, and other reasons.

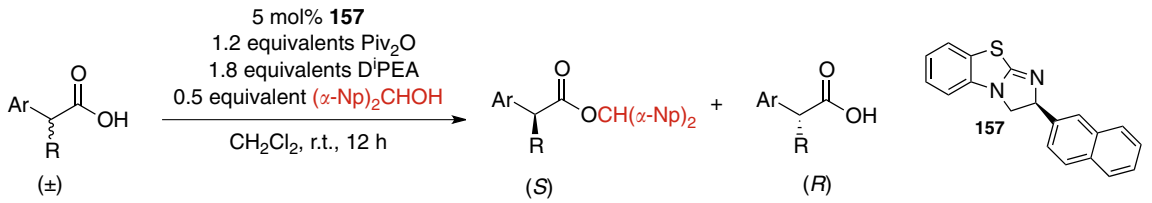
Miller and coworkers synthesized small peptide-based catalysts containing a nucleophilic moiety to transfer acyl groups onto substrates.[33,34,77,78] The peptide backbone should provide a chiral environment for selective substrate recognition. In this context they discovered a D-Pro-Aib-*β*-turn motif as an excellent scaffold for the synthesis of highly selective catalysts. After optimization of the peptides for the KR of **196** the highest enantioselectivities for the resolution of racemic *trans*-1,2-acetamidocyclohexanol were obtained using peptide **198**. A drawback of this catalyst may be its rather high molecular weight of 946 g mol^{-1} and the narrow scope for monoprotected 1,2-amino alcohols.[79]

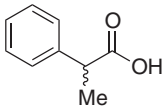
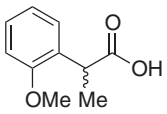
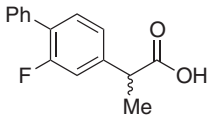
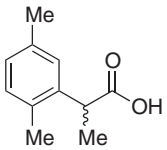
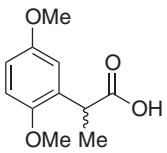
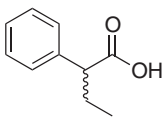
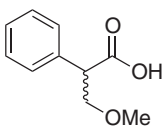
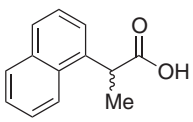
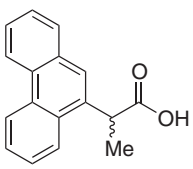


(9)

Qu and Chen modified the backbone of Miller's tetrapeptide by introducing a thioamide instead of the amide in the *β*-hairpin-structure[80] and the resulting catalyst **200** was compared with **199** in the KR reaction of **196**; **200** provides a higher *S*-value (Table 26).[80] A possible explanation might be the formation of a more constrained *β*-hairpin structure. Qu succeeded in

Table 21 KR of chiral carboxylic acids with bis(α-naphthyl)methanol mediated by catalyst **157**

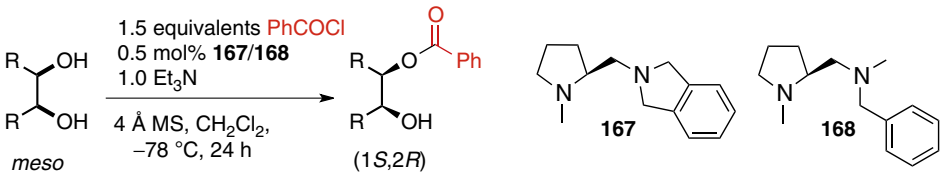


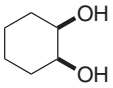
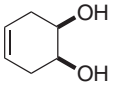
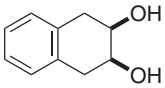
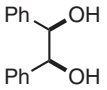
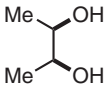
Entry	*Substrate*		ee *(%) acid*	*Yield (%) acid*	ee *(%) ester*	*Yield (%) ester*	S-*value*
1		**158**	59	51	92	45	44
2		**159**	73	30	89	48	193
3		**160**	67	42	87	46	29
4		**161**	99.5	43	98	40	484
5		**162**	73	38	98	47	235
6		**163**	46	35	75	45	11
7		**164**	39	47	88	37	24
8		**165**	82	41	96	48	136
9		**166**	86	49	98	48	361

the synthesis of a smaller, highly efficient catalyst for the KR of **196**, but the substrate scope is still limited to *trans*-1,2-acetamidocycloalkanols.

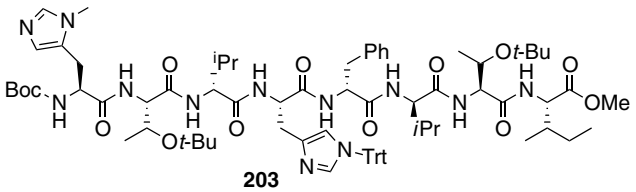
A big advantage of peptide catalysts is that they can be easily modified and the synthesis of a great number via solid phase peptide synthesis (SPPS) is possible in a rather short period of time. A broad range of natural and nonnatural amino acids are available and therefore a large number of combinations can be envisaged. Peptide libraries can be prepared and their members tested for various

Table 22 Efficiency of catalyst **167** and **168** in the desymmetrizations of *meso*-alcohols

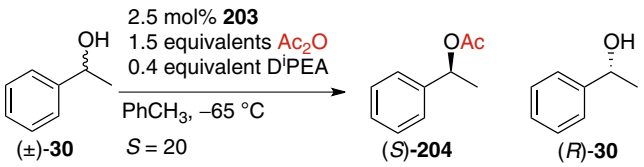


Entry	*Substrate*		*Catalyst*	*Yield (%) ester*	ee *(%) ester*
1		**72**	**167**	62	95
			168	83	96
2		**169**	**167**	78	96
			168	81	90
3		**170**	**167**	89	48
			168	89	66
4		**71**	**167**	68	64
			168	80	60
5		**109**	**167**	80	91
			168	85	94

substrates by using, for example, fluorescence-based assays for high-throughput identification of active catalysts.[81,82] Miller and coworkers identified peptide **203** as an efficient catalyst for the KR of secondary alcohols by using such a screening method.[81,83]



203



(10)

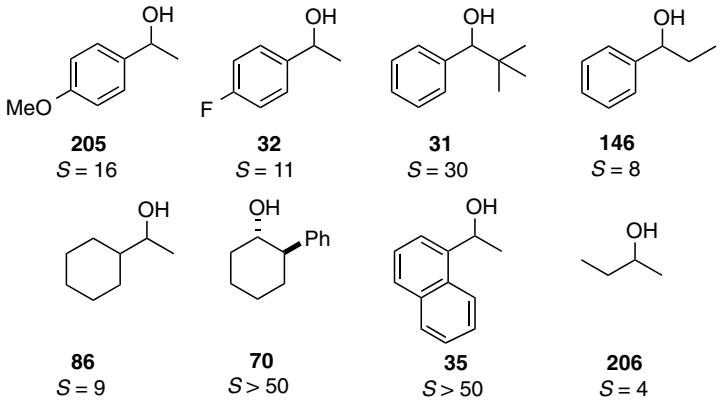
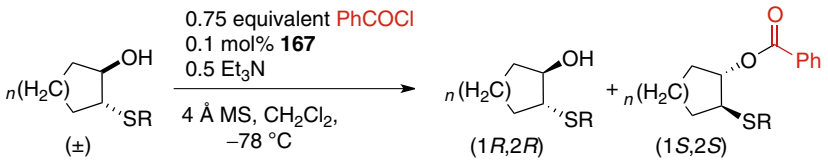
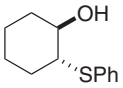
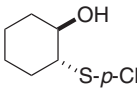
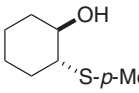
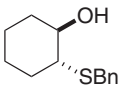
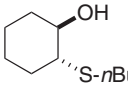
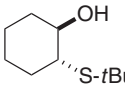
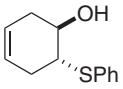
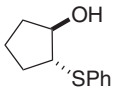
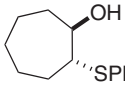
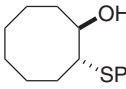
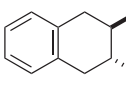
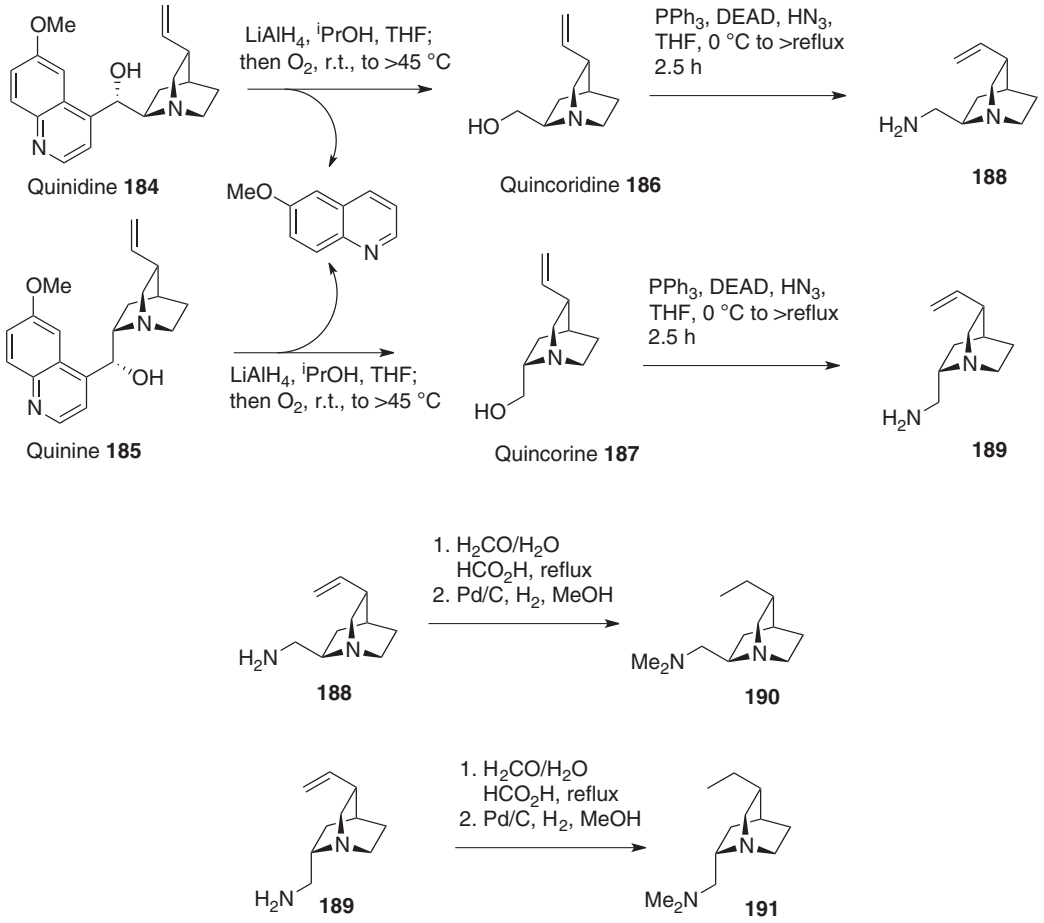


Table 23 Efficiency of catalyst **167** in the KR of β-hydroxy sulfides

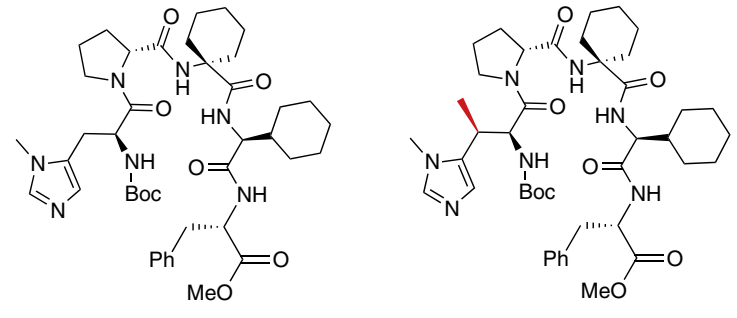


Entry	*Substrate*		ee *(%) alcohol*	*Yield (%) alcohol*	ee *(%) ester*	*Yield (%) ester*	S-*value*
1		**171**	96	49	97	50	280
2		**172**	94	49	98	49	360
3		**173**	97	47	96	49	160
4		**174**	99	48	96	49	160
5		**175**	93	43	92	46	57
6		**176**	73	44	98	42	210
7		**177**	93	47	94	50	160
8		**178**	69	48	68	48	10
9		**179**	97	47	97	48	200
10		**180**	99	48	95	49	160
11		**181**	81	49	86	49	34

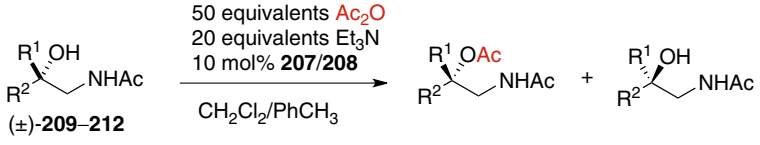
Equation 10 shows the high selectivity of **203** in the KR of (±)−**30**. In contrast, **203** was less efficient when substrates without an aryl moiety were used. This study shows again the high chemoselectivity of peptide catalysts. Although the KR of secondary alcohols especially of *rac*-**30** is widely known and can also accomplished with enzymes, examples for KRs of tertiary alcohols are rare. Even enzyme-catalyzed reactions are not known. Miller et al. achieved the KR of **209**–**212** with moderate to good selectivities. Comparison of the *S*-values generated with catalyst **207**and **208** shows the large effect of small modifications on peptide catalyst systems (equation 11, Table 27). Simply replacing the π-methyl histidine residue of peptide **207** by a methylated β-methyl-π-methyl histidine moiety increased the selectivity. A reason for this observation may be the restricted rotational freedom around the C^{β}–C^{γ} bond of the β-branched π-methyl histidine moiety. ^{1}H-NMR measurements exhibited evidence for the restriction of the rotation for the Boc-protected β-methyl-π-methyl histidine, but did not show evidence for restriction of the rotation for the unprotected β-methyl-π-methyl histidine. Hence, Miller proposed that either a remote steric effect or a hydrogen bonding interaction associated to the Boc-group is responsible for the dihedral angle restriction.[78,84]



Scheme 12



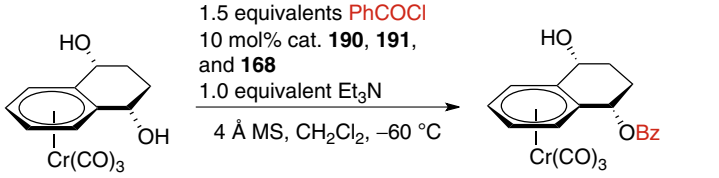
(11)



The desymmetrization of *meso*-compounds has become a powerful tool in asymmetric synthesis. In contrast to KRs, desymmetrization reactions can achieve 100% theoretical yield. Peptide **213**, a modification of **207**, enables the desymmetrization of

meso-glycerol derivative **214**, which presents a formidable challenge.[85] These examples show the manifold applications of small peptide catalysts, because primary, secondary, and tertiary OH-groups can be acylated.

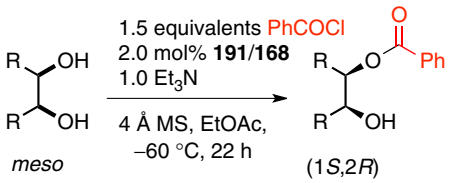
Table 24 Efficiency of catalysts **168**, **190**, and **191** in the desymmetrization of *meso*-**192**



meso-**192** (–)-**193** (shown) or (+)-**193**

Entry	*Catalyst*	*Time (h)*	*Yield (%)* ***193***	ee *(%)* ***193***
1	**168**	22	78	95(–)
2	**190**	23	80	94(+)
3	**191**	22	76	99(–)

Table 25 Efficiency of catalyst **191** in the desymmetrization of *meso*-1,2-diols compared with the results obtained by catalyst **168**



meso (1*S*,2*R*)

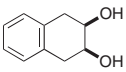
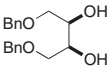
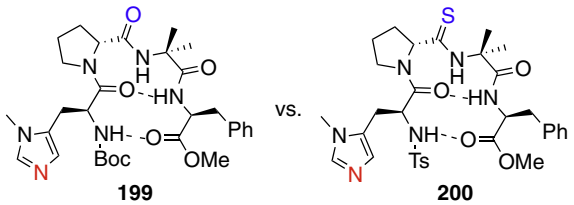
Entry	*Substrate*		*Catalyst*	*Yield (%) ester*	ee *(%) ester*
1		**72**	**191**	92	97
			168	83	96
2		**169**	**191**	79	84
			168	81	90
3		**170**	**191**	65	83
			168	89	66
4		**71**	**191**	82	13
			168	80	60
5		**109**	**191**	82	90
			168	85	94
6		**110**	**191**	87	78
7		**111**	**191**	84	77
8		**194**	**191**	86	77
9		**195**	**191**	51	93

Table 26 KR of *trans*-1,2-acetamidocycloalkanols with catalyst **199** and **200**



199 **200**

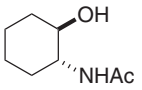
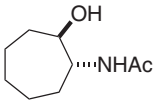
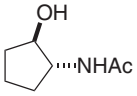
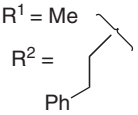
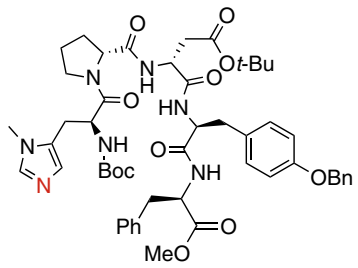
Entry	*Substrate*		*Catalyst*	*Conversion (%)*	S-*value*
1		**196**	**199**	49	28
2			**200**	50	109
3		**201**	**199**	51	17
4			**200**	48	75
5		**202**	**199**	56	6
6			**200**	44	9

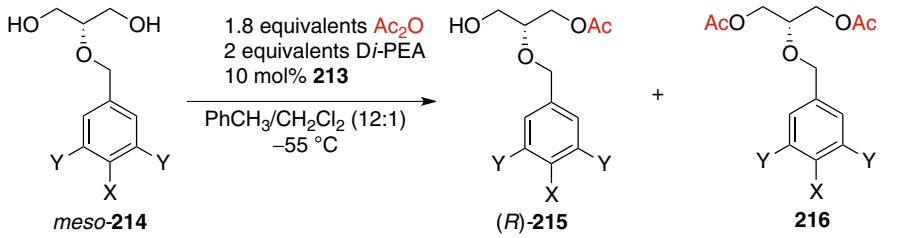
Table 27 Comparison of catalyst **207** and **208** in the KR of tertiary alcohols

Entry	*Substrate*		*Catalyst*	*Conversion (%)*	S-*value*
1	R^1 = Me	**209**	**207**	33	9
2	R^2 = Cy		**208**	53	> 50
3	R^1 = Me	**210**	**207**	39	10
4	R^2 = *p*-NO_2–C_6H_4		**208**	60	24
5	R^1 = Me	**211**	**207**	32	3
6	R^2 = 		**208**	65	18
7	R^1 = CO_2Me	**212**	**207**	21	1.6
8	R^2 = Ph		**208**	43	2.8



213

(12)

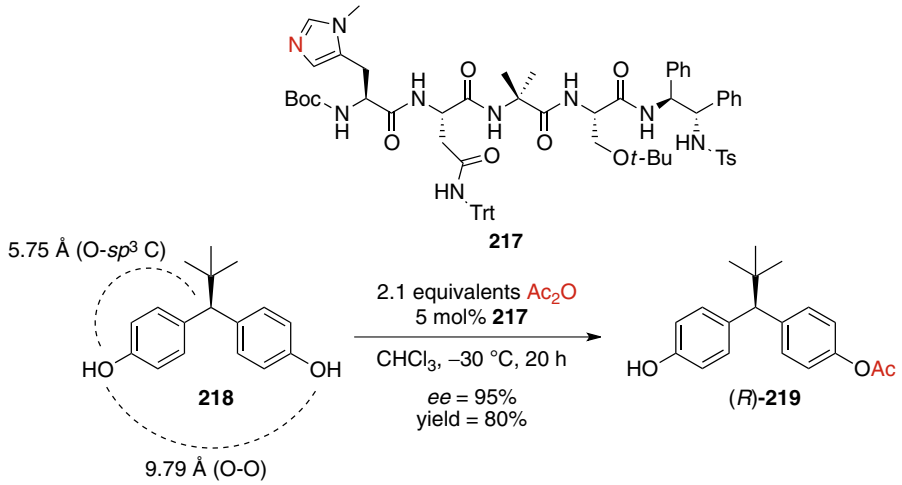


meso-**214** (*R*)-**215** **216**

X = H; Y = H — Yield = 37; *ee* = 91% — 215/216 ratio = 39:61

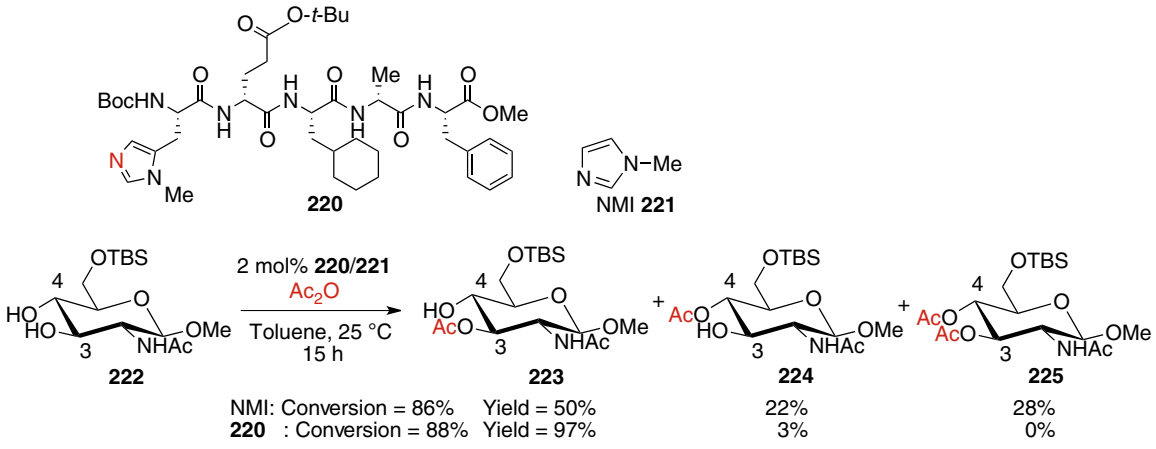
X = H; Y = OMe — Yield = 34; *ee* = 95% — 215/216 ratio = 37:63

In 2006 Miller and coworkers found a catalyst that was effective in the enantioselective acylation of substrate **218**. This substrate was challenging because of the large distance between the two OH-groups (approximately 10 Å) and also between the OH-group and the prostereogenic center (approximately 6 Å). Enzymes seem to be the best choice to solve such a difficult problem, because their macromolecular structure generates a chiral environment, which provides the potential for enantioselective recognition even if the prostereogenic center and the enantiotopic phenol oxygens of the substrate are far away from each other. In this rare case a chemical method (catalyst **217**) shows better results than enzymatic approaches.[78,86,87]



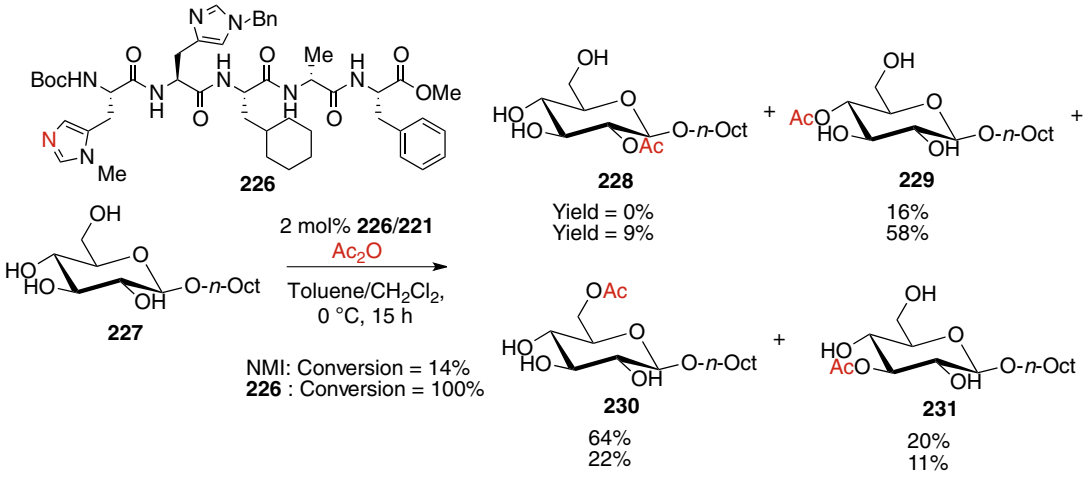
(13)

Site-selective functionalization of substrates containing more than one functional group is synthetically useful but difficult. Hence, enzymatic approaches for chemo- and site-selective transformations are known, but limited to a narrow substrate scope. Miller et al. tested catalyst **220** and *N*-methylimidazole [NMI, (**221**)] in the site-selective acylation of the glucosamine derivative **222**. Although achiral NMI produced a mixture of **223**–**225**, catalyst **220** achieved site selective acylation and **223** was obtained in 97% yield as the major product.[78,88]



(14)

Glucoside **227** was then chosen as a more challenging substrate containing four unprotected OH-groups. NMI **221** as catalyst achieved poor selectivities (three of the four possible products formed) and low conversion (14%). Peptide **226** (a modification of **220**) showed higher activity and provided mono acetate **229** in 58% yield; however, the chemoselectivity was moderate.[78,88]



(15)

Miller and Lewis achieved the selective acylation of a less reactive OH-group in the presence of more reactive OH-groups in erythromycin A (**233**) utilizing pentapeptide **232**.[78,89] The most reactive hydroxyl-group (C2′) can be selectively acylated by simply using NMI (**221**) as catalyst and 1 equivalent of anhydride (product **234**). The next reactive position in the molecule is the C4″ hydroxyl-group. In the presence of 2 equivalents of anhydride the C2′ and C4″ positions were acylated and addition of MeOH selectively cleaved the acetate in the C2′ position. Under these conditions **235** is the major product. A triacetate (C2′, C4″, and C11 acylated) forms after prolonged reaction time and even after 3 days <30% of **233** is converted into **235** and **237** (ratio=4:1). Tertiary hydroxyl groups do not react under these conditions.

In contrast, peptide **232** is more reactive and a reversal of the inherent selectivity was observed; a ratio of 1:5 of **235** and **237** was estimated by NMR integration. These three examples illustrate on the one hand the potential of small peptides as highly efficient and readily modified catalyst for site-selective natural product synthesis, but on the other hand the complexity and catalyst structure sensitivity for selectively transferring a moiety onto a certain functional group. To identify a suitable peptide for the chemoselective transformation (see equation 14), a peptide library containing 150 peptides was tested, and for transformation shown in equation 15, a library including 36 peptides was tested (**Scheme 13**).

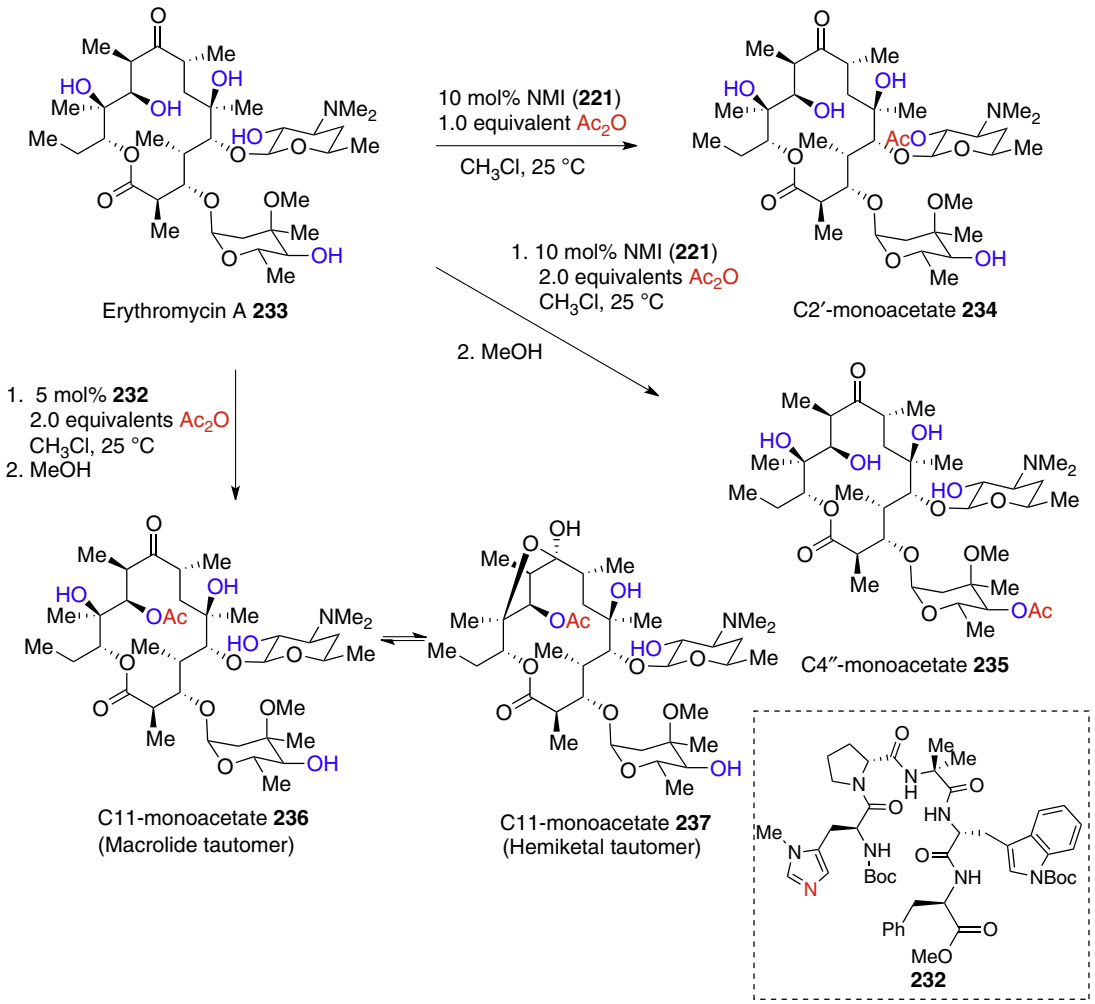
Schreiner and coworkers introduced another approach for the design of peptide catalysts in 2008.[27,34] They did not try to form a stable β-hairpin structure by using L-proline/D-proline to generate secondary structure. This approach introduced a rigid and lipophilic nonnatural γ-adamantane amino acid as the structure forming building block in peptide catalyst **238**. The KRs of various *trans*-cycloalkane-1,2-diols were realized with *S*-values >50 (**Table 28**). In this rare case, the efficiency of a small organic catalyst is superior to enzymatic approaches. Various *Pseudomonas* lipases were tested and displayed low activities and poor selectivities in the KR of *trans*-cyclohexan-1,2-diol (**121**).[90] Enantioselective monobenzoylation of the same substrate was accomplished by Cu(II)-bisoxazoline-complexes,[91–93] the obtained selectivities ranged from 14 to 22. Computations by Sunoj and Shinisha[94] confirmed the hypothesis of Schreiner et al. that it is not a secondary structure formed by the peptide, but hydrogen bond between a carboxyl group of the peptide backbone and one hydrogen atom of the diol that is responsible for the observed selectivity. Subsequently, catalyst **238** was utilized in the first enantioselective Steglich esterification protocol.[67] Here, Schreiner and coworkers used carboxylic acids as electrophiles, which react *in situ* with a substituted carbodiimide to form the corresponding anhydride. This method is superior when the chosen anhydride is not stable or not commercially available; the enantioselectivities were high.

The desymmetrization of *cis*-cycloalkane-1,2-diols (*meso*-diols) was also successfully accomplished by peptide **238** (**Table 29**).[95] A general drawback of this reaction is the configurationally lability of the monoacylated products via 1,2-acyl migration. Racemization occurs during the work up and lowers the enantiomeric excesses of the isolated products. For this reasons Schreiner et al. devised a protocol for the *in situ* organocatalytic oxidation of the unacetylated hydroxy function to produce the corresponding α-acetoxy ketones as valuable chiral building blocks.

Some enzymatic approaches for the desymmetrization of *meso*-cyclohexane-1,2-diol (**72**) are known from the literature. *Pseudomonas* lipase catalyzed this reaction with isopropenyl acetate as the electrophile. An *ee* of 81% was observed and 81% of the product could be isolated.[90] Porcine pancreas lipase catalyzed the desymmetrization of **72** with methyl acetate with an *ee* of 84%.[96] In both cases catalyst **238** can compete with the enzymatic approaches. Organocatalytic methods using chiral 4-pyrrolidinopyridine (PPY) analogs (65% *ee*, 61% conversion, isobutyric anhydride), *N*,*N*-DMAP-based atropisomeric biaryl derivatives (77% *ee*, 20% yield, isobutyric anhydride), or chiral phosphine (67% *ee*, 66% conversion, acetic anhydride) led to lower enantioselectivities.

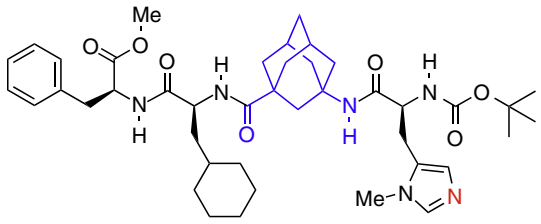
Ishihara at al. (2004)[97,98] as well as Qu and coworkers (2008)[99] followed a nonpeptidic biomimetic acylation approach by introducing catalysts **245** and **246**. Both catalysts proved to be highly efficient in the KR of racemic monofunctionalized 1,2-diol and amino alcohols. The only drawback of these reactions is that best selectivities were obtained in CCl_4, which is highly toxic. A variety of substrates is presented in **Table 30**.[34]

One advantage of peptides or small molecules as catalysts is the possibility to modify them easily, especially because peptides can be readily synthesized via automated SPPS. In all cases the catalysts are highly chemoselective and may therefore serve as

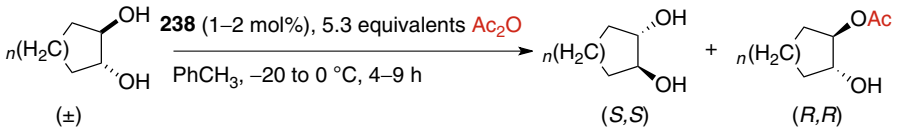


Scheme 13

Table 28 KR of *trans*-1,2-cycloalkanediols with peptide catalyst **238**

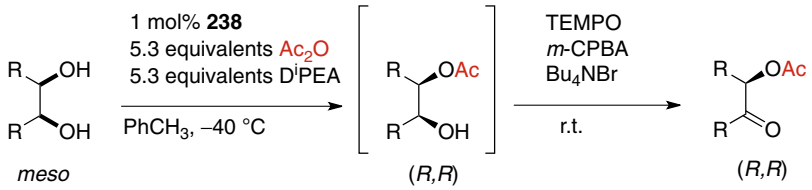


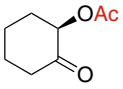
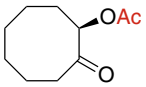
Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe (**238**)



Entry	n		ee *(%) alcohol*	ee *(%) ester*	*Yield (%) alcohol*	S*-value*
1	1	**122**	>85	49	37	>8
2	2	**121**	>99	78	37	>50
3	3	**239**	>99	79	41	>50
4	4	**240**	>99	85	44	>50

Table 29 Desymmetrization and direct oxidation of *meso*-diols **241–244** under optimized conditions



Entry	Product		Yield α-acetoxy ketones (%)	ee α-acetoxy alcohol (%)	ee α-acetoxy ketones (%)
1		**241**	69	80	64
2		**242**	70	88	88
3		**243**	97	84	94
4		**244**	42	84	81

catalysts for selective acylation of polyols. Unfortunately, rational catalyst design of oligopeptides, which are capable of specific functionalizations, is difficult as the structures are far too complex to predict their selective recognition abilities of substrates. Peptide libraries and fluorescence-based assays can help identify active peptides for the acylation of substrates, but the preparation and testing of such libraries is time-consuming and a better conceptual understanding of these oligopeptides is highly desirable.

6.08.1.1.1.2.5 *N*-Heterocyclic carbenes as catalysts for enantioselective acyl transfer

Wanzlick isolated the first NHC-dimer in 1960[100,101] and eight years later the first metal-carbene-complex was synthesized by Öfele.[102] In 1988 Bertrand reported the first stable phosphinocarbene.[103] Three years later Arduengo introduced crystalline 1,3-diadamantyl substituted imidazole-2-ylidene.[104] The discovery of this first stable NHC caused a lot of excitement, because carbenes were no longer considered to be short-lived but could be employed as structural motifs with unique properties. Now NHCs are widely used as ligands in organometallic complexes[105] or as organocatalysts.[106] In addition to the utility as catalysts for Umpolung reactions,[107] NHCs are also capable of transferring acyl groups. Bakhtiar and Smith reported the first achiral acyl transfer reactions in 1994 (see Section 6.08.1.1.1.1).[108] Ten years later, Suzuki et al. published the first enantioselective KR mediated by NHCs.[109] Carbenes **254–263** achieved only moderate selectivities (S≤5) in the KR of *sec.* alcohols.[110] Suzuki et al. proposed the following mechanism (**Scheme 14**).

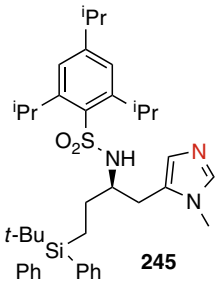
Selective acyl transfer mediated by NHCs seems to proceed via the same nucleophilic catalysis mechanism proposed for DMAP, DMAP-derivatives, *N*-alkyl imidazole-derivatives, amidines, amines, phosphines, and phosphinites (*vide supra*). Instead of a nucleophilic nitrogen or phosphorus atom, the *in situ* generated highly nucleophilic carbene carbon atom attacks the acyl donor and transfers the acyl moiety onto the alcohol. In addition to the properties of the nucleophile, the selectivity can also be affected by the chemical properties of the acyl source. In 2005 Maruoka and coworkers increased the enantioselectivity of the acylation process by using vinyl diphenyl acetate as acylating agent.[111] Under optimized conditions a variety of secondary alcohols were acylated (**Table 31**).

Allylic alcohols as well as aryl alkyl carbinols can be selectively acylated by catalysts **258** and **264**. The selectivity is not affected by electron-donating or electron-withdrawing groups on the aromatic ring. In contrast to the KR of allylic *sec.* alcohols catalyzed by DMAP or *N*-alkylimidazole derivatives, no base is needed because vinyl acetates were used as acyl source instead of anhydrides or acyl chlorides. The *S*-values were comparable to the *S*-values achieved by Fu's catalyst **28** (see Section 6.08.1.1.1.2.1), but the conversions 20% higher on average.

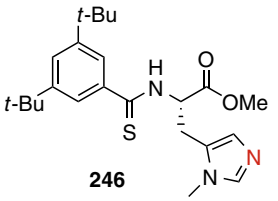
In 2011 Studer et al. published the first KR of *sec.* alcohols by NHC-catalyzed oxidative esterification using aldehydes as the acyl source.[112] They applied an external organic oxidant for their resolution process. Catalyst **265** achieved moderate selectivities in the KR of *sec.* allylic alcohols. Various aromatic *para*-substituted electron-poor aldehydes were

tested. Selectivities up to 60 for *para*-bromobenzaldehyde at 65% conversion were obtained. The carbene was generated *in situ* from **265** using DBU as base.

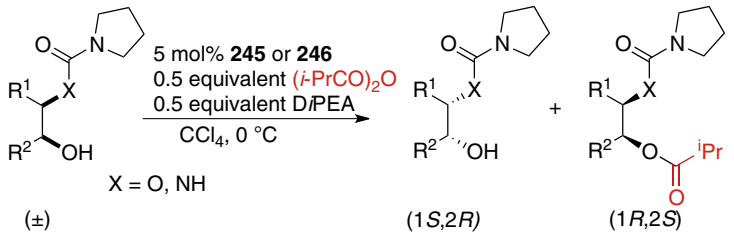
Table 30 Comparison of catalyst **245** with **246** in the KR of various racemic secondary alcohols

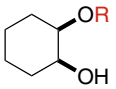
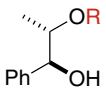
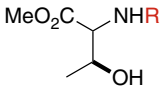
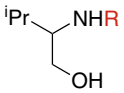
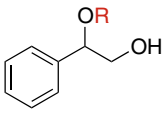
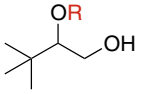


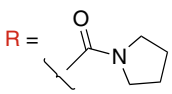
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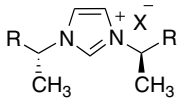


246

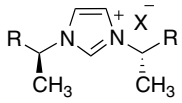


Entry	*Substrate*		*Catalyst*	*Conversion (%)*	ee *(%) alcohol*	ee *(%) ester*	S*-value*
1		**247**	**245** **246**	52 52	97 97	90 90	87 80
2		**248**	**245** **246**	47 44	82 68	93 86	68 28
3		**249**	**245**	49	80	82	25
4		**250**	**245**	39	51	80	15
5		**251**	**245**	50	88	86	39
6		**252**	**246**	53	88	76	23
7		**253**	**246**	52	98	88	91

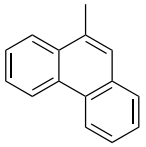




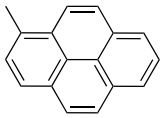
(R,R)-**254**; X = Cl, R = 1-naphthyl
(R,R)-**255**; X = Cl, R = cyclohexyl
(R,R)-**256**; X = Cl, R = phenyl
(R,R)-**257**; X = BF_4, R = 1-naphthyl
(R,R)-**258**; X = BF_4, R = 2-naphthyl
(R,R)-**259**; X = BF_4, R = 9-anthryl
(R,R)-**260**; X = BF_4, R = 1-anthryl
(R,R)-**261**; X = BF_4, R = 1-(2-methoxynaphthyl)
(R,R)-**262**; X = BF_4, R = 1-pyrenyl



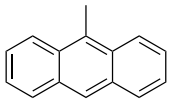
(*S,S*)-**263**; X = BF_4, R = 9-Phenanthryl



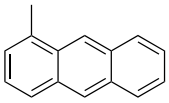
9-Phenanthryl



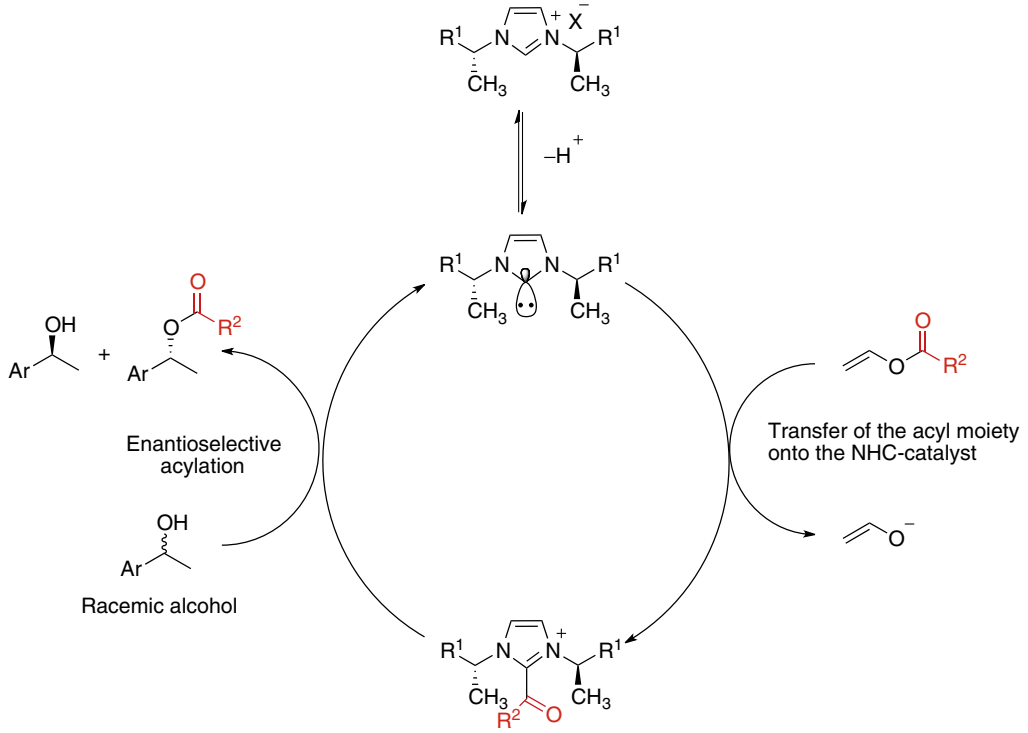
1-Pyrenyl



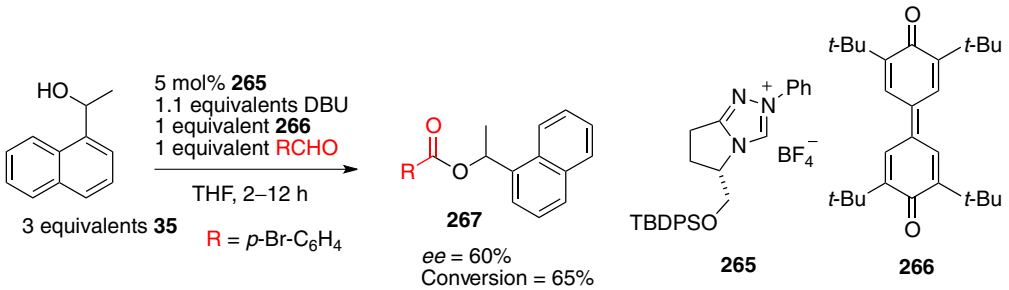
9-Anthryl



1-Anthryl



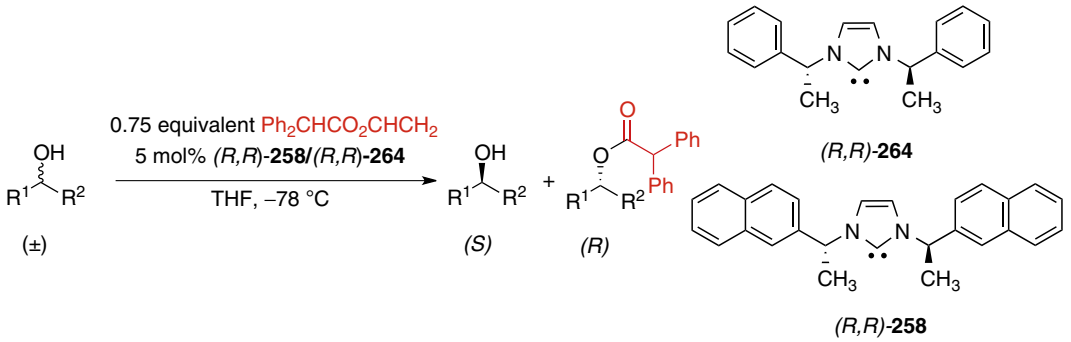
Scheme 14

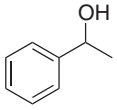
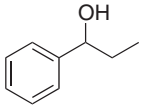
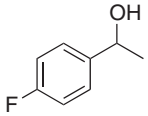
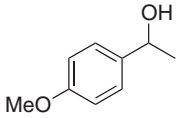
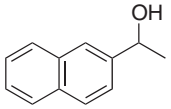
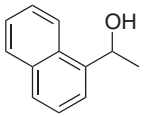
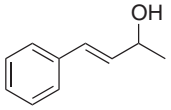
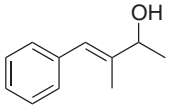


(16)

Studer et al. proposed following mechanism. In the first step the aldehyde reacts with the NHC and is oxidized by an external oxidation agent (**266**) to form a chiral acyl azolium ion. The alcohol then attacks the acylazolium ion to form adduct **A**. At the end of the process adduct **A** fragments into NHC and the product ester (Scheme 15).

Table 31 Performance of **258** and **264** in the KR of *sec.* alcohols

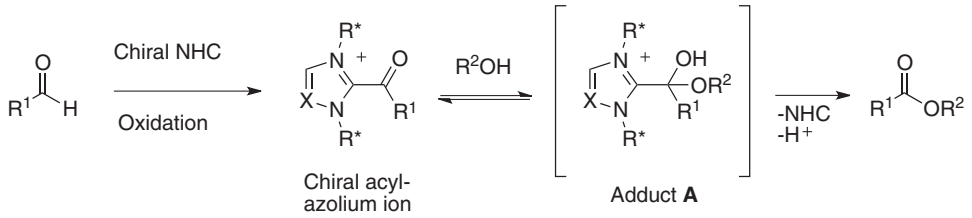


Entry	*Substrate*		*Catalyst*	ee *(%) ester*	*Yield (%) ester*	S-*value*
1		**30**	*(R,R)*-**258** *(R,R)*-**264**	96 93	32 33	80 46
2		**146**	*(R,R)*-**258**	92	33	38
3		**32**	*(R,R)*-**258** *(R,R)*-**264**	91 90	39 35	42 33
4		**205**	*(R,R)*-**258**	94	30	48
5		**98**	*(R,R)*-**258** *(R,R)*-**264**	95 93	27 35	56 46
6		**35**	*(R,R)*-**258**	94	29	47
7		**85**	*(R,R)*-**264**	84	27	16
8		**102**	*(R,R)*-**264**	87	33	22

An advantage compared to other KRs is the possibility to use simple aldehydes as acyl source instead of anhydrides, acid chlorides, or vinyl acetates. Drawbacks of this approach at present are the low *ee*s and the necessity of having to use 1 equivalent of an external oxidizing agent. Yashima and coworkers solved these problems by applying an NHC/flavin system (**Table 32**).[113] The enantiomeric excesses were still moderate, but only 10 mol% of the oxidant is needed, because it can be regenerated by areobic oxidation.

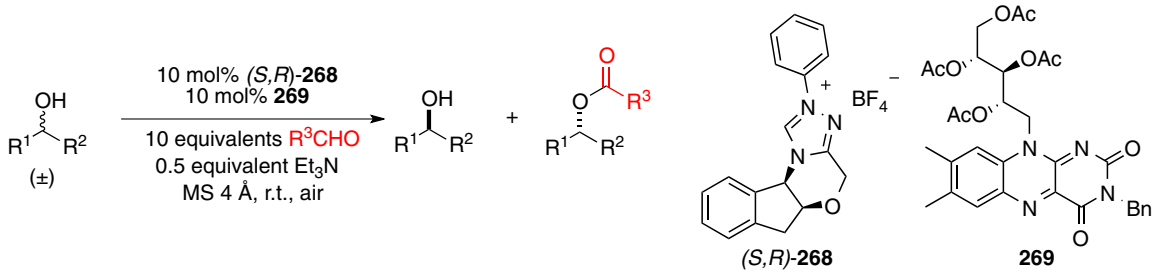
6.08.1.1.1.2.6 Enantioselective ring opening of *meso*-anhydrides by cinchona alkaloid derivatives

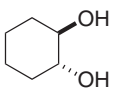
The selective ring opening of *meso*-anhydrides[114] mediated by cinchona alkaloids was first reported by Oda in the 1980s.[115] Shortly thereafter, Aitken et al. reported the conversion of a *meso*-anhydride into a lactone mediated by quinine (57%, 76% *ee*).[116,117]



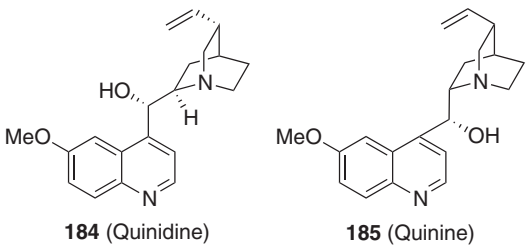
Scheme 15

Table 32 Efficiency of a NHC/flavin system in the KR of secondary aryl alcohols



Entry	*Alcohol*		R^1	R^3	*Conversion (%)*	ee *(%) alcohol*	S-*value*
1		**30**	Ph	Ph	65	43	2.3
2		**35**	1-Naphthyl	Ph	55	44	3.2
3		**98**	2-Naphthyl	Ph	72	66	3.1
4		**30**	Ph	1-Naphthyl	50	32	2.6
5		**30**	Ph	2-Naphthyl	47	39	3.7
6		**121**		Ph	62	75	5.6

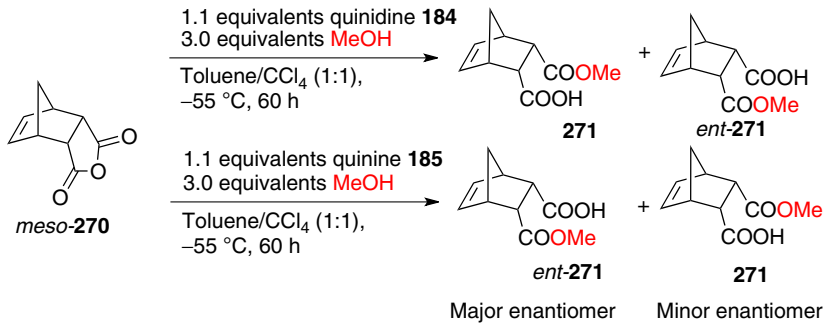
In 1999 Bolm et al. presented a method for the enantioselective ring opening of bi- and tricyclic *meso*-anhydrides by commercially available quinidine (**184**) and quinine (**185**) (Scheme 16).[33,114,118] The desymmetrizations of various cyclic anhydrides utilizing catalysts **184** and **185** proceeded with excellent enantiomeric excesses and high yields (Table 33).

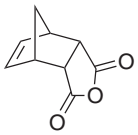
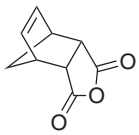
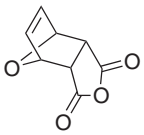
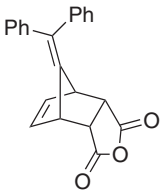
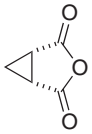
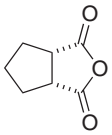
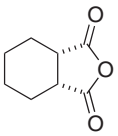


Scheme 16

A drawback of this approach is the high 'catalyst' loading of 110 mol%, and Bolm et al. investigated the ring opening by catalytic amounts of **184** and **185**.[33,119] They first tested the reaction under optimized conditions with just 10 mol% of quinidine

Table 33 Desymmetrization of *meso*-anhydrides utilizing commercially available cinchona alkaloid **184** and **185**

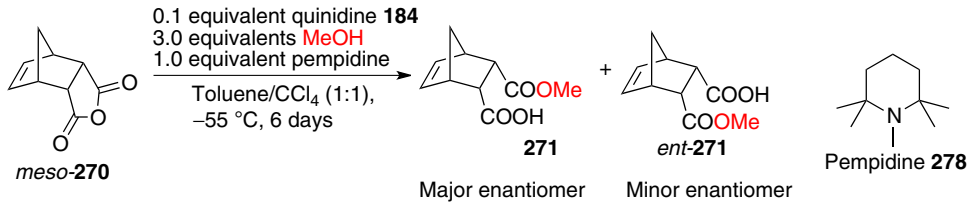


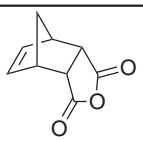
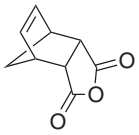
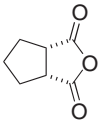
Entry	*Substrate*		*Catalyst*	*Yield (%) of major enantiomer*	ee *(%) of hemiester (major enantiomer)*
1		**270**	**185**	92	99
2			**184**	98	99
3		**272**	**185**	94	93
4			**184**	96	96
5		**273**	**185**	71	75
6			**184**	61	93
7		**274**	**185**	96	92
8			**184**	95	95
9		**275**	**185**	95	85
10			**184**	96	85
11		**276**	**185**	99	93
12			**184**	97	95
13		**277**	**185**	91	87
14			**184**	98	93

(**184**) without additional base and the reaction stopped at 50% conversion (35% *ee*). Bolm et al. proposed following scenario. After the opening of the anhydride by **184** the resulting acid transfers its proton onto the alkaloid, afterwards the protonated alkaloid and the carboxylate of the hemiester form an acid-base complex.[120] In addition, the protonated catalyst **184** adopts the open(3)-conformation, which is catalytically active, but less selective.[116,117,121] They tested various auxiliary bases to avoid the protonation of **184** and identified pempidine (**278**, Table 34) as the base, which in combination with **184** showed the highest *ee*.

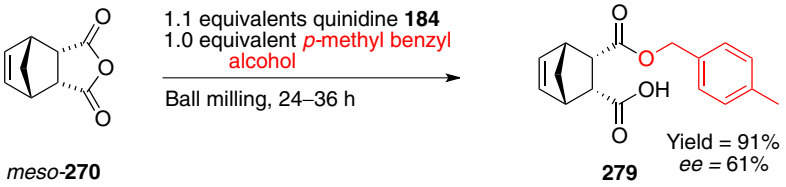
The selectivities and yields were still high (Table 34). A drawback of the method utilizing 10 mol% of **184** is the long reaction time (6 days compared to 60 h) and that pempidine is more expensive than **184**. Although **184** and pempidine can be recovered, the latter method is not practical.

Table 34 Efficiency of catalytic amounts of quinidine in the desymmetrization of *meso*-anhydrides



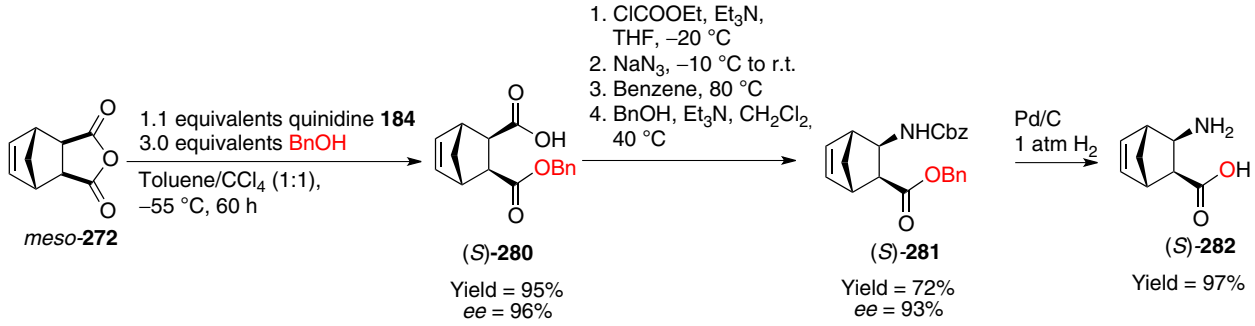
Entry	*Substrate*		*Yield (%) of hemiester*	ee *(%) of hemiester*
1		**270**	98	90
2		**272**	94	91
3		**276**	96	89

Bolm and coworkers also reported a solvent-free approach under ball milling conditions.[122] Structure **184** (1.1 equivalents), the solid *meso*-anhydride (1.0 equivalent), and *p*-methyl benzyl alcohol (1.0 equivalent) were added to a micro mill and were milled for 24–36 h (equation 17). The achieved selectivities were comparable to the selectivities observed in solution under otherwise similar conditions.



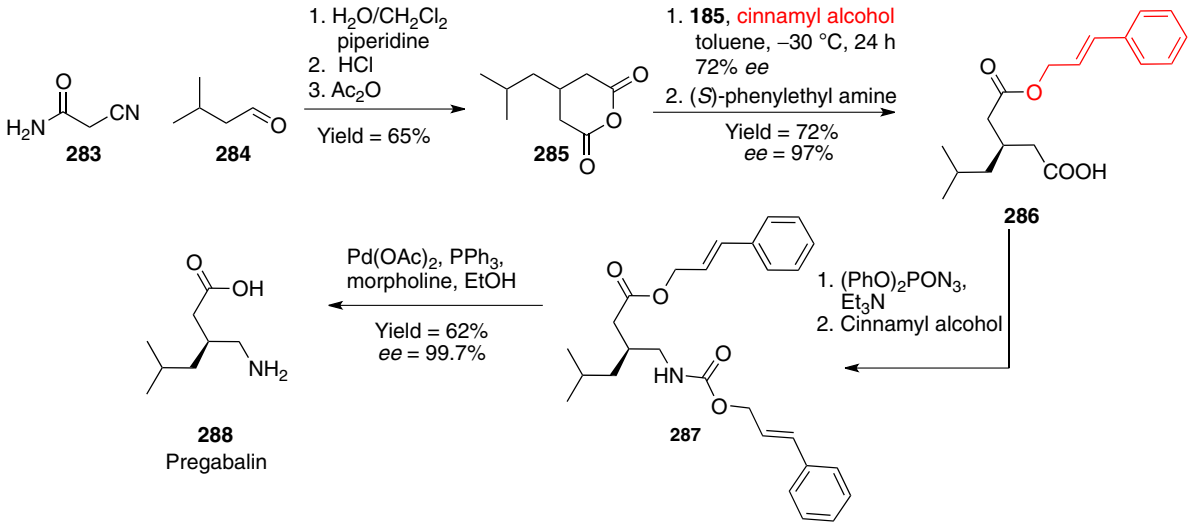
(17)

The enantiopure hemiesters, generated using **184** or **185**, can be converted into enantiomerically enriched *β*-amino acids by Curtius degradation followed by hydrogenation (Scheme 17).[33,123]



Scheme 17

The enantioselective ring opening of *meso*-anhydrides introduced by Bolm et al. enabled an improved synthesis of both enantiomers of *trans*-cyclohex-4-ene-1,2-dicarboxylic acid accomplished by Bernardi et al.,[124] and the synthesis of enantiopure alicyclic *β*-amino acids reported by Hamersăk.[125] Furthermore, the enantioselective ring opening of cyclic *meso*-anhydrides displays the key step in the enantioselective synthesis of the cyclopentyl core of axinellamines reported by Carreira and coworkers.[126] Hamersăk et al. applied the desymmetrization of *meso*-anhydrides mediated by quinine in the synthesis of pregabalin.[127] (*S*)-3-Aminomethyl-5-methylhexanoic acid (pregabalin) was designed as a potential drug for the treatment of epilepsy and neuropathic pain.[128] Bolm's method provided 72% *ee* with cinnamyl alcohol as nucleophile. Further enantiomeric enrichment was achieved by classic salt formation with chiral amines.[127] With the (*S*)-phenylethylamine salt an *ee* of 97% was achieved.[127] Enantioselective ring opening of *meso*-anhydrides presents a powerful tool for the synthesis of enantiopure hemiesters and has been presented as a practical method in *Organic Synthesis* (Scheme 18).[33,129]



Scheme 18

In 2000 Deng and coworkers applied the commercially available 'Sharpless-ligands' $(DHQD)_2AQN$ (**289**) and $(DHQ)_2AQN$ (**290**) in the desymmetrization of cyclic *meso*-anhydrides.[130] The selectivities obtained with **289** and **290** were excellent.[33,130,131] The substrate scope ranges from monocyclic to tricyclic *meso*-anhydrides. A big advantage of cinchona alkaloid catalysts is the possibility to generate both enantiomers in good yields by choosing the quinidine- or quinine-derived catalyst. The catalysts can be quantitatively recovered, which makes this approach synthetically useful (Table 35). Catalyst **290** is not shown but the selectivities are as good as those obtained with **289** (the product (*R*)-hemiester is the major enantiomer).

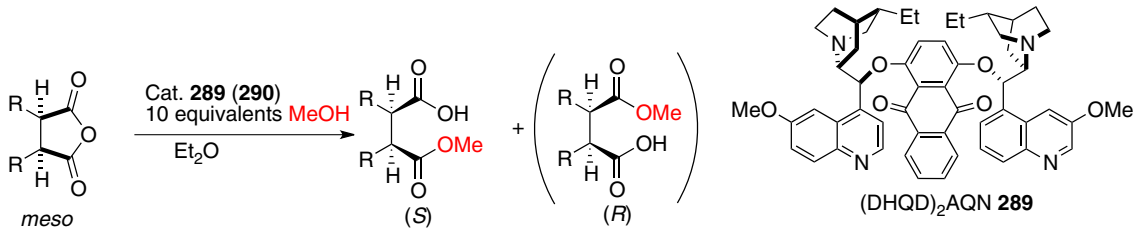
Deng performed the parallel KR of racemic 2-aryl and 2-alkyl succinic anhydrides utilizing catalyst **289** (Table 36).[131,132] The best results were obtained with trifluoroethanol as the nucleophile. The yields and selectivities obtained by catalyst **289** were excellent. Parallel KRs of 2-aryl-, as well as 2-alkyl-succinic anhydrides proceeded under mild conditions and the catalyst could be quantitatively recovered.

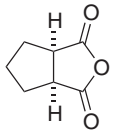
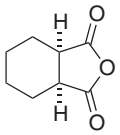
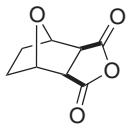
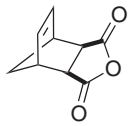
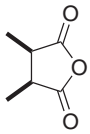
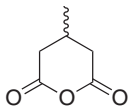
After Deng and coworkers successfully applied modified cinchona alkaloids in the desymmetrization of cyclic *meso*-anhydrides, and the KR of 2-aryl- and 2-alkyl succinic anhydrides, they were interested in the KR of urethane-protected *α*-amino acid-*N*-carboxyanhydrides,[133] which can be easily synthesized from racemic amino acids. The reaction generates a carbamate-protected amino ester and the unreacted urethane-protected *α*-amino acid-*N*-carboxyanhydride enantiomer. The latter can be hydrolyzed to the enantiomerically enriched protected amino acid. The products and the catalyst can be separated through extraction. This approach allows the preparation of enantiomerically enriched protected *α*-amino acids and the protected *α*-amino acid esters in high yields and excellent selectivities (Table 37).[33,131,133]

As DKR can theoretically produce 100% of product, Deng and his group were interested in converting the KR of urethane protected *α*-amino acid-*N*-carboxyanhydrides into a dynamic KR (Table 38). The racemization process needs to be faster than the selective transformation of the starting material. Owing to this requirement, Deng and coworkers increased the reaction temperature and utilized allyl alcohol in the alcoholysis. The achieved selectivities and yields were high (yield up to 95% and *S*-value up to 92).[33,131,134]

The same strategy afforded the DKR of 5-aryl-1,3-dioxolane-2,4-diones to prepare optically pure *α*-hydroxy carboxylic acid derivatives in the range of 61–85% yield (Table 39).[135] The enantioselectivities obtained with catalyst **289** were good to excellent for substrates containing aromatic moieties substituted in *para*- or *para* and *meta*-position. In contrast, enantioselectivities decreased for substrates bearing an *ortho*-substituted phenyl group.

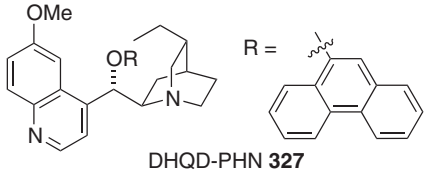
Table 35 Efficiency of catalyst **289** and **290** in the desymmetrization of cyclic *meso*-anhydrides



Entry	*Substrate*		*Catalyst (mol%)*	*Temperature (°C)*	*Yield (%)*	ee *(%)*
1		**291**	8 (8)	–30	99 (90)	95 (93)
2		**292**	5 (5)	–20	97 (95)	97 (93)
3		**293**	15 (15)	–20	88 (85)	96 (94)
4		**270**	10 (20)	–30 (–20)	82 (82)	95 (90)
5		**294**	5 (5)	–20	93 (88)	98 (98)
6		**295**	30 (30)	–40 (–35)	70 (56)	91 (82)

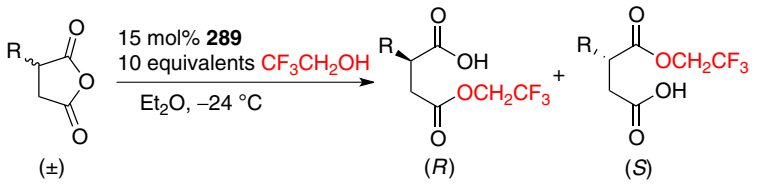
The results in parenthesis are obtained with $(DHQ)_2AQN$ as catalyst. The hemiesters were synthesized with the opposite absolute configuration.

To demonstrate the practical utility of their approach, the synthesis of (+)-biotin (333) was chosen as a test sequence. Deng followed the approach of Sternbach and Goldberg and increased the selectivity by utilizing catalyst **327** for the enantioselective ring opening of **330**. High *ee*s and excellent yields were obtained (Scheme 19).[136]



In 2008 Connon and coworkers introduced bifunctional cinchona alkaloid/thiourea-derived catalyst **334**[137] and utilized it in the desymmetrization of *meso* or prochiral mono, bi, and tricyclic anhydrides at room temperature at low catalyst loadings (1 mol%).[137] They proposed that the thiourea moiety activates the anhydride by hydrogen-bonding, whereas the cinchona moiety promotes general base catalysis. The yields for various substrates range from 93 to 98% and the obtained selectivities were high (Table 40).

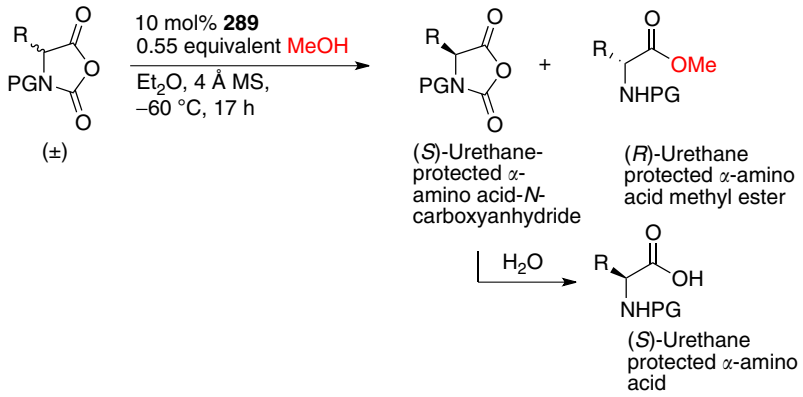
Table 36 Parallel KR of 2-aryl- and 2-alkyl-succinic anhydrides mediated by catalyst **289**



Entry	*R*		*Yield of (R)-hemiester (%)*	*Yield of (S)-hemiester (%)*	*ee of (R)-hemiester (%)*	*ee of (S)-hemiester (%)*
1	Me	**296**	41	36	80	93
2	Et	**297**	50	38	70	91
3	*n*-Octyl	**298**	41	38	66	98
4	Allyl	**299**	49	40	82	96
5[a]	Ph	**300**	32	44	87	95
6[a]	*m*-MeO–C_6H_4	**301**	30	45	83	96
7[a]	*p*-Cl–C_6H_4	**302**	29	44	76	96

[a]Yields obtained after the conversion of (*R*)-hemiester and (*S*)-hemiester into the β-aryl-γ-lactones.

Table 37 KR of urethane-protected α-amino acids-*N*-carboxyanhydrides utilizing catalyst **289**

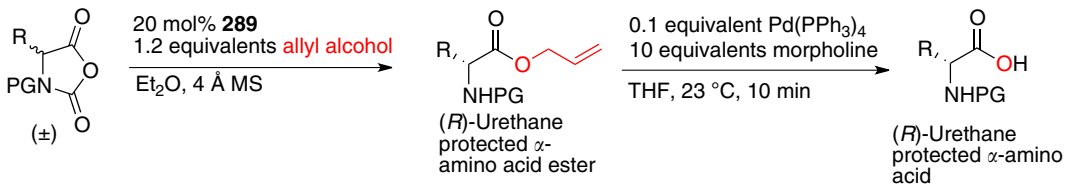


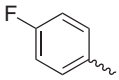
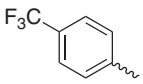
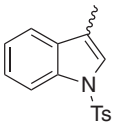
Entry	*R*	*PG*		*Time (h)*	*Temperature (°C)*	*Conversion (%)*	*ee %/ (% yield) of amino acid ester*	*ee %/ (% yield) of amino acid*	*S-value*
1	$PhCH_2$	Cbz	**303**	17	–60	51	93 (48)	98 (48)	114
2	4-F-$C_6H_4CH_2$	Cbz	**304**	31	–78	50	92 (48)	93 (42)	79
3	$BnOCH_2$	Cbz	**305**	72	–78	52	89 (49)	96 (44)	69
4	$(CH_3)_2CH$	Cbz	**306**	22	0	59	67 (58)	96 (40)	19
5	Ph	Cbz	**307**	16	–78	46	97 (45)	84 (46)	170
6	$PhCH_2$	Fmoc	**308**	46	–78	51	92 (50)	96 (47)	93
7	$PhCH_2$	Boc	**309**	15	–40	59	67 (56)	98 (41)	19
8	$PhCH_2$	Alloc	**310**	15	–60	50	91 (45)	91 (45)	67

The reaction mechanism of selective ring opening of cyclic anhydrides mediated by cinchona alkaloids was widely discussed in the literature.[138] Nucleophilic catalysis or general base catalysis are theoretically possible, but most of the evidence supports the latter mechanism.

Cinchona alkaloid-derived catalysts are capable of enantioselective ring opening of various cyclic anhydrides, 5-aryl-1,3-dioxolane-2,4-diones,[135] urethane-protected α-amino acid-*N*-carboxyanhydrides,[133] 2-aryl- and 2-alkyl-succinic anhydrides.[132] The selectivities and yields were consistently good to excellent. Deng's DKR is a powerful tool to generate enantioselectively enriched protected α-amino acid esters and protected α-amino acids from racemic α-amino acids. An advantage of the methods introduced by Bolm, Deng, and Connon is the ability to recover the catalysts quantitatively. All catalysts are commercially

Table 38 Efficiency of **289** in a dynamic KR of urethane-protected α-amino acids-*N*-carboxyanhydride using allyl alcohol as nucleophile



Entry	*R*	*PG*		*Time (h)*	*Temperature (°C)*	*Yield (%) of ester*	ee *(%) of ester*	*Yield (%) of acid*	ee *(%) of acid*
1		Cbz	**307**	1	23	97	91	91	90
2		Cbz	**311**	1	23	96	90	93	90
3		Cbz	**312**	1	23	95	90	88	90
4		Cbz	**313**	2	–30	93	92	93	92
5		Cbz	**314**	0.5	23	98	91	86	89
6		Cbz	**315**	1.5	0	95	90	95	89
7		Fmoc	**316**	1	23	98	90	92	90

available or can be easily prepared from available starting materials. In contrast to catalysts **184** and **289**, catalyst **334** gave excellent selectivities in the desymmetrization of cyclic *meso*-anhydrides at room temperature and did not require cooling such as needed for **184** (–55 °C) and **289** (–40 to –20 °C).

6.08.1.1.2 Metal complex-mediated enantioselective synthesis of esters

The second part of the chapter will introduce on the one hand metal complexes, which are capable acyl transfer catalysts and on the other complexes that serve as racemization catalysts to accomplish DKRs.

6.08.1.1.2.1 Cu-complex-mediated acylation reactions

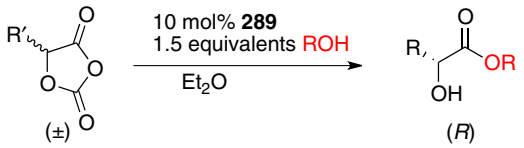
RajanBabu et al. introduced an yttrium-salen complex as a catalyst capable of selective acyl transfer onto secondary alcohols.[139] The obtained *S*-values were poor and ranged from 1.5 to 4.8. In 2003 Matsumura et al. reported the first synthetically useful KR of vicinal diols mediated by a Cu(II)-ion associated with a chiral (*R,R*)-Ph-box ligand **336**.[93] They proposed a coordination of the 1,2-diol with a metal-ion (M^{n+}) to form a reactive intermediate **A**. In the next step **A** is transformed to a metal alkoxide **B** by a weak base and reacts with an acyl halide to form product **C** (Scheme 20). In contrast to Fu's planar chiral DMAP-ferrocene derived catalyst **28**, in which the iron ion only acts as a structure-forming element, the copper ion of Matsumura's catalyst is involved in the acyl transfer.

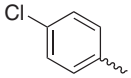
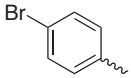
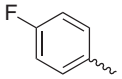
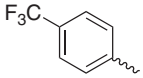
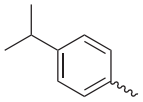
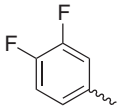
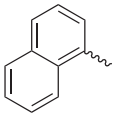
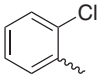
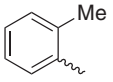
6.08.1.1.2.1.1 KR utilizing Cu-complexes

The first applications of catalyst **336**·$CuCl_2$ were in the KR of hydrobenzoin derivatives and racemic cyclic 1,2-diols (Table 41).[93] The Cu-complex gave extraordinary high enantioselectivities for the hydrobenzoins (*S*-value > 645). The selectivities for the cycloalkane 1,2-diols are good, but much lower compared to organocatalytic approaches (e.g., Schreiner's catalyst **238** with $S > 50$ for the enantioselective acylation).

In 2005 Reiser and coworkers reported the KRs of racemic 1,2-diols, hydrobenzoin, and α-hydroxycarbonyl compounds mediated by Cu(II)-aza-(bisoxazolines)-complexes (Table 42).[92] The yields and selectivities obtained for the substrates strongly depended on the type of ligand used in the reaction. The yields and selectivities achieved by Reiser's approach for hydrobenzoins

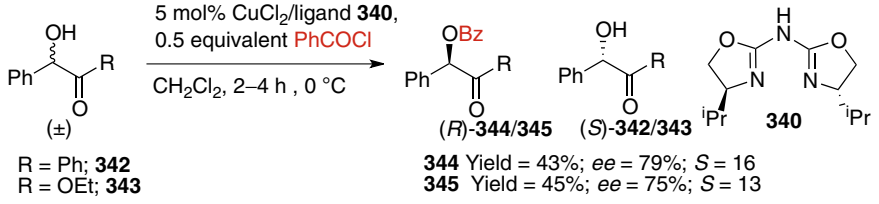
Table 39 Dynamic KR of 5-aryl-1,3-dioxolane-2,4-diones mediated by catalyst **289**



Entry	*R'*		*R-OH*	*Time (h)*	*Temperature (°C)*	*Yield (%) of ester*	ee *(%) of ester*
1		**317**	EtOH	24	–78	71	95
2		**318**	EtOH	24	–78	70	96
3		**319**	EtOH	24	–78	80	96
4		**320**	EtOH	24	–78	65	95
5		**321**	EtOH	24	–78	85	93
6		**322**	EtOH	8	–20	68	91
7		**323**	EtOH	24	–78	65	94
8		**324**	^{n}PrOH	14	–40	74	91
9		**325**	EtOH	10	–60	66	62
10		**326**	EtOH	4	–20	61	60

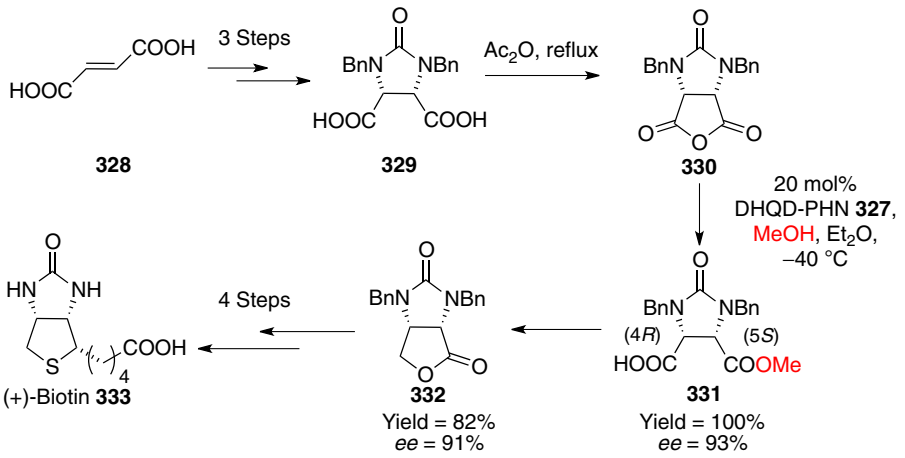
and *trans*-cycloheptane-1,2-diol are comparable to those obtained by Matsumura.[92] In contrast, the selectivities for the benzoylation of *trans*-cyclohexane-1,2-diol are higher.

Although the selectivities for substrates bearing two vicinal hydroxy groups obtained by Cu(II)-complexes (ligands: **339**, **340**, and **341**) were good to excellent, for α-hydroxycarbonyl compounds the achieved selectivities were only moderate (equation 18).



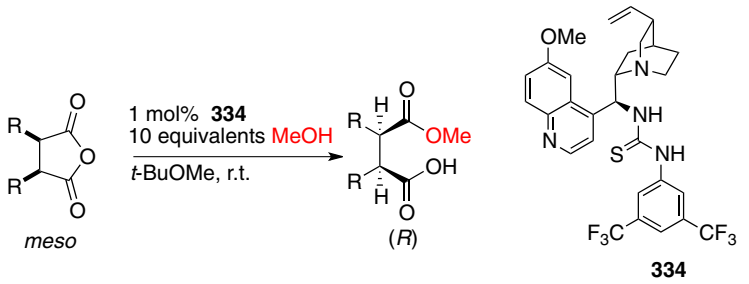
(18)

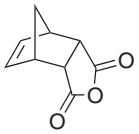
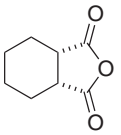
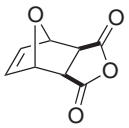
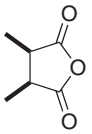
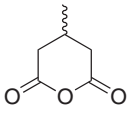
In 2006 Pfaltz and coworkers applied a Cu(II)-ion coordinated to a boron-bridged bisoxazoline (borabox) ligand as catalyst in the KR of racemic hydrobenzoin (equation 19), cyclohexane-1,2-diol (equation 20), 1,2-phenylethanediol (equation 21), and pyridyl alcohols (Table 43).[91]

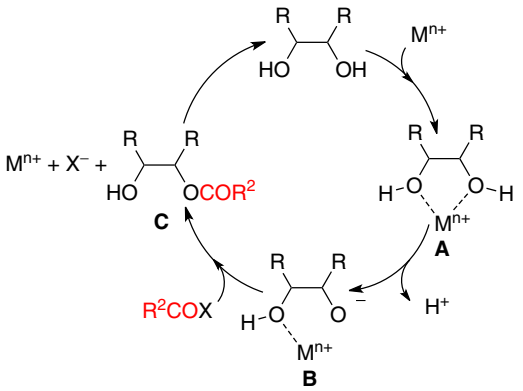


Scheme 19

Table 40 Desymmetrization of cyclic *meso*-anhydrides utilizing bifunctional catalyst **334**

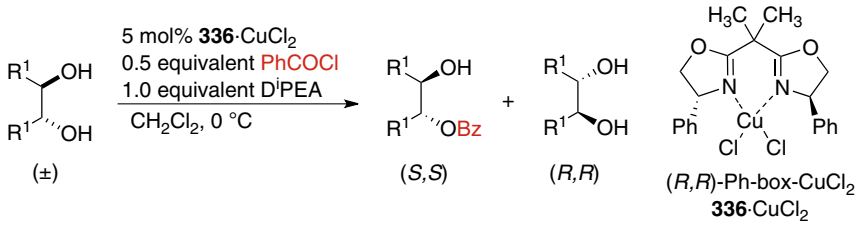


Entry	*Substrate*		*Time (h)*	*Yield (%) of hemiester*	ee *(%) of hemiester*
1		**270**	100	93	96
2		**277**	30	98	93
3		**273**	130	90	85
4		**335**	14	98	92
5		**295**	18	98	83



Scheme 20

Table 41 KR of hydrobenzoins and cyclic 1,2-diols mediated by catalyst **336**·$CuCl_2$



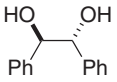
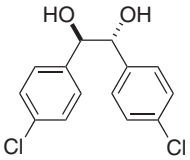
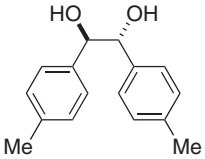
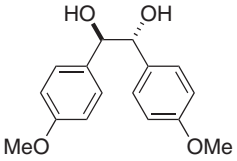
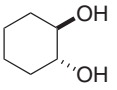
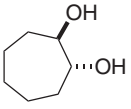
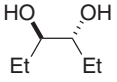
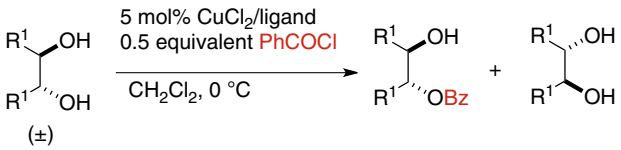
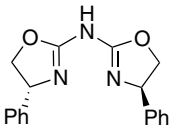
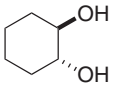
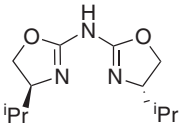
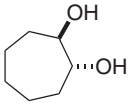
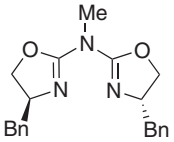
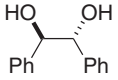
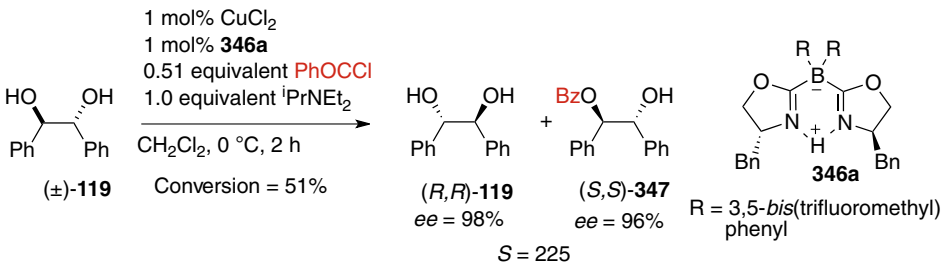
Entry	*Substrate*		*Yield (%) of ester*	ee *(%) of ester*	S-*value*
1		**119**	48	>99	>645
2		**120**	48	>99	>645
3		**337**	47	97	183
4		**338**	49	98	356
5		**121**	37	80	14
6		**239**	49	84	28
7		**339**	44	77	14

Table 42 Efficiency of Cu(II)-aza-(bisoxazoline)-complexes in the KR of racemic cyclic 1,2-diols and hydrobenzoin

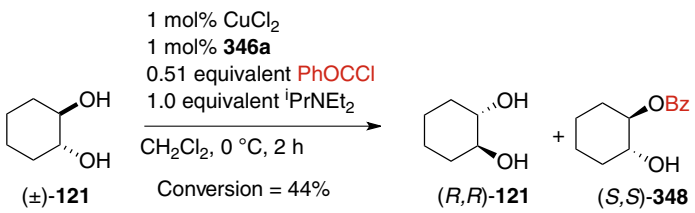


Entry	Ligand		Substrate		Yield (%) of ester	ee (%) of ester	Configuration	S-value
1[a]		**339**		**121**	46	83	*S,S*	22
2[b]		**340**		**239**	46	82	*R,R*	21
3[a,c]		**341**		**119**	49	99	*R,R*	751

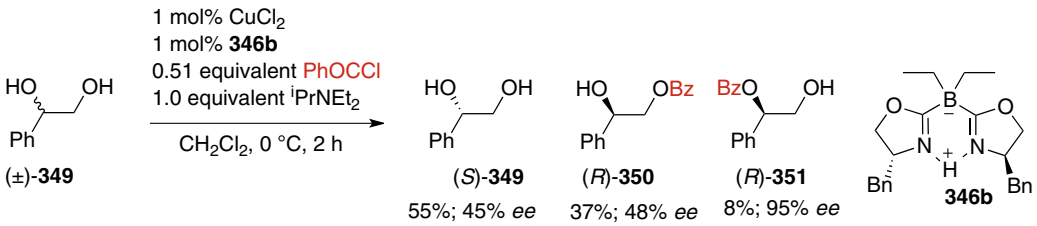
[a]Reaction time = 2 h.
[b]Reaction time = 3 h.
[c]Catalyst loading: 0.5 mol% $CuCl_2$/ligand.



(19)

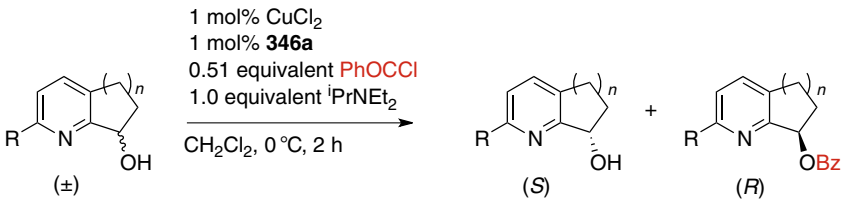


(20)



(21)

Table 43 Efficiency of catalyst **346a** in the KR of pyridyl alcohols



Entry	*R*	n		*Conversion (%)*	ee *(%) of alcohol*	ee *(%) of ester*	S-*value*
1	H	1	**352**	46	5	5	1
2	Ph	1	**353**	45	76	91	51
3	H	2	**354**	52	83	76	19
4	Ph	2	**355**	42	70	97	125
5	Cl	2	**356**	47	58	65	8

The selectivities for hydrobenzoin were excellent even at low catalyst loadings (1 mol%). The results for the borabox ligand **346a** and **346b** are comparable to those obtained with box-ligands (**336**, **339**, **340**, and **341**). Pyridyl alcohols containing a phenyl moiety at the pyridine ring can be resolved with high selectivities by catalyst **346a**.

6.08.1.1.2.2 Desymmetrization of meso*-1,2-diols mediated by Cu(II)-complexes*

Desymmetrization of *meso*-1,2-diols utilizing a copper(II)-ion coordinated by (*R,R*)-Ph-box ligand **336**·Cu(OTf)$_2$ was achieved with moderate to good selectivities (Table 44).[140] A drawback of this method is the high catalyst loading of 10 mol%. Organocatalytic approaches (e.g., Kündig's diamine-based catalyst **191**[75] or Oriyama's catalyst **168**[71] mediated the desymmetrization of similar substrates with higher *ee*s (e.g., substrate **110**; yield = 87%, *ee* = 78% with catalyst **191**).

Pfaltz applied the Cu(II)-borabox-derived catalyst **346a** to the desymmetrization of *meso*-1,2-diols and obtained increased selectivities compared to the Cu(II)-(*R,R*)-Ph-box catalyst **336**·Cu(OTf)$_2$ (Table 45).[141] The reaction proceeds at low catalyst loadings of 1 mol% and with enantioselectivities up to 94%. The ligands can be synthesized from readily accessible oxazolines. The borabox ligand structure can be assembled and varied by the reaction of metalated oxazoline with a diaryl or dialkylhaloborane.

6.08.1.1.2.3 Combination of metal complexes and enzymes in the DKRs of racemic alcohols

As mentioned in the 'Introduction,' the disadvantage of a KR is the limitation to 50% yield for the acylated substrate. Desymmetrizations can produce a theoretical yield of 100%, but they require *meso* or prochiral compounds as starting materials. To overcome the drawback of KR, fast racemization of one of the enantiomeric substrates is needed. In DKR the starting material racemizes, whereas one enantiomer gets selectively acylated. In a dynamic KR 100% theoretical yield is feasible (Scheme 21).

Examples for DKR utilizing just one catalyst (e.g., a chiral organic molecule, enzymes, or metal complexes) are rare. More common is a combination of two catalysts.[14] Possible racemization techniques were categorized by Zwanenburg et al.[142]: base-catalyzed racemization, Schiff base-mediated racemization, acid-catalyzed racemization, enzyme-mediated racemization as well as redox and radical induced racemization processes. Additionally, transition metals are also capable catalysts for the racemization of alcohols. In combination with enzymes usually metal complexes or base are applied to the racemization of the substrate and enzymes provide the enantioselective transfer of the acyl moiety. In the case of the base-catalyzed racemization, the substrate scope is mainly limited to molecules bearing an acidic proton at the stereogenic center.[14]

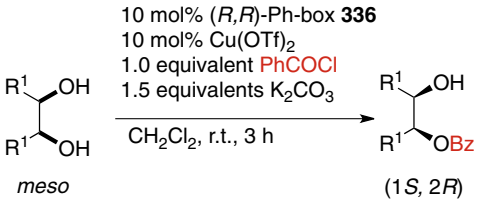
6.08.1.1.2.3.1 DKR of alcohols utilizing ruthenium-complexes for racemization and enzymes for selective acyl transfer

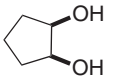
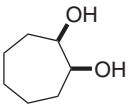
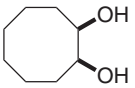
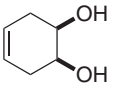
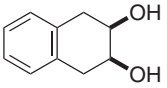
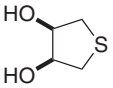
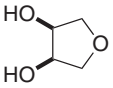
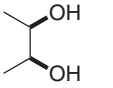
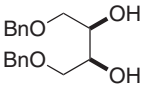
Iridium, rhodium, and ruthenium complexes are known to provide rapid racemization of secondary alcohols via hydrogen transfer, but just a few complexes are compatible with an enzymatic reaction.[14,143,144] It has been proposed that metal hydrides are the reactive intermediates in the hydrogen transfer reaction between metal catalyst and alcohol (Scheme 22).

In 1996 Williams and coworkers were the first to use a combination of a rhodium-catalyst and a lipase for the DKR of secondary alcohols.[145] The obtained selectivities were, however, moderate. In 1997 Bäckvall et al. reported a DKR of secondary alcohols mediated by a ruthenium catalyst and an immobilized lipase at 70 °C;[10] in 2005 an improved method for the dynamic KR of *sec.* alcohols at room temperature and at short reaction times was published.[146] The observed selectivities and yields were excellent and a wide range of secondary alcohols can be deracemized using this approach (Table 46). They proposed the following ruthenium complex **359** catalyzed racemization mechanism (Scheme 23).

Upscaling issues were addressed for the DKR of racemic 1-phenylethanol **30**.[147] At 1 mol scale, applying 0.05 mol% of ruthenium catalyst **359** and small amounts of enzyme after 20 h at 40 °C, 159 g (97% yield) of (*R*)-1-phenylethanol acetate (99% *ee*) were isolated.[147] The high efficiency was proved by carrying the reaction out at a 10 mol scale. The catalysts loadings of the

Table 44 Desymmetrization of *meso*-1,2-diols utilizing catalyst **336**·$Cu(OTf)_2$

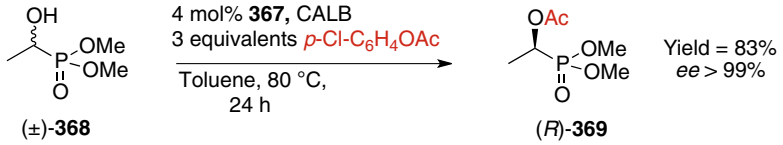


Entry	*Substrate*		*Yield (%)*	ee *(%)*
1		**110**	47	3
2		**357**	88	58
3		**194**	85	65
4		**169**	68	93
5		**170**	92	80
6		**358**	63	8
7		**111**	81	Racemic
8		**109**	78	97
9		**195**	36	96

ruthenium-complex **359** (0.01 mol%) and the biocatalyst were lowered and the reaction was performed in a more highly concentrated reaction mixture. After 21 days 1.43 kg (87% yield) of the product were isolated in excellent enantiomeric purity (97% *ee*).

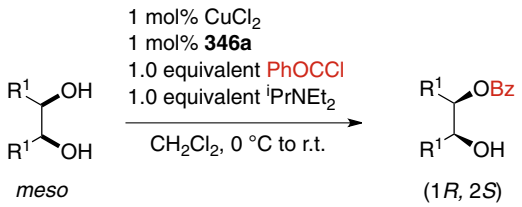
Bäckvall and Pàmies applied his approach to the DKR of various substrates such as α- and β-hydroxyphosphonates (equations 22 and 23)[148] as well as β-azido alcohols (equation 24).[14,143] The yields and selectivities for the α-hydroxyphosphonate and β-azido alcohol were high and the reactions were carried out under mild reaction conditions. β-Azido alcohols can serve as precursors for the synthesis of enantiopure β-amino alcohols. In the case of β-hydroxyphosphonates keto-byproduct **372** formed. Addition of 2,4-dimethyl-3-pentanol decreased the amount of **372**, but did not increase the amount of product.

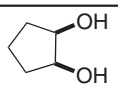
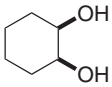
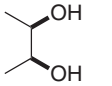
Dynamic kinetic resolution of racemic α-hydroxyphosphonates

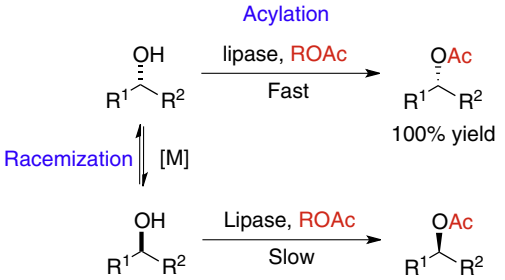


(±)-**368** (*R*)-**369** (22)

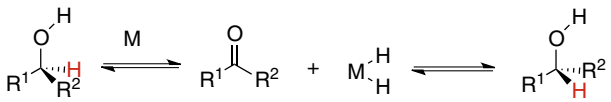
Table 45 Efficiency of catalyst **346a** in the desymmetrization of cyclic *meso*-diols



Entry	*Substrate*		*Yield (%)*	ee *(%)*
1		**110**	73	76
2		**72**	83	90
3		**109**	65	94

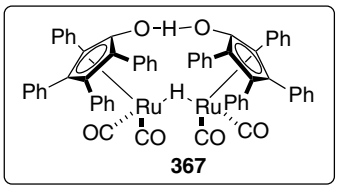


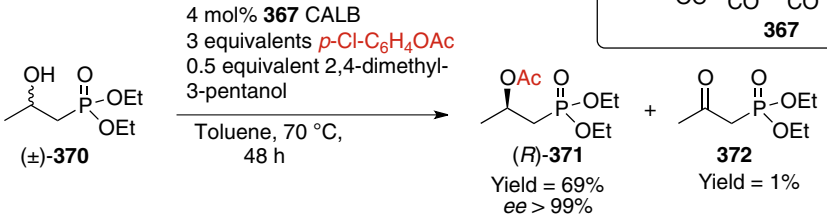
Scheme 21



Scheme 22

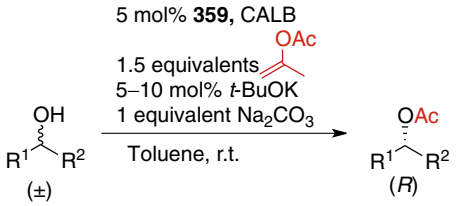
Dynamic kinetic resolution of β-hydroxyphosphonates

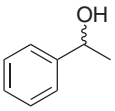
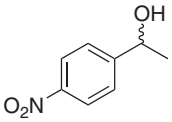
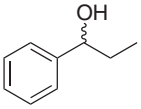
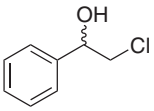
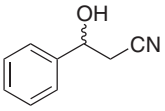
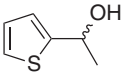
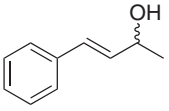
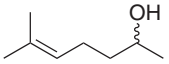
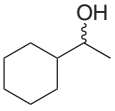
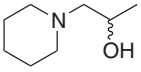
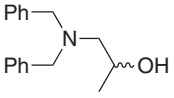




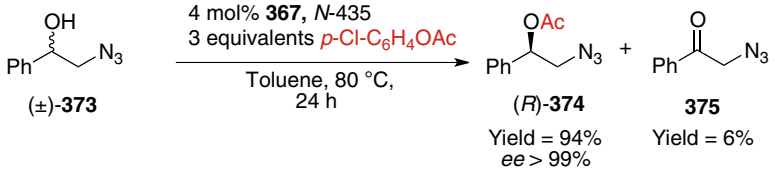
(23)

Table 46 Efficiency of catalyst **359** and CALB (*Candida Antarctica* lipase B) in the DKR of various secondary alcohols

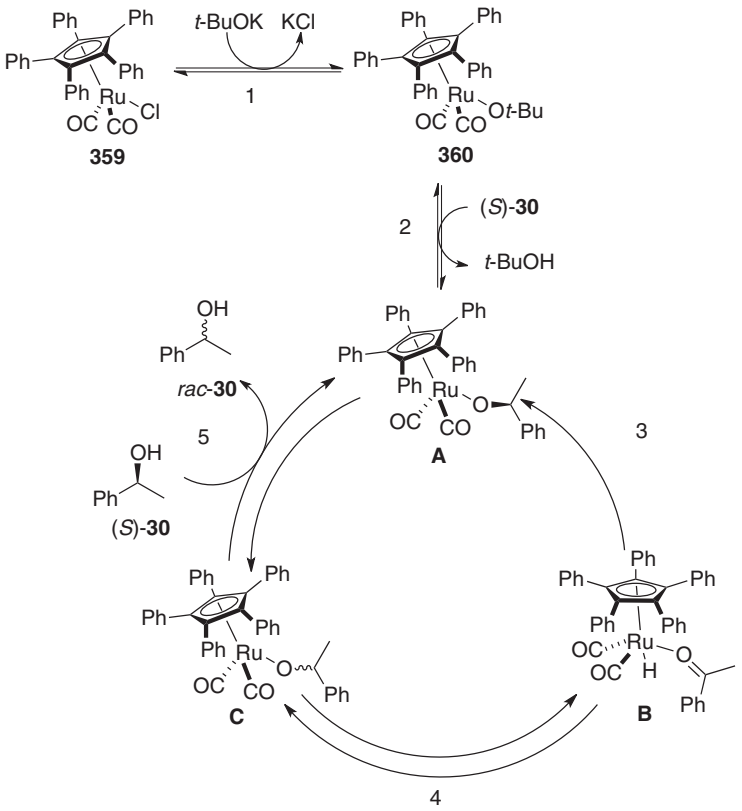


Entry	*Substrate*		*Time (h)*	*Yield (%)*	ee *(%)*
1		**30**	3	95	>99
2		**361**	20	99	>99
3		**146**	17	92	>99
4		**34**	13	83	>99
5		**362**	6	85	97
6		**363**	6	98	>99
7		**85**	18	89	>99
8		**364**	72	92	98
9		**86**	17	98	>99
10		**365**	5	>99	99
11		**366**	5	97	97

Dynamic kinetic resolution of β-azido alcohols



(24)

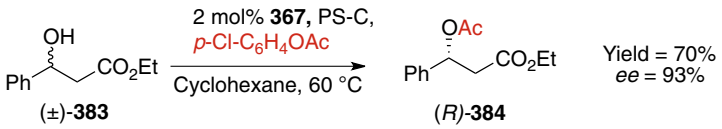


Scheme 23

To broaden the substrate scope, Bäckvall and coworkers optimized the conditions to afford an efficient DKR of α-hydroxy acid esters.[14,149] The best results were obtained utilizing catalyst **367** and *Pseudomonas cepacia* lipase applying 4-chlorophenyl acetate as acyl donor and cyclohexane as solvent.[149] The selectivities were good and the yields were high for substrates bearing an aryl moiety or a secondary carbon atom in β-position (Table 47). In contrast, the selectivities for substrates with a primary carbon atom in β-position and without aromatic substituent were poor ($ee = 30$; entry 6).

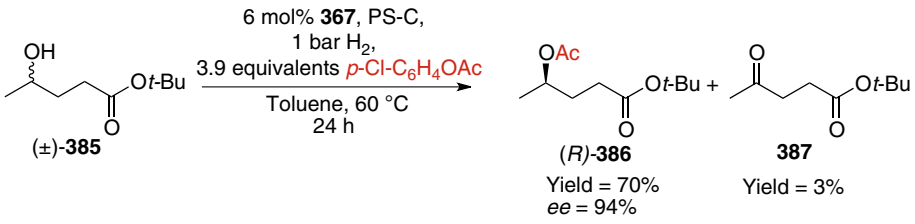
Subsequently, β-,[150] γ-,[151] and δ-hydroxy acid esters[152] were deracemized. The obtained selectivities were very good and the yields high. For γ- and δ-hydroxy acid esters H_2 as additional hydrogen source improved the yield (equations 25, 26, and 27).[14]

Dynamic kinetic resolution of β-hydroxy acid esters



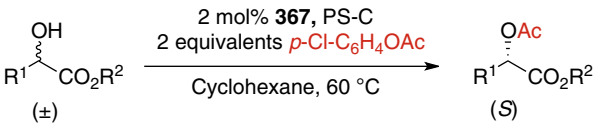
(25)

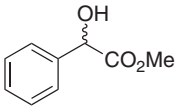
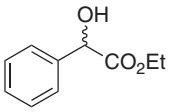
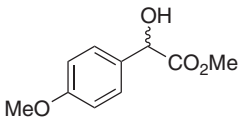
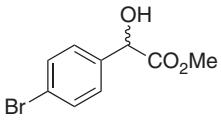
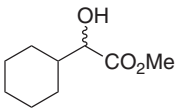
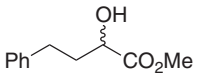
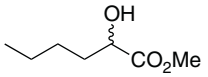
Dynamic kinetic resolution of γ-hydroxy acid esters



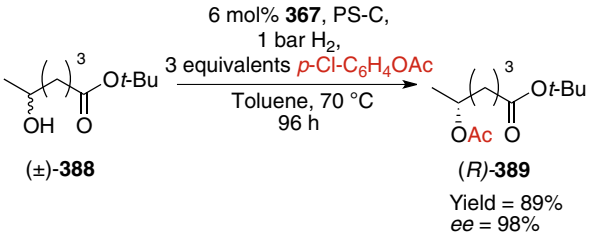
(26)

Table 47 Dynamic KR of α-hydroxy acid esters mediated by catalyst **367** and PS-C



Entry	*Substrate*		*Time (h)*	*Yield (%)*	ee *(%)*
1		**376**	48	80	94
2		**377**	72	74	96
3		**378**	48	76	94
4		**379**	72	69	98
5		**380**	48	80	98
6		**381**	48	62	30
7		**382**	24	60	80

Dynamic kinetic resolution of δ-hydroxy acid esters

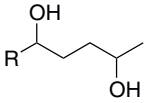
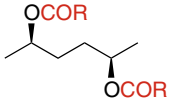
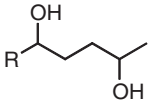
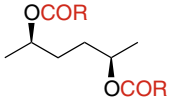
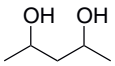
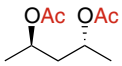
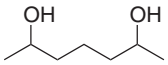
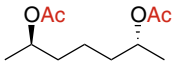
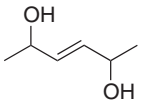
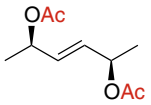
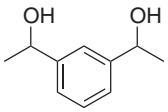
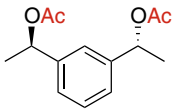
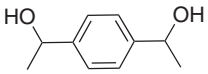
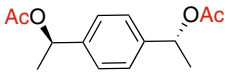
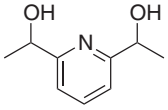
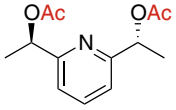


(27)

Bäckvall and coworkers used their approach for dynamic KRs of 1,3-, 1,4- and 1,5-diols.[14,153] In the case of 1,3-diols an intramolecular acyl transfer produced the undesired *meso* diacetate in 62% yield (Table 48; entry 3); 1,4- and especially 1,5-diols were obtained in good yields and high selectivities. This approach offers advantages compared to KR, because the resolved diols are usually available as a mixture of the racemic and the *meso* forms of the substrates. Hence, the theoretical yield of a KR would be 25% even under optimized reaction conditions.

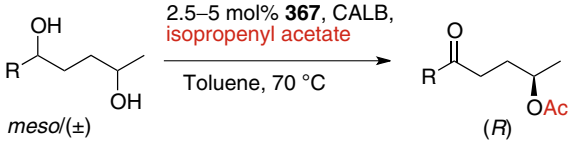
1,4-Diols can be converted into γ-hydroxy ketones with good selectivities and in high yields also utilizing catalyst **367** and CALB under modified reaction conditions (Table 49).[154] In contrast to the reaction conditions (acyl donor=*p*-chlorophenyl acetate) used to generate acylated 1,4-diols, Bäckvall and coworkers utilized isopropenyl acetate as acyl donor to obtain γ-hydroxy ketones as products. In the first step the enzyme acylates the less hindered alcohol function of the diol and acetone forms from isopropenol (keto-enol tautomerism), which is the leaving group of the acylation agent (isopropenyl acetate). Bäckvall proposed that the oxidation of the sterically more hindered OH-group of the diol mainly occurs because acetone is reduced more rapidly by

Table 48 Selective acylation of various diols coupled with a ruthenium-complex **367** introduced isomerization

Entry	*Substrate*		*Product*		*Time (h)*	*Yield (%)*	ee *(%)* (R,R/meso)
1		**390**		**397**	48	63	>99 (86/14)
2		**390**		**398**	1	47	>99 (96/4)
3		**391**		**399**	24	90	>99 (38/62)
4		**392**		**400**	24	63	97 (90/10)
5		**393**		**401**	24	43	>99 (74/26)
6		**394**		**402**	24	76	>99 (98/2)
7		**395**		**403**	24	77	>99 (98/2)
8		**396**		**404**	24	78	>99 (100/0)

Notes: Reaction conditions: 4 mol% **367**, 3 equivalents *p*-chlorophenyl acetate, CALB, toluene.

Table 49 Dynamic kinetic asymmetric transformation of 1,4-diols into γ-hydroxy ketones utilizing a ruthenium complex **367** and lipase

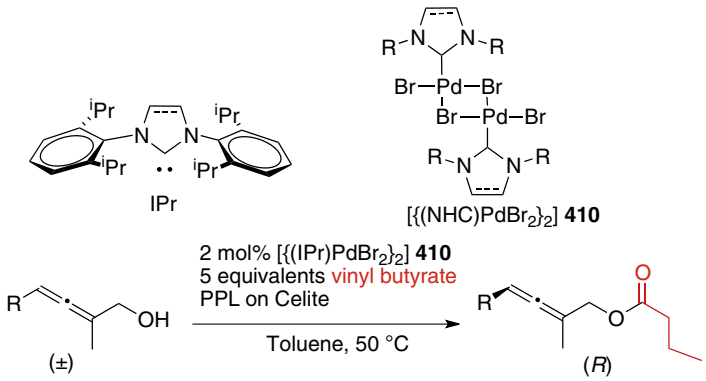


Entry	*R*		*Acyl donor (equivalent)*	*Time (h)*	*Yield (%)*	ee *(%)*
1	Ph	**405**	10	20	75	84
2	*i*-Pr	**406**	20	18	77	89
3	Cy	**407**	20	17	73	90
4	2-Naphthyl	**408**	10	18	82	79
5	*p*-F-C_6H_4–	**409**	10	36	75	86

the ruthenium complex **367** than the hindered OH-function of the 1,4-diol and therefore the γ-hydroxy ketone accumulates in the system.

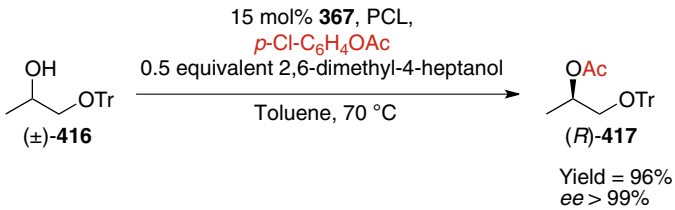
Allenes present a synthetically very useful class of axially chiral compounds.[155] Yet, short synthetic routes for the enantioselective synthesis of axial, helical, and planar chiral allenyl derivatives are rare. Deska and Bäckvall introduced the first DKR of allenols mediated by a palladium complex in combination with the enzyme porcine pancreatic lipase (PPL).[156] The yields are good and the obtained *ee*s ranged from 66 to 89% (Table 50). Enantioenrichment of the allenols can be achieved by enzymatic hydrolysis (*ee*=99%; yield=91% for **411**).

Table 50 Efficiency of catalyst **410** and porcine pancreatic lipase (PPL) in the dynamic version of KR (DKR) of allenols



Entry	*R*		*Time (h)*	*Yield (%)*	ee *(%)*
1	Ph	**411**	23	81	86
2	3-Tolyl	**412**	27	70	89
3	4-Chlorophenyl	**413**	24	83	89
4	2-Naphthyl	**414**	21	80	87
5	*n*-Pentyl	**415**	20	87	66

Park and coworkers used ruthenium catalyst **367** in combination with lipase to deracemize mono-protected 1,2-diols via DKR.[157] A trityl-protected diol acetate was obtained in excellent yield and *ee* = 99% (equation 28); 2,4-dimethyl-3-pentanol was added as to avoid the formation of the ketone byproduct.



(28)

6.08.1.1.2.3.2 DKR of alcohols utilizing an aluminum complexes for racemization and enzymes for selective acyl transfer

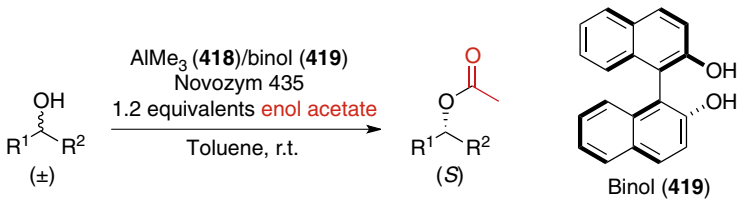
In 2006 Berkessel et al. reported a new system for DKR of secondary alcohols.[158] Instead of an expensive ruthenium complex for the racemization of the alcohol, Berkessel utilized an *in situ* generated aluminum complex. The enantioselective acylation of secondary alcohols was mediated by Novozym 435 and good to excellent *ee*s were obtained (**Table 51**). The aluminum complex was generated *in situ* from readily available substrates (e.g., $AlMe_3$ (**418**), binol (**419**)). The best yields and selectivities were obtained for $AlMe_3$ with binol as ligand. The reported substrate scope is limited to secondary aryl–alkyl and alkyl alcohols.

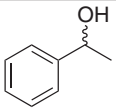
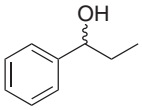
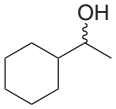
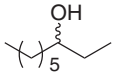
DKRs utilizing a ruthenium/aluminum complexes for the racemization of alcohols and a lipase for the selective acyl transfer offer the opportunity to generate enantiomerically enriched products in high yields (100% theoretically yield). A broad substrate scope can be deracemized by these approaches. Tolerating various functional groups (e.g., azides, halides, acid esters, and nitriles) DKR can serve as the key step for synthesizing complex enantiopure substrates (e.g., amino alcohols). The ruthenium complexes **359** and **367** as well as the lipases Novozym 435 and PS-D are commercially available. Catalysts **418**/**419** can be generated *in situ* by mixing commercially available reagents (binol and $AlMe_3$).

6.08.2 Conclusions and Outlook

In the past 20 years various catalyst families for selective acyl transfer have been developed. Today, metal complexes as well as organic molecules still can compete with enzymatic approaches in some asymmetric acylation reactions (e.g., Fu's KR step in the total synthesis of epothilone,[38] Deng's enantioselective ring opening of a *meso*-anhydride in the synthesis of biotin,[136] and Schreiner's KR of cyclic *trans*-1,2 diols[27]). Especially KRs or desymmetrizations of secondary alcohols are excellent entry points for producing stereochemically pure building blocks and many catalyst systems capable of enantioselective acyl transfer in this

Table 51 Efficiency of an *in situ* generated $AlMe_3$/binol-complex in combination with Novozym 435 in the dynamic KR of secondary alcohols



Entry	*Substrate*		*$AlMe_3$ (equivalent)*	*Time (h)*	*Yield (%)*	ee *(%)*
1		**30**	0.1	3	96	96
2		**146**	0.1	18	99	98
3		**86**	0.2	19	97	99
4		**87**	0.2	18	93	80
5		**420**	0.2	18	95	95

substrate class have been developed in the last decade. In stark contrast, examples of KRs of primary and tertiary alcohols are rare (see Miller's peptide catalyst for the acylation of a tertiary alcohol[84] and Oriyama's KR of a glycerol derivative[73]) and the identification of new catalysts for these substrate classes would be desirable. Although the identification of new catalysts for enantioselective or site-selective transformations is generally challenging, it still is a highly desirable goal. The examples presented in this chapter show the potential of asymmetric acyl transfer as a tool for the synthesis of enantiopure substrates. All catalysts are highly chemoselective and therefore their substrate scope is limited, yet this limitation offers applications as catalysts for late-key-steps in natural product synthesis. Examples for the successful utilization of small organic catalysts for enantioselective acyl transfer in natural product synthesis were reported by Fu (epothilone, (–)-baclofen),[38] Birman (lobeline),[64] Hamersăk (pregabalin),[127] and Deng (biotin).[136] Miller and Griswold impressively demonstrated the potential of peptide catalysts in the site selective functionalization of substrates containing different OH-groups as present in glucosamines, glucosides,[88] and erythromycin A.[89] Furthermore, peptides represent, to the best of our knowledge, the only catalyst family that was successfully utilized in the selective acyl transfer onto primary, secondary, and tertiary alcohols. These examples give hope that further investigations may lead to highly chemoselective catalysts capable of selective acylation of a specific OH-group in a polyol such as vancomycin. Nature uses enzymes for such complex problems. Hence, the design of a chemoselective catalyst is maybe the biggest challenge in asymmetric synthesis, as enzymes are known to be complex macromolecules displaying secondary, tertiary, and quaternary structure.

The combination of two catalysts is also a powerful tool for asymmetric acyl transfer reactions. Bäckvall et al. showed the practical use of his approach (DKR via combination of Ru-catalyst and enzyme) by performing large-scale experiments (up to 10 mol). The obtained selectivity (*ee* = 97%) and yield (87% = 1.43 kg) for (*R*)-1-phenylethanol acetate were still good on large scale.[147]

To date catalysts are mostly identified through trial and error approaches or by using time consuming screening methods, but the investigation of processes for chemical recognition of the substrate by the catalyst have become more important. In the cases of Birman's amide-based catalysts **127**/**128** and Schreiner's peptide catalyst **238**[94] computations were able to shed some light onto the selective acyl transfer process. Although for **127**/**128**[61] π–π interactions seem to be responsible for the chemical recognition and the selective acylation, in peptide **238** hydrogen bonding as well as attractive dispersive interactions between the peptide backbone and the substrate seems responsible of the differentiation between the two enantiomers. Other groups (e.g., Yamada et al., Fuji et al., and Connon et al.) investigated the conformational change of their free catalysts and the acylium ion adduct. All three proposed an 'induced fit' process for which NMR-experiments provided some evidence.[44,49,50]

Although the first steps to a better understanding of the acyl transfer as well as the substrate recognition mechanism of the catalyst have been made, we are still far from rational catalyst design. Much more work on the insights of these complex processes will be needed to achieve this goal. Improved computational and analytical methods may prove critical in this endeavor.

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6.09 Synthesis of Esters and Lactones

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Glossary

Activated esters Derivatives of carboxylic acids, not necessarily only esters, with enhanced reactivity toward the formation of esters and lactones are commonly called activated esters.

Carboxyl group activation (CGA) It describes the esterification or lactonization with activation of the carboxyl group before reaction of the activated species with the requisite alcohol.

Hydroxyl group activation (HGA) It describes the esterification or lactonization with activation of the hydroxyl group before reaction of the activated species with the requisite carboxylic acid.

Kinetic resolution It describes the separation of two enantiomers of a racemic mixture via a chemical reaction where the enantiomers react with different reaction rates.

Transesterification It describes the formation of an ester or a lactone from another ester or lactone via an equilibrium-driven process.

6.09.1 General Information

Esters and lactones are of crucial importance and omnipresent in natural and synthetic products. Some of the most important naturally occurring esters and lactones and synthetic intermediates are outlined in Figure 1. Triglycerides, such as **F1-5** are of utmost biological relevance, whereas myricyl palmitate (**F1-2**) is the main ingredient of beeswax. Ethyl formate (**F1-1**) is of fruity flavor and used as olfactory component. Furthermore, this ester is employed on large scale as solvent for cellulose acetate, cellulose nitrate, and various oils. Whisky lactone (**F1-3**) is another important substance used for perfumes as well as the flavoring of liquor, whereas aspartame (**F1-6**) is an artificial sweetener. Important drugs contain ester functional groups: acetylsalicylic acid (**F1-4**, analgesic), enalapril (**F1-7**, ACE-inhibitor), and taxol (**F1-8**, mitotic inhibitor used in cancer chemotherapy) are exemplarily shown in Figure 1.

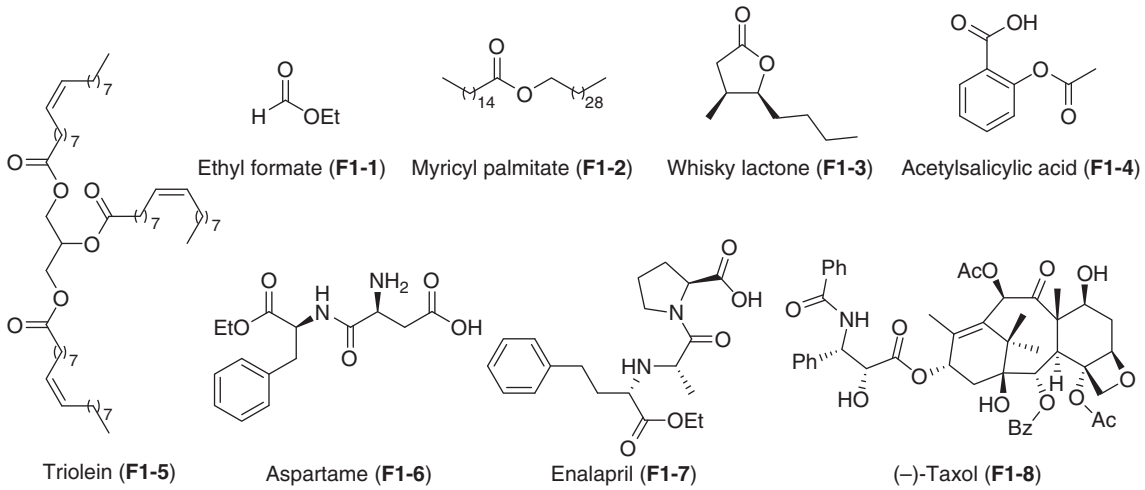


Figure 1 Examples of important esters and lactones.

Although the compounds displayed in Figure 1 represent only a tiny fraction of biologically and industrially important esters, it becomes absolutely obvious that the formation and further elaboration of this functional group is of utmost importance. At present various methods for the selective esterification and lactonization belong to the most basic synthetic operations in the repertoire of organic chemists. After Fischer's seminal publication on the acid-catalyzed esterification of carboxylic acids with alcohols in 1895,[1] the way was paved to this highly fertile research area. Since then, numerous methods have been developed to mildly convert acids and alcohols into the corresponding esters or lactones, mostly after intermediary activation of either reaction partner.

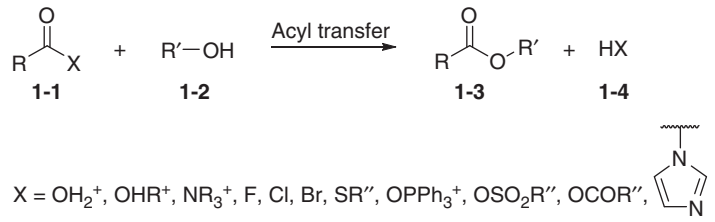
Several review articles on esterification and lactonization have appeared and they are cited at the appropriate places. Furthermore, a chapter on the formation of esters and activated esters has been included in the first edition of Comprehensive Organic Synthesis (Synthesis of Esters, Activated Esters and Lactones).[2] This present chapter serves as an update to the previously reported chapter in Comprehensive Organic Synthesis.

6.09.2 Formation of Esters and Activated Esters

6.09.2.1 Synthesis of Esters by Acyl Transfer to Alcohols (Carboxyl Group Activation)

The most common methods for the preparation of esters and lactones proceed via carboxyl group activation (CGA) and subsequent reaction with a suitable alcohol. The simplest example of such a CGA reaction is represented by direct reaction of carboxylic acids and alcohols to yield the corresponding ester via acid catalysis (Fischer esterification). However, as this procedure also offers severe disadvantages for more complex and/or acid-sensitive substrates, various other protocols have been developed. Scheme 1 provides a general overview of different methods, which are discussed within this section of the chapter.

In any case, the mechanistic background for the esterification is quite similar. The alcohol is often reacted with an activated derivative of the carboxylic acid and the activating group X is replaced by the alcohol moiety. The reaction proceeds through either

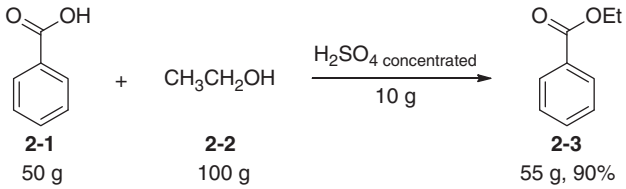


Scheme 1 General concept of CGA reactions.

an addition–elimination via attack of the incoming nucleophile at the sp^2 carbon atom or an elimination–addition sequence. Importantly, the configuration of the alcohol remains intact during the reaction. X must be a good leaving group to maximize the efficiency of the esterification protocol by minimizing electron donation to the carbonyl functional group.

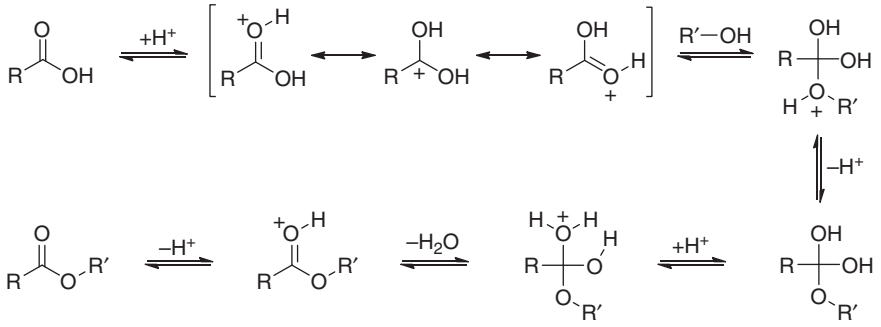
6.09.2.1.1 Esters from carboxylic acids and alcohols under acid catalysis

Initial experiments toward the esterification of simple carboxylic acids and alcohols, catalyzed by relatively large amounts of mineral acids were first reported in the second half of the nineteenth century. In 1895, Fischer examined these methods and made a first attempt to improve on previously reported protocols.[1] Fischer observed that satisfactory yields of the requisite esters were obtained when the corresponding carboxylic acid and the alcohol were mixed and heated to reflux for several hours in the presence of catalytic amounts of strong acids, such as hydrochloric acid or preferably sulfuric acid. Besides the esterification of benzoic acid (**2-1**) and ethanol (**2-2**), outlined in Scheme 2, Fischer successfully employed these conditions for various other acids known at that time and prepared various carboxylic esters. At present, Fischer esterification is commonly employed in undergraduate teaching laboratory courses. In a typical procedure, the alcohol not only serves as substrate but also as solvent for this simple procedure.



Scheme 2 Fischer esterification – original procedure.

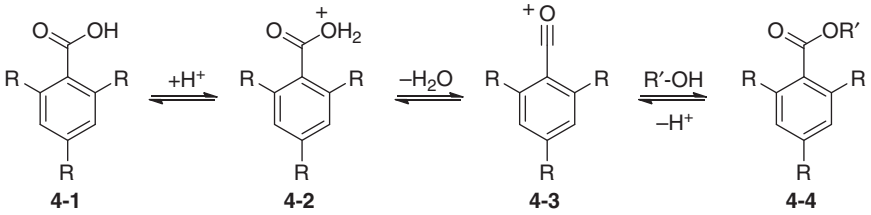
In most cases, the Fischer esterification proceeds via an $A_{AC}2$ mechanism (A=acid catalyzed; AC=acyl transfer; 2=bimolecular) as shown in Scheme 3. Initial activation of the carboxyl functional group is followed by the rate-determining attack of the alcohol at the positively polarized carbon atom before proton transfer and elimination of water release the ester.



Scheme 3 CGA esterification – the $A_{AC}2$ mechanism.

An alternative mechanism for the acid-catalyzed esterification reaction is outlined in Scheme 4. This $A_{AC}1$-mechanism (where, A=acid catalyzed; AC=acyl transfer; 1=unimolecular) is observed when the carboxylic acid is sterically congested as demonstrated on trisubstituted aromatic substrate **4-1**.[3–6] Protonation of the carbonyl group is then followed by the formation of an acylium cation (**4-3**), which reacts with the alcohol present in the reaction medium. The $A_{AC}1$-mechanism is not observed when the aromatic substituents exhibit a strong M^+-effect as in such cases the aromatic ring undergoes substitution (e.g., sulfonation).

Although this method is extremely simple, it cannot be applied to acid- or temperature-sensitive substrates. Furthermore, the esterification is a completely reversible process with the equilibrium far from unidirectional. Thus, complete conversion can only



Scheme 4 CGA esterification – the $A_{AC}1$ mechanism.

be obtained when one component, in most cases the alcohol, is used in large excess. Alternatively, the yield can also be increased by constant removal of water formed during the esterification and this can be achieved either via addition of molecular sieves or via azeotropic distillation using a Dean–Stark apparatus.

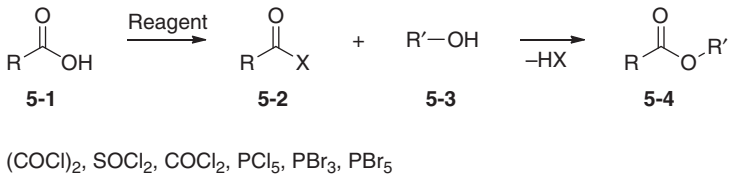
Another drawback of the acid-catalyzed esterification according to the $A_{AC}2$-mechanism is the significantly reduced yield when sterically hindered carboxylic acids are used. Also, α- or β-branched alcohols are not appropriate substrates as often dehydration is observed.

Fischer esterification has been successfully carried out with a variety of different acids as not only strong mineral acids are catalytically active. Most noteworthy, graphite bisulfate, *p*-toluenesulfonic acid, ferric sulfate, and more recently, Lewis acids such as $HfCl_4$[4–6] and $ZrCl_4$ have been employed. An overview of these reactions is also provided in the first edition of Comprehensive Organic Synthesis.[2]

6.09.2.2 Acyl Transfer via Anhydrides and Activated Esters

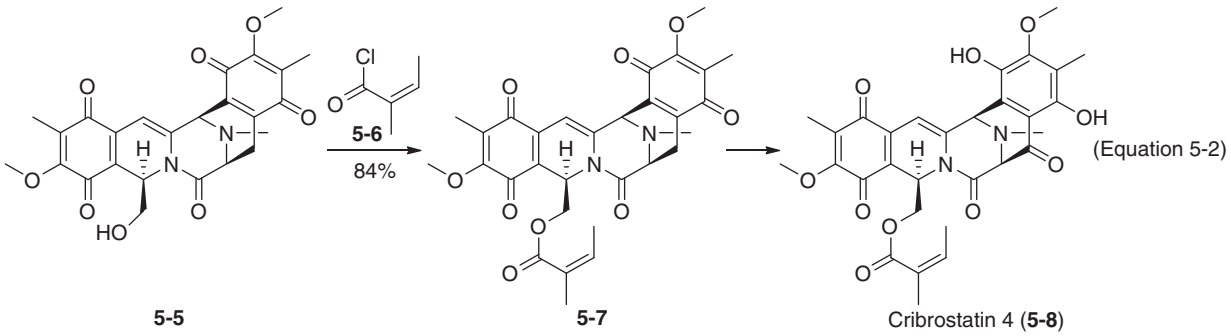
6.09.2.2.1 Acyl transfer via acid halides

Quite early, the reaction of acid halides with alcohols was recognized as a very powerful method for the formation of esters. The activated species is produced and subsequently reacted with a suitable alcohol (see equation 5-1, Scheme 5). Most importantly, in contrast to the Fischer esterification discussed in Section 6.09.2.1.1, complete conversion and thus high yields of the desired reaction products can be achieved. However, the conversion of carboxylic acids to the corresponding acid halides with reagents such as thionyl chloride, phosphorus trichloride, phosphoryl chloride, or oxalyl chloride results in the formation of highly acidic by-products (hydrogen chloride or hydrogen bromide), which can cause decomposition of acid-labile starting materials, reaction with acid-sensitive functional groups, or epimerization of α-chiral substrates.



(Equation 5-1)

$(COCl)_2$, $SOCl_2$, $COCl_2$, PCl_5, PBr_3, PBr_5

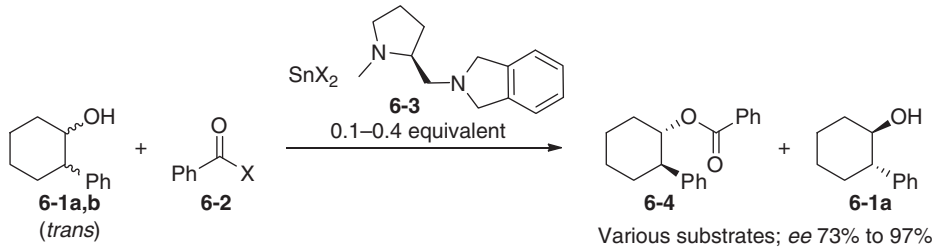


(Equation 5-2)

Scheme 5 Formation of esters via acid halides and application in the synthesis of (±)-cribrostatin 4 (**5-8**).

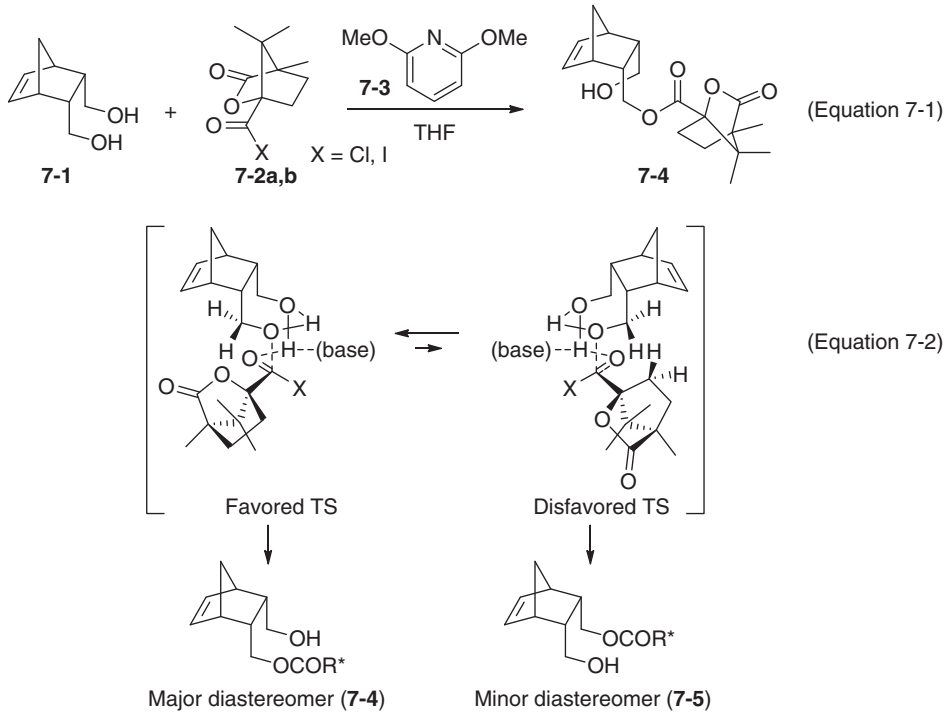
Although this simple method was developed many decades ago and despite considerable progress in this area, acid halides are still commonly employed reagents, as evidenced by Saito's synthesis of racemic cribrostatin 4 (**5-8**),[7] outlined in Scheme 5.

Oriyama developed an enantioselective acylation method that allowed the desymmetrization of *trans*-racemic alcohol **6-1a,b** (Scheme 6),[8] applying chiral proline-derived diamine complex **6-3**. Catalyst loadings of 0.1–0.4 equivalent and fair-to-excellent *ee* (73–97%) were reported for various substrates.



Scheme 6 Desymmetrization of racemic alcohols via esterification with acid halides in the presence of chiral amines.

Yamamoto developed a different approach toward the desymmetrization of *meso*-diols, utilizing optically active camphanoyl halides **7-2a,b** as acylating reagent, as exemplarily shown in Scheme 7.[9] The corresponding monoacylated derivatives were isolated in acceptable yields (51–84%) with moderate-to-good diastereoselectivities (*de* 74–88%). The unexpectedly high level of enantioselectivity was explained via the hydrogen-bonded transition-state model in Scheme 7 (equation 7-2). The favored product **7-4** is obtained via the sterically less demanding transition state.

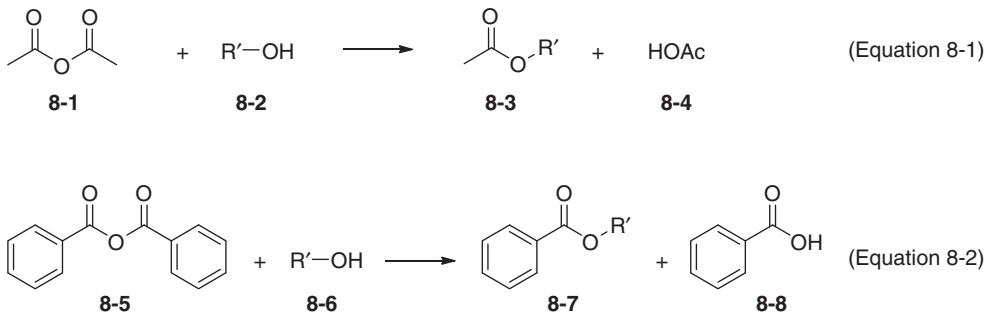


Scheme 7 Desymmetrization of *meso*-diols with camphanoyl halides.

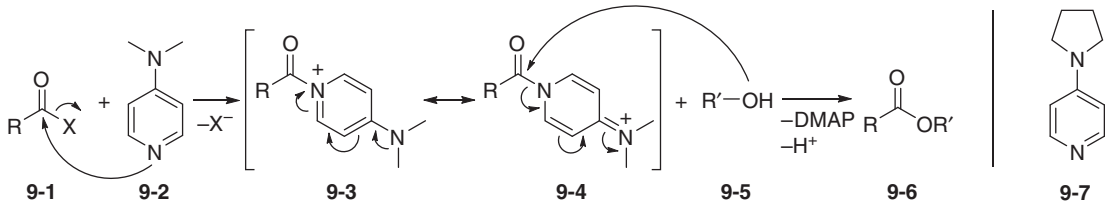
6.09.2.2.2 Acyl transfer via anhydrides

When anhydrides are employed in the esterification reaction, 50% of the acid component is lost as only one of the acid moieties is converted to the desired ester. Thus, this method is only recommended for simple, inexpensive carboxylic acids with a low degree of functionalization, such as acetic anhydride (**8-1**) or benzoic anhydride (**8-5**, Scheme 8). Routinely, esterification with anhydrides is carried out in pyridine. Acid chlorides are commonly converted to the corresponding esters in dichloromethane with pyridine or amine bases such as triethylamine.

In the late 1960s, Steglich observed a tremendous rate acceleration when a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP; **9-2**) was added to the reaction medium.[10] The effect was even more pronounced when 4-pyrrolidinopyridine (**9-7**) was employed as catalyst.[11–15] The mechanistic explanation for the catalytic activity of **9-2** and **9-7** is outlined in Scheme 9. Nucleophilic attack of the aromatic nitrogen onto the carbonyl group is facilitated by the lone pair at the nitrogen atom in *para*-position to the aromatic heteroatom, resulting in resonance-stabilized activated intermediate **9-3**/**9-4**. Next, the requisite alcohol reacts with the activated species and the desired ester is formed with concomitant release of the acylation catalyst. A rate acceleration of up to four orders of magnitude can be observed when DMAP is added to the reaction mixture.

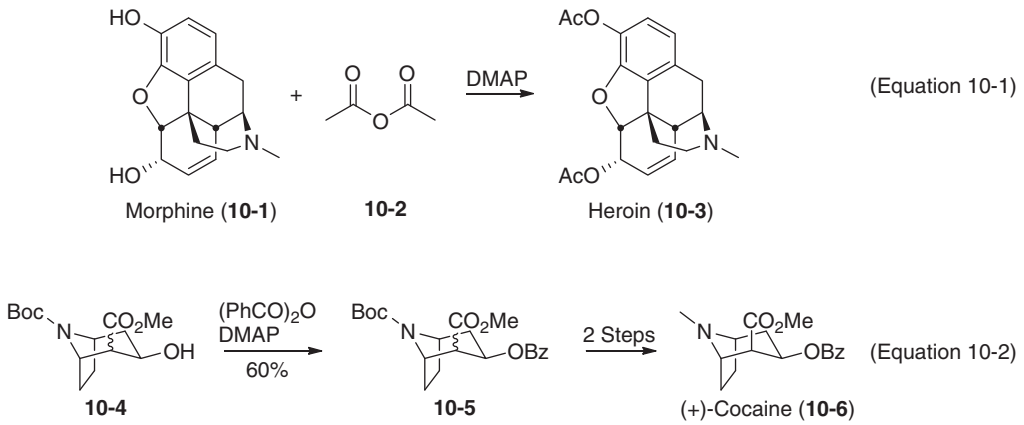


Scheme 8 Esterification using commercially available anhydrides.



Scheme 9 Rate acceleration in esterification protocols with DMAP.

Anhydrides of simple carboxylic acids are commercially available and acetates and benzoates often serve as protecting group for hydroxyl moieties. Many natural products or derivatives thereof contain esters and the installation of these groups employing anhydrides is easy and straightforward, as demonstrated by Wright's synthesis of heroin (**10-3**) from morphine (**10-1**), published in 1874 (DMAP was added in more recent protocols),[16] or Pearson's synthesis of cocaine (**10-6**).[17] Both examples are displayed in Scheme 10.



Scheme 10 Preparation of heroin (**10-3**) and cocaine (**10-6**) via esterification with anhydrides.

As DMAP was identified as a highly versatile and efficient acylation catalyst, several research groups investigated the development of a chiral version of this catalyst. The most prominent examples of such chiral acetylation catalysts are summarized in Figure 2. Chiral DMAP–ferrocene derivatives have been employed (**F2-1**–**F2-4**; Fu),[18–21] additionally, pyridine derivatives with chiral side chains were found to express enantioselectivity as well as catalytic activity (**F2-5**, **F2-6**; Connon).[22] Fuji published the application of **F2-7** as chiral catalyst for the desymmetrization of *meso*-diols.[23] In 1998, Connon reported the preparation of a magnetic nanoparticle-supported chiral DMAP analog (**F2-8**), which allowed the kinetic resolution of racemic alcohols in high selectivity.[24] The magnetic properties of the catalyst nanoparticles allow easy recovery of the catalyst after completion of the reaction.

The application of chiral ferrocene-based DMAP analog **F2-3** is shown in Scheme 11 with the kinetic resolution of racemic benzylic alcohol **11-1**.[19]

Vedejs and Chen also developed a chiral DMAP derivative for kinetic resolutions of racemic alcohols.[25] Chiral reagent **12-1** was prepared from DMAP via a five-step sequence, before reaction with chloroformate **12-2** delivered the chiral acylating reagent **12-3**, equation 12-1, Scheme 12. Formation of **12-3** as active species is required as reaction of **12-1** with isobutyl chloroformate and the

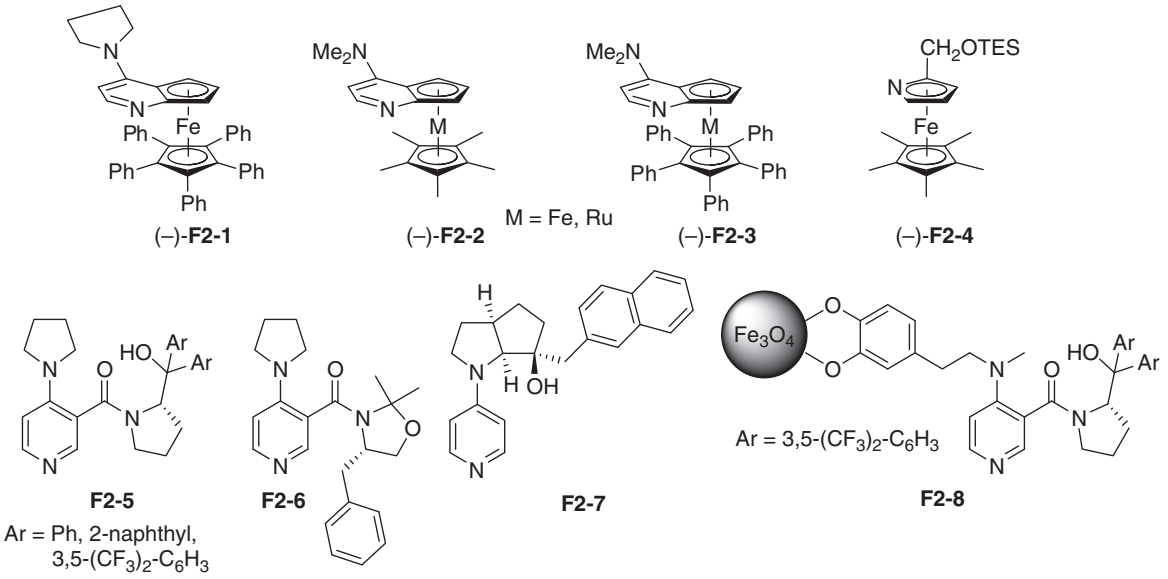
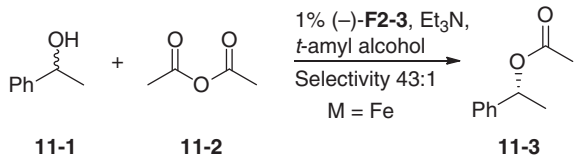
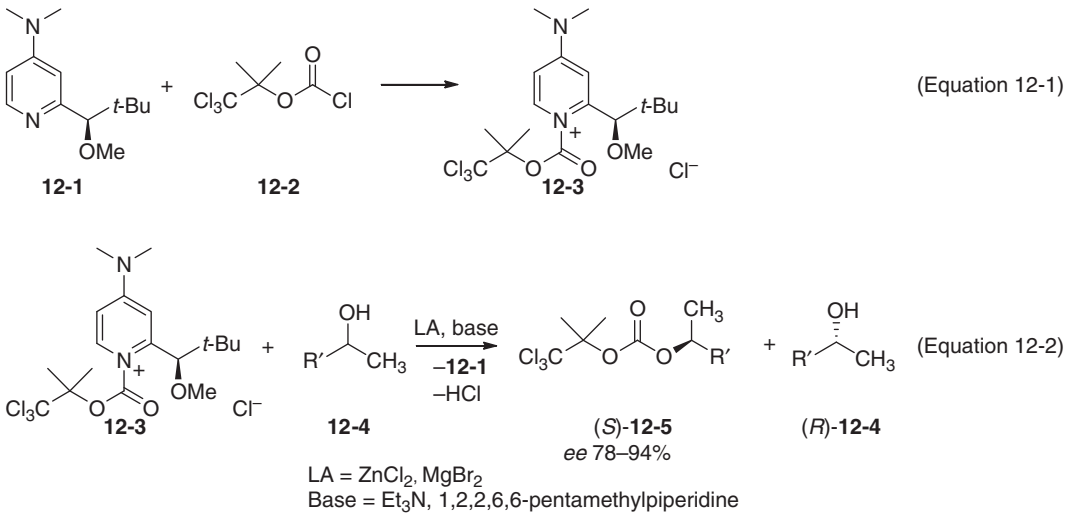


Figure 2 Chiral derivatives of DMAP.



Scheme 11 Kinetic resolution of racemic **11-1** with chiral DMAP-catalyst **F2-3**.

racemic alcohol in the presence of Lewis acids and triethylamine only gave minimal product *ee*. Vedejs was able to isolate the desired mixed carbonates in good *ee* (78–94%), depending on the substrate, reaction time, and conversion rate.

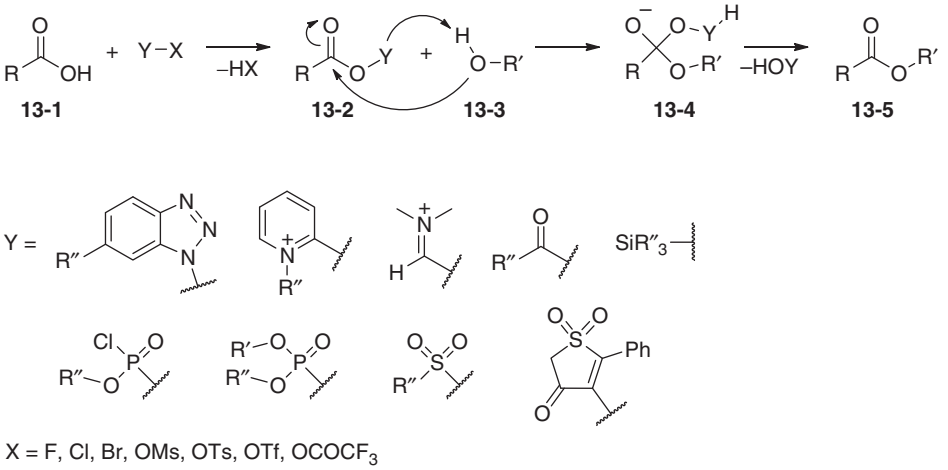


Scheme 12 Vedejs' chiral DMAP derivative.

Besides DMAP as acylating catalyst, various other methods have been developed. It is noteworthy that most protocols include the application of weak protic acids or Lewis acids (among others: TMSOTf, Procopiou[26]; $CoCl_2$, Iqbal[27]; $Sc(OTf)_3$, Yamamoto[28,29]; $TaCl_5$, Chandrasekhar[30]; $MgBr_2$, Vedejs[31]; silica gel[32]; zeolite, Sartori[33]; and montmorillonite, Li[32]).

6.09.2.2.3 Acyl transfer via mixed anhydrides and activated esters

Acylation via mixed anhydrides and activated esters are the most important methods for the esterification of carboxylic acids. During the course of the reaction, as shown in Scheme 13, the carboxylic acid is reacted with the activating agent X–Y and **13-2** is obtained. Subsequently, addition of the alcohol delivers the desired ester after nucleophilic displacement of the previously installed leaving group. If the activating group contains an acyl functional group, the activated species is called mixed anhydride; otherwise the intermediate is called an activated ester. The electrophilicity of the carbonyl moiety is enhanced by the electron-withdrawing character of Y, which increases the electropositive nature of the carbonyl carbon in **13-2**. Furthermore, as shown in the scheme, the nucleophilicity of the alcohol is improved as Y is able to accept the proton of the hydroxy group.



Scheme 13 Mixed anhydrides and activated esters.

When mixed anhydrides are formed, Y has to be devised in such a way as to ensure transfer of the desired acyl group. This can be achieved either by increasing the steric bulk around the activating group, thus leading the attack onto the less crowded carbonyl moiety, or by increasing the leaving group quality of Y, for example, via the formation of resonance-stabilized fragments.

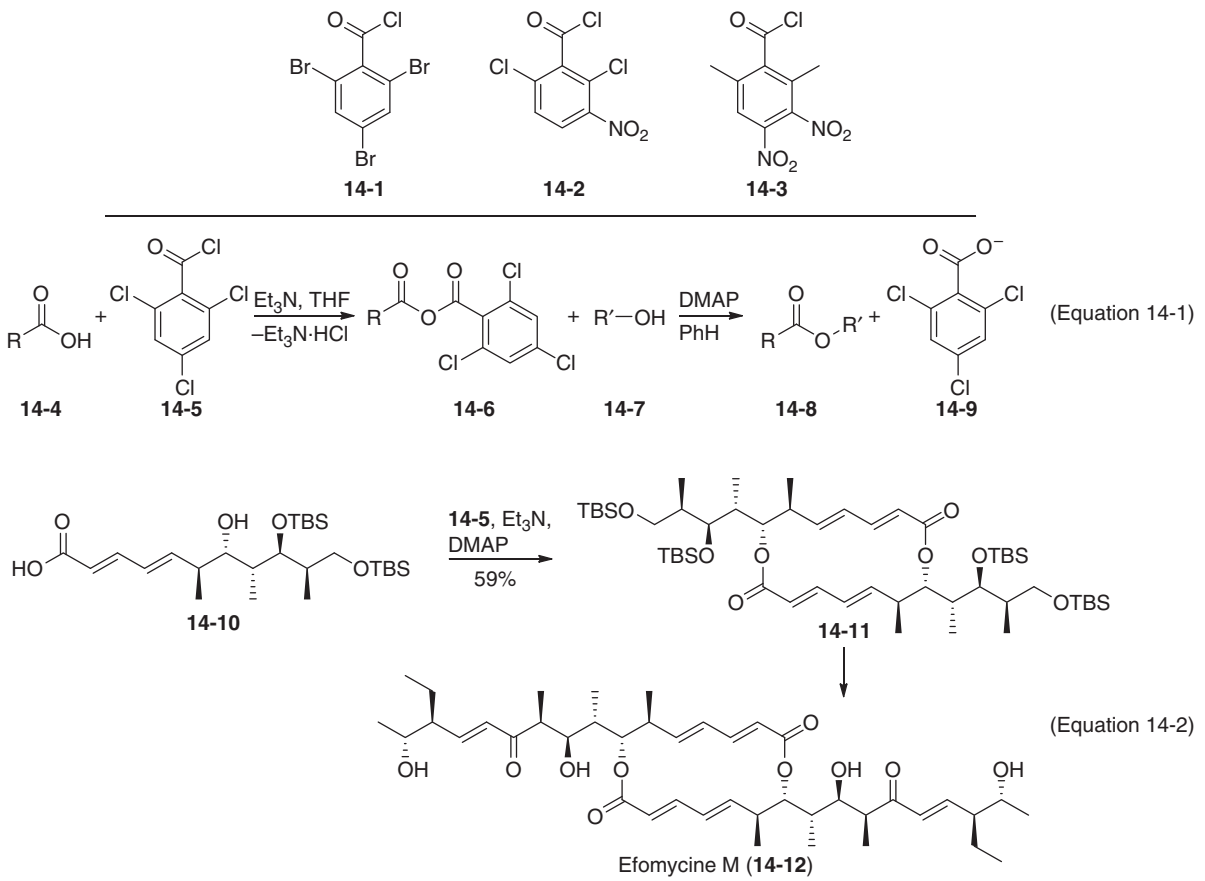
Different aromatic acid halides and anhydrides have been developed for the preparation of mixed anhydrides, which meet the criteria discussed in the previous paragraph. Steric hindrance, efficiently effected by the *ortho*-substituents at the aromatic ring, also often improve the electronic properties of the designated leaving group. The best known example is 2,4,6-trichlorobenzoyl chloride (**14-5**), also known as Yamaguchi reagent. The compound was identified as efficient esterification reagent, especially for macrolactonization reactions.[34] The acylating activity of related reagents has also been evaluated and a representative overview of potent acid chlorides is presented in Scheme 14, along with a general reaction scheme and a recent application of this highly versatile reagent in the preparation of efomycine M (**14-12**).[35]

Benzoic anhydrides with electron-deficient aromatic rings in the presence of Lewis acids have also been used for the preparation of mixed anhydrides. Shiina reported the application of 4-(trifluoromethyl)benzoic anhydride (**15-5**) and catalytic amounts of Lewis acids.[36,37] Yamamoto published the application of $Sc(OTf)_3$ as suitable and mild Lewis acid along with benzoic anhydrides,[29] whereas, a few years later, Shiina used $Hf(OTf)_4$ as powerful catalytically active Lewis acid.[38]

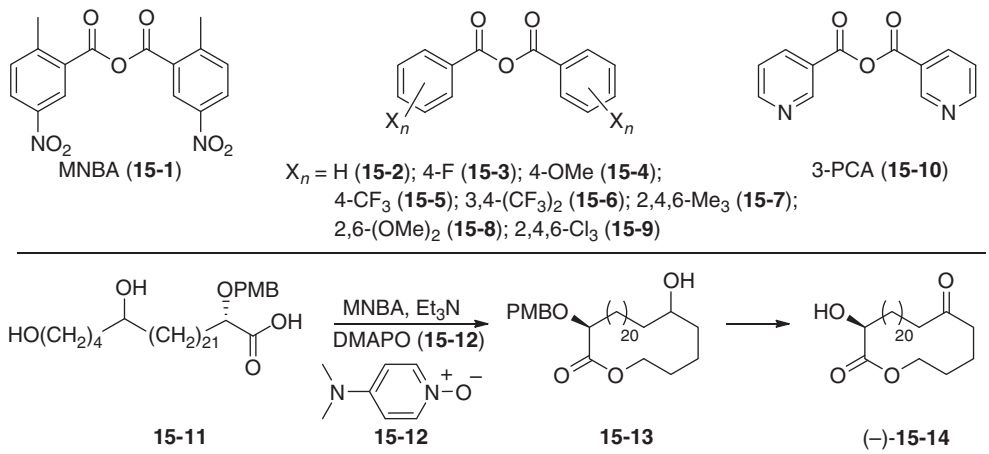
During the course of a more extensive study on activating agents, 2-methyl-6-nitrobenzoic anhydride (MNBA; **15-1**) was identified as a highly promising esterification reagent.[39,40] The advantage of **15-1** over Yamaguchi's esterification reagent was the isolation of the desired ester in good yields even when nearly equimolar amounts of acid and alcohol were used in the reaction. Furthermore, all components could be mixed simultaneously, whereas Yamaguchi had reported a stepwise protocol with the initial formation of the mixed anhydride before the alcohol was added to the reaction. MNBA and related anhydrides with different substitution patterns as well as pyridine-3-carboxylic anhydride (**15-10**) are displayed in Scheme 15, along with the application of this reagent in the synthesis of (−)-2-hydroxy-24-oxooctasanolide (**15-14**).[41,42] MNBA as well as the Yamaguchi reagent are commonly employed in macrolactonization reactions.

Carboxylic acids can be conveniently converted into carbonates, which act as activated species toward the formation of esters. A variety of different reagents for the preparation of carbonates have been described.[43–47] Carbonates are prone to decarboxylation, either on heating or after activation with Lewis acids to yield the desired ester as shown in Scheme 16. In most cases, the reaction proceeds as outlined in equation 16-1. The substituent R^1 present at the carbonate moiety acts as internal nucleophile. However, when the reaction is carried out with an alcohol as solvent, Takeda observed that especially Moc_2O- and Boc_2O-derived carbonates also undergo solvolysis and the reaction proceeds as shown in equation 16-2 with the alcohol acting as external nucleophile.[48] This concept was successfully employed in the synthesis of different macrocyclic lactones with Boc_2O and DMAP serving as the lactonization reagent.[49]

The introduction of the ester-linked side chain of taxol (**17-3**) definitely comprises a nontrivial problem in the synthesis of this important and most complex antitumor drug. Mukaiyama[50] employed di(2-pyridyl) thiocarbonate (DPTC; **16-13**) as an effective



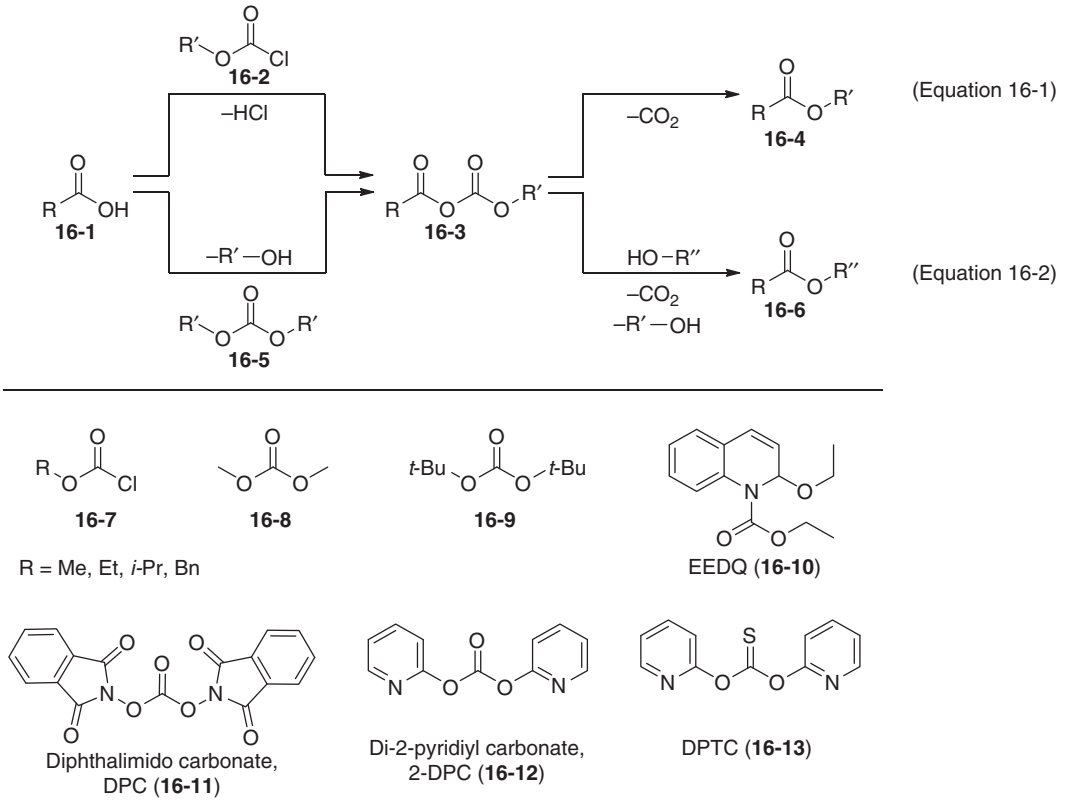
Scheme 14 Esterification using Yamaguchi's reagent.



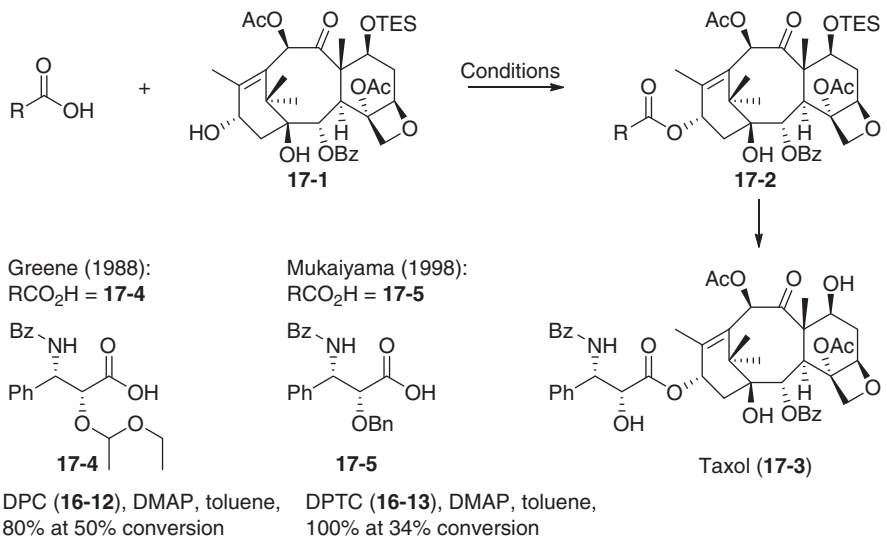
Scheme 15 Esterification reaction with MNBA (**15-1**) and similar reagents.

reagent for this tricky esterification reaction, outlined in Scheme 17. Likewise, Greene[51,52] used di-2-pyridyl carbonate (2-DPC; **16-12**) on a similar substrate with comparable efficiency.

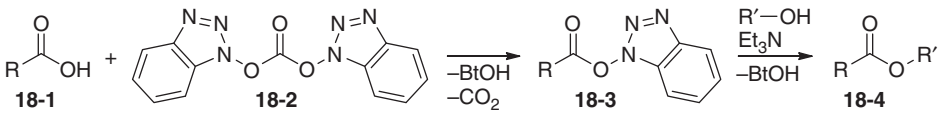
Hydroxybenzotriazole has been identified as a highly versatile reagent for the activation of various functional groups.[53,54] Ueda et al. employed benzotriazole-based carbonate **18-2** for the preparation of esters and amides Scheme 18.[55] Reaction of the carboxylic acid with carbonate **18-2** affords activated ester **18-3**, which then delivers the desired ester on reaction with a suitable alcohol.



Scheme 16 Decarboxylative esterification via carbonates as intermediates.

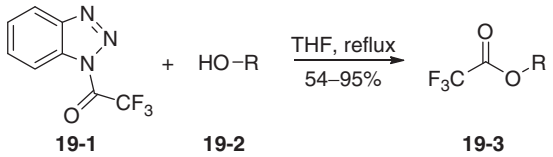


Scheme 17 Synthesis of Taxol (**17-3**) with carbonates as esterification reagents.



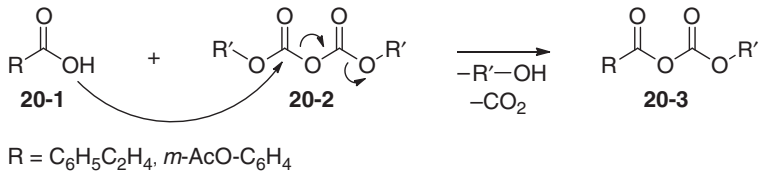
Scheme 18 Benzotriazole carbonates as esterification reagents.

(Trifluoroacetyl)benzotriazole (**19-1**; Scheme 19) has been described as a convenient trifluoroacetylating reagent by Katritzky et al.[56] The desired acylation proceeds smoothly when **19-1** and the alcohol are allowed to react in tetrahydrofuran (THF) at reflux. Importantly, addition of Lewis acids or other activating reagents is not required, which also allows the acylation of sensitive substrates.



Scheme 19 Trifluoroacetylation with benzotriazole derivative **19-1**.

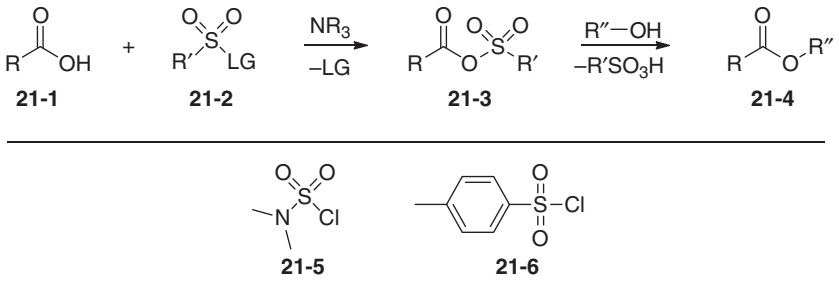
Diaryl dicarbonates can also be employed as reagents for the esterification of carboxylic acids as recently demonstrated by Gooßen and Döhring.[57] As it is outlined in Scheme 20, reaction of the carboxylic acid yields the requisite carbonate in this case on decarboxylation. The desired ester is delivered after a second extrusion of CO_2. The reaction is catalyzed by various Lewis acids, such as $Sc(OTf)_3$, $Mg(ClO_4)_2$, or $Cu(OTf)_2$.



R = $C_6H_5C_2H_4$, *m*-AcO-C_6H_4

Scheme 20 Esterification with diaryl dicarbonates.

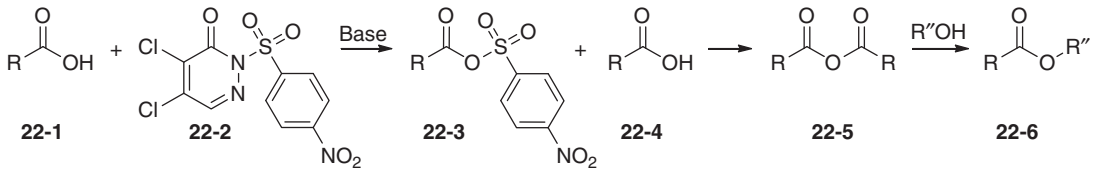
Carboxylic acids can also be successfully activated with sulfonyl chlorides. Subsequent reaction with the requisite alcohol allows the isolation of the desired ester. The method is outlined in Scheme 21. Different protocols have been published, for example, reaction of a carboxylic acid with *p*-toluenesulfonyl chloride (**21-6**) in the presence of *N*-methylimidazole[58] or pyridine,[59] and the application of dimethylsulfamoyl chloride (**21-5**) and *N*,*N*-dimethylamines.[60,61] 4,5-Dichloro-2-[(4-nitrophenyl) sulfonyl]pyridazin-3(2H)-one (**22-2**) has been reported as an extremely mild reagent for the formation of anhydrides.[62] It can be employed to efficiently perform esterification, most likely via intermediary formation of the corresponding anhydrides, along with structurally related activating reagents (**22-7**–**22-12**), Scheme 22.[63] Aromatization of the heterocyclic ring serves as a driving force and enhances the leaving group qualities of the 2H-pyridazinone moiety.

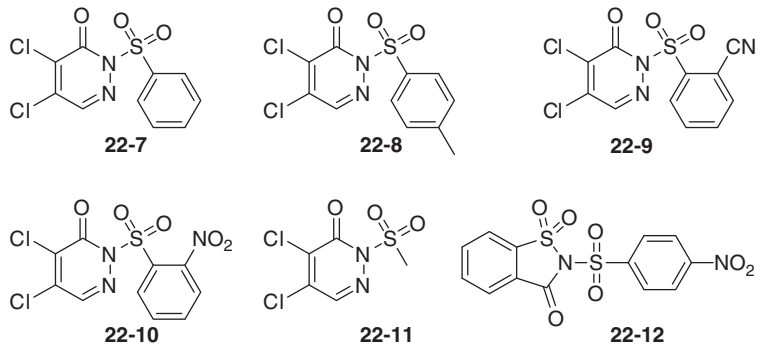


Scheme 21 Sulfonyl chlorides as esterification agents.

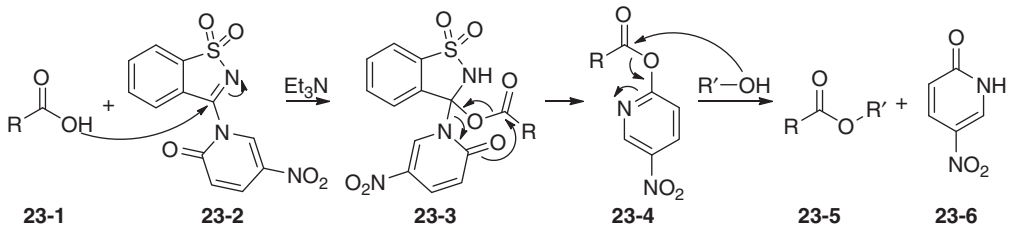
Kinoshita employed benzoisothiazole derivative **23-2** as an effective reagent for the preparation of esters and lactones (Scheme 23) with yields often greater than 90%.[64] Initial attack of the carboxylate results in the formation of adduct **23-3**, which immediately rearranges to acyl derivative **23-4**. Next, attack of the alcohol onto the electrophilic carbonyl moiety results in the formation of the desired ester and 5-nitropyridone (**23-6**) as the by-product.

(Chlorophenylthiomethylene)dimethylammonium chloride (CPMA; **24-2**)[65] was introduced by Mioskowski as a new coupling reagent for ester and amide formation, see Scheme 24.[66] The carboxylic acid reacts with CPMA (**24-2**) and an activated intermediate **24-3** is formed with concomitant loss of HCl. Thus, addition of a base is essential to shift the equilibrium toward the desired product and to prevent the solution from turning too acidic. Next, the alcohol attacks the activated intermediate and the carboxylic ester is obtained, along with thiocarbonate **24-6** as a side product. With this mild method, primary as well as secondary alcohols can be successfully acylated. However, tertiary alcohols fail to react with carboxylic acids. It is noteworthy that α-chiral substrates employed in the CPMA-mediated esterification do not undergo racemization.

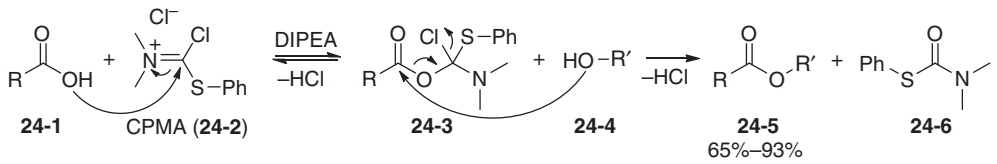




Scheme 22 Esterification via sulfonamide containing activated esters.

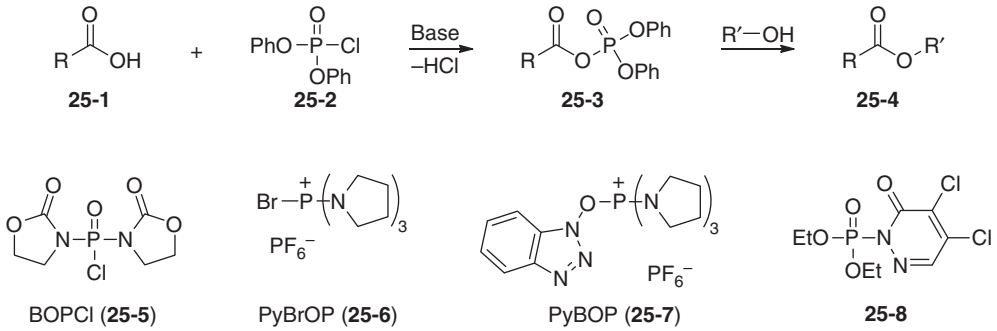


Scheme 23 Esterification using benzoisothiazole derivative **23-2**.



Scheme 24 CPMA-mediated esterification. DIPEA, *N,N*-diisopropylethylamine.

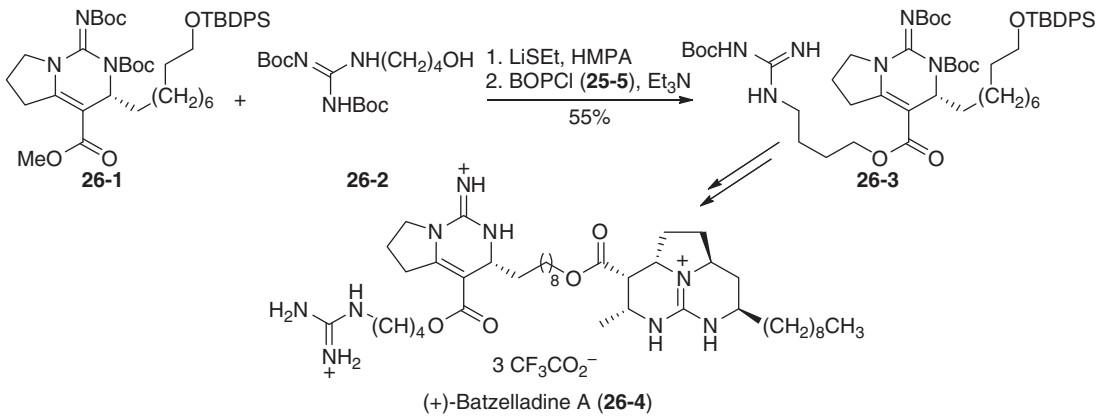
Although phosphorus-based reagents for the activation of carboxylic acids have mostly been used in the synthesis of amides and peptides, these reagents are also extremely useful for the preparation of esters and macrolactones as outlined in Scheme 25 with diphenylchlorophosphonate (25-2). Whereas mechanistically all phosphonates react in complete analogy, bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl; Palomo's reagent; 25-5) has evolved as the most prominent reagent.[67] Other



Scheme 25 Phosphorus-based reagents for esterification.

important examples are bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrOP; **25-6**))[68] and benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (**25-7**; PyBOP).[69] In analogy to **22-2** (shown in Scheme 22) used for the formation of sulfonates as activated intermediates, Lee and Yoon described the application of (4,5-dichloro-6-oxo-6H-pyrazin-1-yl) phosphoric acid diethyl ester (**25-8**).[70] Various other phosphonates have been used as activating reagents for carboxylic acids.[71]

A good example for the utility of BOPCl in the preparation of esters is given by Gin's synthesis of the guanidine natural product (+)-batzelladine A (**26-4**), where **25-5** serves as an activating reagent for the incorporation of the side chain, Scheme 26.[72]



Scheme 26 Gin's synthesis of (+)-batzelladine A (**26-4**).

In analogy to other protocols, the presence of Lewis acids often improves the outcome of the esterification reaction with phosphorous-based activation agents. Kluger reported a significant rate enhancement in the monoacylation of monosaccharides with benzoyl methyl phosphate in the presence of lanthanum salts.[73,74] Addition of magnesium triflate to the reaction mixture increased the observed effect, likely via chelation to the by-product of the acylation reaction, namely, methyl phosphate, and concomitant release of the catalytically active lanthanum(III) cation.[75]

In 1993, Vedejs introduced tributylphosphine as a highly active acylation catalyst with similar or even better rate enhancement than observed with DMAP.[76] Attempts to isolate and characterize the activated intermediate furnished X-ray data of a quite remarkable structure as outlined in Figure 3. Crystals obtained from a solution of neat tributylphosphine in glacial acetic anhydride confirmed nuclear magnetic resonance (NMR) studies that suggested a phosphorus bound to a carbon–carbon double bond. A more detailed study on the scope of phosphine-catalyzed acylation appeared later in the same year.[77]

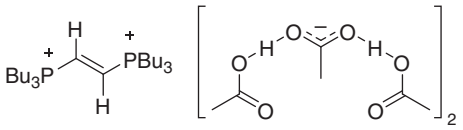


Figure 3 Structure of the phosphine-acyl complex.

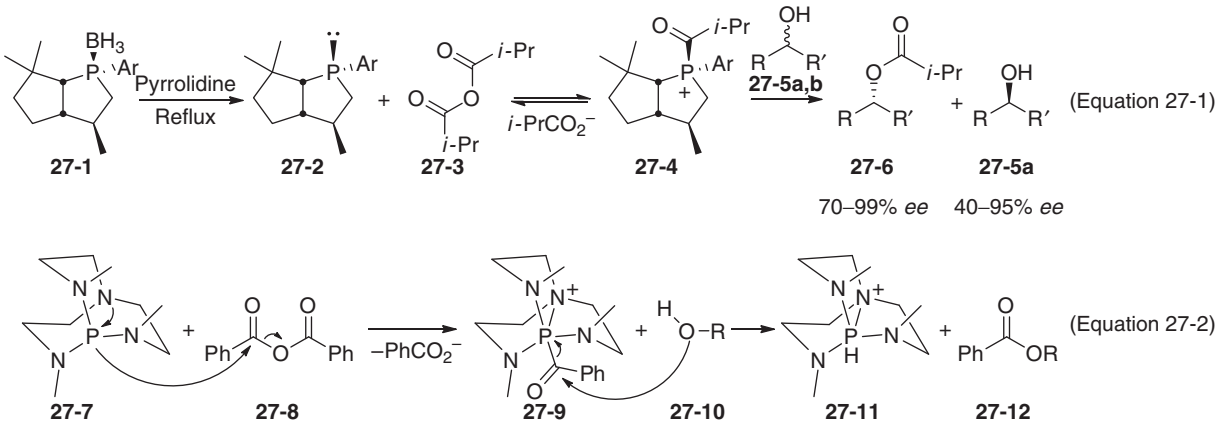
A few years after the seminal disclosure on the catalytic acylating activity of tributylphosphine, Vedejs reported the utilization of chiral phosphine catalysts.[78,79] Several structurally different chiral phosphines were examined.[78] The best results were obtained with 2-aryl-4,4,8-trimethyl-2-phosphabicyclo[3.3.0]octanes (**27-2**) as outlined in equation 27-1, Scheme 27.[79] Reaction of anhydride **27-3** with chiral phosphine **27-2**, derived from **27-1** by warming with pyrrolidine, resulted in the formation of the acylating reagent **27-4**. Addition of racemic alcohol **27-5a,b** then delivered enantiomerically enriched ester **27-6** and alcohol **27-5a** in good-to-excellent yield and stereoselectivity via kinetic resolution.

Verkade demonstrated that hindered alcohols can be successfully acylated with anhydrides in the presence of a strong nonionic Lewis base such as phosphazene **27-7**, displayed in equation 27-2, Scheme 27.[80] Various esters were prepared via this protocol with good-to-excellent yield (57–99%).

6.09.2.2.4 Acyl transfer via substituted methyl and ethyl esters

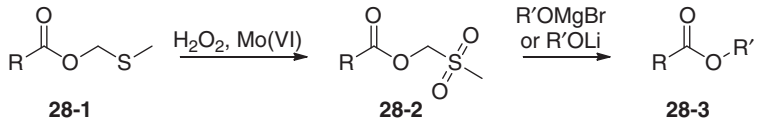
Various substituted methyl and ethyl esters have been successfully employed as activated intermediates toward the mild and selective esterification of carboxylic acids.

The application of methyl thiomethyl esters as activated species for the esterification reaction is outlined in Scheme 28. Formation of the methyl thiomethyl ester proceeds smoothly, for example, via addition of chloromethyl methyl sulfide to the carboxylate.[81,82] Next, oxidation of the sulfide then generates the corresponding sulfone and thus activates the ester toward further



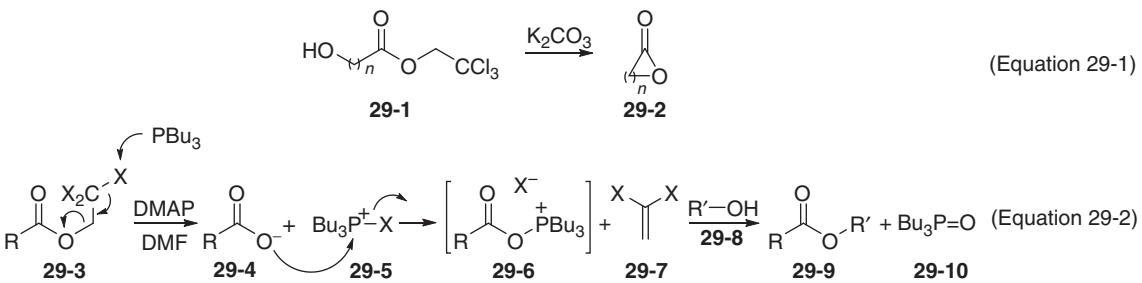
Scheme 27 Esterification via chiral phosphine catalysts.

manipulations. The desired ester is formed upon reaction of the sulfone with the deprotonated alcohol.[83] Narasaka employed this strategy in the racemic synthesis of the 12-membered macrocyle of integerrimine (40% yield for the macrolactonization step).[84]



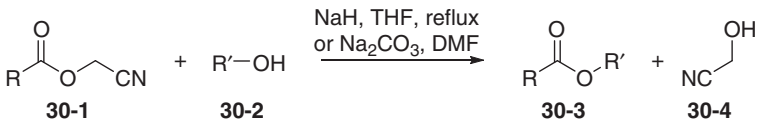
Scheme 28 Esterification via methyl thiomethyl esters as activated species.

Burke described the potassium salt-mediated macrolactonization of trichloroethyl esters and employed the method in the preparation of unnatural hydropyran-containing macrocycles. As shown in equation 29-1, Scheme 29, reaction of trichloroethyl ester (**29-1**) with potassium carbonate delivers the corresponding macrolactone.[85] Another transacylation pathway is outlined in equation 29-2, Scheme 29, where addition of tributylphosphine to the trihaloethyl ester induces dehalogenation and subsequent fragmentation of the substrate. Reaction of the activated acyl species with the hydroxy compound then concludes the sequence with the formation of the desired ester.[86]



Scheme 29 Trihaloethyl esters as esterification precursors.

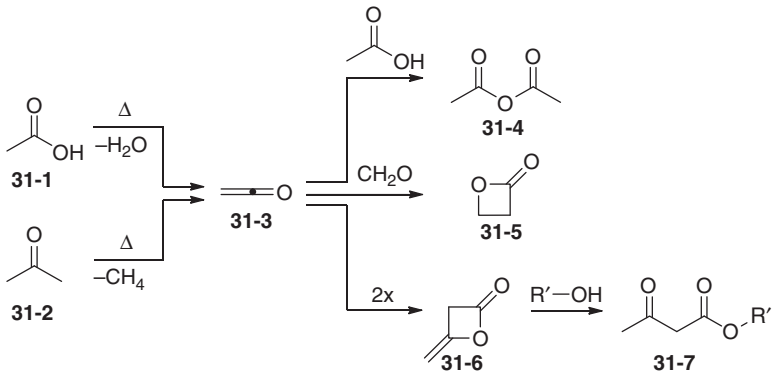
Cyanomethyl esters also serve as activated esters and have been employed in the preparation of macrocyclic natural products such as (–)-lobatamide C (43% yield for esterification)[87] or (–)-apicularen A (80% yield for esterification).[88] As outlined in Scheme 30, the cyanomethyl ester **30-1**, available from the carboxylic acid with chloroacetonitrile, is allowed to react with the requisite alcohol and bases such as sodium hydride or potassium carbonate. The desired ester is obtained from the reaction mixture, along with **30-4** as side product.



Scheme 30 Cyanomethyl esters as activated species for esterification reactions.

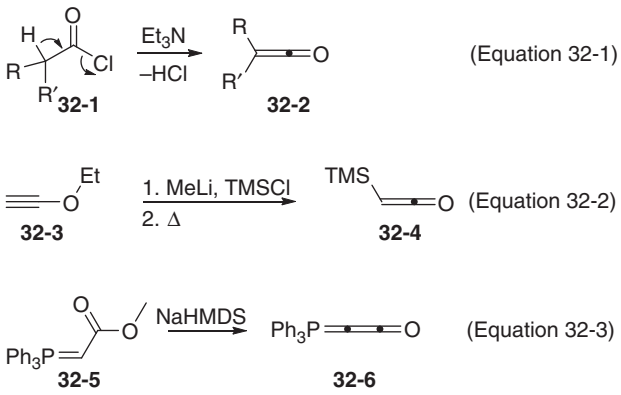
6.09.2.2.5 Acylation via ketenes

Ketenes have not been commonly employed as synthons for the preparation of carboxylic esters on laboratory scale. However, ketenes can act as highly reactive acylating intermediates. Ketene itself (**31-3**) is prepared on industrial scale from acetic acid or it can be obtained via thermolysis of acetone, respectively (Schmidlin ketene synthesis).[89] Ketene is used in the production of acetic anhydride **31-4** (Scheme 31). Reaction of ketene (**31-3**) with aldehydes affords β-lactones via a [2+2]-cycloaddition. The synthesis of propiolactone (**31-5**) from **31-3** and formaldehyde is outlined in Scheme 31. Dimerization of **31-3** results in the formation of diketene (**31-6**), which is used to acylate alcohols to esters of acetoacetic acid (**31-7**).



Scheme 31 Large-scale preparation of ketene (**31-3**) and diketene (**31-6**); application of ketene in the synthesis of acetic anhydride (**31-4**), propiolactone (**31-5**), and esters of acetoacetic acid (**31-7**).

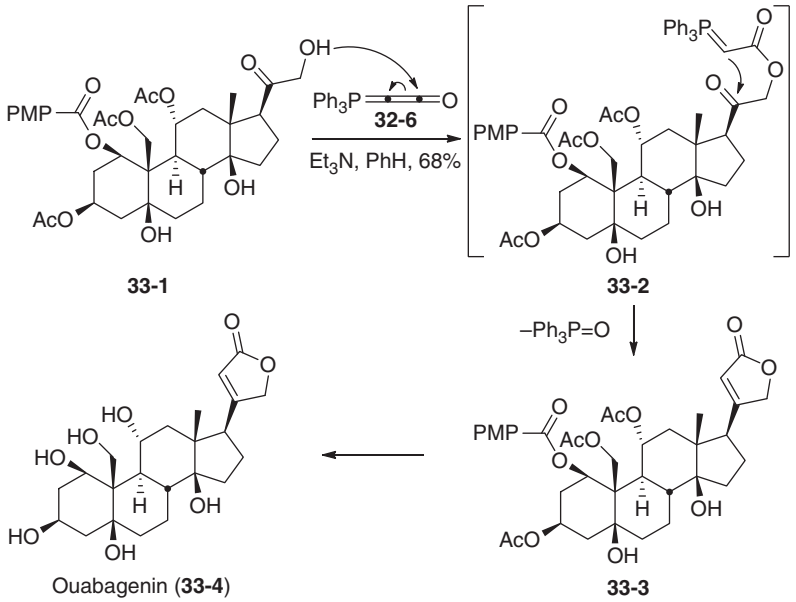
On laboratory scale, different strategies can be applied to prepare ketenes (Scheme 32). A general and mild method is β-elimination of acid chlorides with amine bases such as triethylamine (equation 32-1).[90] Trimethylsilylketene (**32-4**) is a valuable reagent for various applications and also useful for the preparation of β-lactones via the aforementioned [2+2]-cycloaddition with carbonyl functional groups. Another route involves a retro-ene reaction via thermolysis of freshly prepared silylated ethoxy acetylene as it is outlined in equation 32-2.[91] Triphenylphosphoranyl ketene (**32-6**), accessible from methoxycarbonylmethylenetriphenyl phosphorane (**32-5**) and NaHMDS (equation 32-3),[92] is a powerful tool for the synthesis of butenolides. This route includes reaction of the alcohol moiety of α-hydroxyketones with the ketene, and subsequent HWE-olefination. The reagent has been employed by Bohlmann in the synthesis of cardenolides,[93] and by Deslongchamps in the synthesis of ouabagenin (**33-4**), displayed in Scheme 33.[94]



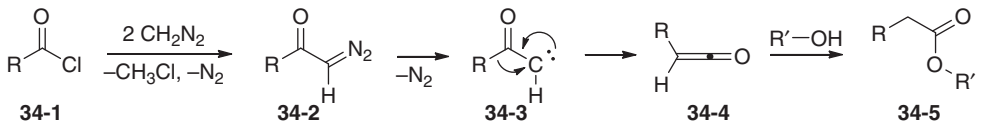
Scheme 32 Preparation of ketenes on laboratory scale.

Ketenes serve as intermediates in the Arndt–Eistert homologation.[95,96] As outlined in Scheme 34, exposure of acid chlorides to excess of diazomethane affords the corresponding α-diazo methylketone (**34-2**), which then rearranges to ketene **34-4** (Wolff-rearrangement, for detailed discussion, *see* Chapter 3.19). Next, reaction of an alcohol with the ketene intermediate concludes the sequence and allows the isolation of the desired ester.

In combination with suitable catalysts, diketene **35-2** has been utilized in the kinetic resolution of racemic alcohols (Scheme 35). Fu employed chiral ferrocene- and azaferrocene-based catalysts, such as **35-4**, to resolve secondary aromatic alcohols.[21] Reaction of racemic alcohols with **35-2** and catalytic amounts of chiral ferrocene derivative **35-4** allowed the isolation of

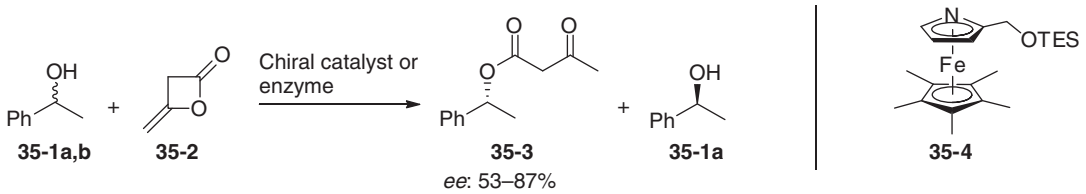


Scheme 33 Deslongchamps' synthesis of ouabagenin (**33-4**).



Scheme 34 Arndt-Eistert homologation.

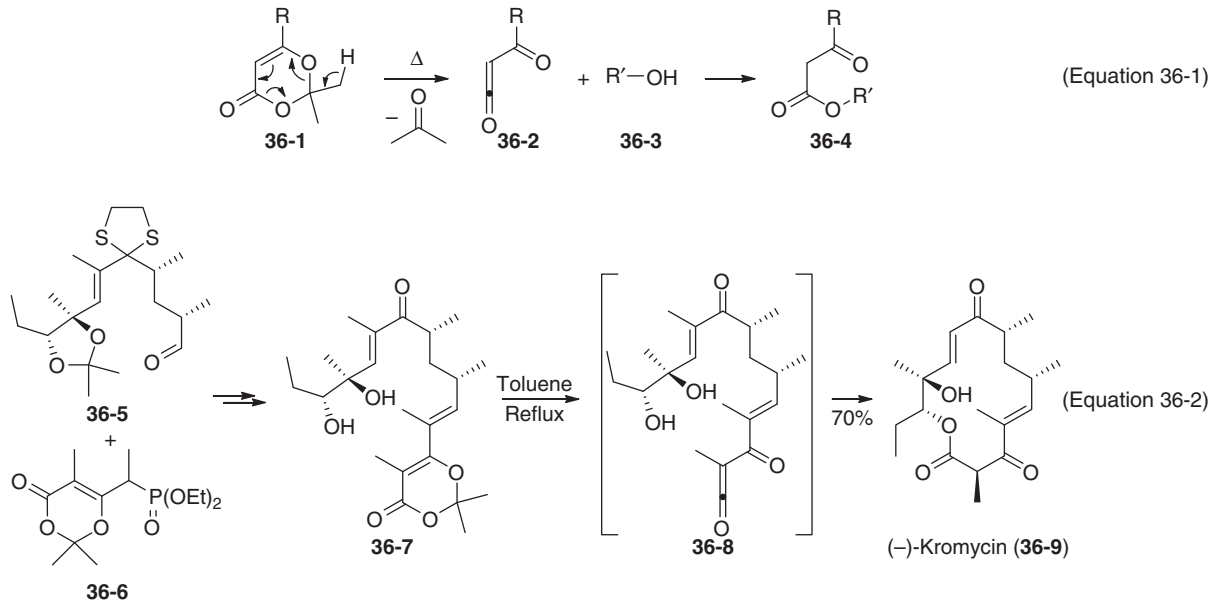
enantiomerically enriched β-keto ester **35-3** in moderate selectivity (*ee* 53–87%). Jeromin used *Pseudomonas* sp. lipase (PL) for this partial kinetic resolution.[97] Both methods delivered the corresponding enantiomerically enriched alcohols.



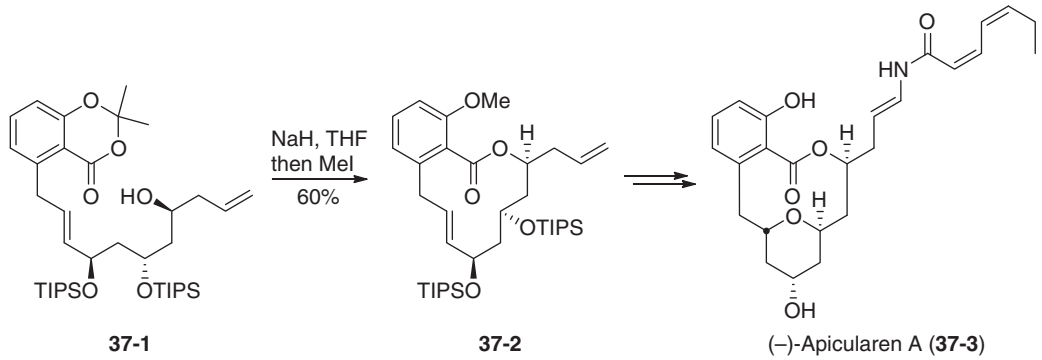
Scheme 35 Kinetic resolution of alcohols via ketenes.

Thermolysis of dioxolenone (**36-1**) results in the formation of β-acetylketene (**36-2**), which can be directly converted to the desired β-ketoesters or β-ketolactones via nucleophilic attack of the corresponding alcohol (equation 36-1, **Scheme 36**).[98] Boeckman recognized this method as a powerful tool for the preparation of various medium-ring lactones and presented a formidable application with the preparation of (–)-kromycin (**36-9**), shown in equation 36-2, **Scheme 36**.[99] Thus, advanced aldehyde **36-5** was converted to dioxolenone diol **36-7** on reaction with dioxolene phosphonate **36-6** and subsequent deprotection of one acetonide, before the desired macrolactonization via ketene intermediate **36-8** was accomplished in refluxing toluene. Kromycin was obtained as a sole product with the newly generated chiral center in α-position to the lactone functional group being identical to the one present in the natural product. A recent review summarizes advantages and synthetic applications of the esterification reaction via acylketenes.[100]

Although the mechanism differs, the lactonization of acetonide-protected salicylates is conceptually closely related to the thermolytic acylketene formation. On exposure of such a salicylate to sodium hydride, the desired lactone is formed under concomitant formation of acetone. Independently introduced by Rizzacasa[101–103] and De Brabander,[104,105] this lactonization protocol was employed in the preparation of several natural products. The key macrolactonization in Rizzacasa's synthesis of (–)-apicularen A (**37-3**) via the aforementioned sodium hydride-mediated reaction is outlined in **Scheme 37**.[103]



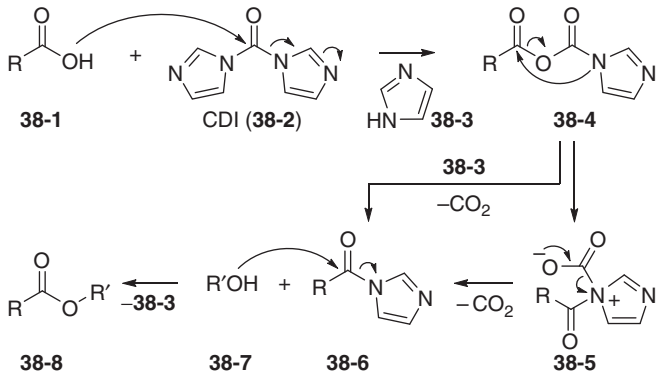
Scheme 36 Formation of β-ketoesters via thermolytic cleavage of dioxolenones and its application in total synthesis.



Scheme 37 Rizzacasa's synthesis of (–)-apicularen A (**37-3**).

6.09.2.2.6 Acylation with N*-acylimidazoles*

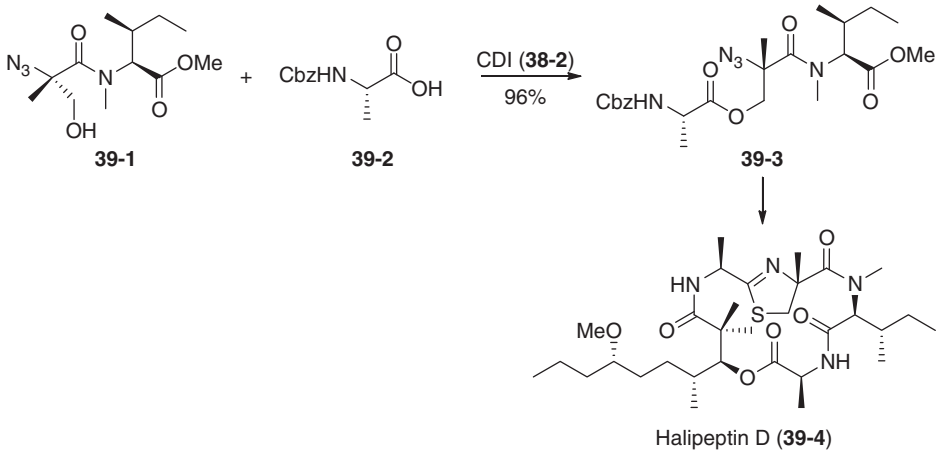
The utilization of *N*-acylimidazoles for the mild and efficient esterification of primary, secondary, and tertiary alcohols was first reported by Staab in 1959.[106,107] The protocol is simple: first, the carboxylic acid is allowed to react with carbonyldiimidazole (**38-2**; CDI) to afford acylimidazole **38-6** after elimination of CO_2 (Scheme 38), either via intermediate **38-5** or direct attack of the



Scheme 38 *N*-Acylimidazoles as catalysts for esterification reactions.

released imidazole on **38-4**. Addition of the alcohol then results in nucleophilic displacement of a second imidazole unit with concomitant formation of the desired ester.[108]

Carbonyldiimidazole (**38-2**) has been employed in the synthesis of various structurally complex natural products. An example of the esterification of a sterically demanding primary alcohol is provided in **Scheme 39**. The esterification served to elaborate ester **39-3**, an important intermediate on the way to halipeptin D (**39-4**).[109]



Scheme 39 Total synthesis of halipeptin D (**39-4**).

Different derivatives of CDI with even better leaving group qualities have been designed. A selection of modified coupling reagents is provided in **Figure 4**.[110,111]

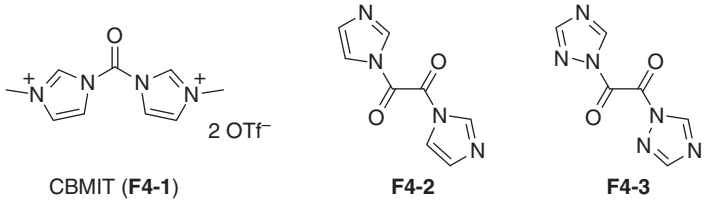
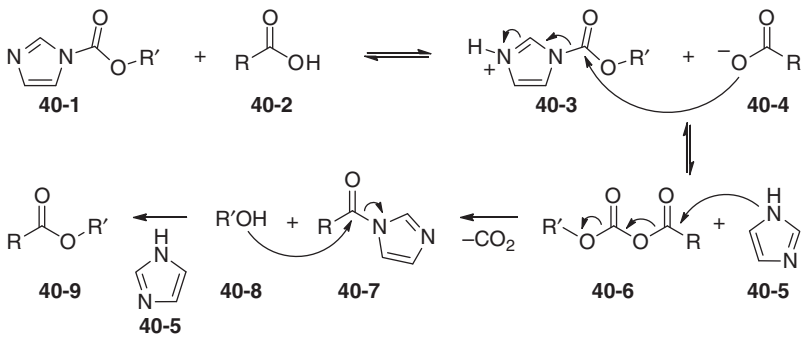


Figure 4 Derivatives of *N*-acylimidazoles as esterification reagents.

Batey employed various imidazole-based ureas for the preparation of carbamates and amides.[112] Sarpong modified and expanded the protocol to also allow the synthesis of esters.[113,114] Treatment of the requisite carboxylic acid with an imidazole carbamate (**40-1**) provides *N*-acyl imidazole **40-7** via the intermediary formation of carbonate **40-6**. Nucleophilic displacement of the imidazole moiety concludes the sequence and delivers ester **40-9** as outlined in **Scheme 40**.

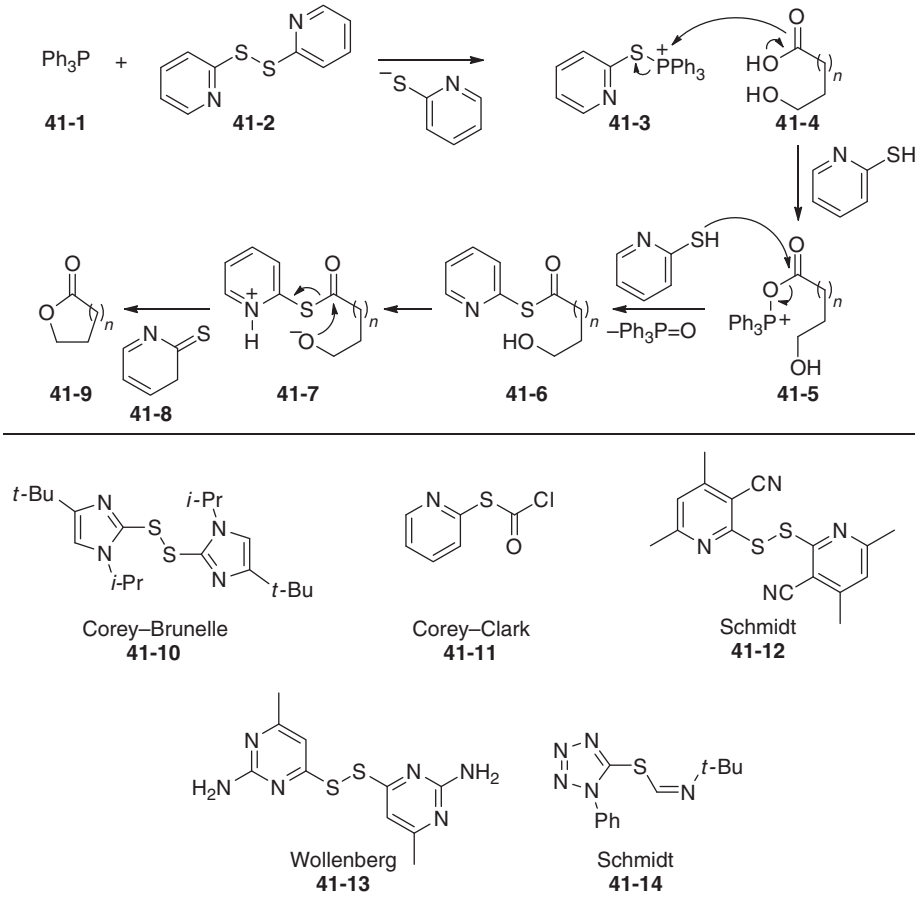


Scheme 40 Mechanistic rationale for the esterification catalyzed by *N*-acyl imidazoles.

6.09.2.3 Double Activation

6.09.2.3.1 Esterification via thioesters

In 1974, Corey and Nicolaou published the application of 2,2'-dipyridyl disulfide (**41-2**) for the efficient formation of esters and lactones (yield often greater than 90%).[115] The method, outlined in Scheme 41, has evolved to one of the most efficient reactions for macrolactonization, and numerous natural products have been prepared following this protocol. On reaction of triphenylphosphine with disulfide **41-2**, activated phosphonium species **41-3** is formed, which is readily attacked by the carboxylic acid. The pyridyl nitrogen plays an important role as the thioester is stabilized via hydrogen bonding (**41-7**) after internal proton transfer from the hydroxyl group. Thus, the thioester is activated for nucleophilic attack and at the same time, the nucleophilicity of the resulting alkoxide is strongly increased. After reaction with the alcohol, the thioester is cleaved and 2-pyridinethione (**41-8**) is released.



Scheme 41 Mechanistic consideration for the Corey-Nicolaou esterification/lactonization protocol; various sulfides for esterification.

A few years later, diimidazoylsulfide **41-10** was reported as efficient reagent for the activation of carboxylic acids.[116] The *tert*-butyl group on the imidazole ring was essential to prevent the formation of stable *N*-acyl derivatives, which then fail to deliver the desired ester or lactone.

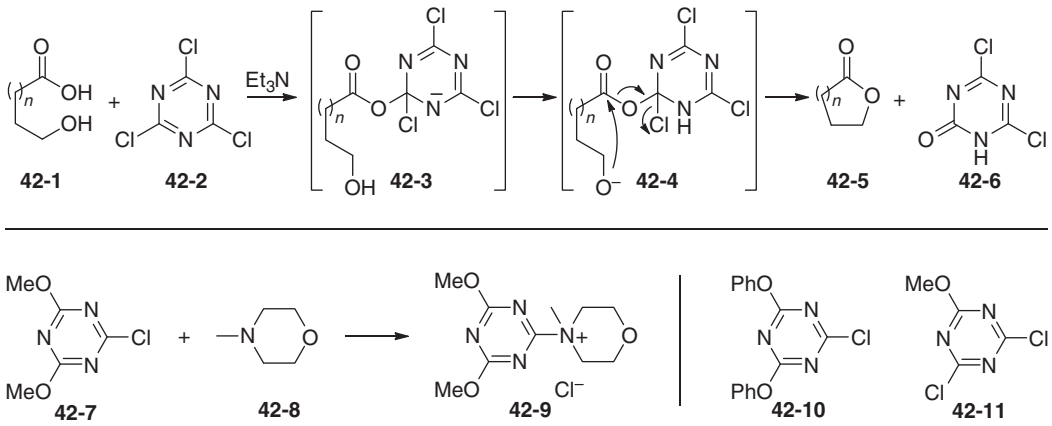
A major drawback of the Corey–Nicolaou protocol lies in the elimination of triphenylphosphine oxide, resulting from the activation of the disulfide. A variation of the protocol was developed by Corey and Clark,[117] who employed thionylchloroformate **41-11** instead of disulfide **41-2**. Other variations of the Corey–Clark reagent (**41-11**) were developed by Schmidt[118,119] or Wollenberg,[120] see Scheme 41. All reagents were reported to deliver the desired ester or lactone in good-to-excellent yields (often greater than 90%), depending on the substrates employed in the reaction.

Addition of metal ions such as silver(I),[121] mercury(II),[122] or copper(I)[123] to the reaction mixture was reported to strongly increase the rate of the esterification/lactonization,[124] presumably via coordination of the metal ion to the sulfur with a concomitant increase of electrophilicity of the thioester.

6.09.2.3.2 Esterification using cyanuric chloride

Mechanistically and conceptually closely related to thioesters is the use of cyanuric chloride (**42-2**) as the esterification/lactonization also proceeds via a double-activation mechanism. Introduced for macrolactonization in 1979 by Venkataraman,[125,126] the

reagent, although cheap and readily available, has not been extensively used in the total synthesis of natural products and only few examples have been reported. The mechanism for the lactonization using cyanuric chloride (**42-2**) is outlined in Scheme 42.

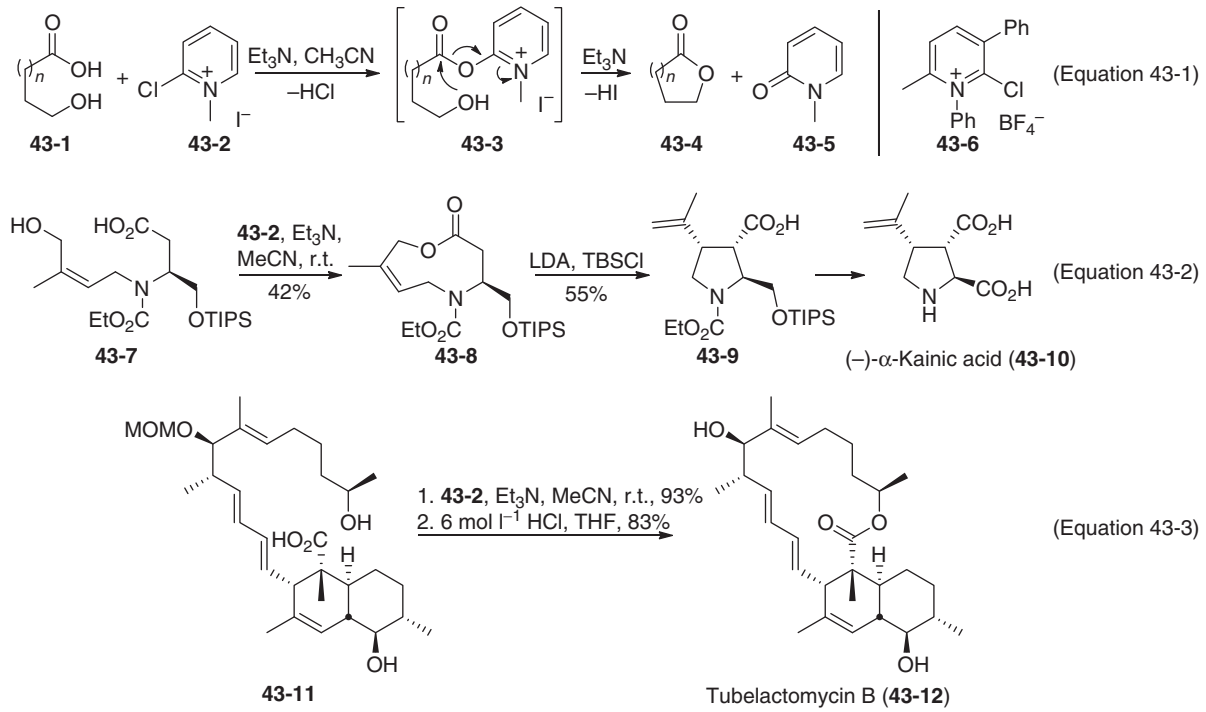


Scheme 42 Cyanuric chlorides as lactonization catalysts.

Applications of derivatives of cyanuric chloride have been described and employed in the formation of esters and lactones, most noteworthy methoxy- and phenoxy-substituted compounds such as **42-7**, **42-10**, and **42-11**.[127,128] Additon of *N*-methylmorpholine (**42-8**) to triazine **42-7** allows the isolation of morpholinium chloride **42-9**, which was also found to promote esterification of carboxylic acids under mild conditions. Enhanced leaving group qualities of the charged heterocycle explains the efficiency of the reagent.[129]

6.09.2.3.3 Esterification with Mukaiyama's salt

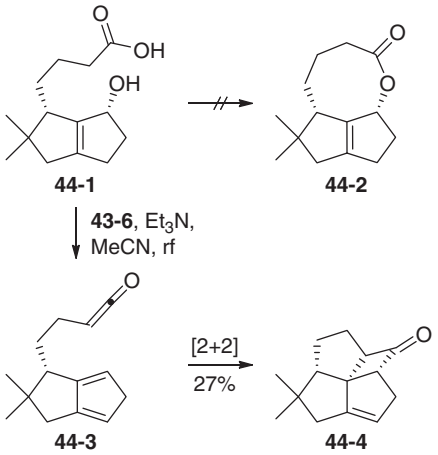
In 1976, Mukaiyama described the application of 1-alkyl-2-halopyridinium salts for the lactonization of ω-hydroxy acids.[130,131] As shown in equation 43-1, Scheme 43, with 1-methyl-2-chloropyridinium iodide (**43-2**; Mukaiyama's salt), the acid is activated via substitution of the chlorine by the carboxylate and highly reactive acyloxypyridinium salt **43-3** is generated. Intramolecular nucleophilic displacement affords the macrolactone **43-4**.



Scheme 43 Mukaiyama's salt as reagent for macrocyclization reactions. Mechanism and application in the total synthesis of α-kainic acid (43-10) and tubelactomycin B (**43-12**).

Mukaiyama's salt was successfully employed in the preparation of (–)-α-kainic acid (**43-10**) (equation 43-2, Scheme 43).[132] The macrolactonization reaction established the precursor for the key Claisen rearrangement to construct the pyrrolidine ring of the alkaloid. The late stage macrolactonization of ω-hydroxy acid **43-11** in the synthesis of the antimicrobial 16-membered macrolide (+)-tubelactomycin B (**43-12**) is another more recent example for the utility of this method (equation 43-3, Scheme 43).[133]

Usually, the reaction is carried out with excess of triethylamine at elevated temperature. Under these conditions, Mukaiyama's salt was found to be unstable and with the isolation of 2-chloropyridine or ammoniopyridinium salts, which are unreactive toward activation of the carboxylic acid, partial decomposition was confirmed. Furthermore, another possible side reaction includes the formation of ketenes,[134] as evidenced by the isolation of cyclobutanone **44-4** instead of the desired macrolactone **44-2**, Scheme 44. To circumvent these problematic side reactions, 2-chloro-6-methyl-1,3-diphenylpyridinium tetrafluoroborate (**43-6**, Scheme 43) was presented as an alternative activating reagent for carboxylic acids.[135,136]



Scheme 44 [2+2] Cycloaddition as undesired side reaction in the lactonization catalyzed by 2-chloropyridine.

6.09.2.3.4 Tin-based esterification

The first report on the tin-mediated esterification of alcohols and carboxylic acids was published in 1980 by Steliou and Hanessian.[137] The authors observed that ω-hydroxy acids were efficiently converted to the corresponding lactones in the presence of small amounts of *n*-Bu_2SnO (**F5-1**). Later, various different tin derivatives, outlined in Figure 5, were evaluated for their catalytic activity. Some tin derivatives were found to be exceptionally active with respect to the esterification, namely, di-*n*-butyltin diethoxide (**F5-5**) or di-*n*-butyltin diimidazole (**F5-6**), thus allowing the reaction to be carried out with highly satisfying yields even at room temperature.[138] Otera described the application of distannoxanes **F5-7** and **F5-8** as catalysts for esterification reactions.[139]

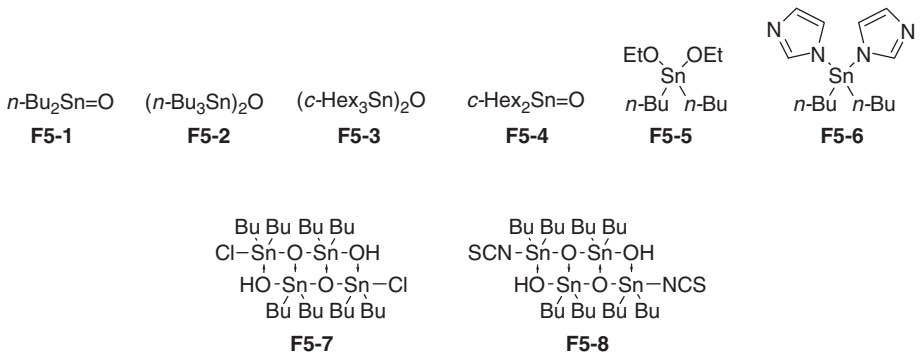
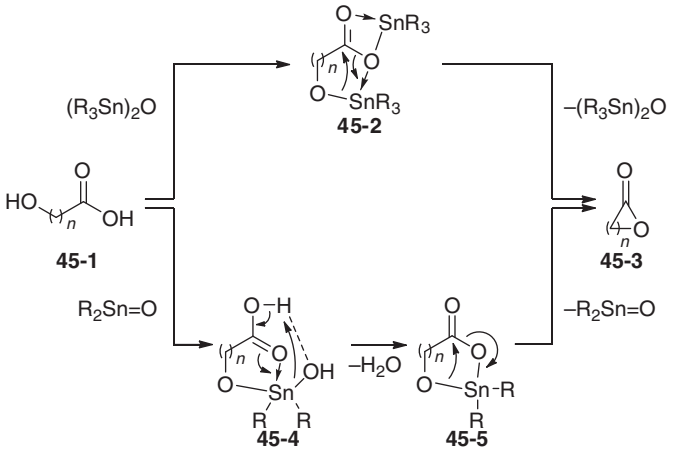


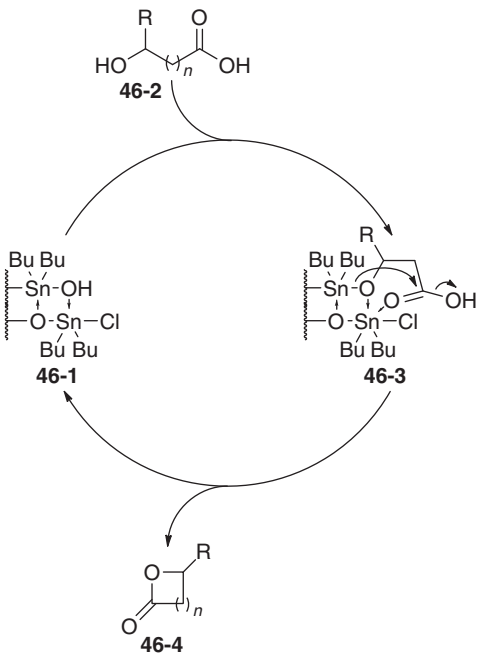
Figure 5 Various reagents for tin-mediated esterification reactions.

Mechanistically, the tin-mediated esterification was proposed to proceed via double activation of the acid and the alcohol with two different tin species as shown in Scheme 45.[137,138] Internal coordination favors the formation of cyclic alkoxystannylene carboxylates **45-2** or **45-5** before the desired lactone and the active catalyst are released. Undesired side reactions such as polymerization and intramolecular esterification can be successfully suppressed under high dilution conditions.



Scheme 45 Mechanistic consideration of tin-mediated lactonization reactions.

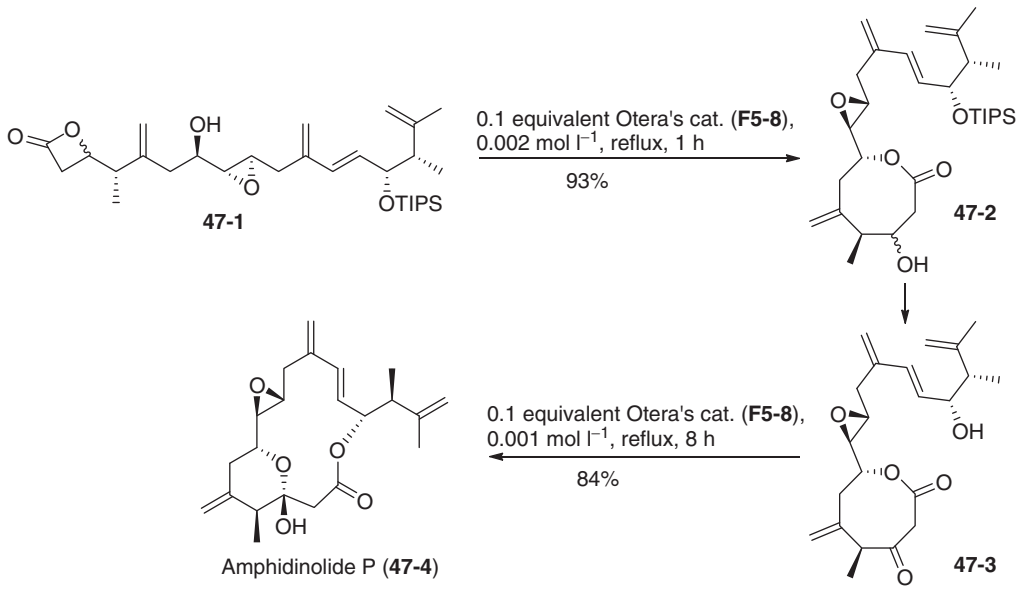
The mechanism of the lactonization with Otera's catalyst (Scheme 46) was postulated in complete analogy to the esterification protocol with dibutyltin oxide (Scheme 45). Again, the high efficiency of the catalyst can be explained by double activation of the acid and the alcohol moiety.



Scheme 46 Catalytic cycle for the tin-mediated lactionization.

Besides the lactonization of ω-hydroxy acids, Otera's catalyst has also been employed in selective transesterification reactions.[140–142] A recent application of Otera's catalyst (**F6-8**) in the synthesis of macrolides is outlined in Scheme 47.[143] The tin catalyst was used for the intramolecular transesterification of β-lactone **47-1** to eight-membered lactone **47-2** and the elaboration of the amphidinolide P skeleton (**47-4**).

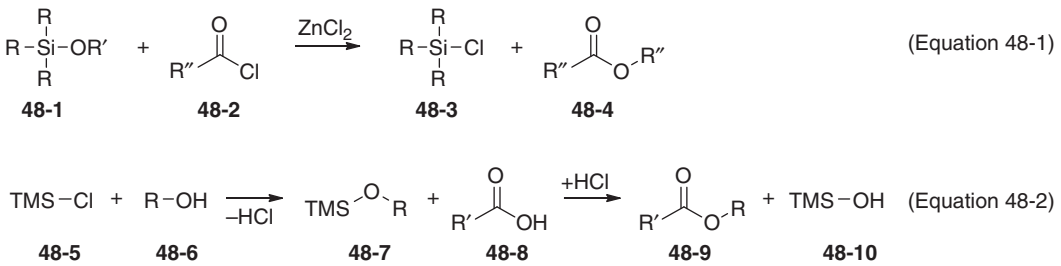
The advantage of Otera's catalysts over dibutyltin oxide or related compounds is the irreversible course of the lactonization reaction. Thus, molecular sieves, or a Dean–Stark apparatus, are not required for the esterification to proceed to completion.[139] Although Otera's catalyst is perfectly suited for the lactonization of ω-hydroxy acids with various ring sizes, the esterification is less efficient.[141] To obtain an acceptable yield of the desired ester, the requisite alcohol must be added in excess, and often up to 20 to 30 equivalents are necessary to get satisfying results. Despite all of the synthetic advantages of Otera's catalyst, the problematic toxicity of tin and its derivatives cannot be denied. Although highly useful in total synthesis, this method is not suited for industrial application or the preparation of biologically relevant samples.



Scheme 47 Application of Otera's catalyst in the synthesis of amphidinolide P (**47-4**).

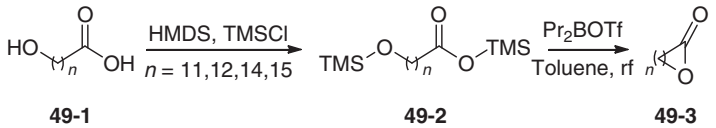
6.09.2.3.5 Silicon-based esterification

The efficient esterification of acid chlorides with silylated alcohols in the presence of zinc chloride as Lewis acid has been described in the early 1960s (Scheme 48, equation 48-1).[144] Later, the procedure has been modified and simplified to directly allow the formation of various esters from primary or secondary alcohols and the requisite acids on addition of chlorosilanes (Scheme 48, equation 48-2).[145] It is noteworthy that TMSCl not only silylates the alcohol as displayed in Scheme 48, but also serves as catalytically active Lewis acid when used in substoichiometric amounts, suggesting a more complex or ambivalent reaction mechanism.



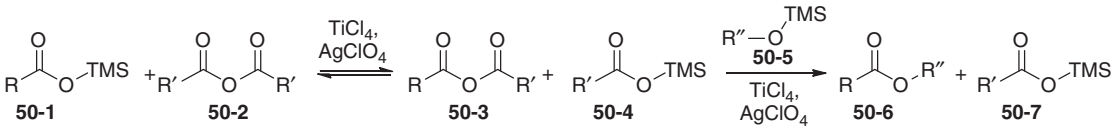
Scheme 48 $ZnCl_2$ and TMSCl-mediated esterification reactions.

Chlorosilanes have also been employed in the preparation of macrolides, see Scheme 49. Exposure of the corresponding ω-hydroxy acid **49-1** to hexamethyldisilazane (HMDS) and TMSCl delivers the bis-protected (or bis-activated) intermediate **49-2**, which on Lewis-acid activation with Pr_2BOTf allows the isolation of the desired lactone **49-3**. Alternatively, the same result was obtained when ω-hydroxy acids were treated with excess of TMSOTf in the presence of boron trifluoride etherate.[146]



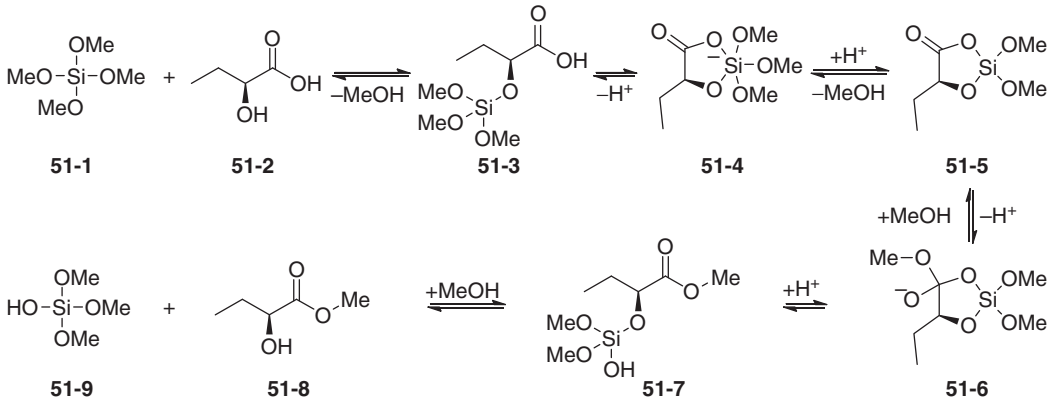
Scheme 49 Lactonization via TMSCl- and Lewis acid-catalysis.

Carboxylic esters and lactones were also prepared via silyl activation of carboxylic acids and subsequent reaction with mixed anhydrides in the presence of a silylated alcohol and Lewis acids, Scheme 50. This protocol was employed in the preparation of macrolactones.[36,37,147]



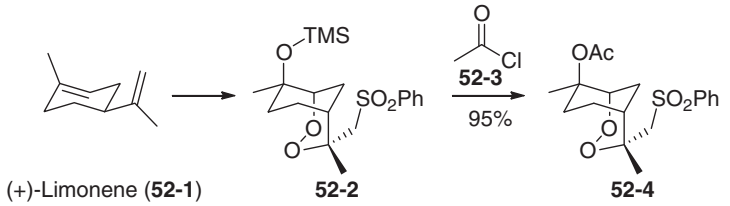
Scheme 50 Esterification via trimethylsilyl (TMS)-activated carboxylic acids.

A mechanistically interesting concept for the selective esterification of α-hydroxycarboxylic acids is described in Scheme 51.[148] When allowed to react with tetramethylorthosilicate (**51-1**), α-hydroxycarboxylic acids **51-2** afforded the corresponding methyl ester in good yield. Both, alcohols as well as carboxylic acids readily react with chlorosilanes to the corresponding alkoxy- or acyloxysilanes, respectively. However, as the stability of alkoxysilanes is higher than the stability of acyloxysilanes, the selectivity of the esterification toward α-hydroxycarboxylic acids can only be explained via complexation and formation of cyclic intermediate **51-4**. Methanol, which is released during the formation of **51-5** then attacks the carbonyl moiety and α-hydroxy ester **51-8** is obtained after hydrolysis of the silyl group. The mechanism outlined in Scheme 51 is closely related to the mechanistic explanation of the boronic acid-mediated esterification, which is described in Section 6.09.2.3.6.[149]



Scheme 51 Silicon-mediated esterification of α-hydroxy carboxylic acids.

Bachi employed the silicon-based esterification in his synthesis of sulfones with antimalarial properties, Scheme 52.[150] Thus, limonene (**52-1**) was converted to TMS-ether **52-2**, which on reaction with acetyl chloride delivered the desired acetate in 95% isolated yield. Reaction of the tertiary alcohol with acetyl chloride in the presence of pyridine and a catalytic amount of DMAP also furnished the desired ester with lower yields (yield not reported).

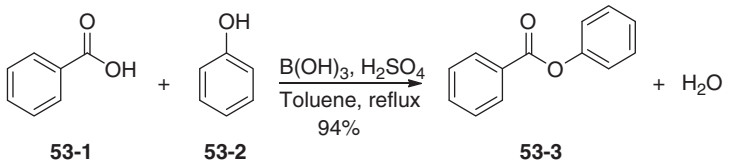


Scheme 52 Application of silicon-based esterification in the preparation of sulfones with antimalarial activity.

6.09.2.3.6 Esterification with boric acid/boronic acid

An early example for the application of boric acid in the esterification of phenols with various carboxylic acids was published by Lowrance in 1971.[151] In a typical procedure, a mixture of acid and phenol was heated to reflux in toluene in the presence of boric acid and sulfuric acid. Water was removed by means of azeotropic distillation and the desired esters were isolated in good yields (58–94%). An example of the protocol is shown in Scheme 53. According to the author, direct esterification of phenols and aromatic carboxylic acids failed without addition of boronic acid.

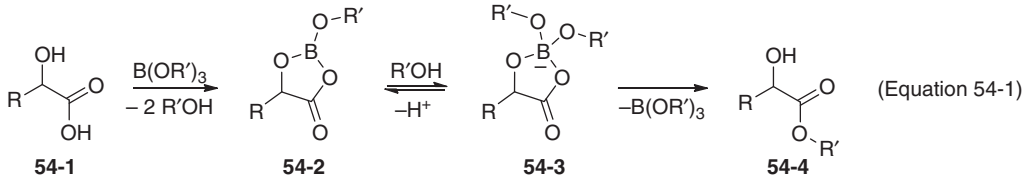
A few years ago, Houston reported the boric acid-mediated chemoselective esterification of α-hydroxycarboxylic acids.[149] Methyl-, ethyl-, and isopropyl-esters were isolated in good-to-excellent yield when the α-hydroxycarboxylic acid was exposed to the corresponding alcohol in the presence of boric acid, *see* equation 54-1, Scheme 54. In a fashion similar to the one discussed for the selective esterification of α-hydroxycarboxylic acids with tetramethylorthosilicate (Section 6.09.2.2.5),[148] a cyclic borate is



53-1 53-2 53-3

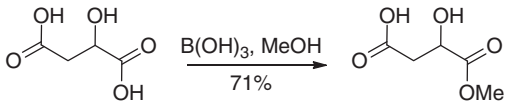
Scheme 53 Esterification catalyzed by boric acid.

suggested as a key intermediate. The chemoselectivity that can be observed in reactions of diacids can be explained by these cyclic intermediates (equation 54-2).



54-1 54-2 54-3 54-4

(Equation 54-1)



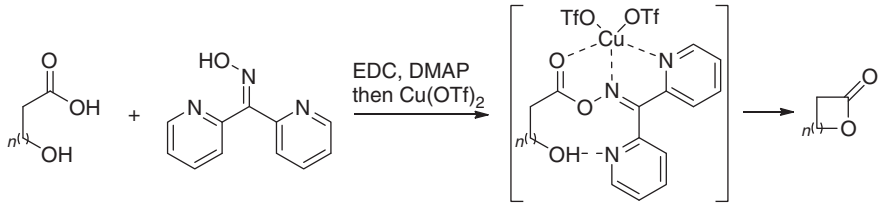
Malic acid (**54-5**) **54-6**

(Equation 54-2)

Scheme 54 Boric acid-mediated esterification of α-hydroxy carboxylic acids.

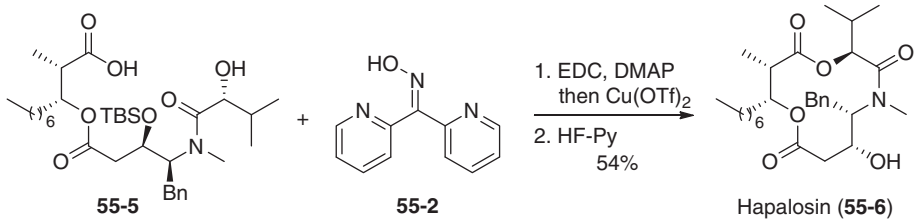
6.09.2.3.7 Esterification via ketone oxime esters

Originally developed for peptide synthesis,[152] Palomo employed *di*-2-pyridyl ketone oxime esters **55-3** in the presence of EDC and DMAP as well as $Cu(OTf)_2$ for the preparation of macrolactones as outlined in **Scheme 55**.[153] Again, double activation of the carboxylic acid and the hydroxy moiety drives the reaction to completion. Whereas *di*-2-pyridyl ketone oxime esters are perfectly stable and no cyclization is observed, addition of copper triflate in stoichiometric amounts triggers the formation of the desired lactone. This observation can be rationalized by the formation of intermediate **55-3**.The protocol was successfully employed in the preparation of hapalosin (**55-6**), a 12-membered macrocyclic bis-lactone.[153]



55-1 **55-2** **55-3** **55-4**

(Equation 55-1)



55-5 **55-2** Hapalosin (**55-6**)

(Equation 55-2)

Scheme 55 Total synthesis of hapalosin (**55-6**) via ketone oxime catalysis.

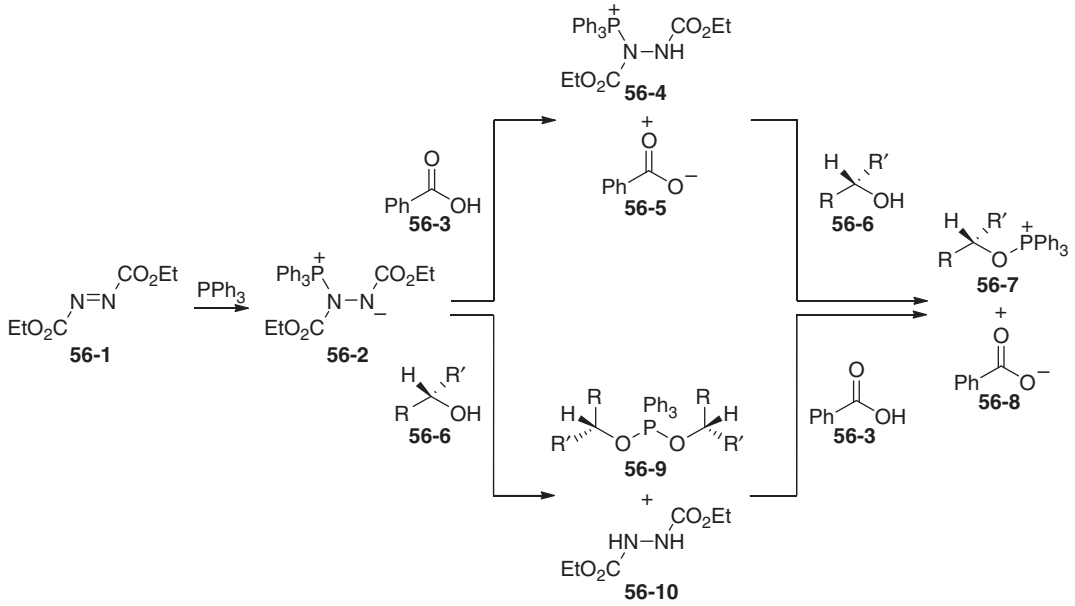
6.09.2.4 Synthesis of Esters via Hydroxyl Group Activation (HGA)

6.09.2.4.1 Mitsunobu reaction

In 1967, Mitsunobu et al. described the synthesis of esters of phosphoric acid by the reaction of trivalent phosphorous compounds with diethyl azodicarboxylate (DEAD; **57-1**) and alcohols.[154] Only a few months after this seminal disclosure, the method was

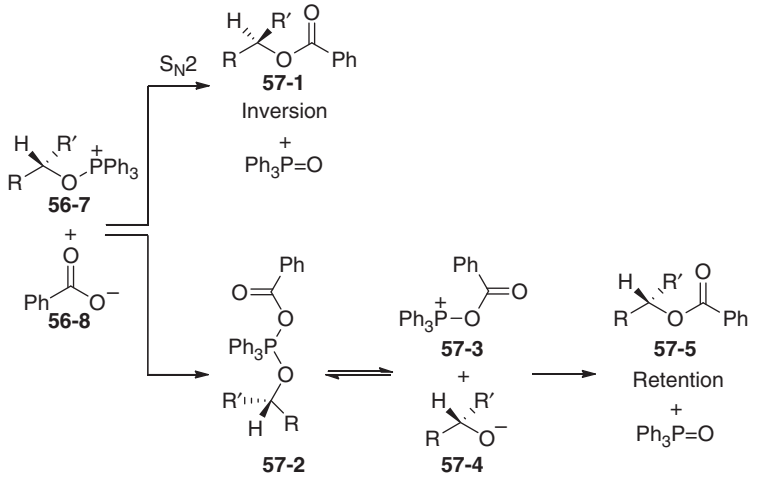
extended and carboxylic esters were successfully prepared.[155] This new method quickly evolved to one of the most important procedures for the efficient esterification and lactonization, mainly because of the high degree of stereospecificity and regioselectivity. The extremely mild reaction conditions make the Mitsunobu reaction a perfect tool for the synthesis of highly complex and sensitive natural products and their intermediates.[156] Furthermore, modification of the reaction conditions allows the installation of various other functional groups, such as amines, organic sulfides, and many more.

Despite the importance of the Mitsunobu reaction for organic synthesis, the mechanistic background is still not completely resolved. An important early observation was the inversion of the configuration of chiral alcohols via the Mitsunobu protocol. The proposed mechanism starts with the formation of betaine **56-2** (Morrison-Brunn-Huisgen betaine)[157,158] from DEAD (**56-1**) and triphenylphosphine as depicted in Scheme 56. The betaine deprotonates the carboxylic acid to form ionic species **56-4**/**56-5**, before reaction with the alcohol delivers alkoxyphosphonium salt **56-7**/**56-8**. Alternatively, the same intermediate can also be obtained if betaine **56-2** initially reacts with the alcohol to afford phosphorane **56-9**, which then reacts with the carboxylic acid to deliver key intermediate **56-7**/**56-8**.



Scheme 56 Mechanism of the Mitsunobu esterification resulting in inversion of the stereocenter of the alcohol moiety.

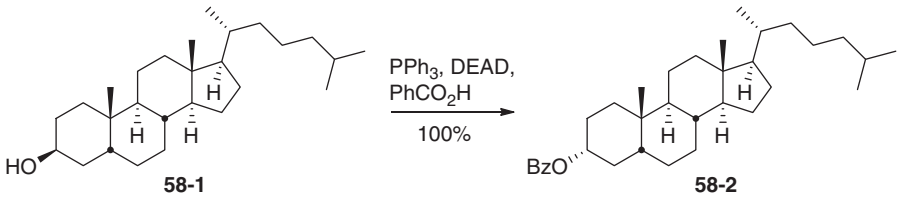
As pointed out in the previous paragraph, the intrinsic synthetic advantage of the Mitsunobu reaction is the clean inversion of configuration at the secondary alcohol. With the formation of key intermediate **56-7**/**56-8**, this observation can easily be explained (Scheme 57). Displacement of the oxophosphonium ion by a carboxylate by means of a S_N2-reaction with concomitant formation of triphenylphosphine oxide allows the isolation of the carboxylic ester with inverted stereoconfiguration.



Scheme 57 Mechanistic considerations of the stereocontrol in the Mitsunobu esterification.

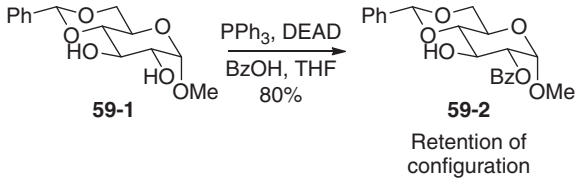
Esterification with retention of the stereochemistry via the Mitsunobu protocol is only favored if the alcohol is sterically hindered. In such case, the ester can be formed from oxophosphonium ion **56-7** via the equilibrium with **57-2**/**57-3**/**57-4** as intermediates.

This Mitsunobu protocol was first successfully employed by Bose in the synthesis of steroids as outlined in Scheme 58. The facile inversion of the stereocenter remains one of the most obvious advantages of this procedure.[159]



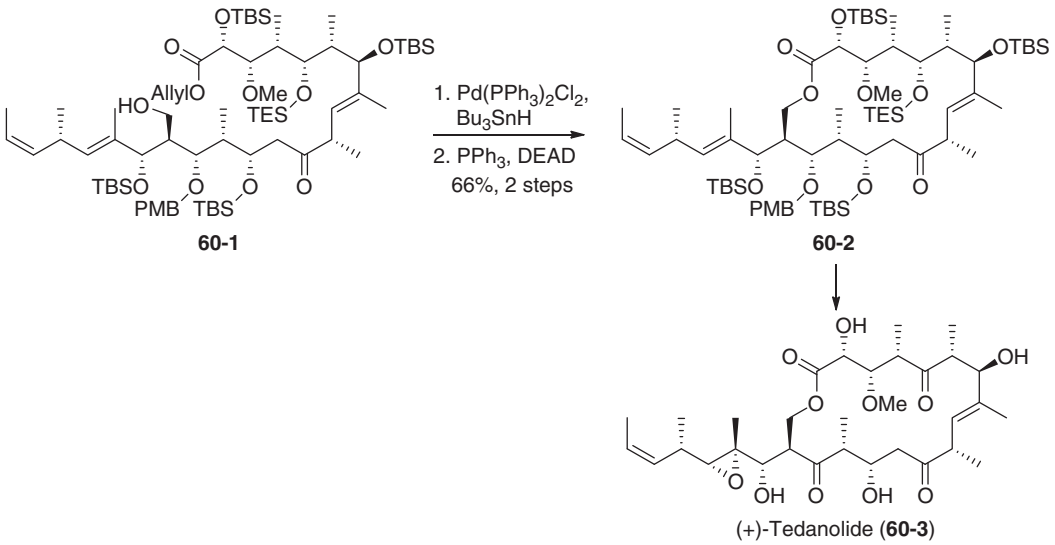
Scheme 58 Bose's synthesis of steroids via Mitsunobu esterification.

An application of the Mitsunobu reaction with retention of configuration in the synthesis of a protected monosaccharide is presented in Scheme 59.[160]



Scheme 59 Esterification of a monosaccharide with retention of configuration.

The Mitsunobu esterification has also been employed as a powerful tool for the formation of macrolactones. A recent example for the synthetic power of this reaction was published by Kalesse and coworkers (Scheme 60), who employed the Mitsunobu conditions to the *seco*-acid from **60-1** (after cleavage of the allyl ester) and obtained the desired macrolactone **60-2** in excellent yield as late-stage intermediate in the synthesis of (+)-tedanolide (**60-3**). Notably, this protocol was superior to other macrolactonization reactions, such as the Keck–Boden protocol (DCC/DMAP, see Section 6.09.2.4.1) or the Yamaguchi esterification (Scheme 14).[161]



Scheme 60 Kalesse's total synthesis of (+)-tedanolide (**60-3**).

A major practical issue is the difficult work-up of the reaction mixture and the separation of the reaction products from by-products such as triphenylphosphine oxide or diethyl hydrazinedicarboxylate (DEAD-H_2; **57-10**). Different water-soluble phosphines, as well as diazo-compounds, have been developed to circumvent this problem (a small selection of reagents is shown in Figure 6).[162–165] Additionally, polymer-supported reagents are available to secure improved work-up and easy removal of by-products via filtration.

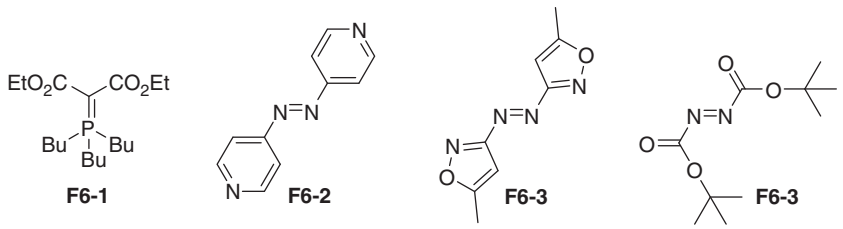
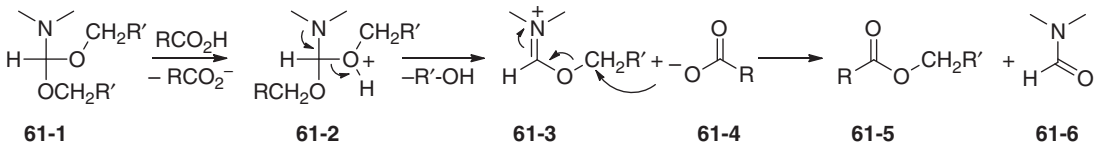


Figure 6 Different water-soluble phosphines and diazo compounds.

6.09.2.4.2 Eschenmoser–Vorbrüggen reaction

Nearly simultaneously, Vorbrüggen[166] and Eschenmoser[167,168] reported that reaction of *N*,*N*-dimethylformamide (DMF) dialkyl acetals (**61-1**) with carboxylic acids delivers the corresponding carboxylic esters **61-5**. The mechanism (Scheme 61) involves protonation of the acetal with subsequent elimination of one equivalent of alcohol. The carboxylate then reacts with the HGA-iminium species **61-3** and affords the ester with concomitant release of one equivalent of DMF (**61-6**). Importantly, only S_N2-active R'-groups can be transferred, such as methyl, ethyl, and benzyl.

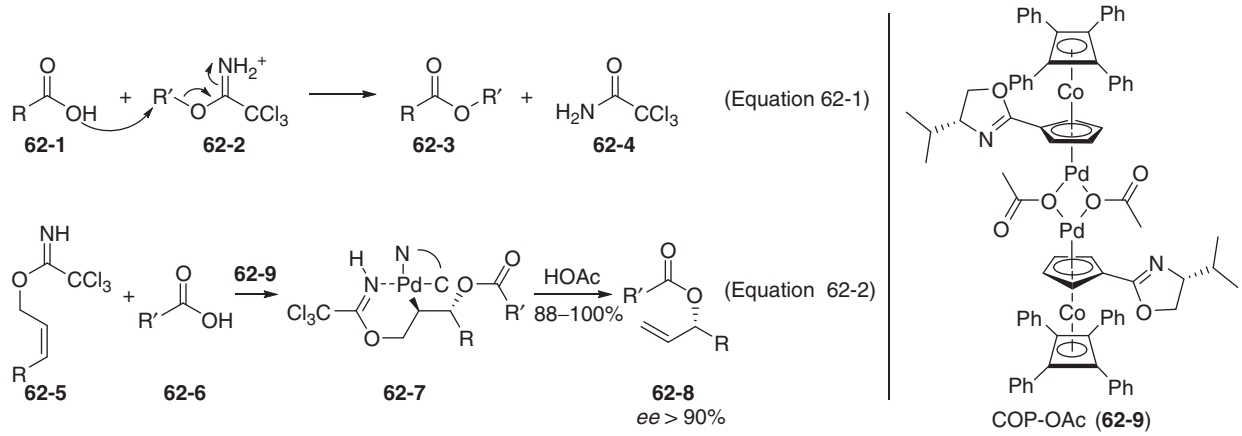


Scheme 61 Eschenmoser-Vorbrüggen esterification.

A few years after the seminal publication, Vorbrüggen and Krolikiewicz published an application of this method in the synthesis of macrolactones. The desired lactones were obtained in 40–50% yield.[169]

6.09.2.4.3 Alcohol activation via trichloroacetimidates

Trichloroacetimidates have been widely used as convenient reagents for the protection of alcohols, which are routinely converted to their benzyl and allyl ethers following the procedure developed by Bundle and coworkers.[170,171] However, as outlined in equation 62-1 (Scheme 62), the same procedure can also be applied to the preparation of carboxylic esters in a very mild manner under neutral reaction conditions. Thus, reaction of carboxylic acids with trichloroacetimidates allows the isolation of the corresponding carboxylic esters as first demonstrated by Jackson in 1988 for the preparation of tertiary butyl esters.[172] Kokotos

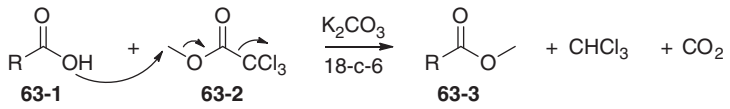


Scheme 62 Alkyl trichloroacetimidates in the preparation of carboxylic esters.

described the synthesis of benzyl and allyl esters with the requisite trichloroacetimidates. However, in this case, addition of a catalytic amount of $BF_3 \cdot Et_2O$ was required to obtain the acylated material in acceptable yield.[173]

Overman published the application of *Z*-allylic trichloroacetimidates for the preparation of allylic esters; equation 62-2, Scheme 62.[174] The palladium catalyst (**62-9**) employed in this reaction is believed to activate the carbon–carbon double bond. Next, nucleophilic attack of the carboxylate and elimination of the trichloroacetimidate moiety releases the allylic ester. Importantly, chiral palladium-catalysts allow the isolation of chiral allylic esters with high *ee* (>90%) and good yield (typically >90%).

Conceptually similar to the application of trichloroacetimidates is the reaction of carboxylic acids with methyl trichloroacetate, Scheme 63.[175] In the presence of potassium carbonate and crown ether, the corresponding methyl esters are obtained in good yield. The irreversible formation of chloroform and carbon dioxide drives the reaction to completion.

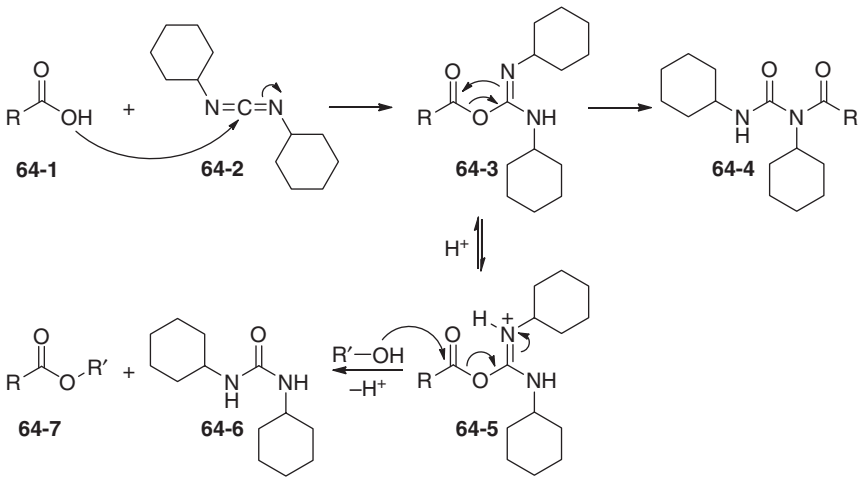


Scheme 63 Utilization of methyl trichloroacetate in the preparation of methyl esters.

6.09.2.5 Esterification via CGA or HGA Pathways

6.09.2.5.1 Esterifcation with carbodiimides

Quite early, dicyclohexylcarbodiimide (**64-2**; DCC) was employed in the preparation of esters of sugars and some amino acid derivatives.[176–183] However, beside the low and irreproducible yields, a major drawback of this method was the considerable formation of *N*-acylurea derivatives (**64-4**) as undesired side products via *O*,*N*-acyl migration as outlined in Scheme 64. Acylurea formation not only diminishes the overall yield of the process, but also complicates work-up and isolation of the desired ester. Different modifications of the procedure have been suggested, which suppress the formation of side products, such as addition of pyridine[184] or *p*-TsOH.[185]

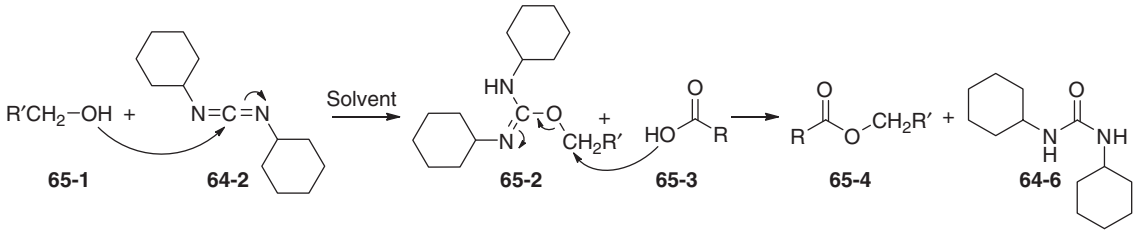


Scheme 64 Mechanistic considerations in the esterification with DCC (**64-2**).

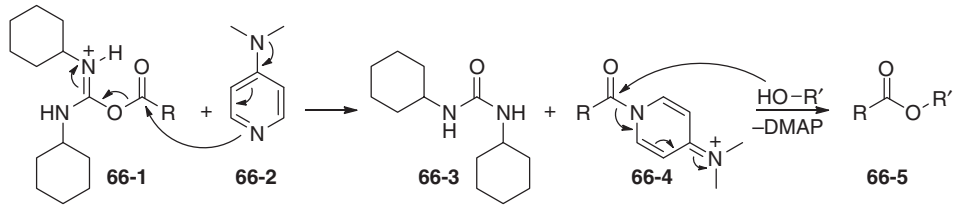
DCC also allows the formation of esters via HGA, Scheme 65. Reaction of the alcohol with the carbodiimide affords isourea **65-2**, a process often mediated by copper catalysis, which delivers the desired ester after addition of the carboxylic acid.[186] Although not commonly employed, alcohol activation presents a possibility to suppress the formation of isoureas.

Despite all efforts, esterification reactions mediated by dicyclohexylcarbodiimide and related reagents only evolved as a general method after Steglich introduced DMAP (**66-2**) as a highly efficient catalyst.[11–15] Reaction of intermediate **66-1** with DMAP (**66-2**) affords activated ester **66-4**, which then delivers the desired ester on reaction with the corresponding alcohol. Keck reported further improvement when DMAP–HCl was employed in esterification and macrolactonization reactions and thus confirmed the importance of the proton-transfer in this process[187] described by Holmberg a few years earlier.[185] With regard to Keck's contribution, the application of the Steglich protocol to the formation of macrolactones is often referred to as Keck macrolactonization (Scheme 66).

Importantly, carboxylate anions react with DCC (**64-2**). Thus, this method can also be used in the acylation of alcohols with symmetrical anhydrides with great efficiency as both acyl moieties are transferred.[188]

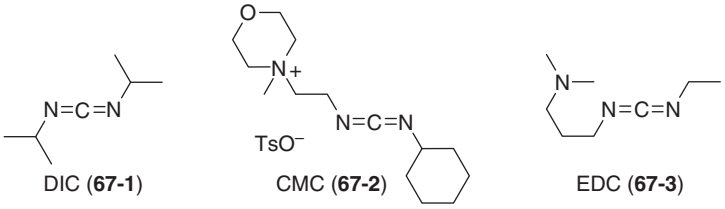


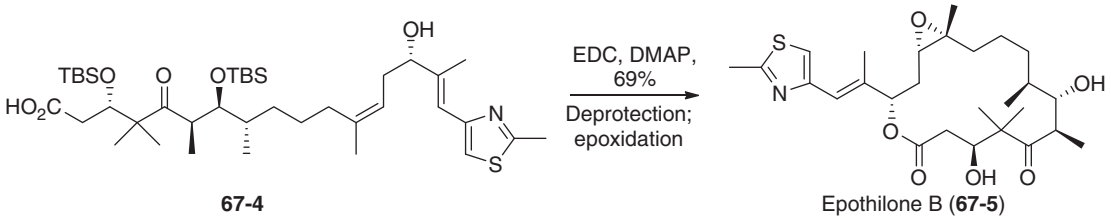
Scheme 65 DCC-mediated HGA esterification.



Scheme 66 Mechanism of the Steglich esterification.

To circumvent the problematic removal of the urea side products – especially on large scale – various carbodiimides have been developed that promise enhanced work-up. A selection of the most prominent reagents is presented in Scheme 67.[189] In this respect, diisopropylcarbodiimide (**67-1**, DIC) is commonly employed, as well as water-soluble variations of the reagent, such as *N*-cyclohexyl-*N*′-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (**67-2**, CMC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (**67-3**, EDC).[186,189] The synthetic utility of EDC was demonstrated by Mulzer et al. who employed the reagent in the late stage macrolactonization of hydroxy acid **67-4** in the synthesis of epothilone B (**67-5**),[190] Scheme 67.



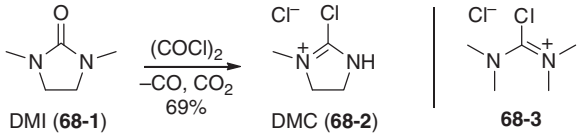


Scheme 67 Application of EDC in the synthesis of epothilone B (**67-5**).

With increased implementation of polymer-supported synthesis, especially for the preparation of peptides, polymer-bound carbodiimide reagents have been developed and investigated intensively.[191–194]

1,3-Dimethylimidazolinium chloride (**68-2**, DMC) has been discussed as an alternative to carbodiimides for the formation of esters and lactones. The reagent can be conveniently prepared from 1,3-dimethyl-2-imidazolidinone (**68-1**, DMI) on reaction with oxalyl chloride in 69% yield (Scheme 68) or alternatively via reaction with diphosgene in 91% yield (not shown). The reagent is relatively stable when stored with exclusion of moisture.[195] DMC acts as a dehydrating agent in a similar fashion to DCC. Thus, slow addition of the hydroxy acid (or the acid and the corresponding alcohol) to a solution of DMC and a base delivers the desired lactone (or ester).

Besides DMC, *N*,*N*,*N*,*N*-tetramethylchloroformamidinium chloride (**68-3**, Scheme 68) and polymer-bound derivatives have been reported.[196]



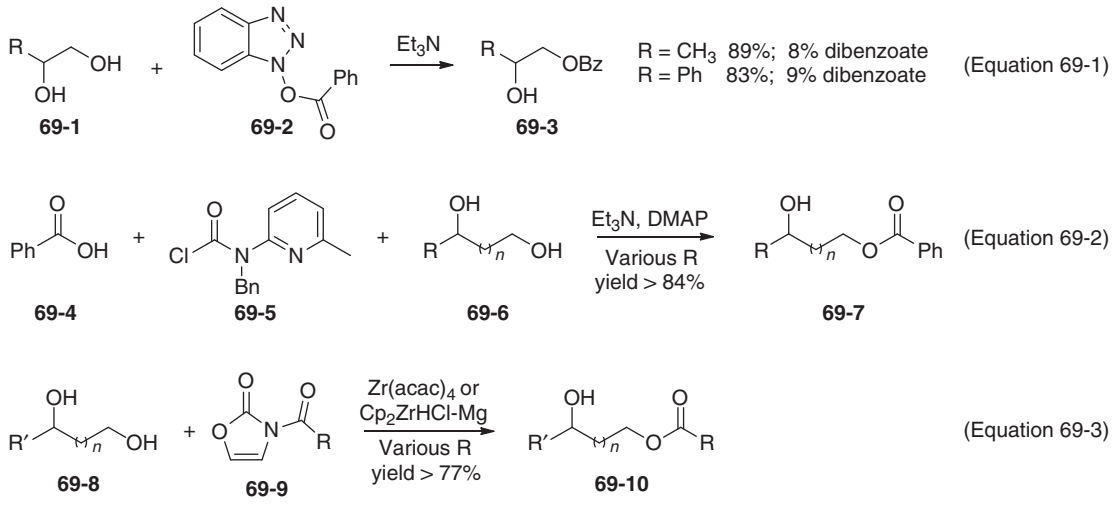
Scheme 68 DMC (**68-2**) as catalyst for esterifications.

6.09.2.6 Selective Monoacylation of Polyols

The synthesis of complex natural products or medicinally important target molecules often requires selective protection and deprotection (acylation and deacylation) of one of several hydroxyl functional groups. Thus, methods to selectively address the desired hydroxyl group are synthetically of great importance; unfortunately, no universally applicable method is available at this time.

Generally, primary alcohols are more reactive toward acylation than secondary, whereas tertiary do not react under standard acylation conditions. Further differentiation is possible when sterically demanding groups are close to the hydroxy moiety. In some cases, even primary alcohols react reluctantly when hindered by large groups.

Several methods have been developed for the selective protection of primary alcohols when secondary hydroxyl groups are present, some of which are outlined in Scheme 69. For example, 1-(benzoyloxy)benzotriazole (**69-2**) was identified as a very mild reagent for the selective esterification of primary hydroxyl groups and polyols have been converted to the corresponding primary benzoates as shown in equation 69-1. The author listed several examples with yields greater than 80% of the desired monobenzoate with minor amounts of the corresponding secondary benzoates.[197]



Scheme 69 Selective acylation of primary versus secondary alcohols.

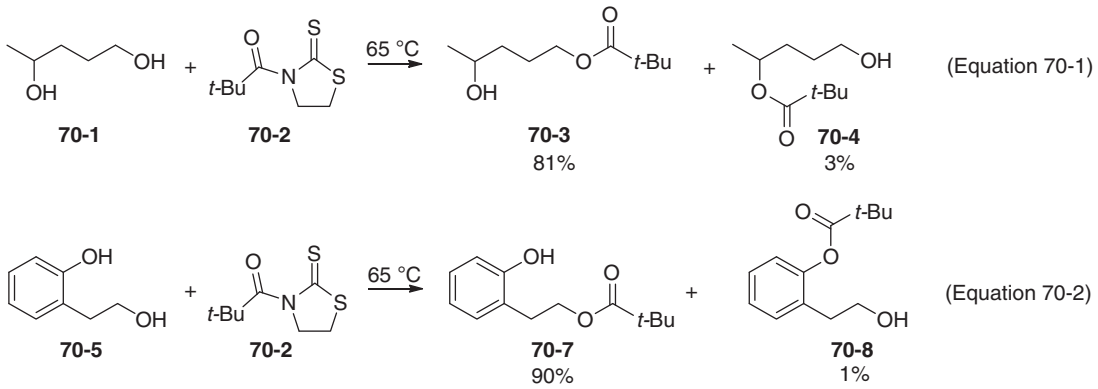
N-Benzyl-2-(6-methyl)pyridinecarbamoyl chloride (**69-5**) is another mild acylating reagent, which can be used for the selective benzoylation of primary alcohols in the presence of secondary and tertiary hydroxyl functional groups (equation 69-2).[198] The typical procedure involves reaction of the desired carboxylic acid with **69-5** to the corresponding activated ester, followed by selective acylation of the primary alcohol in the presence of catalytic amounts of DMAP. The authors reported good yields (>84%) and selectivities (approximately 5–10% of secondary benzoates and dibenzoates formed) for most substrates.

3-Acyl-2-oxazolones (**69-9**) are also effective acylation reagents when used in the presence of certain zirconium complexes (see equation 69-3).[199] Following this protocol, monoacylated diols are accessible in high yield and selectivity comparable to the methods described above.

Various methods for the selective acylation of primary versus secondary alcohols have been published, taking advantage of different acylating reagents, such as benzoyl cyanide,[200] dialkyl acylphosphonates,[201] benzoyl imidazole,[107] benzoyl tetrazole,[202] or even acid chlorides.[203,204] Selective monoacylation of primary alcohols can also be achieved by the Mitsunobu reaction, which is discussed in detail in Section 6.09.2.3.1.[154] Despite all differences, these protocols are conceptually highly similar as all methods employ extremely mild and thus selective acylating reagents. Furthermore, acylating reagents are added in equimolar amount to the reaction mixture to avoid acylation of the less reactive secondary alcohols.

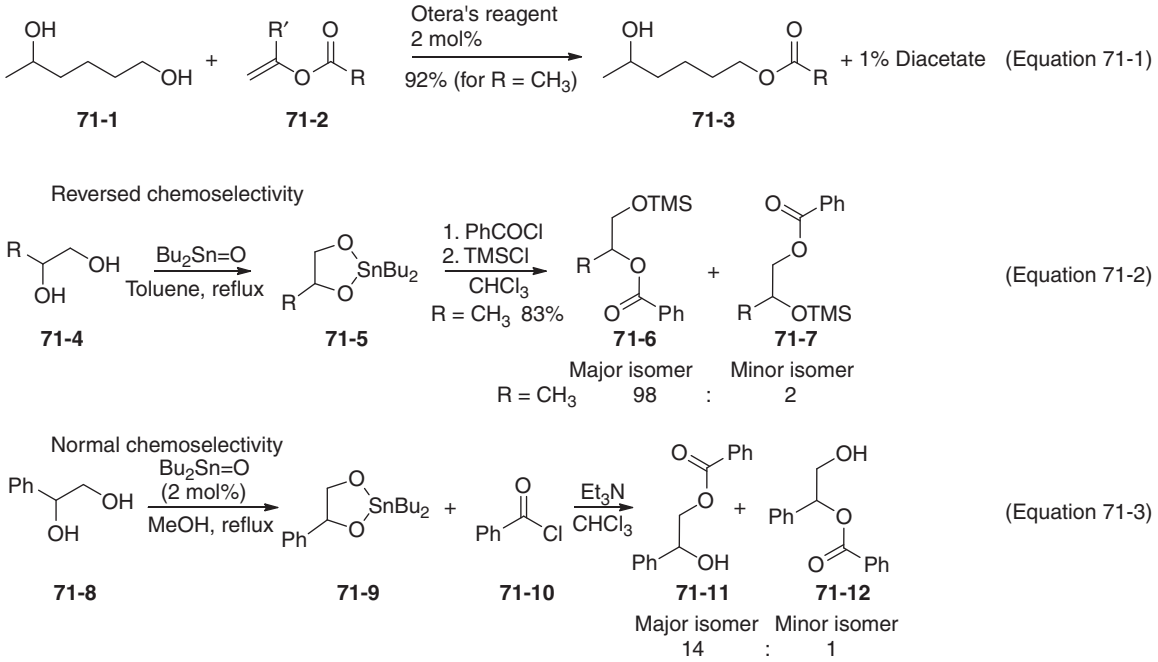
A very mild and selective method for the pivaloylation of primary alcohols was reported by Yamada (Scheme 70).[205,206] Reaction of the diol with 3-pivaloyl-1,3-thiazolidine-2-thione (**70-2**, PTT) in toluene at elevated temperatures (usually between 65 °C and 80 °C) without further activation or use of Lewis acids or bases delivered the desired monoacylated reaction products in

good yield whereas only minor amounts of bis-protected material were isolated (equation 70-1). Selectivities obtained with pivaloyl chloride or pivalic anhydride were significantly lower (**70-3**:**70:4** 3:1 and 8:1, respectively). Monoacylation of substrates with phenolic and alcohol hydroxyl groups is shown in equation 70-2. Whereas the alcohol is acylated nearly exclusively with reagent **70-2**, reaction with pivaloyl chloride and triethylamine afforded the corresponding aryl pivalates (**70-8**) as a major product, although in poor chemoselectivity (**70-7**:**70-8** 45:55; other substrates showed better selectivity in favor of the aryl pivalate). The same selectivity switch was observed when **70-2** was allowed to react with suitable substrates in the presence of base. This observation can be explained by the increased nucleophilic properties of phenols (via phenoxide) under basic conditions.



Scheme 70 Selective pivaloylation using PTT (**70-2**) as reagent.

Tin-based catalysts are mild and highly efficient as already discussed in Section 6.09.2.2.4. Otera's catalyst has also been successfully employed in the selective acylation of primary alcohols, equation 71-1 in **Scheme 71**.[207] Typically, a solution of the alcohol is allowed to react with a large excess of the corresponding alkenyl ester (**71-2**) in the presence of a catalytic amount of the tin species to selectively allow the formation of the desired primary ester in excellent yield. Only traces of the corresponding diester were obtained.

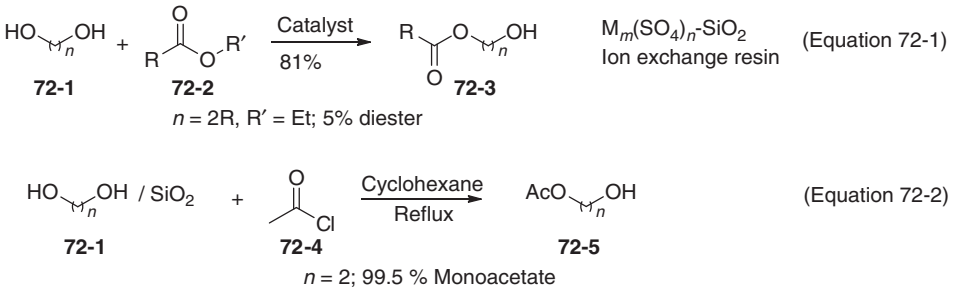


Scheme 71 Chemoselective acylation via the use of tin reagents.

An interesting observation in the tin-based monoacylation of polyols was reported by Roelens and coworkers.[208,209] As outlined in equation 71-2, reaction of unsymmetrical diol **71-4** with equimolar amounts of dibutyltin oxide under azeotropic dehydration conditions delivers dibutylstannylene **71-5**. Next, addition of one equivalent of benzoyl chloride, followed by another equivalent of silyl chloride affords a mixture of silyl-protected monoesters **71-6** and **71-7**. Importantly, the acylation

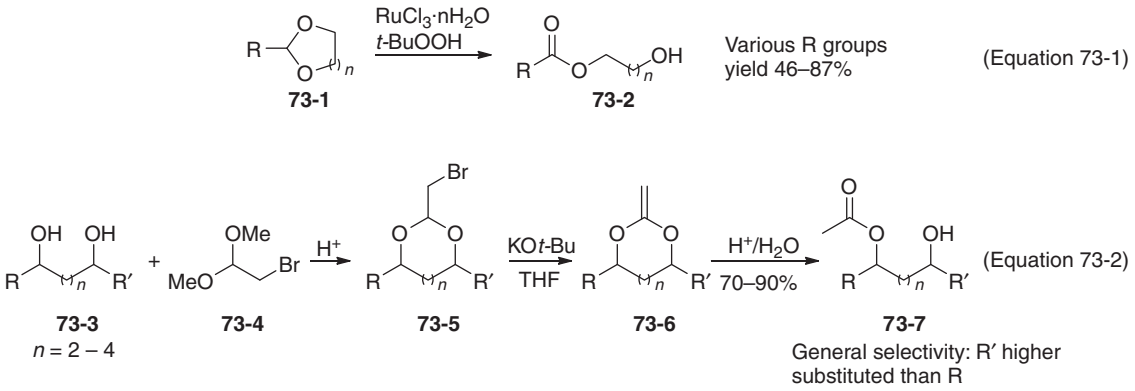
proceeds with inversed chemoselectivity as the major isomer is primary silyl ether **71-6**. However, 'regular' chemoselectivity is observed when diol **71-8** is reacted with a catalytic amount of dibutyltin oxide, followed by slight excess of benzoyl chloride. Hydroxy benzoates **71-12** and **71-13** are obtained with the primary benzoate as the major constituent.[210] The authors suggest that ketal **71-9** reacts with the acid chloride to the desired ester whereas the catalytically active tin species is released. The ratio of regioisomers was determined by NMR spectroscopy without isolation of the reaction products.

Selective monoacylation of symmetrical diols, or polyols with more than one secondary hydroxyl functional group, is a more challenging problem. Several protocols have been developed, taking advantage of different catalysts, such as alumina,[211] distannoxane,[212] phase-transfer catalysts,[213] insoluble polymer supports,[214] or alternatively, careful continuous extraction techniques.[215] Nishiguchi reported the application of metal sulfate-supported silica gel and was able to convert various symmetrical diols into the requisite monoacylated derivatives with high selectivity.[216,217] Strongly acidic ion-exchange resins are equally suited to deliver monoacylated esters. Both methods are represented by equation 72-1, **Scheme 72**.[218] The authors report that esterification of diols was much faster than the esterification of less polar substrates, such as the monoacetylated derivative. A possible reason might be the water layer on the surface of the catalyst. Thus, more polar substrates have a higher probability to be close to the catalytically active surface of the resin. Selective monoacylation of symmetrical polyols has also been achieved via reaction of a suspension of the diols absorbed on silica in cyclohexane at reflux with acetyl chloride as schematically outlined in equation 72-2.[219]



Scheme 72 Selective monoacylation of symmetrical diols.

Alternatively, monoprotection of symmetrical proximal diols can be achieved via oxidation of intermediary-formed acetals as outlined in equation 73-1, **Scheme 73**. Oxidation of the acetal, for example, with *tert*-butyl hydroperoxide and a catalytic amount of ruthenium chloride then results in the formation of a hydroxy ester **73-2**.[220]



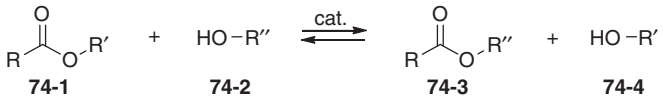
Scheme 73 Cyclic ketene acetals as intermediates in the esterification of diols.

Pittman described the application of cyclic ketene acetals in the esterification of proximal diols as shown in equation 73-2.[221,222] Reaction of the diol with 2-chloro-1,1-dimethoxyethane or 2-bromo-1,1-dimethoxyethane (**73-4**) and subsequent elimination under basic conditions allows the isolation of the desired ketene acetal intermediate **73-6**. Activation of this highly reactive species with aqueous acid results in ring opening and formation of monoester **73-7** in excellent overall yield. The method is highly regioselective as the acylation of the least hindered hydroxy group is strongly favored.

6.09.2.7 Transesterification

Transesterification is a crucial method for the preparation of various esters on laboratory as well as industrial scale.[223] The difficulty of this method lies in the reversible nature of the reaction as discussed in previous sections of this

chapter (e.g., 6.09.2.1.1) as well as outlined in Scheme 74. Thus, it is important to develop strategies to shift the equilibrium to the side of the desired reaction product.

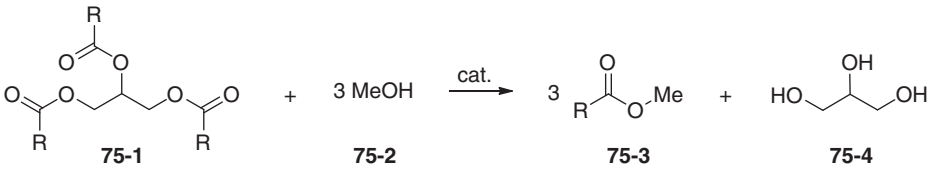


74-1 74-2 74-3 74-4

Scheme 74 Reversibility of transesterification reaction.

Various methods described for the esterification as discussed within this chapter are also suitable for transesterification, and acidic as well as basic catalysts have been employed in this process. Typical reagents include lanthanoids,[224] titanium species,[225] boron tribromide,[226] or amines with catalytic amounts of DMAP.[227] Furthermore, specific esterification catalysts, such as Otera's reagent, are commonly utilized. As these general methods have been covered within the appropriate sections, a repeated discussion is being omitted.

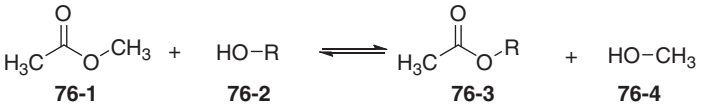
The production of biodiesel emerged to an industrially important process of utmost importance, also evidenced by the huge number of research papers published on this topic within the last few years. Various strategies have been developed to optimize the transesterification of renewable biomass such as natural seed oil. The most important operation employs a methanolic solution containing basic catalysts, such as potassium carbonate on silica,[227–230] calcium carbonate,[229–231] sodium methoxide, or anion-exchange resin.[230–232] Alternatively, transesterification is also possible with supercritical methanol.[231,232] The industrial process is concluded by separation of the desired methyl esters from other valuable by-products, mainly glycerol, Scheme 75.



75-1 75-2 75-3 75-4

Scheme 75 Production of biodiesel from triglycerides via transesterification.

Transesterification of triglycerides as described above is a good example of Le Chatelier's principle in action. Already in the mid 1930s, another example was reported by Adkins. This survey compared the 'replacing power' of different alcohols.[233,234] Adkins observed that the formation of methyl esters is thermodynamically most favored. Furthermore, increasing length of the alkyl chain at the alcohol decreases the replacing power of the reaction partner. The same effect was observed when branched alcohols were compared to unbranched material. Some of Adkins' results are summarized in Scheme 76.



76-1 76-2 76-3 76-4

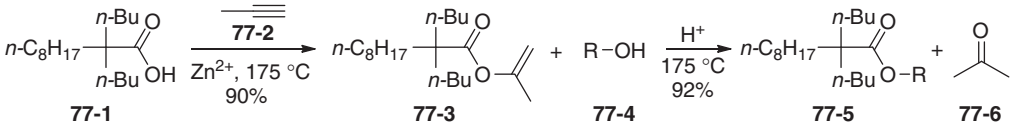
Alcohol	Replacement values $\frac{[CH_3CO_2R]}{[CH_3CO_2CH_3]}$	Equilibrium constant $\frac{[CH_3CO_2R] \times [CH_3OH]}{[CH_3CO_2CH_3] \times [ROH]}$
Methanol	1	1.00
Ethanol	0.81	0.66
1-propanol	0.79	0.62
1-decanol	0.88	0.71
2-Propanol	0.55	0.30
Cyclohexanol	0.57	0.32
Allyl alcohol	0.62	0.38
Benzyl alcohol	0.59	0.35

Scheme 76 Replacement of alkyl groups as determined by alcoholysis of esters.

Generally, the equilibrium can also be efficiently shifted to favor the formation of the desired ester if one reaction partner is continuously removed. If the boiling points of the reactants significantly differ, this can be achieved by means of distillation. Alternatively, azeotropic distillation with certain hydrocarbons or aromatic solvents can be applied to some systems.

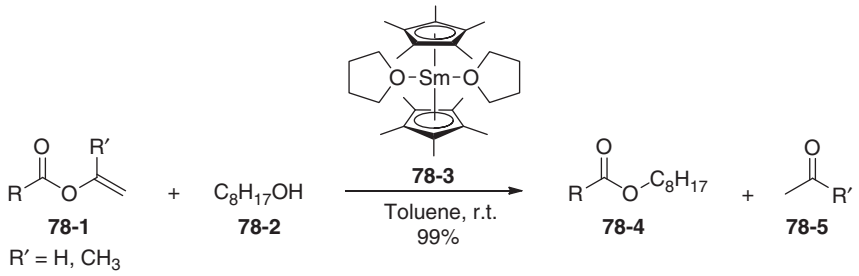
Molecular sieves have been used to selectively remove methanol from the reaction mixture to favor the formation of esters with larger alcohol moieties.[235,236] This protocol seems only suitable for small-scale transesterification.

Another possibility to increase the yield of the desired ester is to allow the formation of a highly stable side product. Different approaches have been developed; some methods are discussed below. Rothman employed isopropenyl esters as starting material for the acid-catalyzed transesterification reaction at elevated temperatures (Scheme 77).[237] The isopropenyl ester (**77-3**) required for this transformation was obtained in excellent yield on reaction of the acid with propyne at 175 °C in the presence of zinc carboxylates.[238] With this highly reactive ester in hand, transesterification proceeded smoothly even with hindered or tertiary alcohols. The distinctive driving force for the acylation of **77-4** can easily be explained by the irreversible nature of the reaction with the formation of acetone as by-product. A major drawback, however, is the use of relatively high temperatures in this protocol, which excludes its application on temperature-sensitive substrates.



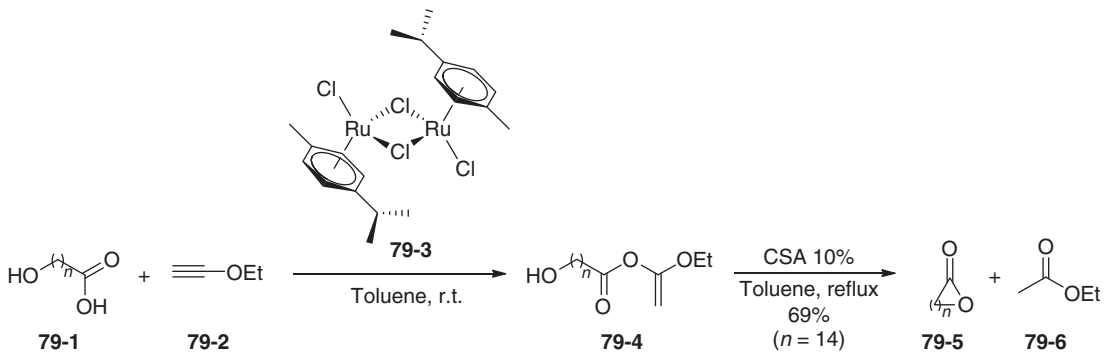
Scheme 77 Transesterification reactions employing isopropenyl esters.

Ishii reported a milder transesterification protocol of vinyl and isopropenyl esters as shown in Scheme 78.[239] Samarium reagents such as $Cp_2{}^*Sm(thf)_2$ (**78-3**)[240] were identified as highly reactive catalysts to promote the desired transesterification reaction. Even sterically demanding alcohols are acylated in high yield (typically greater than 90%). Furthermore, the high temperatures required in Rothman's protocol can be avoided.



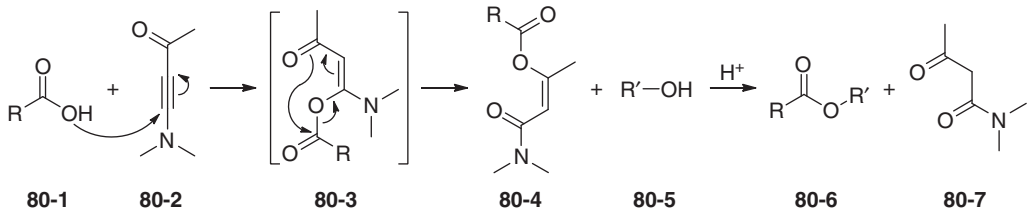
Scheme 78 Application of samarium complex **78-3** in transesterification reactions.

A similar approach for efficient macrolactonization was reported by Trost et al. (Scheme 79).[241] This work was based on Kita's ruthenium-mediated protocol for the formation of 1-ethoxyvinyl esters from carboxylic acids and ethoxyacetylene.[242,243] Formation of vinylic ester **79-4** as a stable and isolable intermediate was followed by the acid-catalyzed esterification of the hydroxyl moiety to deliver the desired ester or macrolactone and ethyl acetate as by-product. Again, the irreversible final step helps to drive the reaction to completion. Macrocycles of different ring sizes can be prepared in satisfying yield (49–70%). Only the formation of 12- and 13-membered rings proved problematic and the corresponding dimers were obtained as major products with only small amounts (4% and 22%, respectively) of the desired macrocycle.



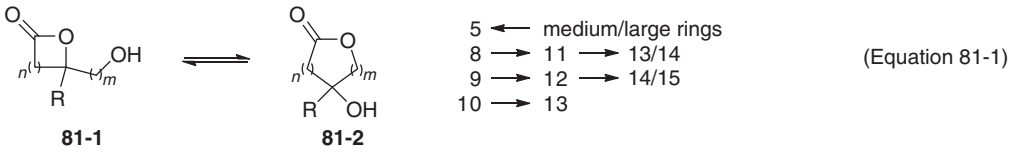
Scheme 79 Transesterification of ethoxyvinyl esters.

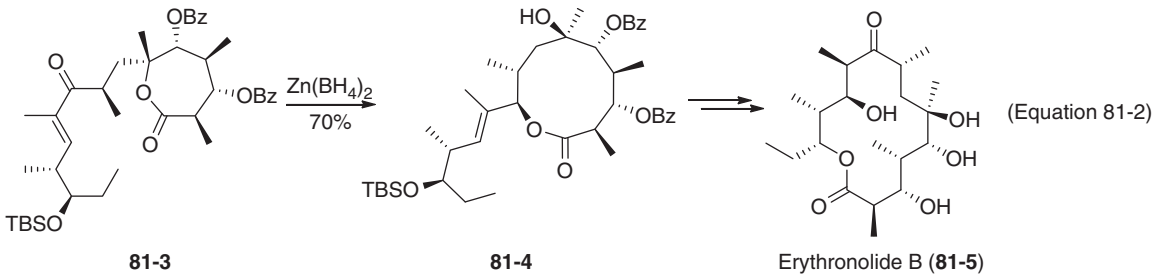
Gais reported the utilization of 4-(dimethylamino)but-3-yn-2-one (**80-2**) in the formation of vinyl esters suited for transesterification as shown in Scheme 80.[244–246] Thus, acid-catalyzed reaction of carboxylic acids with push-pull activated alkyne **80-2** selectively delivers enol ester **80-4** via rearrangement of intermediary formed 1,4-adduct **80-3**. Next, acid-catalyzed addition of the desired alcohol to the rearranged species (**80-4**) allows the isolation of transesterification product **80-6**. The formation of β-ketoamide as a highly stable side-product explains the driving force of this protocol. The only drawback of the method is the tedious preparation of alkyne **80-2**.



Scheme 80 Transesterification via the formation of highly stable side products.

Corey investigated the effect of varying ring sizes on the selective translactonization of cyclic polyols.[247] With the complete reversibility of the transesterification, this study is a direct indication of the stability of lactones with different ring sizes and the inherent ring strains (equation 81-1, Scheme 81). The distance between the hydroxy functional groups is important because the translactonization process requires a cyclic transition state. Thus, index m should be 1, 2, or 3 to get satisfying results. Generally, γ-lactones ($n=2$) are highly stable and formed preferentially over larger rings. Medium-sized rings are not favored and rearrange to thermodynamically more stable larger rings or γ-lactones. Furthermore, the rate of interconversion drops with increasing ring size as the energy difference becomes smaller or negligible.





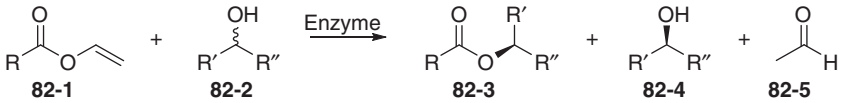
Scheme 81 Total synthesis of erythronolide B (**81-5**) via transesterification.

The concept of selective translactonization has been employed in syntheses of several natural products. The preparation of erythrynolide (**81-5**) via translactonization (7-membered to 10-membered macrocylce; $m=3$) is exemplarily shown in equation 81-2, Scheme 81.[248,249]

Besides purely chemical methods, enzymatic protocols have also been applied in selective transesterification reactions. Enzymatic esterification is discussed in Section 6.09.2.7 and is conceptually similar to enzymatic transesterification reactions.

Different enzymes have been identified to efficiently catalyze transesterifications. In most cases, lipases isolated from microorganisms, such as *Candida antarctica*, *Pseudomonas fluorescens*, or *Alcaligenes* sp. are employed. Additionally, mammalian liver often serves as a source for enzymes and most noteworthy, porcine pancreatic lipase (PPL) is often used. A typical enzymatic transesterification reaction is outlined in Scheme 82 where the ester and the alcohol are allowed to react in the presence of the corresponding enzyme. Importantly, the reaction fulfills multiple purposes and it is most often employed to resolve racemic mixtures of the corresponding alcohol **82-2** as enzymes recognize and differentiate between enantiomers. Vinyl esters are commonly employed as the irreversible formation of acetaldehyde helps to drive the reaction to completion.

The topic of enzymatic transesterification reactions has been extensively covered by several comprehensive review articles.[250–253]



Scheme 82 Enzyme-catalyzed kinetic resolution of alcohols via transesterification.

6.09.2.8 Enzymatic Acylations and Deacylations

A few decades ago, enzymes played only an insignificant role in organic chemistry and most researchers opposed the idea of employing enzymatic reactions for several reasons. However, this picture changed dramatically and at present varieties of enzyme-based protocols and procedures are available and have been added to the standard repertoire of organic chemists, and some methods are suitable for large-scale operations.[250–257] This is also – or especially – true for mild and selective esterification reactions, and this important topic has been extensively covered and highlighted in recent review articles. In this respect, enzymatic methods are important tools for the regioselective esterification of polyols, such as carbohydrate.[255] Essential for this success story and the acceptance of enzymes as useful catalysts or 'reagents' was the development of enzymes capable of tolerating nonaqueous solvent systems.[258,259]

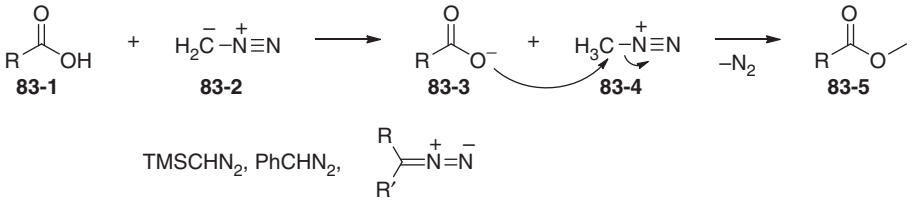
Enzymatic transesterification is briefly discussed in Section 6.09.2.5, and conceptually is highly similar to enzymatic esterification. Generally, as shown in Scheme 82, a suitable ester is allowed to react with an alcohol in the presence of the enzyme, to deliver the desired ester. For a more detailed discussion of this topic, textbooks and review articles on enzymatic methods should be consulted.

6.09.3 Alkylative Esterification

The following section is devoted to different protocols that provide the desired carboxylic esters without the direct use of alcohols. The range of different reagents suitable for such a conversion is immense; herein, the discussion starts with diazomethane and its derivatives and continues with halides and related species. The section concludes with the review of various other electrophiles that can be employed in the preparation of carboxylic esters.

6.09.3.1 Esterification with Diazomethane and Its Derivatives

Although diazomethane (**83-2**) has been identified as a highly toxic and also explosive material, the reagent is commonly employed in laboratory-scale reactions as it is one of the mildest methods for the conversion of carboxylic acids into their corresponding methyl esters.[253,260–262] The mechanism is shown in Scheme 83. Protonation of diazomethane is followed by nucleophilic attack of the carboxylate anion with concomitant loss of nitrogen.



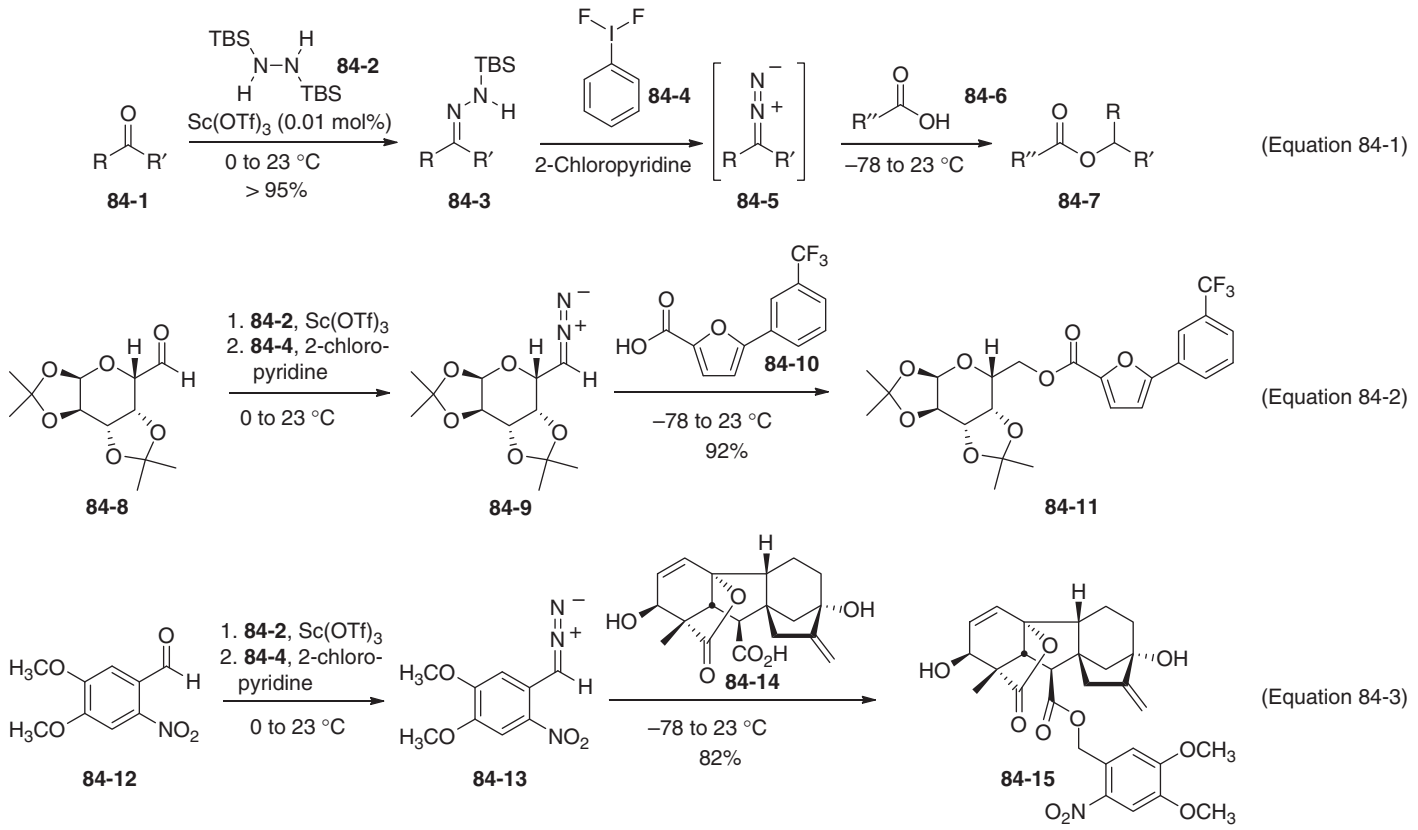
Scheme 83 Esterification of carboxylic acids with diazomethane and its derivatives.

TMS diazomethane serves as a nonhazardous alternative for its toxic and explosive congener. Diazo compounds have also been successfully employed in the synthesis of more complex esters. Reaction of diphenyldiazomethane with carboxylic acids results in the formation of the corresponding benzhydryl ester.[261] A general procedure for the esterification of carboxylic acids with diazoalkanes has recently been reported by Myers (Scheme 84).[262] The requisite diazo compound was generated via oxidation of *N*-TBS-hydrazones (**84-3**) with (difluoroiodo)benzene (**84-4**). The method is tolerant to many different functional groups as demonstrated by the examples outlined in Scheme 84 (equations 84-2 and 84-3).

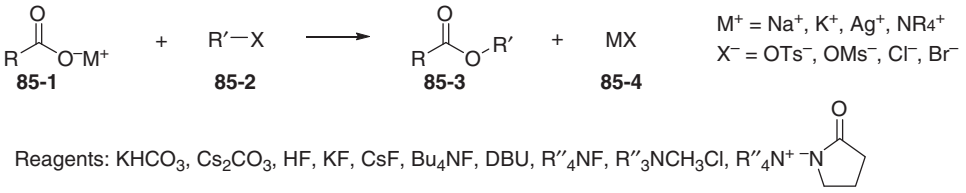
Generally, diazo compounds are extremely reactive species, which is expressed in the facile formation of various side products. In this respect, methylation of other acidic positions such as phenols is commonly observed.

6.09.3.2 Esterification with Alkyl Halides and Related Species

Alkyl halides and related species, such as tosylates, mesylates, or nosylates, are also commonly employed in the preparation of carboxylic esters from the corresponding carboxylates as outlined in Scheme 85. A major drawback, however, is the low nucleophilicity of the carboxylate anion, resulting in an often sluggish reaction.



Scheme 84 Esterification via diazo compounds as intermediates.



Scheme 85 Esterification of carboxylates with alkyl halides and related species.

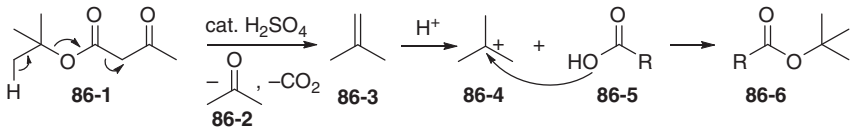
Different cations have been employed as counterion for the carboxylate moiety and the influence of these counterions on the reaction rate has been assessed.[263] Silver carboxylates form insoluble silver halides when allowed to react with alkyl halides, thus driving the reaction to completion.

Additionally, different reagents have been employed in this alkylative esterification of which a small selection is also provided in Scheme 85. The most prominent catalytic systems are hydrogen carbonate and carbonate,[264] fluorides (hydrogen bonding between the hydroxyl moiety and the halide enhances the reactivity),[265–267] various amine bases,[82,268] and phase-transfer catalysts.[269]

Importantly, alkylative esterification can be used to invert the stereochemistry at a secondary carbinol center. Tertiary halides or other sterically congested reaction partners (mainly secondary halides) are prone to elimination and are thus not suitable substrates for the alkylative esterification.

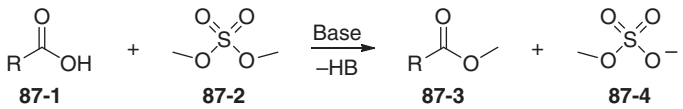
6.09.3.3 Esterification with Other Electrophiles

tert-Butyl esters are accessible from carboxylic acids and isobutylene in the presence of strong acids.[270,271] The major drawback of this method is the impracticable handling of gaseous isobutylene, which needs to be condensed into the reaction mixture at low temperature or increased pressure. This problem can be solved via *in situ* formation of isobutylene from other sources. *tert*-Butanol was identified as precursor for the facile preparation of isobutylene and successfully employed in the synthesis of *tert*-butyl esters.[272,273] Alternatively, as outlined in Scheme 86, *tert*-butyl acetoacetates release isobutylene when allowed to react under acidic conditions.[274]



Scheme 86 Preparation of *tert*-butyl esters via reaction with *in situ*-generated isobutylene.

Dimethyl sulfate has long been known as a highly effective alkylating reagent, which has been mostly employed in the alkylation of phenols. However, the reagent is also a powerful tool for the preparation of methyl esters, with even sterically demanding substrates giving satisfying results.[275,276] The general reaction of carboxylic acids with dimethyl sulfate is presented in Scheme 87. Only one of the methyl groups is transferred from the alkylating agent onto the carboxylic acid.

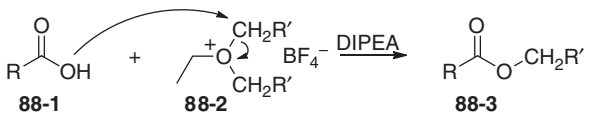


Scheme 87 Preparation of methyl esters via reaction with dimethyl sulfate.

Trialkyloxonium salts represent another class of highly efficient reagents for the preparation of carboxylic esters. Various different reagents have been described, following the pioneering work of Meerwein et al.[277–279] Importantly, most reagents, although somewhat sensitive to moisture, can be stored in the freezer for extended periods without decomposition.

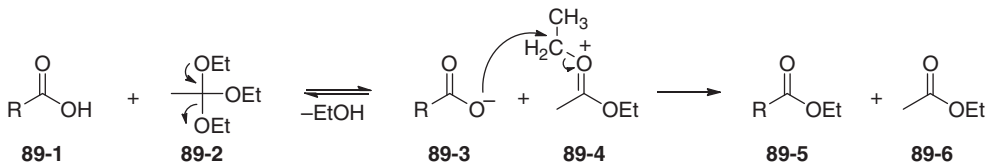
As shown in Scheme 88, the mechanism of the esterification is extremely simple. The desired ester is obtained after nucleophilic attack of the carboxylate onto the activated electrophile. The reaction conditions are very mild and even sensitive substrates can be successfully converted to the desired esters.[279,280]

ortho-Esters are commonly used for the facile preparation of acetals. However, *ortho*-esters can also be employed as synthons for the generation of carboxylic esters.[281] As outlined in Scheme 89, the mechanism is closely related to the esterification with trialkyloxonium salts. Starting from triethyl orthoacetate, ethyl esters become accessible via reaction of the carboxylic acid with *O*-alkylated ethyl acetate (89-4), which is formed as a highly reactive intermediate. Generally, the reactions are carried out under



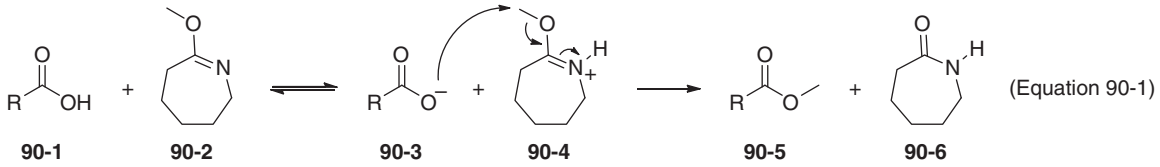
Scheme 88 Esterification reactions with trialkyloxonium salts.

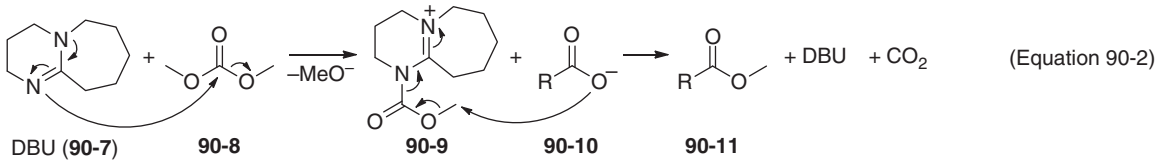
slightly acidic conditions. The side product, namely, ethyl acetate when starting from **89-2** can easily be removed under reduced pressure during work-up.



Scheme 89 Application of *ortho*-esters in the preparation of carboxylic esters.

The reaction of a carboxylic acid with *O*-methylcaprolactim (**90-2**) was described by Mohacsi in the early 1980s (equation 90-1, Scheme 90).[282] When heated as an equimolar mixture without additional solvent, the carboxylic acid was successfully converted to the corresponding methyl ester and *ε*-caprolactam (**90-6**), which is easily removed from the reaction mixture on aqueous work-up.





Scheme 90 *O*-Methylcaprolactim (**90-2**) and DBU (**90-7**) with dimethyl carbonate as esterification precursors.

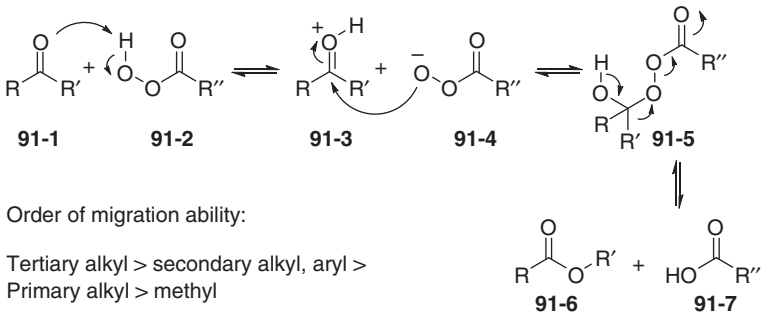
In a similar fashion, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; **90-7**) can also be employed in the esterification of carboxylic acids.[283] In this respect, DBU is allowed to react with dimethyl carbonate (**90-8**) at elevated temperature to preform the activated alkylating carbamate **90-9**, which then affords the desired methyl ester on *O*-alkylation of the requisite carboxylate. The formation of carbon dioxide serves as a driving force in the reaction.

6.09.4 Miscellaneous Methods

6.09.4.1 Synthesis of Esters and Lactones via the Baeyer–Villiger Oxidation

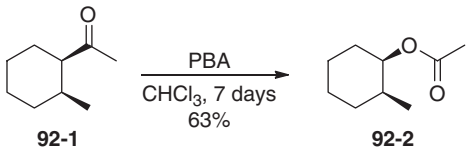
More than 100 years ago, Adolf von Baeyer and Victor Villiger performed a study on the oxidative power of peroxy acids and the newly discovered Caro's reagent.[284,285] As outlined in Scheme 91, exposure of a ketone to peracids results in 'insertion' of oxygen between the carbonyl moiety and the alkyl or aryl substituent with formation of the corresponding ester. Mechanistically, activation of the carbonyl group is followed by nucleophilic attack of the peracid and formation of tetrahedral intermediate **91-5**. Next, the collapse of intermediate **91-5** with concomitant migration of the alkyl or aryl substituent delivers carboxylic ester **91-6**. Importantly, the migrating ability of the substituents correlates with the stability of the migrating group. In this respect, tertiary alkyl groups are more prone to migrate than secondary alkyl groups or aryl substituents. Primary alkyl groups or methyl substituents are least susceptible to migrate.

Commonly, the Baeyer–Villiger oxidation is carried out in the presence of a buffer, such as Na_2HPO_4 or $NaHCO_3$, to prevent undesired transesterification reactions or saponification of the reaction product.



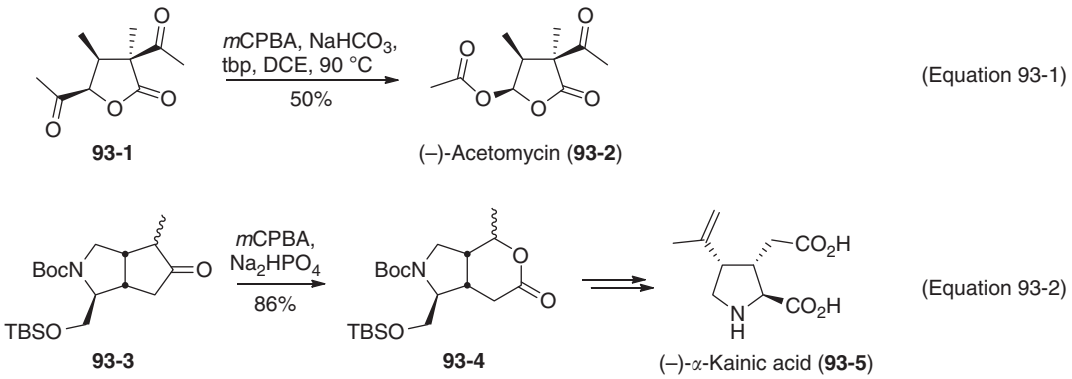
Scheme 91 Mechanistic rationale of the Baeyer–Villiger oxidation.

In 1950, Turner reported the Baeyer–Villiger oxidation of *cis*-and *trans*-1-acetyl-2-methylcyclohexane, as shown in Scheme 92, and revealed that the oxidation occurs with retention of the stereochemistry of the migrating group.[286] In an independent study, published in the same issue of the *Journal of the American Chemical Society*, Gallagher described a similar observation in the peroxybenzoic acid-mediated oxidation of 20-ketosteroids.[287] A few years later, Mislow performed a detailed study on the stereochemical course of the Baeyer–Villiger reaction and confirmed the results obtained by Turner and Gallagher.[288]



Scheme 92 Retention of configuration in the Baeyer–Villiger oxidation of ketones. PBA, phenylboronic acid.

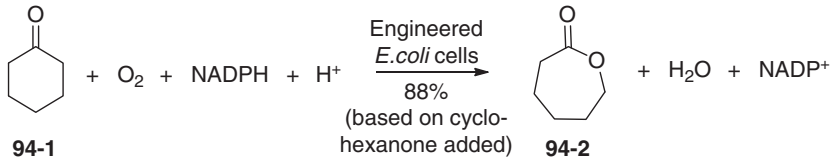
Since its discovery, the Baeyer–Villiger reaction has been applied to a great number of total syntheses of natural products as the esterification method (oxidative rearrangement) of choice. Two examples are outlined in Scheme 93. Ziegler's synthesis of (–)-acetomycin (**93-2**) is an interesting example as it clearly demonstrates the possibility to kinetically differentiate between two methyl ketones.[289] Noteworthy, as discussed in the previous paragraph, the Baeyer–Villiger oxidation proceeds with complete retention of stereochemistry of the migrating group.



Scheme 93 Baeyer–Villiger oxidation in the total syntheses of acetomycin (**93-2**) and α-kainic acid (**93-5**). DCE, 1,2-dichloroethylene.

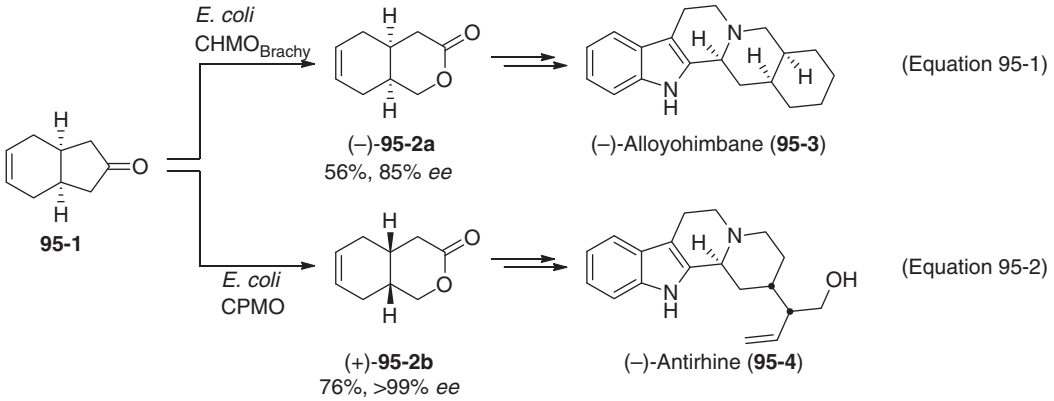
In 2010, Helmchen published an enantioselective total synthesis of (–)-α-kainic acid (**93-5**, equation 93-2, Scheme 93).[290] Bicyclic intermediate **93-3**, prepared via an Ir-catalyzed allylic amination, and a diastereoselective Pauson–Khand reaction as key steps, was allowed to react with meta-chloroperoxybenzoic acid (*m*CPBA) in a buffered solution. Lactone **93-4**, isolated in excellent yield, was converted to the natural product over several steps.

With the growing acceptance of enzymatic methods in traditional organic synthesis and the increasing importance of biotechnological procedures in process chemistry, the most recent variation of the Baeyer–Villiger oxidation is the development of enzymatic protocols. The oxidation of cyclohexanone with engineered nongrowing cells of *Escherichia coli* is outlined in Scheme 94.[291] Whereas typical problems of whole-cell oxidation, such as solubility issues of organic substrates in water or substrate and product inhibition have been discussed, cofactors required for the oxidation reaction are provided from the living organism.



Scheme 94 Example of an enzymatic Baeyer–Villiger oxidation with engineered *E. coli.*

Over the last few years, numerous substrates and enzymes have been screened to reveal the potential of the microbial Baeyer–Villiger oxidation.[292] A good example of the practicability of the enzymatic Baeyer–Villiger oxidation is outlined in Scheme 95. Oxidation of symmetrical bicyclic ketone **95-1** with different strains of biotechnologically engineered *E. coli* delivers antipodal lactones **95-2a** and **95-2b**, which have previously been employed in the total synthesis of (–)-alloyohimbane (**95-3**, equation 95-1) and (–)-antirhine (**95-4**, equations 95-2), respectively.[293,294]

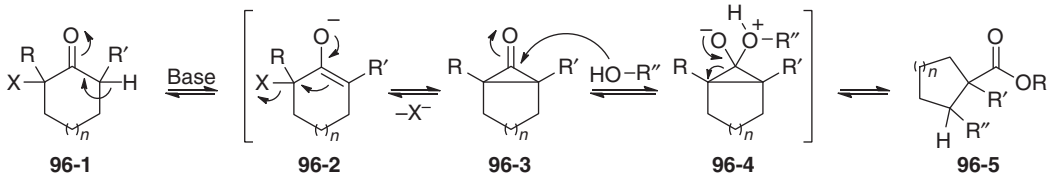


Scheme 95 Preparation of intermediates of the syntheses of alloyohimbane (**95-3**) and antirhine (**95-4**) via an enzyme-catalyzed Baeyer–Villiger oxidation.

6.09.4.2 Favorskii Rearrangement as a Source of Esters and Lactones

Although most commonly recognized as a method for ring contraction, the Favorskii rearrangement is also a suitable method for the synthesis of esters and lactones. Since the seminal disclosure of this important reaction in 1894,[295,296] this rearrangement has been extensively used especially in the preparation of highly branched carboxylic acids and strained polycyclic systems.[296] However, herein we mainly examine the Favorskii rearrangement as a method for the preparation of carboxylic esters. A detailed discussion of the Favorskii rearrangement is provided in Chapter 3.17.

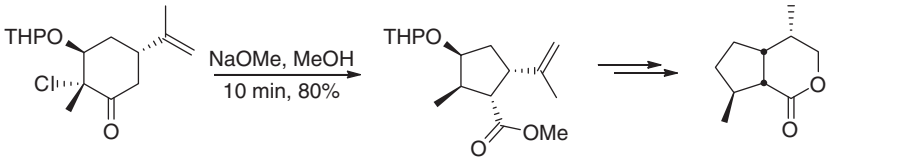
The mechanism of the Favorskii rearrangement is outlined in Scheme 96. The sequence starts with the enolization of α-halo ketone **96-1** under basic conditions. Next, intramolecular alkylation with displacement of the halogen affords cyclopropanone **96-3** which, on addition of a nucleophile, immediately results in a fragmentation and liberation of the carboxylic ester with concomitant ring contraction of the substrate.



Scheme 96 Mechanism of the Favorskii rearrangement.

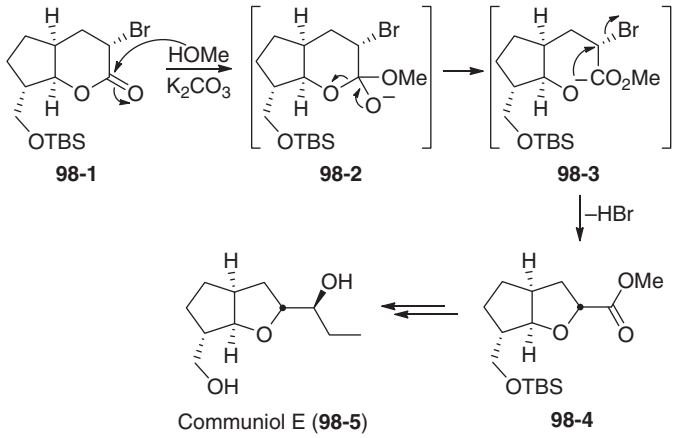
The Favorskii rearrangement served as a key step in Lee's synthesis of (+)-dihydronepetalactone (**97-3**), Scheme 97.[297] Natural carvone was converted to α-chloroketone **97-1**, which then delivered methyl ester **97-2** on exposure to sodium methoxide. The ester was then converted to the natural product over several steps.

In a recent publication, Kobayashi employed an *oxy*-Favorskii rearrangement as a key step in the synthesis of racemic communiol E (**98-5**), Scheme 98.[298] The mechanism of this modification of the rearrangement, also outlined in Scheme 98, commenced with nucleophilic attack onto the ester functional group (**98-1**), which results in the formation of the corresponding carboxylic ester (**98-3**). Next, the intermediary alkoxide displaces the halogen and forms tetrahydrofuranyl ester derivative **98-4**.



97-1 **97-2** (+)-Dihydronepetalactone (**97-3**)

Scheme 97 Favorskii rearrangement in the synthesis of (+)-dihydronepetalactone (**94-3**).

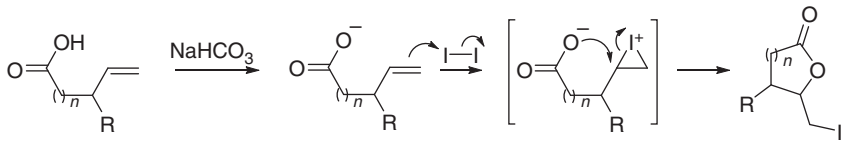


Scheme 98 *oxy*-Favorskii rearrangement in the synthesis of communiol E (**98-5**).

6.09.4.3 Halolactonization

Halolactonization is another excellent and also long-known method for the preparation of lactones with different ring sizes. First described in 1904 by Bougault,[299] the reaction has served as a key step in the preparation of various important natural products.[299–301]

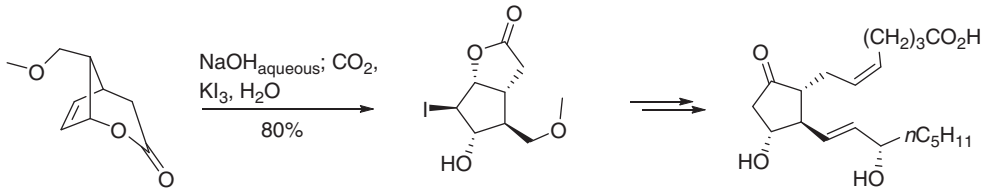
The mechanism of the reaction is simple and straightforward. As outlined in Scheme 99, the formation of the iodonium ion is followed by intramolecular nucleophilic attack of the carboxylate with concomitant formation of the desired lactone. The iodide can then be further manipulated; thus, this esterification method serves multiple purposes, which are also evidenced by the synthetic examples outlined below. The reaction of the halogen is governed by steric and electronic effects, whereas the intramolecular attack of the carboxylate anion and the concomitant formation of the lactone very often follow general rules for ring closure as empirically determined by Baldwin.[300]



Scheme 99 Mechanism of the halolactonization reaction.

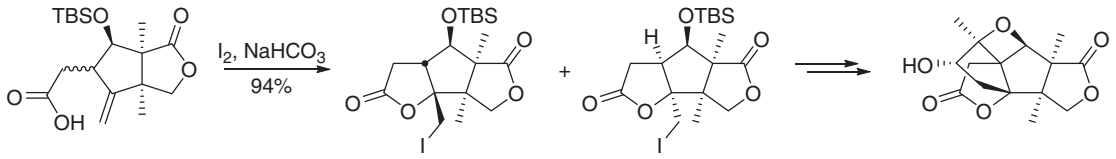
A classic example of the great synthetic potential of the iodolactonization reaction is Corey's route to prostaglandins, outlined in Scheme 100.[302] Saponification of the ester functional group in bicyclic lactone **100-1** was followed by reaction of the intermediary-formed acid with an aqueous solution of potassium triiodide, and iodolactone **100-2** was obtained in good yield. Dehalogenation of **100-2** initiated the endgame of this highly flexible route to the biologically highly important prostaglandins.

In 2002, Danishefsky employed an iodolactonization reaction as one of the key steps in the preparation of merrilactone A (**101-4**).[303] As shown in Scheme 101, the exocyclic double bond in the epimeric mixture of bicyclic intermediate **101-1** served as a scaffold for the formation of the iodonium ion and delivered the corresponding iodolactones **101-2** and **101-3** in good yield. The major product **101-2** was then converted to merrilactone (**101-4**) over a multistep sequence. Danishefsky's synthesis of **101-4** is also a representative example for the dual purpose of halolactonization, as the reaction not only established the lactone ring but also introduced a halogen, which in a subsequent step served as a handle for a Keck allylation.



100-1 **100-2** Prostaglandin E_2 (**100-3**)

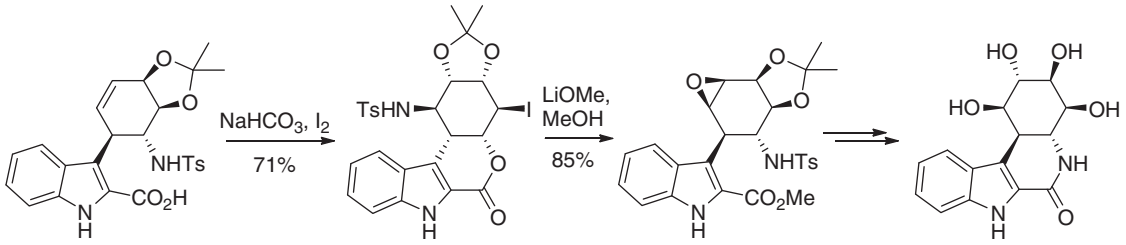
Scheme 100 Iodolactonization in Corey's synthesis of prostaglandin E_2 (**100-3**).



101-1 **101-2** **101-3** Merrilactone (**101-4**)

Scheme 101 Iodolactonization in Danishefsky's synthesis of merrilactone (**101-4**).

Pancratistatin was identified as a highly potent antitumor agent and gained considerable interest from the synthetic community.[304] In 2004, Hudlicky published a short route to a β-carboline-1-on mimic (**102-4**) of this important natural product.[305] This synthesis, outlined in Scheme 102, is another representative example of the synthetic potential of this important lactonization method. The original synthetic plan envisaged epoxidation of the double bond in indole derivative **102-1**. However, as selective epoxidaton could not be achieved because of the indole moiety present in the substrate, an iodolactonization was chosen as an indirect way to generate the desired oxirane **102-3**. Carboxylic acid **102-1** was treated with iodine and **102-2** was obtained in good yield. This material could then be converted into oxirane **102-3** via methanolysis of the lactone.

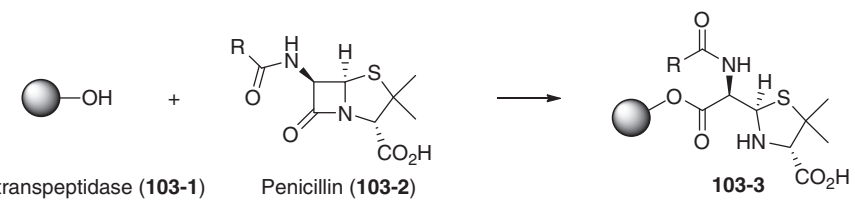


102-1 **102-2** **102-3** **102-4**

Scheme 102 Iodolactonization in Hudlicky's synthesis of an indole mimic of pancratistatin (**102-4**).

6.09.4.4 Esterification using β-lactams

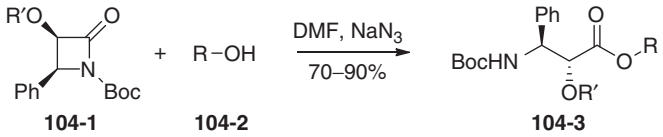
The following section is devoted to a rather specific method for the preparation of certain esters utilizing β-lactams as synthons. Biologically, this process is of utmost importance as it describes the mode of action of penicillin and related β-lactam antibiotics, such as cephalosporins. Mechanistically, as outlined in Scheme 103, the highly strained β-lactam is converted to the corresponding β-amino ester on reaction with a hydroxy moiety.[306–308] This reaction specifically inhibits transpeptidases, which results in the loss of the integrity of cell walls, efficiently killing various microorganisms and consequently confining infectious diseases.



DD-transpeptidase (**103-1**) Penicillin (**103-2**) **103-3**

Scheme 103 Mode of action of penicillin (**103-2**) and related β-lactam antibiotics.

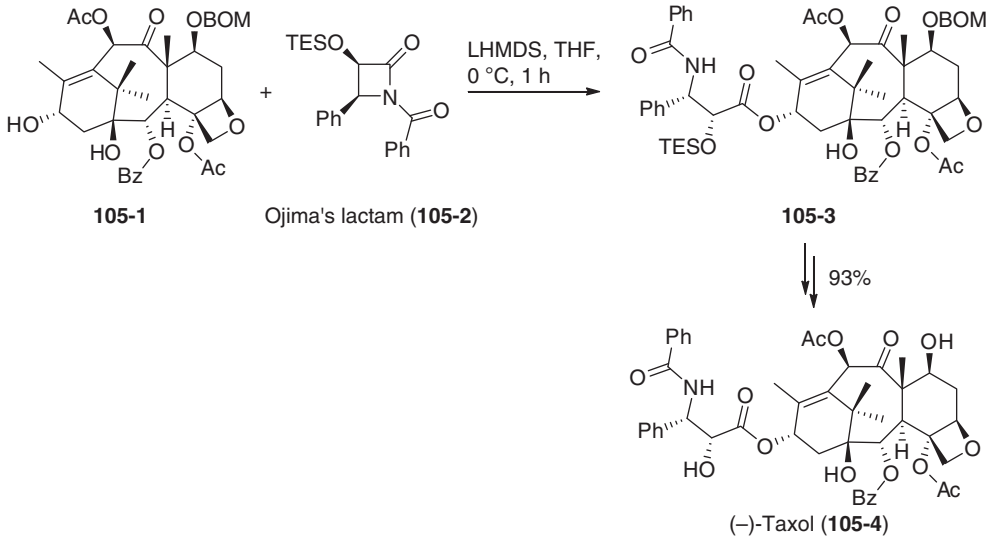
The reactivity of β-lactams toward nucleophiles under acidic or basic reaction conditions led to the utilization of such synthons. Palomo reported a mild method for the alcoholysis of β-lactams, which is shown in Scheme 104.[309] When allowed to react with alcohols in DMF in the presence of sodium azide or cyanide *N*-Boc, protected β-lactams afforded the corresponding β-amino esters in high yield.[309,310]



104-1 **104-2** **104-3**

Scheme 104 Esterification via ring opening of β-lactams.

Ojima et al. contributed to this field and prepared various nonprotein amino acid residues,[311] and most notably utilized β-lactams for the preparation of the side chain of taxol (**105-4**) and the structurally related taxotére.[312] Holton employed this method in the first total synthesis of this extremely important antitumor constituent, outlined in Scheme 105.[313,314]



105-1 Ojima's lactam (**105-2**) **105-3**

(–)-Taxol (**105-4**)

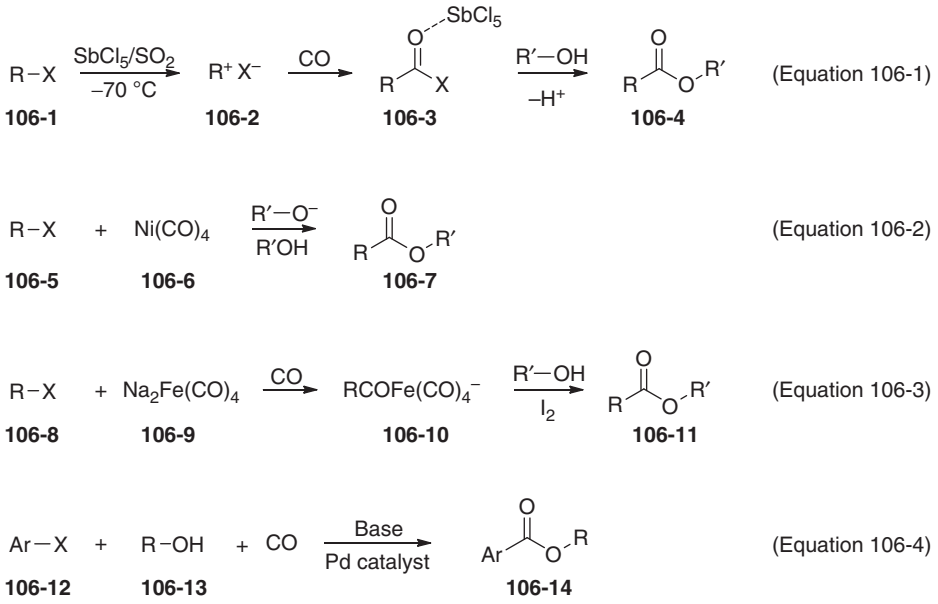
Scheme 105 Application of Ojima's lactam (**105-2**) for the installation of the side chain of taxol (**105-4**).

6.09.4.5 Alkoxycarbonylation

Alkoxycarbonylation reactions constitute an important method for the synthesis of mostly methyl esters. Besides the laboratory-scale application, alkoxycarbonylation reactions are suitable for large-scale preparation of industrially relevant products. A detailed discussion on transition-metal catalyzed procedures as discussed in this section is also provided in Chapters 4.14, 4.15, 4.16, 4.17, and 4.18.

Different possibilities for the conversion of alkyl and aryl halides into the corresponding carboxylic esters have been described and representative examples are outlined in Scheme 106. Equation 106-1 describes the reaction of alkyl halides with $SbCl_5$ in liquid sulfur dioxide.[315] Mechanistically, the process is believed to proceed via an intermediary-formed carbocation. Thus, tertiary alkyl halides deliver the desired ester in higher yields than secondary or even primary halides. Additionally, esters derived from skeletal rearrangements are common side products. Similar results were also described by other research groups. Takahashi employed sulfuric acid to trigger the formation of the corresponding carbocation[316] and Koch and Haaf described the carboxylation reaction of alkenes via intermediary-formed carbocations as early as 1958.[317]

Alkoxycarbonylations of alkyl and aryl halides with nickel complexes (equation 106-2, Scheme 106) follow a different mechanistic pathway. When allowed to react with a suitable alcohol under basic conditions in the presence of nickel tetracarbonyl, the corresponding ester is obtained in good yield (usually 60–95%).[318] The reaction proceeds with the retention of configuration, thus carbocations are not involved in this process. This method can also be applied to the preparation of amides and nitriles. Another possibility for the carbonylative esterification is outlined in equation 106-3. Reaction of the corresponding alkyl halide

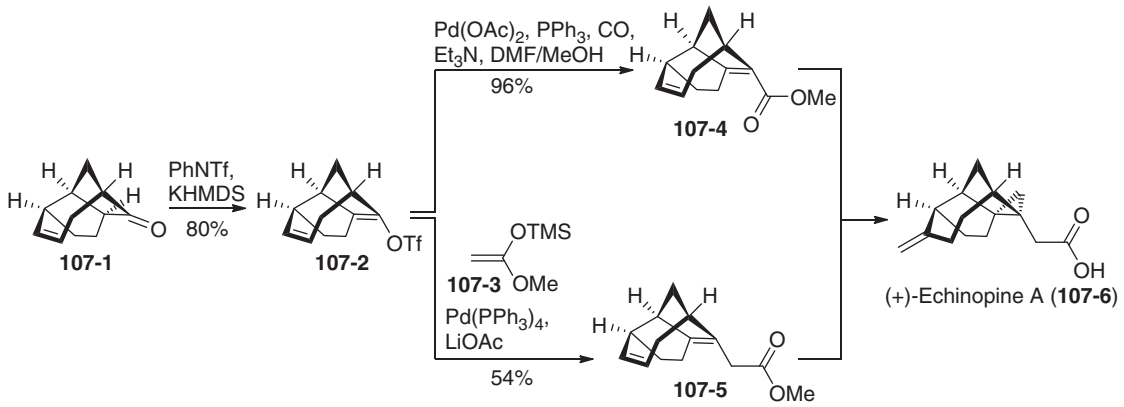


Scheme 106 Alkoxycarbonylation of alkyl and aryl halides.

with sodium tetracarbonylferrate and carbon monoxide delivers the desired carboxylic esters after addition of the requisite alcohol and oxidative work-up with iodine (typically 80% yield).[319,320]

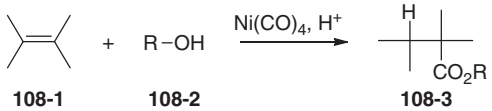
Palladium catalysts (see equation 106-4, **Scheme 106**) and rhodium catalysts have been successfully employed in the carboxylation of alkyl, vinyl, or aryl halides and triflates. Mechanistically, the reaction proceeds via insertion of the catalytically active metal, followed by ligand exchange, oxidative addition, and a final reductive elimination to afford the desired ester.

The palladium-catalyzed carboxylation of vinyl triflate **107-2**, **Scheme 107**, was used as one of the key steps by Mulzer and coworkers in the synthesis of (+)-echinopine A (**107-6**).[321]



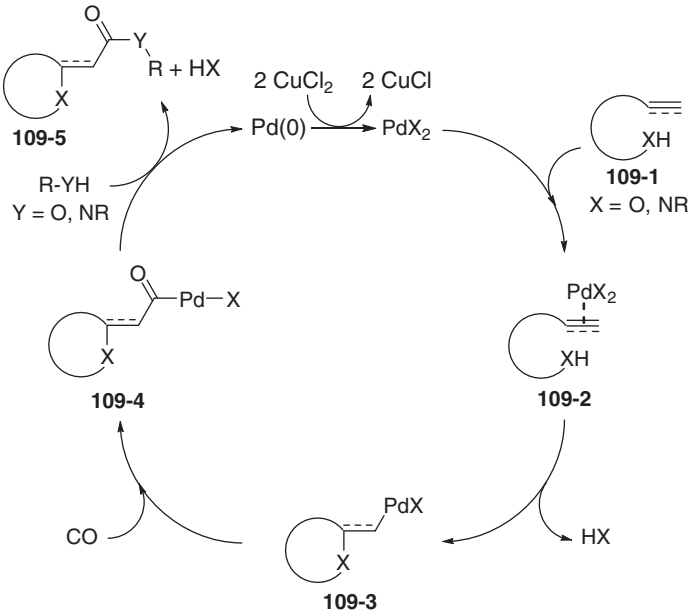
Scheme 107 Palladium-catalyzed esterification in the synthesis of (+)-echinopine A (**107-6**).

Hydroalkoxycarbonylation is a common method for the elaboration of carboxylic esters from alkenes. Again, several metals can be used to successfully convert alkenes to the desired esters, exemplarily shown in **Scheme 108** with nickel tetracarbonyl as catalyst.



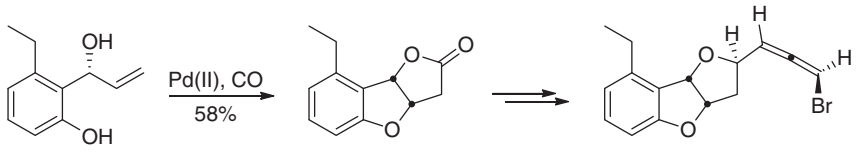
Scheme 108 Hydroalkoxycarbonylation of alkenes with nickel tetracarbonyl.

The mechanism of the alkoxycarbonylation is outlined in Scheme 109. Coordination of the palladium species to the alkene or alkyne moiety (**109-1**) is followed by attack of a nucleophile (alcohol or amine) onto the η^2-Pd(II) complex and formation of the alkoxy- or aminopalladated species (**109-3**). Next migratory insertion of carbon monoxide delivers acyllpalladium species **109-4**, which then reacts with another nucleophile to deliver the desired product (**109-5**). Pd(0) is converted to Pd(II) to close the catalytic cycle.[321–324]



Scheme 109 Catalytic cycle in the palladium-catalyzed alkoxycarbonylation reaction.

An elegant intramolecular alkoxycarbonylation served as one of the key steps in the synthesis of (–)-panacene (**110-3**).[323] The conversion of allylic alcohol **110-1** to tricyclic lactone **110-2** is outlined in Scheme 110.



110-1 **110-2** (–)-Panacene (**110-3**)

Scheme 110 Alkoxycarbonylation as a key step in the synthesis of (–)-panacene (**110-3**).

6.09.5 Synthesis of Lactones

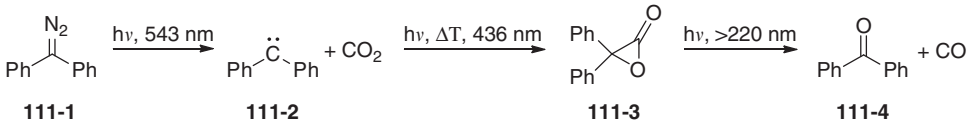
The section discussing the synthesis of lactones is deliberately very short and only intended to provide examples of reactions specifically and solely suitable for the synthesis of lactones with certain ring sizes. In most cases, lactones are prepared simply by applying general esterification protocols, which have been discussed in detail throughout this chapter; thus, a repeated discussion of such general methods is being omitted.

6.09.5.1 Synthesis of α-Lactones

α-Lactones are extremely unstable compounds and of little synthetic importance. Only a few methods have been reported, which grant access to these rather exotic products. For example, Bartlett synthesized α-lactones from ketenes via ozonolysis and later also via autoxidation.[324,325]

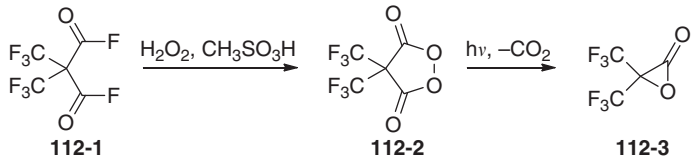
Despite their aforementioned lack of synthetic applicability, the preparation and characterization of α-lactones is of theoretical importance. Amongst others, these highly strained lactones are suitable to probe the reactivity of carbenes. In this respect, Sander described the preparation of diphenyloxiranone (**111-3**) from diphenyldiazomethane (**111-1**) as outlined in Scheme 111.[326] Irradiation of **111-1** in a CO_2-doped Ar or Xe matrix at 10 K resulted in the intermediary formation of carbene **111-2**, which

delivered α-lactone **111-3** on slight warming to 40 K. Further irradiation ($\lambda > 220$ nm) effected decomposition of the unstable material and benzophenone (**111-4**) was obtained.

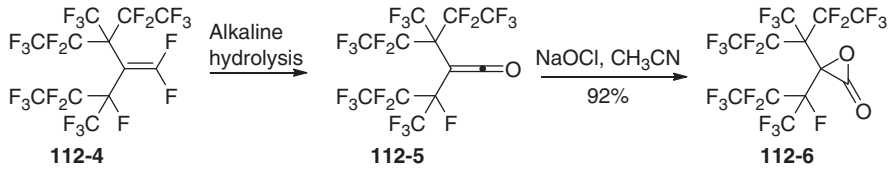


Scheme 111 Preparation of α-lactone **111-3** from diphenyldiazomethane.

Trifluoromethyl moieties exert a stabilizing effect, which can be utilized in the preparation of α-lactones as shown in Scheme 112. When allowed to react with hydrogen peroxide in methanesulfonic acid, bis(trifluoromethyl)malonyl difluoride (**112-1**) afforded bis(trifluoromethyl)malonyl peroxide (**112-2**), which delivered α-lactone **112-3** when irradiated. Again, because of the low stability of the reaction product, the photolysis had to be carried out at low temperatures (77 K) in a matrix, or on a preparative scale in CCl_4 at −15 °C (equation 112-1, Scheme 112).[327]



(Equation 112-1)



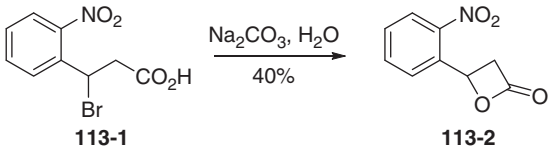
(Equation 112-2)

Scheme 112 α-Lactones from fluorinated substrates.

Another approach toward α-lactones was presented by Coe and Tatlow and coworkers who accessed these labile compounds via sodium hypochlorite-mediated epoxidation of highly fluorinated ketenes (equation 112-2, Scheme 112).[328,329] Ketene **112-5** itself was prepared from alkene **112-4** on alkaline hydrolysis, before reaction with sodium hypochlorite delivered the desired α-lactone.

6.09.5.2 Synthesis of β-Lactones

With a highly strained four-membered ring motif, β-lactones are extremely reactive compounds. As a direct consequence to the inherent ring strain, β-lactones display distinctive differences in reactivity compared to other lactones or esters. Thus, much effort has been devoted to the preparation of β-lactones and the exploration of reactions associated with these systems[330,331](Scheme 113).

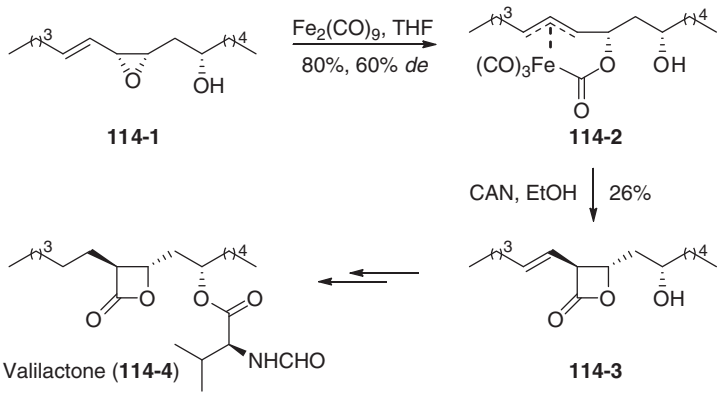


Scheme 113 First synthetic access to β-lactones.

Despite the high ring strains associated with β-lactones and in contrast to α-lactones, most methods described in previous sections of this chapter are applicable to the preparation of four-membered ring lactones as well. Also, β-lactones are long known products as evidenced by the early preparation of 4-(2-nitrophenyl)oxetan-2-one (**110-2**) from the corresponding β-bromocarboxylic acid **110-1** by Einhorn in 1883 (Scheme 110).[332]

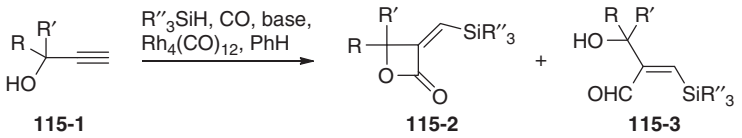
In this section, some of the more specific methods for the preparation of β-lactones are outlined. In the late 1970s and early 1980s, Ley developed a protocol for the formation of β-lactones utilizing iron carbonyl complexes.[333,334] When allowed to react with pentacarbonyl iron (or related iron carbonyl complexes), α,β-unsaturated epoxides deliver the corresponding ferralactone (structural features as shown for compound **114-2**), which on exposure to oxidants such as ceric ammonium nitrate can be

converted to β-lactones. As shown in Scheme 114, this method was successfully employed in the synthesis of valilactone (**114-4**), where unsaturated oxirane **114-1** served as substrate for the diiron nonacarbonyl-mediated lactonization reaction to deliver β-lactone **114-3** in moderate yield after oxidative work-up of the intermediary-formed tricarbonyliron-lactone complex **114-2**.[335]



Scheme 114 Formation of β-lactones via tricarbonyliron-lactone complexes as intermediates.

Another metal-assisted lactonization method is outlined in Scheme 115. Reaction of propargyl alcohols with dimethylphenylsilane, a nitrogen base, CO, and a catalytic amount of tetrarhodium dodecacarbonyl $Rh_4(CO)_{12}$ allowed the isolation of the corresponding α-silylmethylene β-lactone **115-2** and enal **115-3**. The ratio of **115-2** and **115-3** greatly depends on steric as well as electronic factors. A small selection of conditions is outlined in Scheme 115.[336] This modification of the general cyclocarbonylation reaction became attractive as standard palladium-catalyzed reactions did not yield the desired β-lactones from propargyl alcohols.

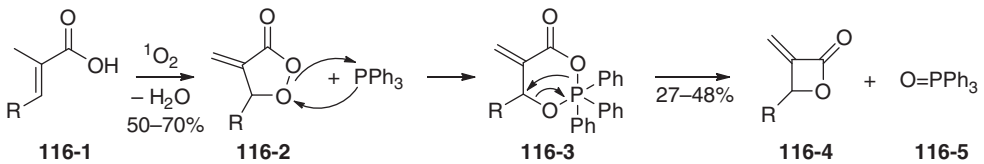


Ratio of **115-2** and **115-3** varies with R groups and base used in the reaction

	115-2	115-3
R = H; R′ = CH_3; Me_2PhSiH; NEt_3	15%	76%
R = H; R′ = CH_3; Me_2PhSiH; DBU	54%	26%
R = H; R′ = CH_3; *t*-$BuMe_2SiH$; DBU	79%	6%

Scheme 115 β-Lactones from propargyl alcohols.

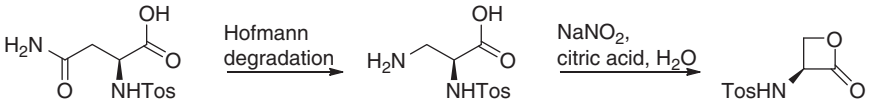
Phosphines and phosphites are able to reduce peroxides via net oxygen atom extrusion and concomitant formation of the corresponding deoxygenated material.[337] This method can also be applied to the preparation of β-lactones as outlined in Scheme 116.[338,339] Reaction of cyclic peroxyester **116-2**, accessible from methacrylic acid derivatives on oxidation with singlet oxygen, with triphenylphosphine resulted in the isolation of α-methylene-β-lactones in moderate-to-fair yield. Interesting from a mechanistic point of view is the fact that reaction of peroxylactones with phosphines results in ketene elimination and decarboxylation (not discussed herein).[338]



Scheme 116 Oxidative phosphine-induced preparation of β-lactones.

The final example discussed within this section, outlined in Scheme 117, has been applied to the preparation of L-α-tosylamino-β-propiolactone (**117-3**).[340] However, this method seems well-suited for the general synthesis of lactones of varying ring sizes as simply the leaving group ability of diazo-functional groups is exploited. In this respect, Hofmann degradation of

N-tosyl-L-aspargine (**117-1**) afforded the requisite starting material for the diazotization with concomitant formation of the desired β-lactone.

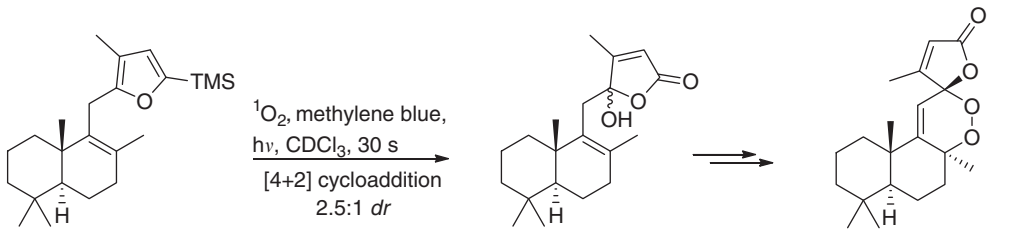


117-1 **117-2** **117-3**

Scheme 117 Formation of β-lactones via diazo intermediates.

6.09.5.3 Synthesis of γ-Lactones

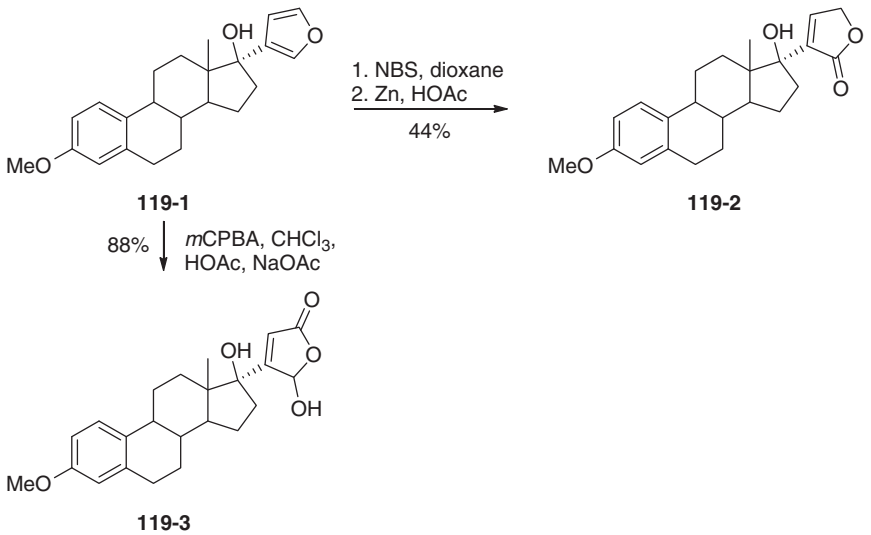
Ring strain is no predominant criterion in the chemistry of five-membered lactones, thus these cyclic esters can be prepared in complete analogy to their open-chain analogs. This section contains only one method that is suitable for the preparation of γ-lactones as furan derivatives are utilized as starting materials, defining the ring size of the requisite reaction product. Formation of γ-lactone **118-2** is one of the key steps in the preparation of (+)-premnalane A (**118-3**) as shown in Scheme 118.[341] Hydroxy butenolide **118-2** was obtained after a [4+2]-cycloaddition reaction of silylated furan **118-1** with singlet oxygen (yield not given).



118-1 **118-2** (+)-Premnalane A (**118-3**)

Scheme 118 Preparation of γ-lactones via furan oxidation.

Another example of the utilization of furan oxidation in the preparation of biologically relevant target molecules is given in Scheme 119.[342] Treatment of substituted furan **119-1** with *N*-bromosuccinimide (NBS) and subsequent zinc reduction afforded butenolide **119-2** in moderate yield. The same starting material was also converted to hydroxy butenolide **119-3** in good yield on *m*CPBA-mediated oxidation of the furan moiety.



119-1 **119-2** **119-3**

Scheme 119 Furan oxidation and butenolide formation in steroids.

6.09.6 Conclusion

Esters and lactones are omnipresent in natural products and synthetic intermediates. The great importance of this functional group is evident by the numerous protocols that have been developed to synthesize esters and lactones since the pioneering work by Emil Fischer in the 1890s. This chapter serves as an update to the review published in the first edition of Comprehensive Organic Synthesis and is intended to provide an overview of the most important and prominent methods for the installation of esters and lactones with strong emphasis on new developments. Despite the title of this book series, a truly comprehensive coverage of this field is not possible because of the huge number of articles that have been published in this area.

Within the past decades, many problems associated with the esterification and lactonization have been addressed and solved. In contrast to early protocols, which required harsh reaction conditions and often high temperatures, newly developed procedures allow the reaction to proceed at room temperature under mild conditions. Activation of alcohols or carboxylic acids before the addition of the requisite reaction partner further increases the efficiency of the esterification or lactonization. Numerous catalysts have been reported and enzymatic procedures are available and have been applied even on industrial scale.

Despite all efforts, several problems still remain to be solved. Selective esterification of diols represents a challenging task and macrolactonization often lacks practicability. In this respect, the field of esterification and lactonization remains a fruitful and vivid research area and we can hope for practical and constructive solutions for these unsolved problems.

6.09.7 Acknowledgment

The authors thank Dr. Nina Tölle for careful proofreading of the document.

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6.10 Synthesis of Thioamides and Thiolactams

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6.10.1 Introduction

Thioamides **1** are the most popular group of thiocarboxylic acid derivatives as they are stable, often solid, and non-malodoriferous.[1–3] Moreover, thioamides are of great interest as synthetic intermediates, especially in heterocyclic synthesis,[4,5] but applications as ligands in coordination compounds[6] and photochemical transformations of thioamides[7] are also noteworthy. The transition from a biologically active amide or lactam to the corresponding near-isosteric sulfur derivative usually brings about remarkable changes in biological activity. This has been shown for nucleotides[8] and β-lactam antibiotics[9] but is particularly interesting for peptides, where the thioxo sulfur in 'endothiopeptides'[10] provides a handle for photochemically induced changes of conformation ('photoswitch').[11]

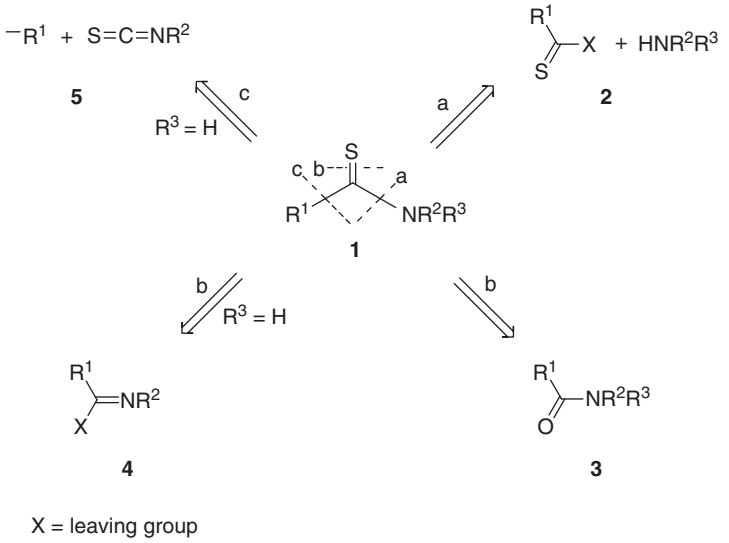
The continued interest in the application of thioamides and thiolactams calls for a constant improvement of the methods of synthesis. Here, a retrosynthetic analysis (Scheme 1) reveals the main routes of thioacylation of amines by thionocarboxylic acid derivatives **2** (bond scission 'a'), of thionation of amides **3** (bond scission 'b'), of thiolysis of imidocarbocyclic acid derivatives **4** (bond scission b; $R^3 = H$), and of the addition of nucleophiles to isothiocyanates **5** or similar thiocarbonic acid derivatives (bond scission 'c'). Although the last mentioned process may be considered as a thiocarbamoylation and so is within the scope of this chapter, the O/S exchange in amides **3** is covered elsewhere (see Vol. 2, Chapter 3.7.2.1 The Eschenmoser Coupling Reaction – alpha-Thioiminium Salt Formation of Compr. Org. Synth. I)[12–14] and so is thioamide synthesis by way of a Willgerodt–Kindler reaction (see Vol. 6, Chapter 2.3.1.7.2 Synthesis of Amides and Related Compounds – Willgerodt of Compr. Org. Synth. I).

6.10.2 Thioacylation of Amines

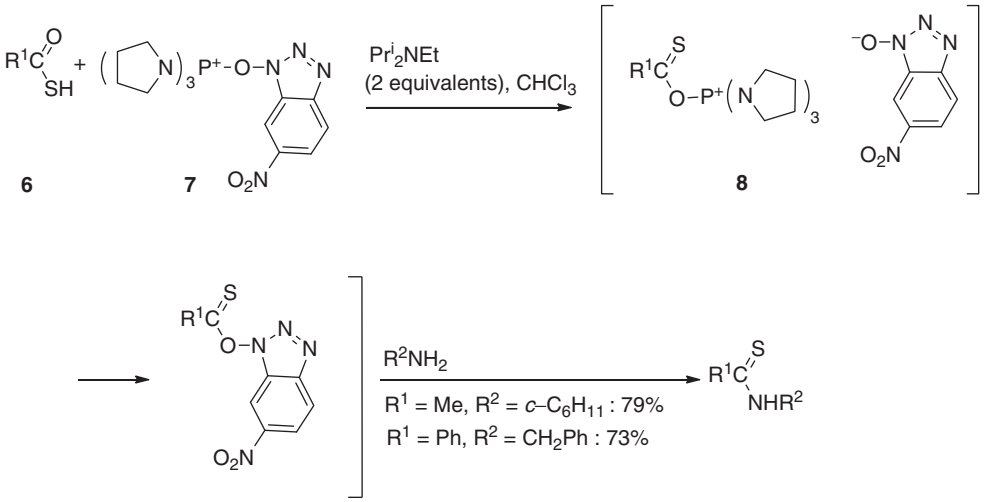
6.10.2.1 Thioacylation with Monothiocarboxic Acids

Normally, monothiocarboxylic acids are acylating rather than thioacylating reagents. However, activation of monothiocarboxylic acids **6** by phosphorus reagents, for example, (6-nitrobenzotriazol-1-oxy)-tris(pyrrolidino)phosphonium hexafluorophosphate (**7**), results in an O–P bond creating a new thioacylating species **8** (Scheme 2). From there, thioacylation to give a thioamide is a smooth process though also some amide is formed due to competing formation of an S–P bond between **6** and **7**.[15,16]

The method is particularly useful for the synthesis of endothiopeptides with essentially preserved amino monothioacid configuration (<2% epimerization)[16] also using other phosphorus reagents.[17]

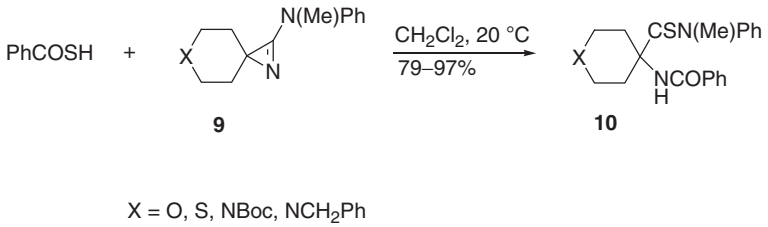


Scheme 1



Scheme 2

A special case is found in the ring-strained azirines such as **9**. Here, the C═N unit is attacked by the nucleophilic sulfur of the thioacid to give after ring-opening thioamides **10** in high yield (equation 1).[18]

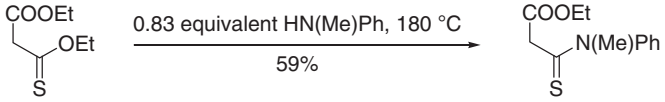


(1)

6.10.2.2 Thioacylation with *O*-Alkyl Thiocarboxylates

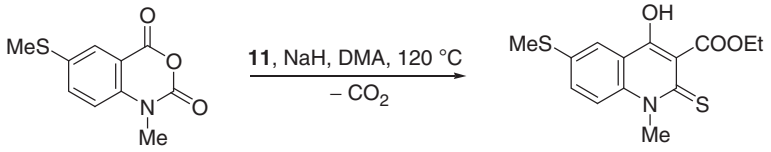
Thioacylation of amines by *O*-alkyl thiocarboxylates is usually a straightforward process. Although aliphatic amines react at room temperature or require only moderate heating, the less nucleophilic aromatic amines react at temperatures above 100 °C. Under these conditions, thionoesters slowly rearrange to their *S*-alkyl isomers and amide formation may compete with thioamide

formation. In the reaction of an *O*,*O*-diethyl monothiomalonate **11** with *N*-methylaniline side reactions can be minimized if a small excess of thioester **11** is used (equation 2).[19]



11 (2)

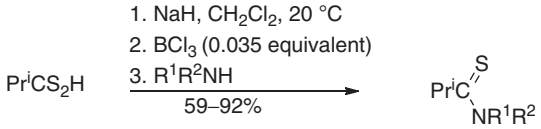
Thionoester **11** and isatoic anhydride **12** react with decarboxylation to give thiolactam **13** (equation 3).[20]



12 **13** (3)

6.10.2.3 Thioacylation with Dithiocarboxylic Acids

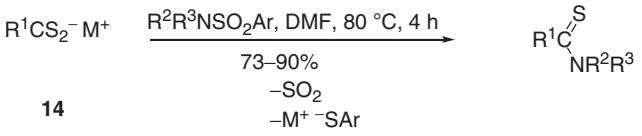
Moderate stability and unpleasant odor make dithiocarboxylic acids less attractive reagents for thioacylation. It is more convenient to employ dithiocarboxylate salts, which are formed by neutralization or generated *in situ* from the appropriate nucleophile and carbon disulfide. Thus, the sodium salt of isobutyrodithioic acid **14**, after activation with boron trichloride, gives a smooth reaction with ammonia, methylamine, dimethylamine, or pyrrolidine to give the corresponding thioamides (equation 4).[21] The approach may be extended to the synthesis of α-phosphonothioamides.[21]



14 (4)

R^1, R^2 = H, Me, $R^1 + R^2 = (CH_2)_4$

A clean reaction of lithium or magnesium dithiocarboxylates is observed on addition of 2,4-dintrobenzenesulfonamides in dimethylformamide (DMF), that is, the amine is introduced in protected form; the ether solvent used to prepare the dithiocarboxylate salt should be evaporated before addition of the sulfonamide (equation 5).[22]



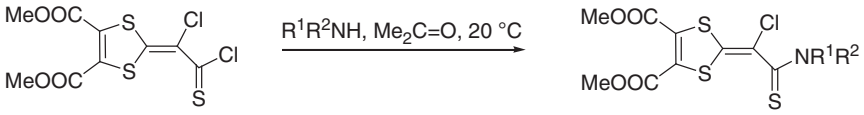
14 (5)

R^1 = Pr^i, H_2C=CH, Ph, 4-ClC_6H_4
R^2 = H, CH_2CH_2OMe
R^3 = CH_2(4-$MeOC_6H_4$)

Ar = 2,4-$O_2NC_6H_3$
M = Li, MgBr

6.10.2.4 Thioacylation with Thioacyl Chlorides or Thioanhydrides

Thioacyl chlorides are not conveniently accessible and exhibit only limited stability, so that normally they are not considered as reagents for thioacylation. An exception is thioacyl chloride **15**, which appears to be stabilized by a bond–no bond interaction of the exocyclic and an endocyclic sulfur atom. This species undergoes a smooth reaction with primary and secondary amines to give thioamides (equation 6).[23]

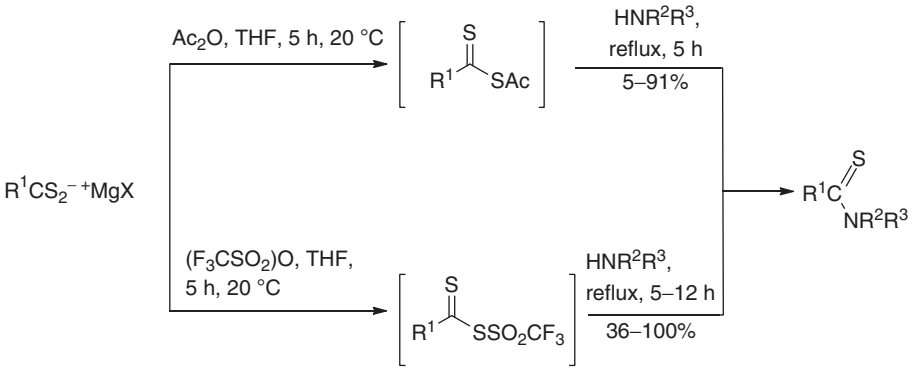


(6)

15

$R^1 = CH_2Ph$, $R^2 = H$: 87%
$R^1 = 3\text{-}MeC_6H_4$, $R^2 = H$: 82%
$R^1 + R^2 = CH_2CH_2OCH_2CH_2$: 60%

Thioanhydrides show a similar reactivity as thioacyl chlorides, but may be conveniently generated *in situ*. Successful applications include the reaction of dithiocarboxylate magnesium salts with acetic anhydride or with triflic anhydride according to Scheme 3; especially the triflic anhydride method was applied for the synthesis involving a broad range of amines.[24]

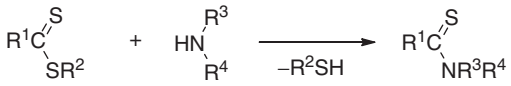


Scheme 3

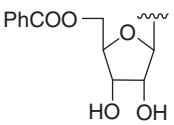
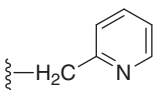
In addition, thioanhydride-type compounds have been generated from carboxylic acids[25] or acyl chlorides[26] and thiophosphate derivatives and used in the synthesis of thioamides.

6.10.2.5 Thioacylation with Dithiocarboxylates

Dithiocarboxylates, R^1CSSR^2, give a smooth reaction with ammonia or amines to yield the corresponding thioamides. The method tolerates the presence of various functional groups as is shown by the synthesis of phosphonothioamides (entries 1,2),[27] of sulfinylthioamides (entries 3,4),[28,29] of *N*-(hydroxyalkyl) thioamides (entry 5),[27,30] and of a nonnatural nucleoside (entry 6; equation 7).[31]

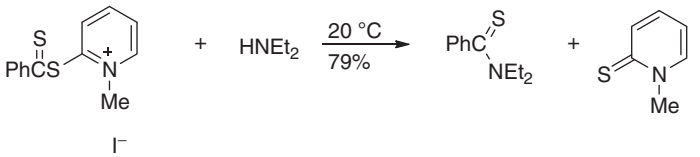


(7)

Entries	*R^1*	*R^2*	*R^3*	*R^4*	*Reaction conditions*	*Yield (%)*	*References*
1	$(EtO)_2P(O)CH_2$	Et	Me	Me	THF, 20 °C	93	27
2	$(EtO)_2P(O)CH_2$	Et	CH_2CH_2–OH	H	THF, 20 °C	87	27
3	$MeS(O)CH_2$	Me	Me	Me	5 equivalents amine, THF, 20 °C	57	28
4	$Pr^iS(O)CH_2$	Me	Me	Me	5 equivalents amine, THF, 20 °C	91	28
5	Pr^i	Me	$CH(Et)CH_2OH$	H	NEt_3, 20 °C	Nearly >95% yield	30
6		Me		H	EtOH, reflux, 2 days	37	31

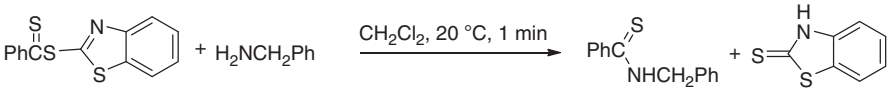
Abbreviation: THF, tetrahydrofuran.

The efficiency of dithiocarboxylates as thioacylating agents is further improved if the eliminated thiol or thiolate is resonance-stabilized making it an excellent leaving-group and allowing thioamide synthesis at temperatures below room temperature. This is seen in the use of 1-methyl-2-thiobenzoylthio-pyridinium iodide or tosylate **16** (equation 8)[32] or of 2-(thiobenzoylthio)benzothiazole (17) (equation 9), which gives a very fast reaction with aliphatic amines at room temperature, but requires refluxing in benzene for the thiobenzoylation of the sterically hindered *tert*-butylamine or the weakly nucleophilic aniline.[33]



(8)

16

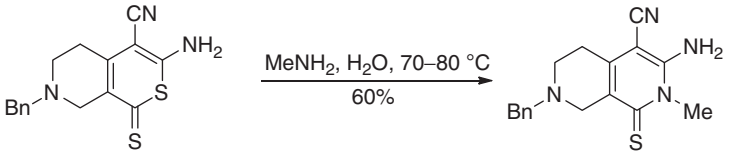


(9)

17

Dithiocarboxylates are also useful for the thioacylation of amino groups in natural products. In the reaction with amino acid derivatives, loss of optical purity may pose a problem.[16] However, for a 4-amino modified phenylalanine, retention of the absolute configuration was observed on reaction with carboxymethyl dithiocarboxylates.[34] Furthermore, it has been shown that amino acid methyl dithioesters may be coupled in the presence of 4-dimethylaminopyridine and salts to a growing peptide chain on a polymeric resin in high yields and with low racemization.[35]

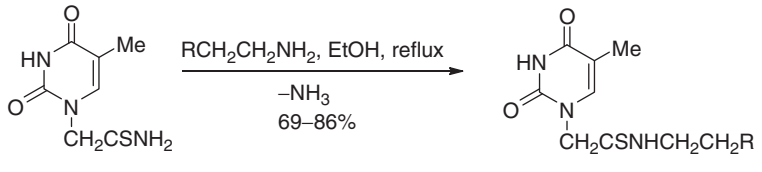
Dithiolactones thioacylate amines analogously to their acyclic congeners. The result may be ring-opening to a thioamide[36] or recyclization to a thiolactam (equation 10).[37]



(10)

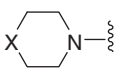
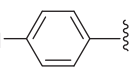
6.10.2.6 Thioacylation with Thioamides

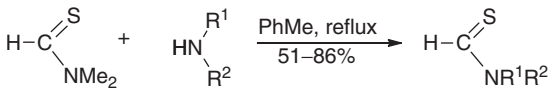
A transamidation between a thioamide and an amine is possible if the amine unit in the thioacylating thioamide is more volatile than the attacking amine. So the primary thioamide in thymine derivative **17** reacts with several primary amines under elimination of ammonia (equation 11); it should be noted that the less nucleophilic nitrogen of an aniline derivative does not react.[38] Similarly, on heating dimethylthioformamide with various high-boiling amines, a new thioformamide is formed (equation 12).[39]



(11)

17

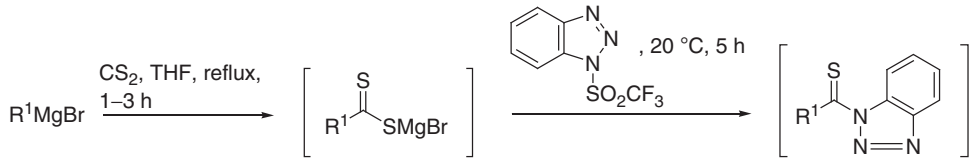
R = $MeNHCH_2$, Me_2NCH_2,  (X = CH_2, O), 



(12)

The transamidation of a thioamide by addition of an amine is further favored if the eliminated amine is a good leaving-group. This quality is seen for several *N*-thioacylated heterocycles with benzotriazoles being the most frequently used example; here, the

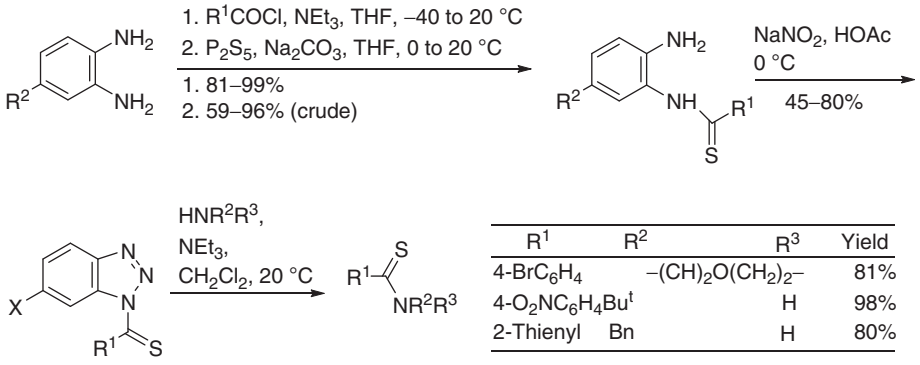
required 1-thioacyl derivatives are generated *in situ* from a dithiocarboxylate and 1-(trifluorosulfonyl)benzotriazole (Scheme 4)[24] or 1-chlorobenzotriazole.[40]



R^1	R^2	R^3	Yield (%)
Bu^n	Bn	H	61
n-C_7H_{15}	CH_2CH_2Ph	H	72
n-C_7H_{15}	Ph	H	79
n-C_7H_{15}	2-Pyridyl	H	45
n-C_7H_{15}	$-CH_2CH_2OCH_2CH_2-$		78

Scheme 4

A 6-nitro group on the benzotriazole apparently improves the stability of the reagent and allows its use also for the synthesis of thionoesters, (di)thiocarbamates, and (di)thiocarbonates.[40] 6-Nitro-1-thioacylbenzotriazoles **18** are conveniently prepared starting from 1,2-diamino-4-nitro-benzene, which is monoacylated and converted into the thioamide with P_2S_5; ring-closure is achieved with nitrous acid. Reagent **18** and amines give *N*-monosubstituted and *N*,*N*-disubstituted thioamides in high yields (Scheme 5).[40] In contrast to the chemistry of Scheme 4, the approach is compatible with functional groups that would not tolerate Grignard conditions. The synthesis of thiopeptides proceeds smoothly in racemization-free reactions[41,42] and the method gave access to a crucial thioamide intermediate in a synthesis of (+)-curacin A, a novel antimitotic metabolite from a cyanobacterium.[43]

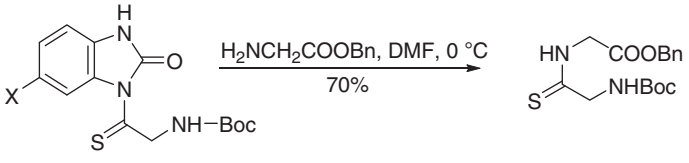


R^1	R^2	R^3	Yield
4-BrC_6H_4	$-(CH)_2O(CH_2)_2-$		81%
4-$O_2NC_6H_4Bu^t$		H	98%
2-Thienyl	Bn	H	80%

18a (X = NO_2)

Scheme 5

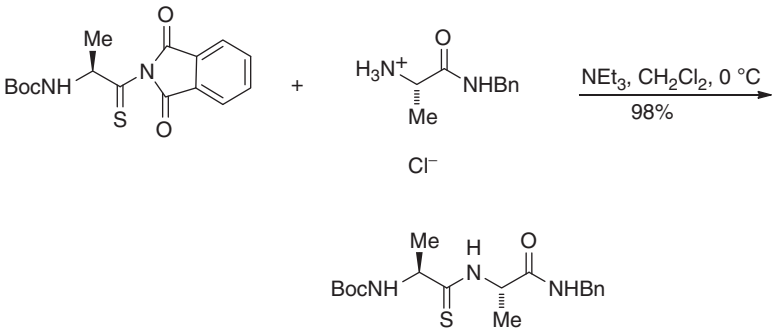
Also 1-thioacylbenzimidazolones are convenient reagents for the thioacylation of amines, amino acids, and peptides, though the benzimidazolinone is a less efficient leaving-group than the 6-nitrobenzotriazole in **18a**.[41,44] The 6-fluoro derivative **18b** shows improved efficiency (equation 13).[45]



(13)

18b (X = F)

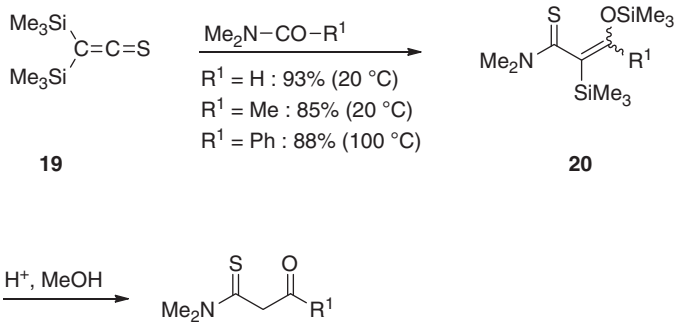
N-thioacylphthalimides represent another type of activated thioamides that has been successfully employed in transamidation reactions. In contrast to reagents **18a**,**b**, these compounds are readily accessible from a primary thioamide and phthaloyl chloride in the presence of potassium carbonate.[46] The method allows coupling of amino acids to endothiopeptides without apparent racemization as shown in equation 14.[46] Amino alcohols are selectively *N*-thioacylated.[47]



(14)

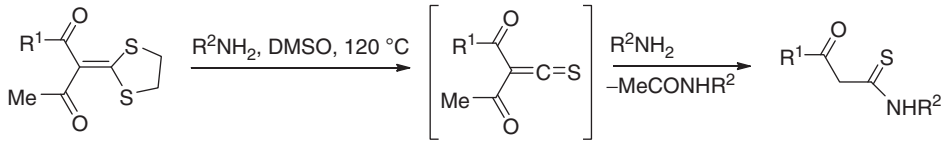
6.10.2.7 Thioacylation with Thioketenes or Thioketene Equivalents

Thioketenes are normally elusive species.[48] However, they are stabilized by silicon substitution making bis(trimethylsilyl)thioketene **19** a convenient reagent; with amides, insertion into the N–C bond occurs to give bis-silylated unsaturated thioamides **20** which, on treatment with acid, give *β*-oxothioamides (equation 15).[49]



(15)

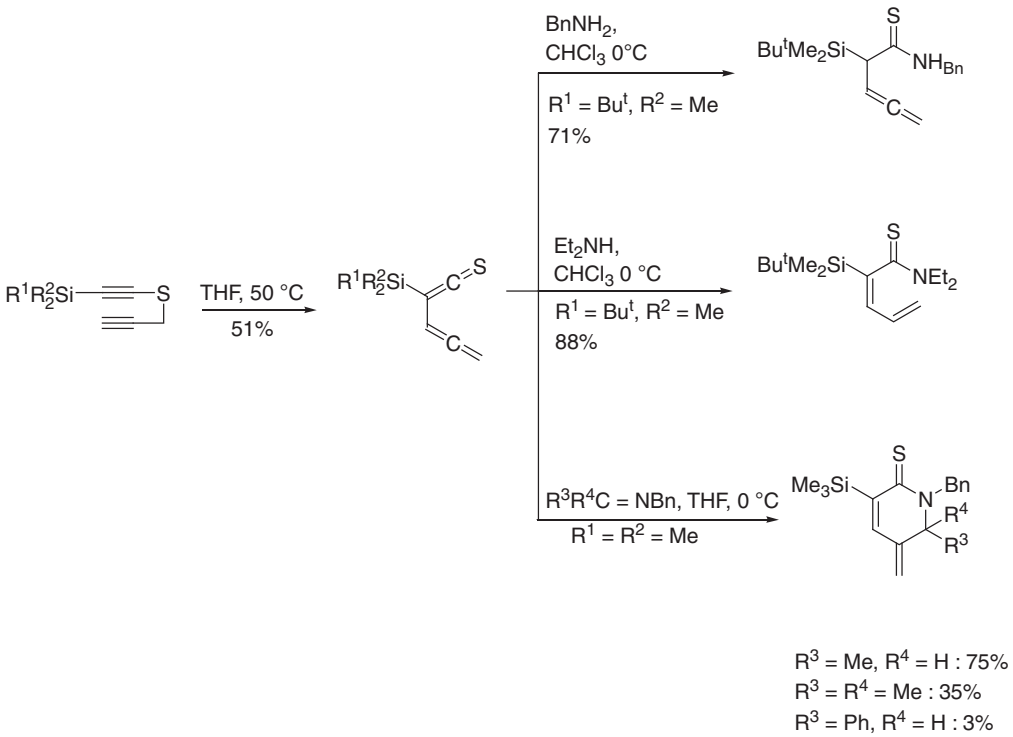
The presence of transient thioketenes in a reaction system is confirmed by their ready reaction with amines. So allenylthioketenes as generated by [3.3] sigmatropic rearrangement of alkynyl propargyl sulfides can be trapped with benzyl- or dimethylamine to give unsaturated thioamides[50] or by Schiff bases in a [4+2] cycloaddition to give *δ*-thiolactams (**Scheme 6**).[51] Anions of 2-alkylidene-1,3-dithiolanes are not stable, but give ring-opening in a 1,3-anionic cycloreversion to generate thioketenes, which are again conveniently trapped by amines[52]; starting from bis-acyl substituted derivatives, an acid cleavage follows to give finally 3-oxothioamides (equation 16).[53]



(16)

R^1 = OEt, R^2 = Bu^n : 87%
R^1 = Me, R^2 = Bn : 84%
R^1 = NHPh, R^2 = Et : 78%

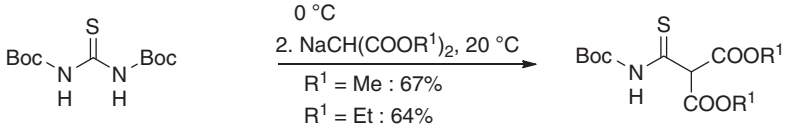
Formation of *β*-thiolactams by [2+2] cycloaddition chemistry is observed on addition of alkynyl silyl sulfides, which act as aldothioketene equivalents, to Schiff bases[54] or of sterically stabilized thioketenes to isocyanates.[55]



Scheme 6

6.10.2.8 Thioacylation with Thioureas

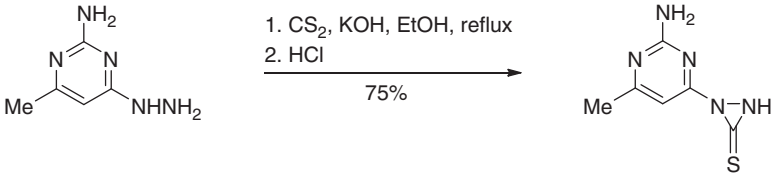
N,N′-di(*tert*-butoxycarbonyl)thiourea is a novel and mild thioacylating agent, especially for alcohols and thiols, whereas for thioamide synthesis only the formation of malonate-derived thioamides was possible (equation 17).[56]



(17)

6.10.2.9 Thioacylation with Carbon Disulfide

Carbon disulfide is usually used for the synthesis of thiocarbonic acid derivatives rather than thioamides. An interesting exception is the synthesis of an α-thiolactam (equation 18).[57]



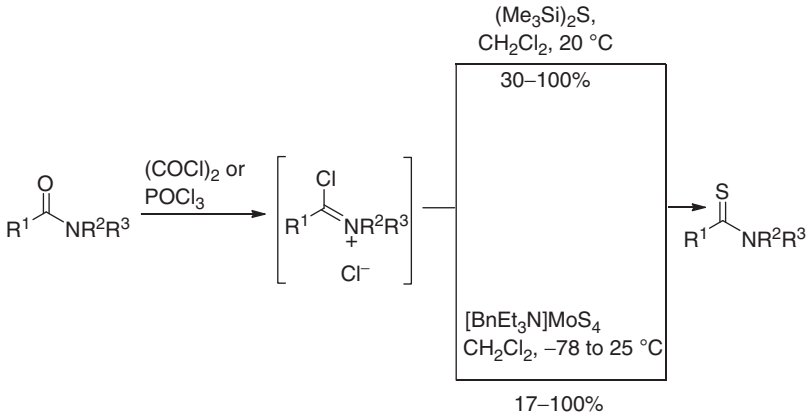
(18)

6.10.3 Thiolysis of Imidocarboxylic Acid Derivatives

6.10.3.1 Thiolysis of Imidoyl Chlorides

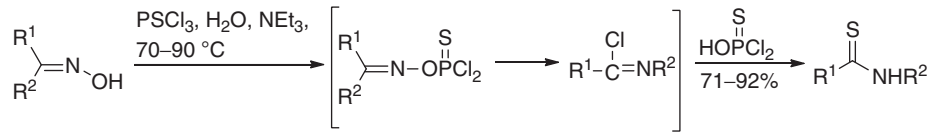
Imidoyl chlorides may be looked upon as activated amides. So their thiolysis to thioamides represents an alternative to the thionation of amides by phosphorus reagents, which often requires harsh conditions and produces major quantities of

phosphorus-containing side-products. In this process, the imidoyl chlorides are often not isolated but used *in situ*. Current reagents for thiolysis are hexamethyldisilathiane[58] or benzyltriethylammonium thiomolybdate[59]; neither reagent works well in the synthesis of primary thioamides (Scheme 7).



Scheme 7

Imidoyl chlorides may also be generated from oximes in a Beckmann rearrangement induced by $HOPSCl_2$ (from $PSCl_3$ and water) and give access to secondary thioamides and thiolactams (equation 19).[60]

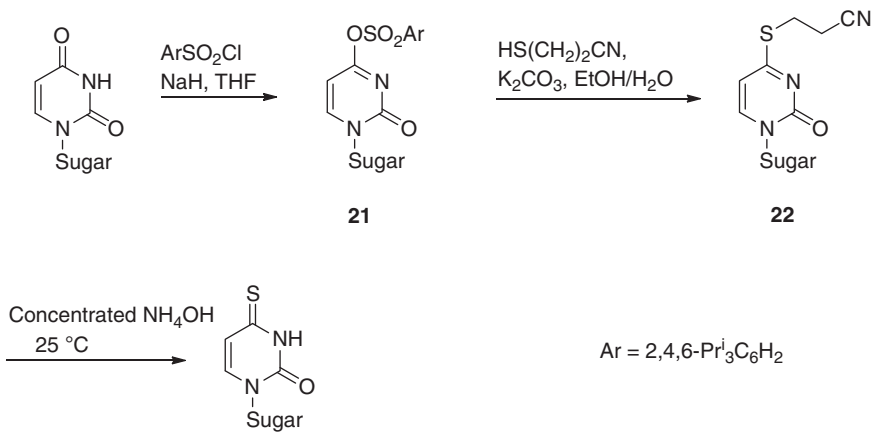


(19)

The Beckmann rearrangement may also be initiated by *O,O*-diethyl dithiophosphoric acid[61a] or by sulfonation of ketoximes and subsequent treatment with thiourea.[61b]

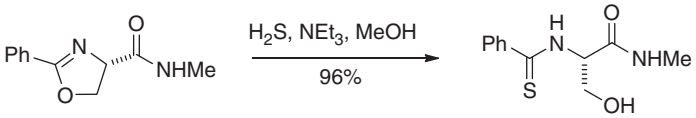
6.10.3.2 Thiolysis of Imidates

An interesting conversion of uridine into 4-thiouridine proceeds via a sulfonyl imidate **21** (equation 20). Substitution of sulfonate in **21** by 3-mercaptopropionitrile gives thioimidate **22**, from where the thione unit is liberated by base treatment in a retro-Michael reaction.[62] This implies that a β-cyanoethyl group can be regarded as a protective group of the thiocarbonyl function.



(20)

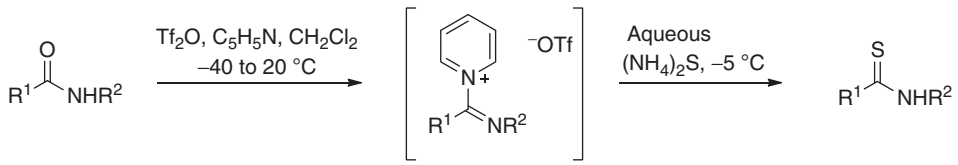
Oxazolines are cyclic imidates and may be converted into isolable thioamides by H_2S (equation 21); the approach is particularly useful for the transition from an oxazoline to a thiazoline.[63]



(21)

6.10.3.3 Thiolysis of Amidines

Another route from amides to thioamides employs the reaction with triflic anhydride in the presence of pyridine to give amidine-type intermediates **23**. From there, thiolysis is achieved with H_2S[64] or with aqueous ammonium sulfide.[65] The latter reagent is easier to deliver in controlled dosage (equation 22).

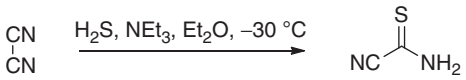


(22)

23

6.10.3.4 Thiolysis of Nitriles

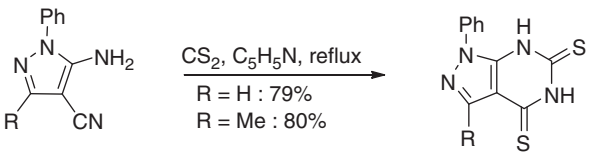
The thiolysis of nitriles by H_2S is a traditional method for the synthesis of primary thioamides. The reaction is usually carried out in the presence of a weak base, with triethylamine and pyridine being most popular.[5,66–68] In this way, the almost 200 years old synthesis of cyanothioformamide by monothiolysis of cyanogen was highly improved (equation 23).[69]



(23)

A recent development is the use of an anion-exchange resin.[70] However, due to the toxicity and experimental inconvenience of using gaseous H_2S, alternative reagents have been developed. These include NaHS generated *in situ*,[71] ammonium sulfide in pyridine[72] or in methanol at room temperature or under microwave irradiation.[73] Thioacetic acid is employed in the presence of pyridine,[74] BF_3OEt_2,[75] or calcium hydride.[76] More sophisticated reagents are $NaSSiMe_3$ as such[77] or in the form of chlorotrimethylsilane in combination with Na_2S as equivalent of $NaSSiMe_3$.[78] Finally, reagents that are more familiar for the thionation of amides may also be applied to convert nitriles into primary thioamides, that is, P_2S_5[79,80] or the Lawesson reagent with catalysis by BF_3OEt_2.[81]

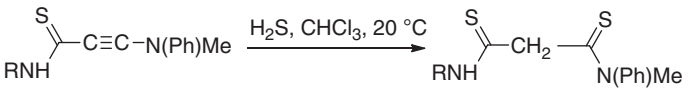
An interesting example of nitrile thiolysis is the reaction of a heterocyclic amine with CS_2, which gives the thiourea as intermediate with liberation of H_2S; this thiolyses the nitrile group present and leads finally to a bis-thiolactam (equation 24).[82]



(24)

6.10.4 Thiolysis of Ynamines

The addition of H_2S to ynamines proceeds conveniently to give the corresponding thioamides (equation 25).[83]

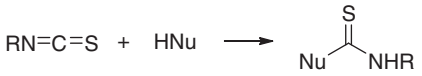


(25)

R = *c*-C_5H_{11} : 73%
R = Ph : 36%

6.10.5 Thiocarbamoylation of Nuclophiles

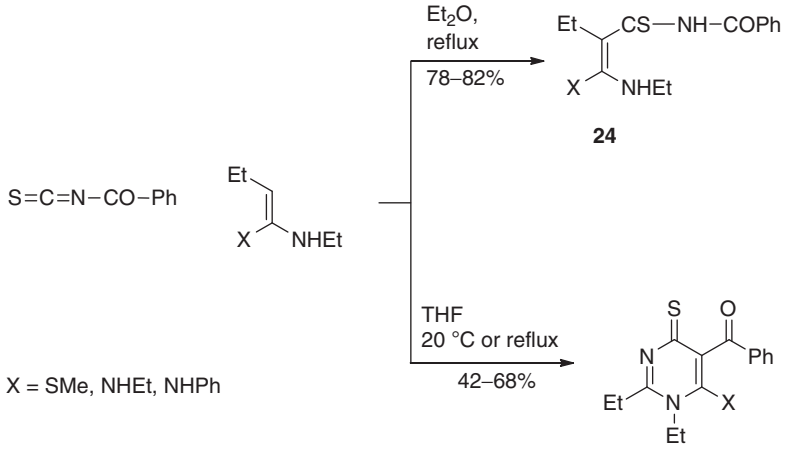
Isothiocyanates are usually stable, but quite reactive electrophiles. Their reaction with nucleophiles can be looked upon as a thiocarbamoylation and so as a special type of thioacylation (equation 26).



(26)

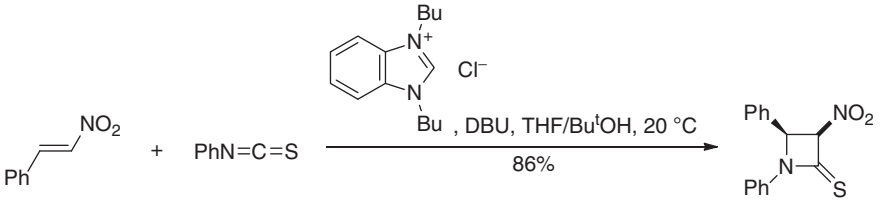
6.10.5.1 Thiocarbamoylation of Electron-rich π-Systems

Nucleophilic π-systems, which react smoothly with isothiocyanates include β-unsubstituted or β-monosubstituted enamines,[84,85] ketene-*O*,*O*-acetals,[86] ketene-*S*,*N*-acetals,[87–90] and ketene-*N*,*N*-acetals.[88] Depending on the substitution pattern and reaction conditions, subsequent or *in situ* cyclization of primary adducts of type **24** to thiolactams may occur (Scheme 8).[88]



Scheme 8

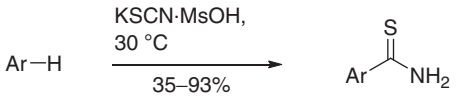
Depending on the substitution pattern, functionalized alkenes may also undergo [2+2][86,91] or [4+2] cycloaddition reactions[92] with isothiocyanates to give thiolactams. This includes NHC-catalyzed reactions of nitroalkenes according to equation 27.[91]



dr 95:5

(27)

Similar to electron-rich alkenes, aromatics may also add to isothiocyanates. For benzene[93,94] or thiophene derivatives,[95] this requires Friedel–Crafts conditions, that is, catalysis by $AlCl_3$. Pyrrole[96] or 2,4-diaminothiazole[97] may react without added catalyst. Although these reactions inevitably lead to secondary thioamides, the action of potassium thiocyanate in methanesulfonic acid on electron-rich arenes or heteroarenes opens up a route to primary thioamides (equation 28).[98]

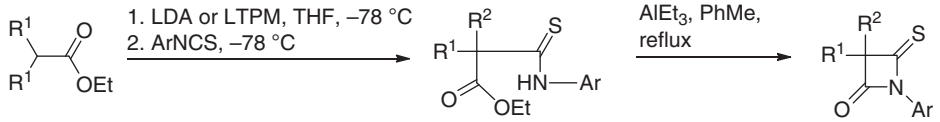


(28)

Ar—H = 2,4-$(MeO)_2C_6H_3$, 2,4-$(EtO)_2C_6H_3$, 4-$MeOC_6H_4$, 2-thienyl, 2-pyrrolyl

6.10.5.2 Thiocarbamoylation of Enolates

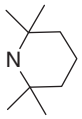
Ester enolates and related anions derived from amides,[20,99] nitriles,[99] or sulfones[99] smoothly add to isothiocyanates to give secondary thioamides. The reaction of malonate anions with isothiocyanates was successfully employed in a synthesis of the cytostatic (+)-vinblastine[100] and gives intermediates **25** for β-thiolactam **26** synthesis as shown in equation 29.[101]



25 **26**

(29)

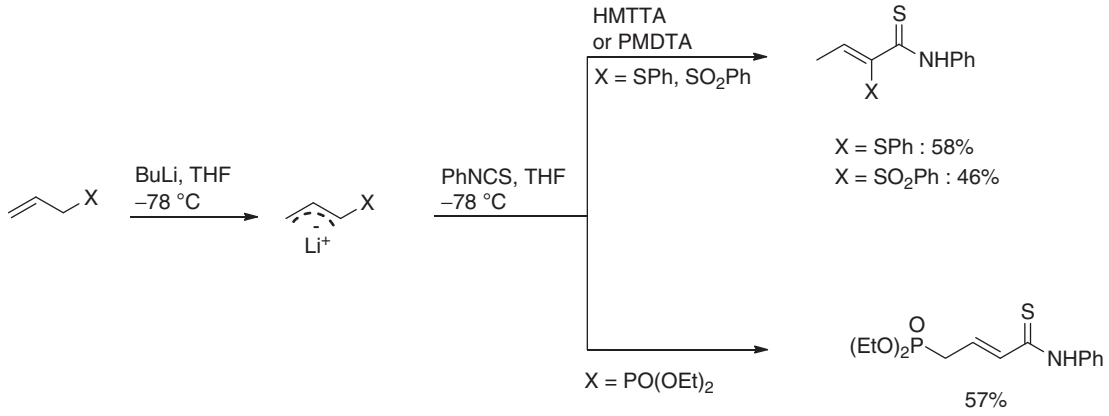
Ar = 4-MeOC$_6$H$_4$

TPM = 

R^1	R^2	% **25**	% **26**
H	Et	56%	18%
Me	Me	94%	85%
Me	Et	64%	72%

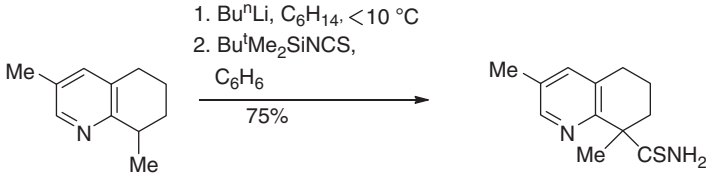
6.10.5.3 Thiocarbamoylation of Carbanions

The addition of organolithiums or Grignard reagents to isothiocyanates is a classical method for the synthesis of secondary thioamides. The organolithiums include common reagents like lithium alkyls or phenyl lithium,[102] but may also be obtained from activated hydrocarbons such as terminal alkynes,[83] phenyl ethers,[103] 1-dimethylaminonaphthalene,[104] heteroarenes,[105,106] allyl sulfides, allyl sulfones, or allyl phosphonates.[107] The last mentioned reagents show an interesting substituent-dependent regioselctivity in the reaction with isothiocyanates as shown in **Scheme 9**. In contrast to isocyanates, the reaction of the sulfur derivatives with the isothiocyanate had to be enhanced by addition of hexamethyltriethylenetetramine (HMTTA) for the allyl sulfide and of pentamethyldiethylenetriamine (PMDTA) for the allyl sulfone. The reactivity of a naphthyllithium derivative can be increased by a lithium/manganese transmetallation.[104] Desilylation is a means to generate a trifluoromethyl ammonium salt, which adds to isothiocyanates to give trifluorothioacetamides.[108]



Scheme 9

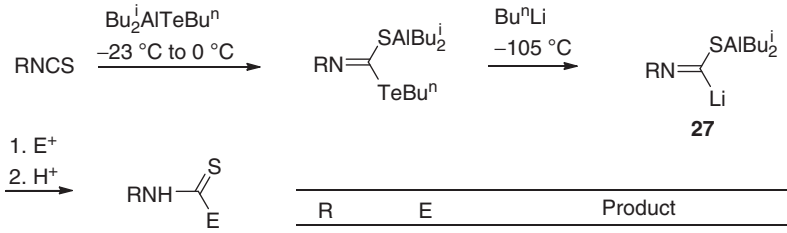
In contrast to the lithium reagents, Grignard reagents usually require room temperature to react with isothiocyanates.[109,110] This is also true for allylsamarium bromide.[111] Although these reactions inevitably lead to secondary thioamides, triphenylphosphine thiocyanate, $Ph_3P(SCN)_2$,[112] or silyl isothiocyanates give primary thioamides as shown in equation 30.[113]



(30)

A thiocarbamoylation of carbanions may not only be achieved using isothiocyanates but also with *N,N*-dimethylthiocarbamoyl chloride[114,115] or with thiuram monosulfides, whereas tetramethylthiuram disulfide gives dithiocarbamates.[116] The reactions with *N,N*-dimethylthiocarbamoyl chloride require catalysis by palladium[114] or nickel.[115] In any case, *N,N*-disubstituted thioamides are formed.

A different use of isothiocyanates is seen in their conversion into thiocarbamoyllithium synthons **27** by the action of an aluminum/tellurium reagent and subsequent addition of butyllithium. The carbanion can be trapped by various carbonyl compounds according to equation 31.[117]

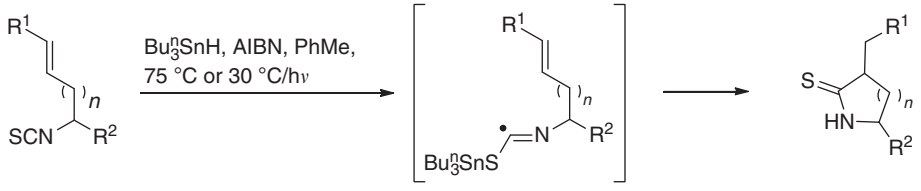


R	E	Product	Yield
Bu^n	O	Bu^nNH, S, HO	60%
Bu^n	$PhCO_2Me$	Bu^nNH, S, Ph, O	73%
Ph	PhCHO	PhNH, S, Ph, OH	91%

(31)

6.10.5.4 Thiocarbamoylation of Carbon Radicals

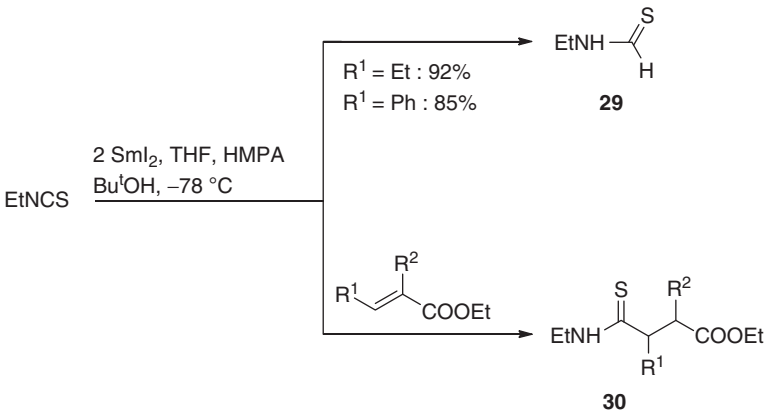
Alkenyl isothiocyanates and tri-*n*-butyltin hydride in the presence of azo-bis(isobutyronitrile) (AIBN) react to give (tri-*n*-butyltin) thioimidoyl radicals **28**, which undergo *exo* cyclization to *γ*- (*n*=1) or *δ*-thiolactams (*n*=2) as shown in equation 32.[118]



(32)

R^1	R^2	*n*	Yield
H	H	1	70%
Me	COOMe	1	94%
Ph	COOMe	2	75%
SPh	Ph	2	69%

Radicals are intermediates in the samarium(II) iodide-induced reduction of isothiocyanates. This is a route to *N*-alkyl thioformamides **29**[119] or, in the presence of an *α,β*-unsaturated ester, to coupling products **30**[120] as shown in Scheme 10.



R^1	R^2	Yield
H	H	77%
Me	H	81%
H	Me	56%
Ph	H	57%

Scheme 10

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6.11 *N*-Acylation Reactions of Amines

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Glossary

Acylating agent A reagent for transferring an acyl group to a substrate.

Coupling agent A reagent used to activate a carbonyl source, usually a carboxylic acid, to make it more susceptible to nucleophilic attack.

Dynamic kinetic resolution (DKR) It occurs in a kinetic resolution reaction when the enantiomers of the racemic substrate are racemizing, which can lead to 100% conversion into a chiral product.

***E*-Value** A value describing the efficiency of an enzyme-catalyzed kinetic resolution reaction that is defined as $E=(\mathrm{kcat}(R)/K_M(R))/(\mathrm{kcat}(S)/K_M(S))$ where the (*R*)-enantiomer is more reactive than its (*S*)-antipode.

Kinetic resolution A kinetic resolution reaction occurs when two enantiomers of a racemic substrate react with different reaction rates with a chiral catalyst or reagent to afford a chiral product and enantioenriched substrate.

Ligation Method of coupling two unprotected peptide fragments together for the convergent synthesis of large peptides or proteins.

***s*-Value** A value describing the efficiency of a kinetic resolution reaction that is independent of conversion that is defined as $s=k_R/k_S$, where $k_R>k_S$ are the rate constants of the reaction of the (*R*)- and (*S*)-enantiomers, respectively.

6.11.1 Introduction

The amide bond is one of the most important in chemistry, with investigations into developing mild method for their syntheses one of the most widely researched topics in organic chemistry. Life is dependent on the formation of amide bonds between amino acids for the biosynthesis at the ribosomal level of peptides and proteins that are integral to many aspects of biology and medicine. The amide bond is also industrially important; a 2008 survey of molecules synthesized for medicinal chemistry applications revealed that just over 50% of all drug candidates contained at least one amide bond.[1] This ensures that the *N*-acylation reaction of amines using activated carboxylic acid derivatives is currently the single-most widely performed reaction carried out throughout the pharmaceutical industry.[1,2] Furthermore, the controlled formation of amide bonds for the preparation of peptides,[3] proteins,[4] and high molecular weight polyamides[5] is also essential to many biomedical and material applications.

There have been many advances in the synthesis of amide bonds over the past 20 years, ranging from improvements to existing coupling processes through to the development of completely new amide bond-forming reactions. The continued development of peptide-coupling methods now allows for the routine automated synthesis of small-to-moderate-sized peptide fragments,[6] whereas recent developments in native chemical ligation technology enables large complex proteins to be prepared chemically.[7,8]

However, despite these impressive achievements, the ACS Green Chemistry Institute has recently voted the area of 'amide formation avoiding poor atom economy reagents' as one of the most important research challenges currently facing organic chemistry.[9] This is because many widely employed amide bond-forming reactions employ relatively expensive reagents have poor atom economy, and generate relatively large amounts of waste. This is particularly true of methods used for the synthesis of peptides and proteins, which currently requires the use of highly protected α-amino acids, polymeric supports, coupling agents, and large excesses of reagents and solvents for their synthesis.[10] Consequently, there is currently much focus on developing catalytic and waste-free amide bond-forming reactions that are as versatile in scope as many of the stoichiometric methods in current use.[8]

This update aims to describe the most widely used *N*-acylation reactions currently employed for amide bond formation, as well as highlighting important or promising advances over the past 20 years. First, established amide bond-forming reactions that employ readily available acylating agents for the synthesis of a wide range of amides are described. Protocols for the generation of highly reactive *N*-acylating intermediates *in situ* will then be discussed, with an emphasis on their application for the racemization-free synthesis of peptide bonds. Approaches for the solution and solid-phase synthesis of medium-sized peptides are then considered, including a brief perspective on exciting developments that employ native ligation amide bond-forming reactions for peptide and protein synthesis. Fast-moving developments on the use of metal catalysts and organocatalytic protocols for carrying out catalytic amide bond formations that have great potential for large-scale synthesis will then be discussed. A brief overview of reaction protocols that have been developed for carrying out macrolactamization reactions is included, as well as important developments where chiral catalysts and biocatalysts have been used for the kinetic resolution of racemic amines using enantioselective *N*-acylation protocols. Given the enormous range of literature concerning amide,[8,11–17] peptide,[3,18–24] and protein synthesis,[7] it has proven necessary to direct interested readers to the many excellent books and reviews available that document this area. Consequently, the authors apologize in advance for being unable to directly cite many of the seminal contributions that have been published in this field and encourage readers to consult the many references cited within the comprehensive reviews referenced herein, as well as the numerous papers that cite them. Although many of the protocols and reagents described herein are potentially applicable to the *N*-acylation of other types of nitrogen nucleophile (e.g., sulfonamides, diketopiperazines, aromatic heterocycles, etc.), space considerations dictate that their *N*-acylation reactions have not been covered.[25,26] Similarly, detailed discussion of important developments involving the synthesis of amidic polymers and the use of amide bonds to attach molecules to the surfaces of materials, polymers, and biomolecules lie beyond the remit of this chapter.[27–30]

6.11.2 Overview of Amide Bond-Forming Reactions

Given their importance, it is unsurprising that a vast array of *N*-acylation methodologies have been developed for the synthesis of amides from amines and carboxylate derivatives. In its simplest form, amide bond formation requires activation of a carboxylic acid donor (or derivative), so that its hydroxyl group is converted into a better leaving group that is replaced by an incipient amine nucleophile. The appropriate choice of acylating agent for amide bond formation is crucial, with many factors affecting the yield of amide product produced. In particular, the reactivity of the parent amine (e.g., primary vs. secondary), the type of functional group present (e.g., chemoselectivity of *N*- vs. *O*-acylation), the presence of potentially labile stereocenters in the coupling partners (e.g., α-amino acid derivatives) can significantly influence the choice of acylation conditions employed. The success of an uncatalyzed amide bond-forming reaction between an amine and a potential acyl donor generally depends on the electrophilicity of the acylating agent and the leaving-group ability of its nucleofuge X^- (**Figure 1(a)**). It will also be dependent on the nucleophilicity of the amine, the physical properties/solubility profiles of both coupling partners and other reaction parameters such as solvent, concentration, and temperature. Simple amides (e.g., aromatic amides for heterocyclic synthesis) are often prepared using robust protocols that couple an amine with a common acylating agent (e.g., an acid chloride, acid anhydride, methyl ester, etc.) in the presence of a base or catalyst. Amide bond formations can also be carried out under milder conditions using dedicated coupling agents that function to generate highly reactive acylating intermediates *in situ* (**Figure 1(b)**), which are particularly useful for the synthesis of complex amides that contain labile stereocenters (e.g., peptides) or multiple functional groups (e.g., amide synthons for natural product synthesis).

Additives are often used in amide bond-forming reactions to improve the reactivity profile of an acylating agent, where they serve to react with a primary acyl donor (e.g., acid chloride, acyl azide, *O*-acylisourea, etc.) to afford a secondary reactive intermediate *in situ* that demonstrates better *N*-acylation properties (**Figure 1(c)**). They are widely used to prevent unwanted racemization/epimerization events during the coupling of *N*-protected α-amino acids in peptide synthesis. The most commonly employed additives are hydroxylamine variants such as *N*-hydroxysuccinimide (NHS), hydroxybenzotriazole (HOBT), and *N*-hydroxyazabenzotriazole (HOAT) whose presence has been shown to improve the performance of many amide and peptide bond-forming reactions (**Figure 2**).[31] Use of these additives can be particularly important for improving the performance of peptide-coupling reactions on solid-phase, where it is essential that iterative peptide bond-forming reactions occur with no loss of stereochemical integrity.[32] Polymer-supported variants of these additives have also been developed (e.g., polystyrene-supported HOBT),[33] which can be useful for the synthesis and purification of peptide bond-forming reactions carried out in solution phase.

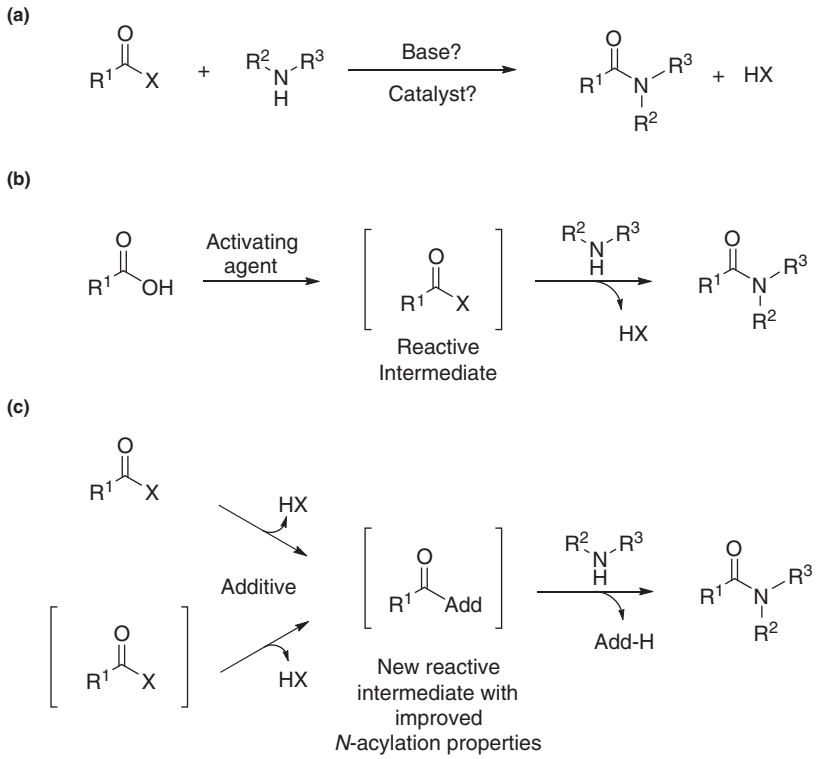


Figure 1 (a) Uncatalyzed or catalyzed acylation reaction of an amine with a stable *N*-acylating agent; (b) coupling agent employed to generate a reactive *N*-acylating intermediate that facilitates amide bond formation; and (c) an additive reacts with an acyl donor to afford a new acylating agent that reacts with an amine to afford an amide bond.

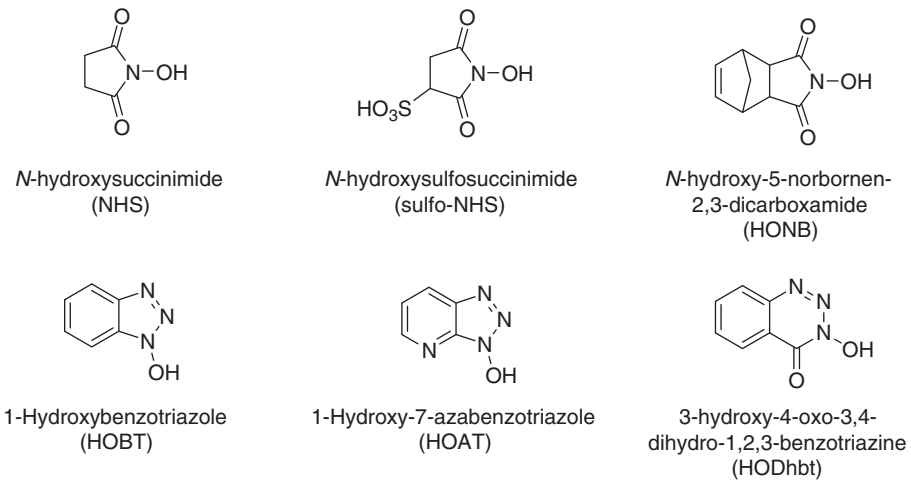


Figure 2 Common additives employed to improve the performance of *N*-acylation reactions.

6.11.3 Stable *N*-Acylating Agents

A wide range of acylating agents (Figure 3) have been developed for the synthesis of amides, which vary greatly in their cost, ease of preparation, stability and reactivity toward amine nucleophiles.[3] Their use depends on the nature of the amide to be prepared, with cheaper *N*-acylating agents (e.g., acid chlorides, methyl esters, etc.) being favored for industrial applications, whereas more expensive acylating reagents (e.g., *N*-succinimidyl esters, *N*-acyl-imidazoles, etc.) are typically used for the synthesis of more complex and/or valuable amide/peptide products.[13]

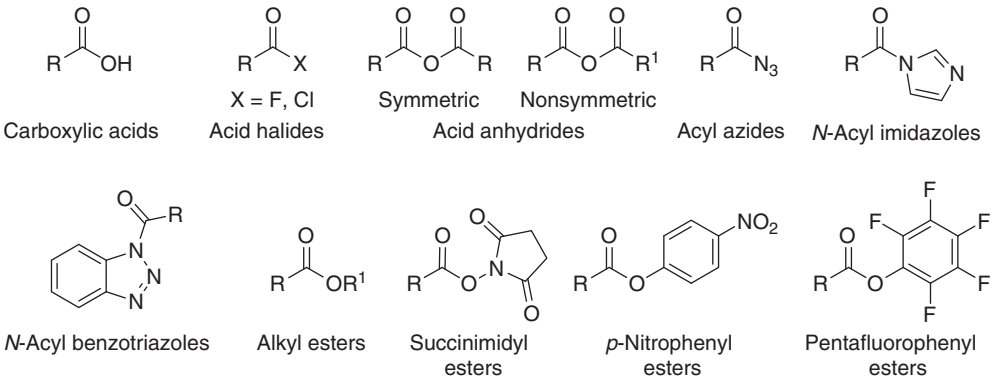


Figure 3 Commonly used *N*-acylating agents.

6.11.3.1 Carboxylic Acids

Carboxylic acids are potentially very useful acylating reagents for amide bond formation that are widely used as parent substrates to prepare the range of acylating agents shown in Figure 3. Direct amide bond formation from reaction of carboxylic acids and amines is generally inhibited by competing formation of their corresponding ammonium carboxylates in polar solvents. These carboxylate salts can react to afford amide bonds at high temperatures (140–180 °C), but the harsh conditions normally required severely limits the substrate scope and yield of this type of amide bond formation.[34] Williams and coworkers have reported the mildest conditions (110–150 °C) for the direct condensation of acids and amines to date, using toluene (or xylene) as a nonpolar solvent to disfavor the formation of charged carboxylate salts (Figure 4).[35] Their conditions gave good conversions of a range of alkyl acids and alkyl amines into amides, however, the *N*-acylation reactions of aryl acids or anilines were limited in scope.

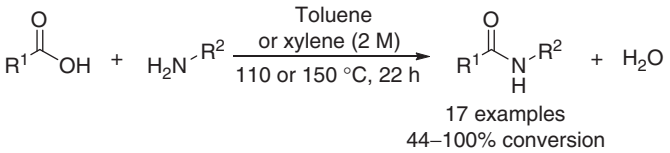


Figure 4 Direct uncatalyzed formation of amides from carboxylic acids and amines.

A number of promising Lewis acid-catalyzed methods for direct amide bond formation from carboxylic acids and amines have been investigated over the past 20 years. In particular, a number of different boron-based Lewis acids have been used to catalyze amide bond formation via formation of (acyloxy)boron species from carboxylic acids *in situ*.[36,37] The first substoichiometric catalytic version using a boron catalyst was reported by Yamamoto and coworkers, who employed 1 mol% of either 3,4,5-trifluorobenzeneboronic acid or 3,5-bis(trifluoromethyl)benzeneboronic acid as catalysts in nonpolar solvents such as toluene, xylene, or mesitylene, using 4 Å molecular sieves contained in a Soxhlet thimble to remove water. This method was reported to be effective for the *N*-acylation of primary and cyclic secondary amines using a range of carboxylic acid donors, as well as for promoting lactamization reactions for the formation of six- and seven-membered lactams.[38] Sterically demanding acids such as 1-adamantanecarboxylic acid could be used as an acyl donor under these conditions (Figure 5), however, a slight amount of racemization was observed when enantiopure (*S*)-(+)-mandelic acid was reacted with benzylamine.[38] A fluorous variant of this catalyst has been developed that enables simple catalyst recycling via its extraction into fluorous solvents,[39] whereas 4,5,6,7-tetrachlorobenzo[*d*][1,3,2]dioxaborol-2-ol[40] and *N*-alkyl-4-boronopyridinium halides[41] have also been reported to be highly effective amidation catalysts.

Hall and coworkers subsequently demonstrated that *ortho*-haloarylboronic acids could be used to catalyze amide bond formation in dichloromethane containing 4 Å molecular sieves at room temperature, although long reaction times (48 h) were required.[42] It was found that 5-methoxy-2-iodophenylboronic acid was the most active catalyst, which was proposed to be due to the *ortho* iodine atom acting as a hydrogen-bond acceptor that stabilizes boron-containing orthoaminal transition state intermediates.[43] Whiting and coworkers have shown that bifunctional amino boranes are particularly effective catalysts for *N*-acylation reactions of aryl carboxylic acids at reflux in toluene,[44] with *N*,*N*-diisopropylbenzylamine-2-boronic acid showing good activity as a catalyst under high dilution at reflux in fluorobenzene.[45] Simple borate esters (e.g., $B(OCH_2CF_3)_3$) have also been shown to catalyze secondary amide bond formation from aliphatic carboxylic acids,[46] whereas boric acid itself has been used for the synthesis of a range of pharmaceutically relevant amides from their corresponding carboxylic acids and amines.[47]

Suzuki and coworkers showed that tris(methoxyphenyl)bismuthanes (e.g., $(2,4,6\text{-}(MeO)_3C_6H_3)_3Bi$) can catalyze the reaction of primary carboxylic acids with primary amines in benzene at reflux,[48] whereas Rao and coworkers have reported that $ZnCl_2$ is an

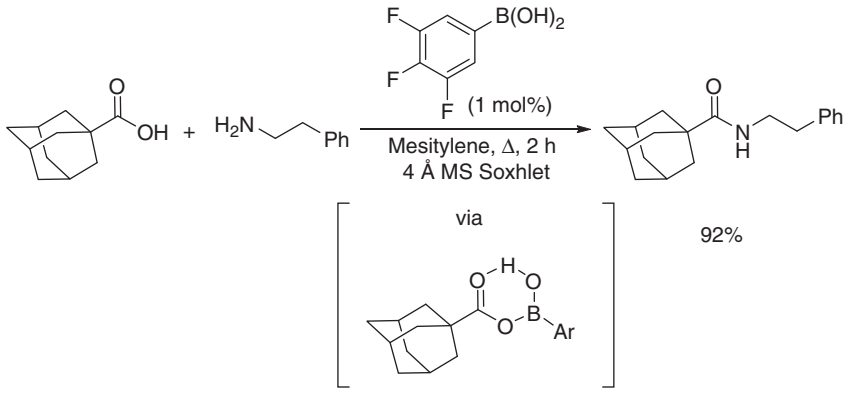


Figure 5 3,4,5-Trifluorobenzeneboronic acid as a catalyst for amide bond formation.[38]

effective Lewis acid catalyst for the formylation of a range of anilines in neat formic acid at 70 °C.[49] More recently, Williams and coworkers screened a number of readily available Lewis acid catalysts for the *N*-acylation of amines with carboxylic acids.[35] They found that zirconium catalysts were most active, with 5 mol% of either $ZrCl_4$ or $ZrCp_2Cl_2$ capable of catalyzing the *N*-acylation of a number of primary amines using a range of different carboxylic acids in good yield (Figure 6). Subsequently, Adolfsson and coworkers reported a related procedure utilizing 2–10 mol% $ZrCl_4$ in tetrahydrofuran (THF) in the presence of molecular sieves at reflux,[50] which enabled electron-deficient *p*-nitrobenzoic acid to be employed as a substrate, and a small number of tertiary amides to be prepared using cyclic secondary amines as nucleophiles.

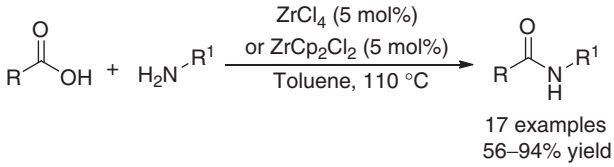


Figure 6 Zirconium-catalyzed acylation of amines with carboxylic acids.[35]

Li et al. have reported that stoichiometric $AlMe_3$ can be used to promote the coupling of a wide range of primary and secondary amines with carboxylic acids to form secondary and tertiary amides via the formation of metal–amide complex intermediates (Figure 7).[51] Notably, highly electron-deficient anilines and sterically demanding secondary amines could be employed as substrates, although 3 equivalents of amine and $AlMe_3$ were required for good yields of amide to be obtained. This method was also limited by its functional group compatibly, with ester, nitro, and cyano groups not tolerated under these conditions.



Figure 7 $AlMe_3$-promoted amide bond formation.[51]

Srinivas and Das have described that Fe^{3+}-K-10 montmorillonite clay catalyzes the acylation of a number of primary secondary amines with both aromatic and aliphatic carboxylic acids.[52] Hosseini-Sarvari and Sharghi have shown that ZnO promotes the *N*-formylation of an impressive number of anilines as well as primary and secondary amines.[53] Importantly, the ZnO catalyst could be easily recovered from the crude reaction product and recycled, although optimal conditions required the use of 50 mol% catalyst (Figure 8).

Amides may be rapidly formed from reaction of primary amines with carboxylic acids under solvent-free conditions using microwave activation without prior activation,[54–56] as well as in the presence of additives such as acidic polysaccharide-derived mesoporous materials,[57] silica, triethylamine, and tosyl chloride,[58] imidazole,[59] and polymer-supported *N*-acylating reagents.[60] Enzymes have also been used to catalyze amide bond formation between amines and carboxylic acids in organic and ionic solvents,[61] with their use as biocatalysts for the formation of specific peptide bonds of particular use (*vide infra*). Although esters are normally employed as acyl donors in enzymatic amide bond-forming reactions, Straathof and coworkers have shown that

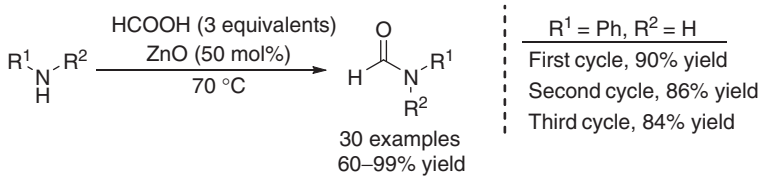


Figure 8 ZnO as a recyclable catalyst for *N*-formylation reactions.[53]

Candida antarctica lipase B (CAL-B) can catalyze the amidation of free carboxylic acids using ammonium bicarbonate in anhydrous methyl isobutyl ketone to afford octanamide and oleamide in good yields.[62] Immobilized CAL-B (Chirazyme L-2) has also been used to catalyze the kinetic resolution of (*rac*)-1-phenylethylamine and (*rac*)-2-phenyl-1-propylamine using fatty acids as acyl donors in ionic liquid solvents, to afford chiral amides and amines with excellent levels of stereocontrol.[63]

6.11.3.2 Acid Chlorides and Fluorides

Acid chlorides are one of the most widely used *N*-acylating agents for amide bond formation that are employed widely throughout both academia and industry. The Schotten–Baumann reaction, first described in 1884, involves reaction of an amine with an acid chloride (or acid anhydride) in the presence of aqueous base.[64] Modern variants of the original reaction conditions have been developed that enable amide bond formation to be carried out in organic solvents, utilizing a range of bases (e.g., Et_3N, $^iPr_2NEt$, *N*-methylmorpholine, DMAP, etc.) to trap the hydrochloric acid that is generated in the reaction. The ease of preparation of acid chlorides from their corresponding acids (e.g., $SOCl_2$, $COCl_2$/DMF, PCl_5, cyanuric chloride, etc.) and the operational simplicity of their *N*-acylation reactions ensures that acid chlorides are very useful reagents for forming a wide range of amide bonds (**Figure 9**). However, problems associated with the reaction of amines with acid chlorides can include highly exothermic reactions, the release of an equivalent of HCl, and premature hydrolysis of sensitive acid chloride reagents. One of the biggest difficulties encountered is the propensity of chiral α-substituted acid chlorides to undergo racemization under basic conditions, which limits the use of acid chlorides as substrates for peptide synthesis. Ketene formation through α-deprotonation of acid chlorides *in situ* can lead to racemization and other unwanted side reactions (**Figure 10(a)**), whereas *N*-acyl-α-amino acid chlorides can undergo racemization via formation of oxazolone intermediates (**Figure 10(b)**).[13] Conditions have been developed to convert FMoc-protected amino acids into their corresponding acid chlorides under mild conditions for racemization-free solid-phase peptide synthesis,[65] however, this approach is normally only applicable to the synthesis of relatively simple peptide sequences.[66]

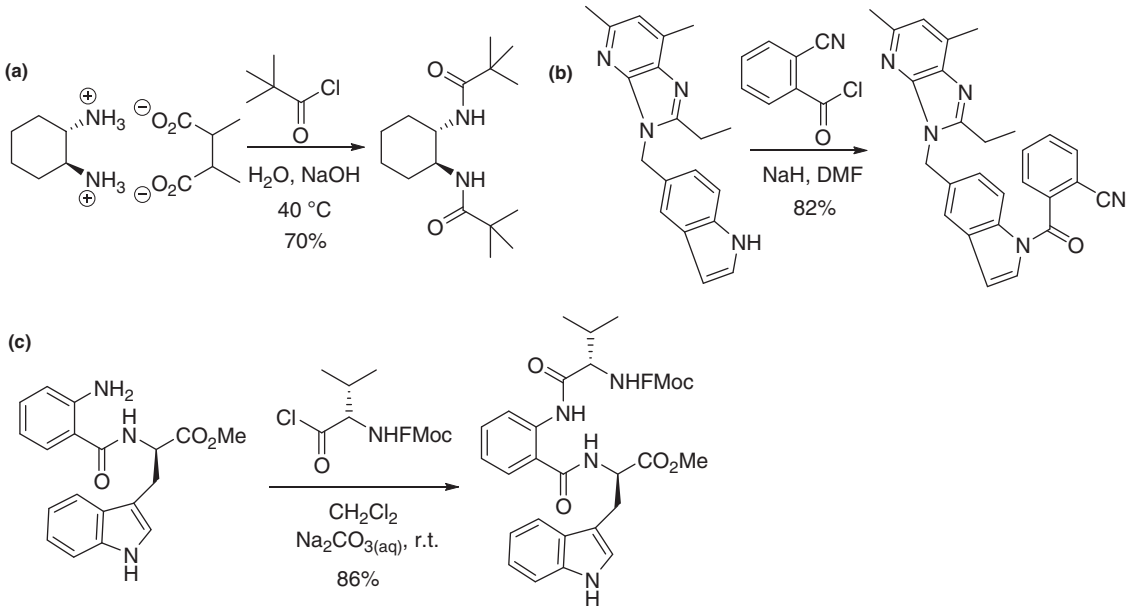


Figure 9 Schotten–Baumann conditions for: (a) synthesis of a chiral *bis*-pivaloylated amide[67]; (b) *N*-Acylation of an indole[68]; and (c) amide coupling reaction for the synthesis of fumiquinazoline alkaloids.[69]

Although uncatalyzed reactions of reactive amines with acid chlorides are often possible, a range of metal-based catalysts have been developed to catalyze their *N*-acylation reactions, including the use of activated zinc[70] and zirconyl chloride.[71] However,

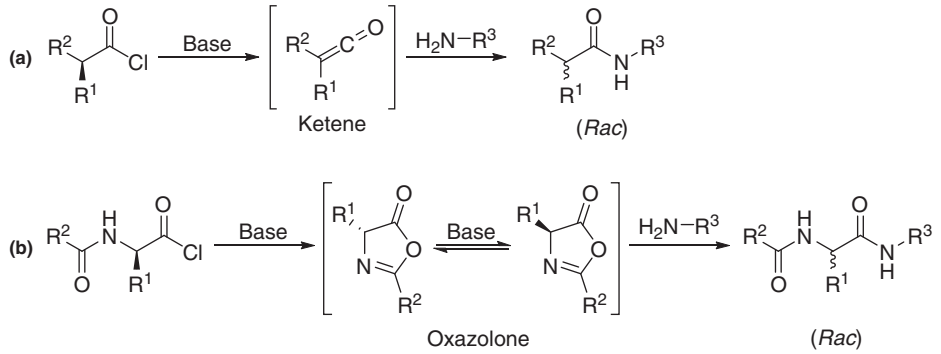


Figure 10 Racemization of acid chlorides through (a) ketene formation or (b) oxazolone formation.

nucleophilic catalysts such as pyridine, 4-dimethylaminopyridine, and 4-pyrrolidinopyridine are routinely employed to catalyze the *N*-acylation reactions of amines with acid chlorides and acid anhydrides (Figure 11).[72–74]

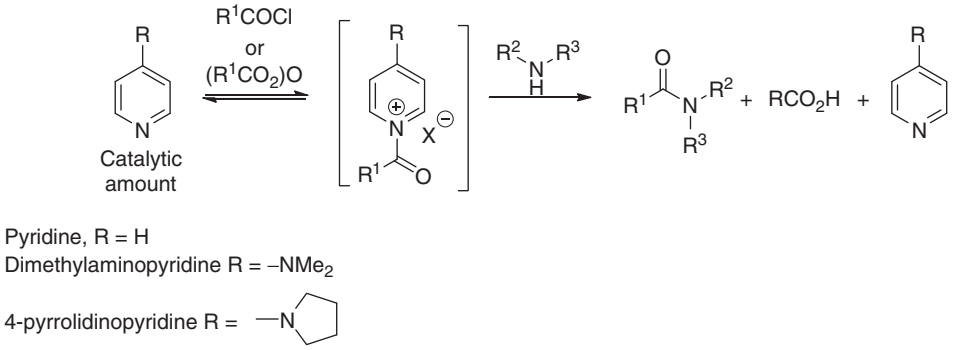


Figure 11 General mechanism of Lewis base-promoted *N*-acylation reactions using pyridine-based catalysts.

Acid fluorides are often crystalline, water-stable reagents that are less prone to base-induced oxazolone formation and racemization when compared with their corresponding acid chlorides that can be particularly useful for peptide synthesis.[66] *N*-Fmoc-amino acid fluorides that contain acid-sensitive *tert*-butyl (^{t}Bu), *tert*-butyloxycarbonyl (BOC), and trityl (CPh_3) side-chain protecting groups can be prepared via the action of fluorinating agents such as cyanuric fluoride[75] and diethylamino sulfur trifluoride (DAST)[76] on the parent acid (Figure 12). Tetramethylfluoroformamidinum hexafluorophosphate is a nonhygroscopic salt that can be used to generate amino acid fluorides *in situ*,[77] whereas benzyltriphenylphosphonium dihydrogen trifluoride (PTF) has also been used as an additive in carbodiimide-mediated coupling reactions to generate reactive acid fluoride intermediates (Figure 12).[78] Amino acid fluorides have been utilized in both solution-phase and solid-phase peptide syntheses (Figure 13),[79] where they have proven to be particularly useful for coupling sterically hindered α,α-disubstituted amino acids.[80] Wenschuh and coworkers have shown that peptide synthesis with acid fluorides can be performed in the absence of base, which can help prevent many of the side reactions associated with the use of acid chlorides.[81] The major disadvantages of using acid fluorides are their limited commercial availability and their potential for releasing hydrogen fluoride during their synthesis and use in amide bond-forming reactions.

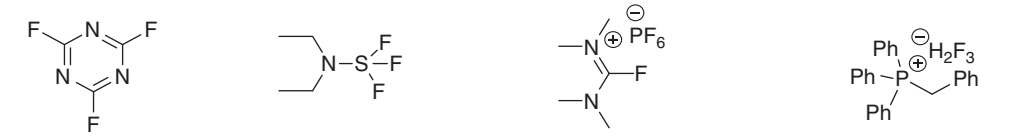


Figure 12 Reagents employed for conversion of carboxylic acids into acid fluorides.

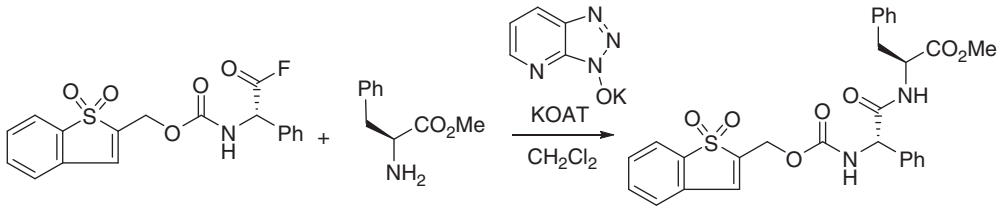


Figure 13 Racemization-free dipeptide synthesis using an *N*-Bsmoc-α-aryl-α-amino acid fluoride as coupling partner in the presence of the potassium salt of 7-aza-1-hydroxybenzotriazole (KOAT).[82]

6.11.3.3 *N*-Acyl Transfer Reagents

Amidic bonds are normally highly stable and they do not normally act as effective acylating agents for amines in the absence of a catalyst, however, a number of specialized *N*-acyl transfer agents have been developed for this purpose. Acyl azides are reactive *N*-acylating agents that react with a wide range of amines, which have been used for peptide coupling reactions because α-substituted *N*-acyl azides are not generally prone to racemization (Figure 14(a)).[83] Diphenylphosphoryl azide (DPPA) has been introduced as a reagent to carry out experimentally convenient 'one-pot' acyl azide protocols,[84] as well as for facilitating macrolactamization reactions to afford cyclic peptides such as dendroamide A (Figure 14(b)).[85] However, the widespread use of *N*-acyl azides for amide bond formation is generally limited by concerns about their safety and their tendency to undergo competing Curtius rearrangement reactions.

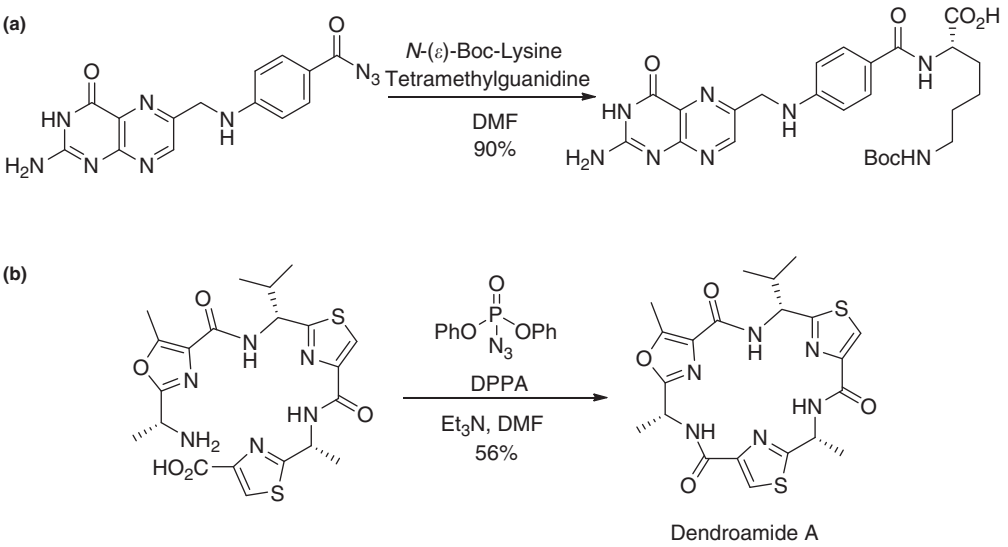


Figure 14 (a) Synthesis of a folic acid derivative using a reactive acyl azide intermediate[83] and (b) DPPA-mediated macrolactamization reaction to afford the cyclic peptide dendroamide A.[85]

N-Acyl imidazoles are one of the most important *N*-acylating reagents as they are commercially available for both amide and peptide bond synthesis (Figure 15(a)). They are often used as coupling agents in the presence of activators such as HOBT, with 2-hydroxy-5-nitropyridine having recently being recommended as a safe additive for their use in large-scale reactions.[86] *N*-Acyl imidazoles are normally prepared *in situ* from reaction of the corresponding acid with carbonyl diimidazole (CDI), with subsequent addition of the required amine affording the desired amide bond. *N*-Acyl imidazole intermediates are known to react with a wide range of primary and secondary amines and have been shown to be tolerant of the presence of a number of different functional groups,[13] enabling their use for the synthesis of pharmaceutical intermediates on an industrial scale (Figure 15(b)).[87] Interestingly, Batey and coworkers have recently demonstrated that structurally related *N*-carbamoylimidazolium salts derived from secondary amines are highly effective reagents for converting acids into secondary amides (Figure 15(c)).[88] Nucleophilic catalysts such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) have also been employed to improve the yields of amide bond-forming reactions using *N*-acyl imidazoles as coupling agents, particularly for the acylation reactions of sterically hindered acids and electron-poor anilines (Figure 16).[89]

Katritzky et al. have prepared a large number of crystalline and stable *N*-acyl benzotriazoles via reaction of benzotriazole with either an acid chloride or using coupling reactions with a carboxylic acid.[91] These *N*-acyl benzotriazole reagents react with

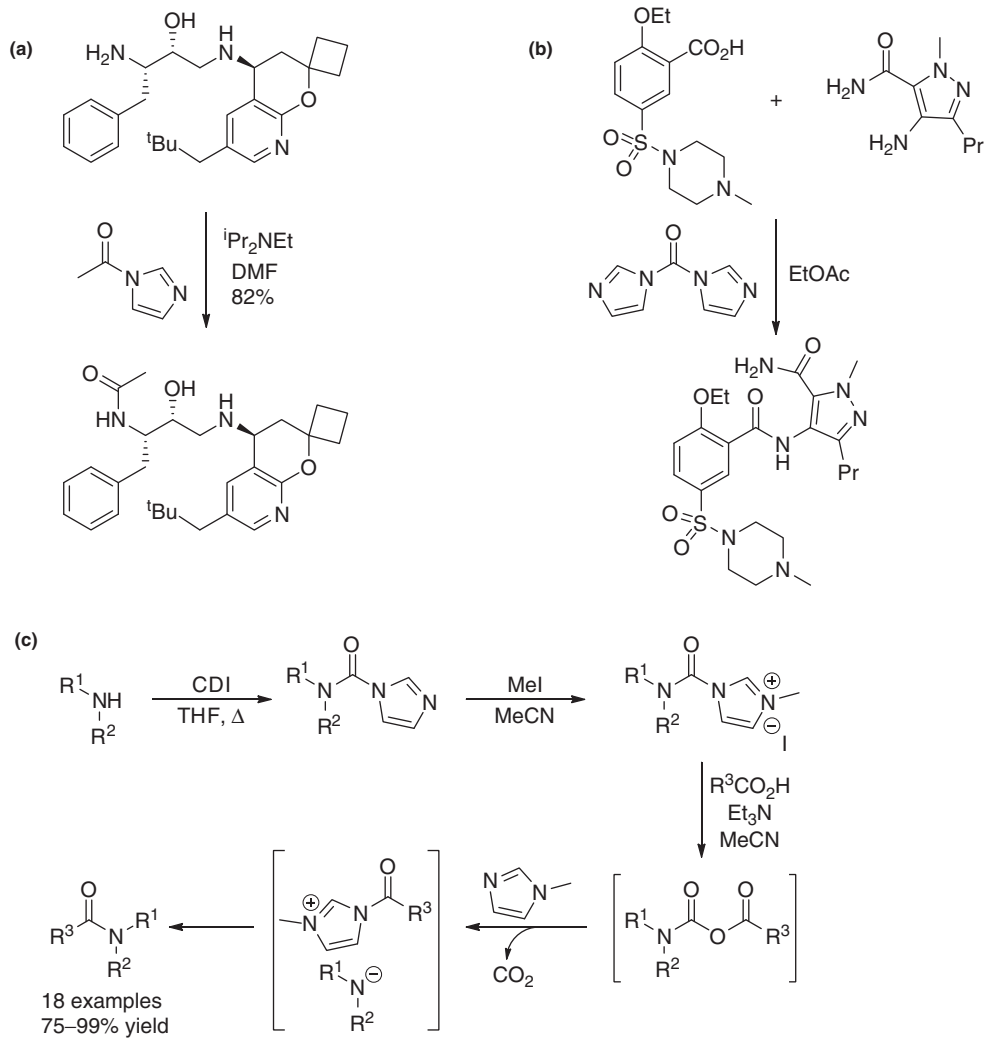


Figure 15 (a) Synthesis of a β-secretase inhibitor using commercially available *N*-acetyl imidazole as an acyl donor[90]; (b) CDI coupling step used in the industrial process to make Sildenafil[87]; and (c) use of *N*-carbamoylimidazolium salts for amide bond formation.[88]

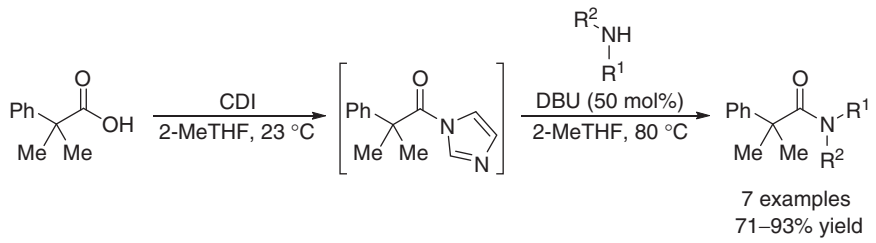


Figure 16 DBU-catalyzed amidation reactions of *N*-acyl imidazole intermediates.[89]

ammonia and a wide range of primary and secondary amines to afford primary, secondary, and tertiary amides in high yields,[92] with lower reactivities observed for formation of sterically demanding tertiary amides (Figure 17).[93] The benzotriazole byproduct produced in these *N*-acylation reactions is conveniently removed from crude reaction products by simply washing with aqueous base. More recently, Katritzky et al. have focused on the use of *N*-acyl benzotriazole derivatives of amino acids for the syntheses of peptides. *N*-protected α-amino acids can be converted into air-stable benzotriazole derivatives without racemization and used as efficient *N*-acylating agents in peptide bond-forming reactions.[94] For example, 36 different *N*-protected *N*-aminoacyl benzotriazole derivatives comprised of 18 natural amino acid variants, protected with either Fmoc, Cbz, or Boc groups, were reacted with free amino acids to give 94 different dipeptides in good yields (Figure 17(b)).[95] Other potentially useful *N*-acyl transfer agents

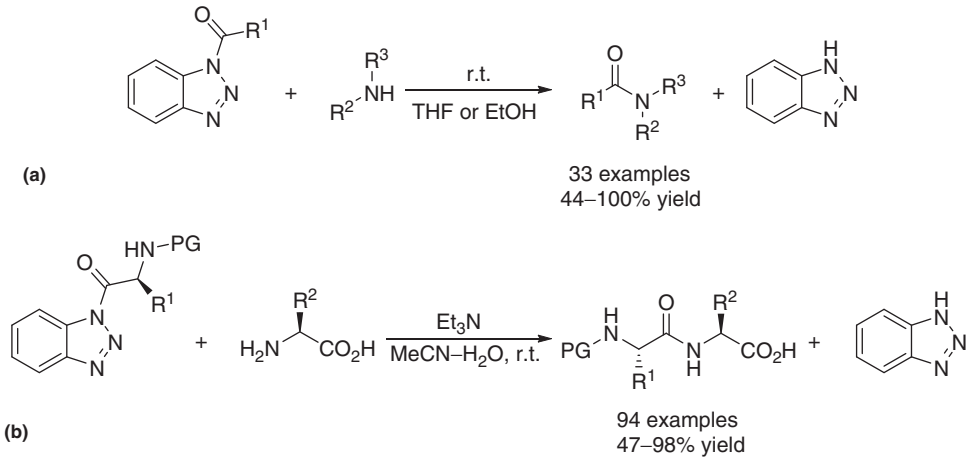
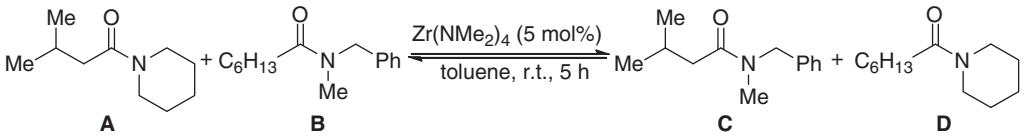


Figure 17 *N*-Acyl benzotriazoles as *N*-acylating agents for amide[93] and peptide bond[95] formation.

have been employed for amide bond formation including the use of *N*-acyl pyrroles,[96] *N*-acyl-1,5-diazabicyclo(4.3.0)non-5-ene (DBN) salts,[97] 2-acylpyridazin-3-ones,[98] *N*-acyl-oxazolidin-2-ones,[99] and *N*-methoxydiacetamide.[100]

A limited number of metal-catalyzed transamidation reactions of amides have been developed, which is generally considered to be a difficult reaction to catalyze due to the inherent stability of carboxamide groups. Bertrand and coworkers have reported that $AlCl_3$–amine complexes can catalyze transamidation reactions of primary, secondary, and tertiary amides.[101] This method allowed stoichiometric amounts of $AlCl_3$ to be used to *N*-acylate primary and secondary amines using activated *N*-tosyl, *N*-benzoyl, and *N*-pivaloylamides as acyl donors. Gellman and coworkers have described a series of metal-catalyzed equilibrium-controlled transamidation reactions of primary and secondary amines using secondary and tertiary amides as acyl donors,[102–104] with $Zr(NMe_2)_4$ found to be a particularly efficient catalyst for the transamidation of secondary amines using tertiary amides (Figure 18).[104] Impressively, this catalytic system also promoted tertiary amide metathesis at room temperature, affording transamidation protocols with significant potential for dynamic combinatorial chemistry applications.[104]



At equilibrium: **A**:**B**:**C**:**D** = 26:20:28:26

Figure 18 $Zr(NMe_2)_4$-catalyzed tertiary amide metathesis.[104]

Myers and coworkers have published a transamidation protocol whereby primary amides are treated with *N*,*N*-dialkylformamide dimethyl acetals to generate *N*′-acyl-*N*,*N*-dialkylformamidine intermediates *in situ*, which then react with amines in the presence of zirconium chloride to afford secondary and tertiary amides (Figure 19).[105] It was found that the *N*′-acyl-*N*,*N*-dialkylformamidine intermediates were stable enough to be isolated enabling their use as isolable *N*-acylating reagents for amines in the presence of 10 mol% scandium triflate.

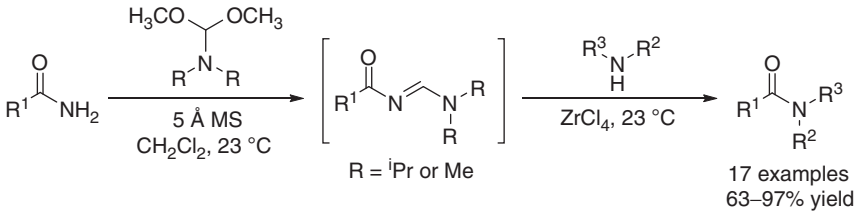


Figure 19 Zirconium chloride-mediated transamidation of *N*′-acyl-*N*,*N*-dialkylformamidine.[105]

Beller and coworkers have shown that $Cu(OAc)_2$ catalyzes the transamidation of primary amines with primary amides and ureas at high temperature (140 °C) (Figure 20(a)),[106] whereas Williams and coworkers have recently reported the transamidation of primary amines with primary amides under milder conditions (80 °C) using $ZrCp_2Cl_2$ as a catalyst (Figure 20(b)).[107] Both of

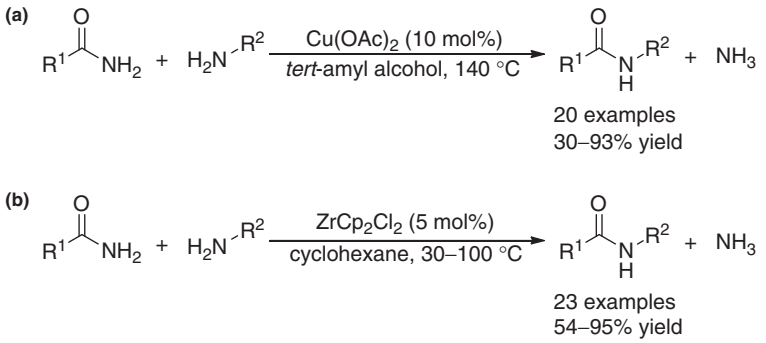


Figure 20 Transition metal-catalyzed transamidation reactions.

these transamidation approaches facilitate the *N*-acylation of a range of primary amines, including anilines, as well as nucleophilic cyclic secondary amines. These reactions are thought to proceed via attack of the amine on the catalyst to form a metal–amide complex, with coordination of the acyl donor amide then resulting in intramolecular amine transfer and ligand exchange to release the transamidation product and ammonia.

Recently, Shimizu and coworkers have found that CeO_2 is an effective catalyst for the transamidation of primary amides with alkyl amines under solvent-free conditions at high temperature (Figure 21).[108] Mechanistic studies suggest that the CeO_2 surface acts as a bifunctional catalyst, with Lewis acidic sites activating the carbonyl group of the primary amide and adjacent Lewis basic sites activating the amine toward nucleophilic attack.

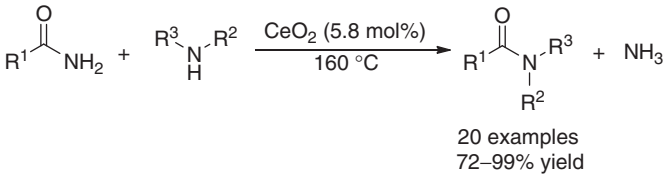


Figure 21 CeO_2-catalyzed transamidation of primary amides.[108]

Williams and coworkers reported that 10–50 mol% of hydroxylamine hydrochloride can catalyze the transamidation of primary amides with primary or secondary amines at reflux in toluene (Figure 22(a)).[109] Alkyl primary amides were found to be more reactive than aryl amides with anilines generally affording lower yields of amide product. Notably, 30 mol% hydroxylamine hydrochloride was found to catalyze the formylation of benzylamine with formamide at room temperature. Mechanistic studies revealed that hydroxylamine hydrochloride is likely to activate the primary amide through formation of a hydrogen-bonded complex (Figure 22(b)), thus increasing the reactivity of the carbonyl toward nucleophilic attack by the amine. Boric acid also catalyzes transamidation reactions with primary and secondary amines at high temperature (150 °C), with a number of different primary, secondary, and tertiary amides used as acyl sources, including formamide for the *N*-formylation of amines (Figure 23(a)).[110] A lipase from *Candida cylindracea* has also been shown to demonstrate promising activity for the transamidation of a range of secondary amides with benzylamine in methyl *tert*-butyl ether as solvent (Figure 23(b)).[111]

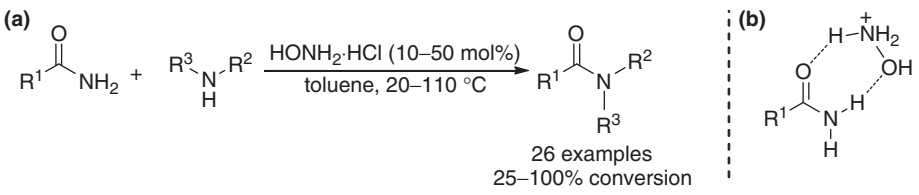


Figure 22 Transamidation of primary amides using hydroxylamine hydrochloride as a catalyst.[109]

6.11.3.4 Symmetric Acid Anhydrides

Symmetric acid anhydrides are easily prepared and widely used as *N*-acylating reagents for amines, with acetic anhydride being widely used in uncatalyzed *N*-acetylation reactions.[64] Acid anhydrides have also been widely used as *N*-acyl donors in the presence

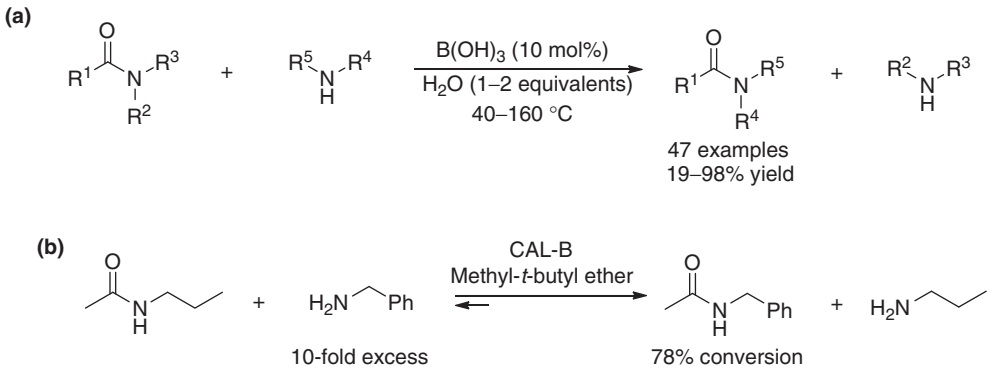


Figure 23 (a) Boric acid-catalyzed transamidation reactions[110] and (b) CAL-B-catalyzed transamidation of amides.[111]

of both Lewis acids and Lewis bases (e.g., DMAP), however, they are often reactive enough to afford amides in uncatalyzed reactions (Figure 24(a)). For example, Temperini et al. have shown that a number of primary and secondary amines can be *N*-acylated with commercially available anhydrides in ethyl acetate at room temperature.[112] These acylation reactions were shown to be both regio- and chemoselective, with amino alcohols undergoing selective *N*-acylation, and primary amine groups being regioselectively acylated in the presence of a secondary amine functional group. Sato et al. have also shown that selective uncatalyzed *N*-acylation reactions with symmetric acid anhydrides can be efficiently performed in microreactor systems.[113] Although many simple symmetric acid anhydrides are commercially available, structurally more complex ones need to be prepared and are normally used immediately. A major drawback of their use is that they display poor atom efficiency, because half of their acylating equivalent is wasted as a carboxylate leaving group, which can be problematic when using valuable acyl donors (Figure 24(b)).[13] The amide bond-forming reactions of acid anhydrides using primary amines as substrates may also form stable imides as unwanted side products.[16] There are numerous reports of homogenous metal-catalyzed reactions using acid anhydride donors, with many metal complexes being used at very low catalyst loadings under mild conditions for the acetylation

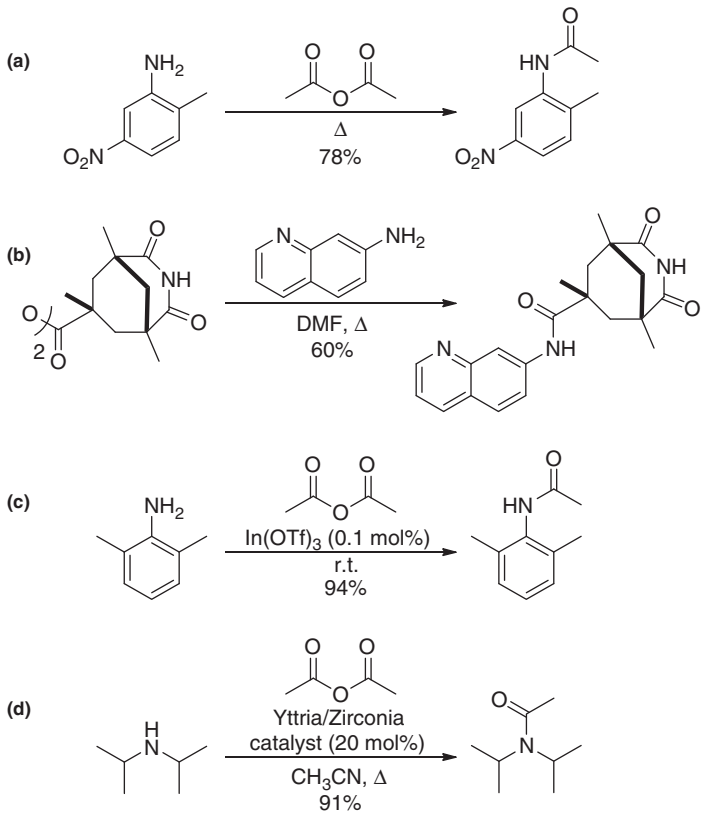


Figure 24 Symmetric anhydrides used in protocols for: (a) *N*-acylation of electron-deficient amines[118]; (b) *N*-acylation of an arylamine using a sterically hindered anhydride[119]; (c) indium triflate-catalyzed *N*-acylation of amines[114]; and (d) solid-supported yttria/zirconia-catalyzed synthesis of a tertiary amide.[116]

of electronically and sterically demanding amines.[17] Notable reports of effective *N*-acylation catalysts that employ acid anhydrides as acyl donors include the use of indium triflate (Figure 24(c)),[114] zinc oxide,[115] heterogeneous yttria/zirconia (Figure 24(d)),[116] and MoO_2Cl_2.[117]

6.11.3.5 Mixed Acid Anhydrides and Carbonates

The use of a mixed anhydride as an acyl donor avoids wasting half of the desired acylating equivalent, with the spectator carboxylate leaving group ideally being cheap and easy to remove from the amide product. The major problem with this approach is controlling the regioselectivity of amine addition to the different acyl fragments of the mixed acid anhydride donor. Mixed pivalic anhydrides are often generated *in situ* to carry out highly regioselective *N*-acylation reactions of amines, with the steric demand of their *tert*-butyl groups preventing nucleophilic attack at their proximal carbonyl groups (Figure 25(a)). Inexpensive isobutyl chloroformate has proven to be particularly useful for the generation of mixed anhydride species on an industrial scale, and for the synthesis of complex amides of use in natural product synthesis (Figure 25(b)). Mixed alkoxycarbonyl-, phosphinic-, and phosphorous anhydrides have also been used to carry out selective *N*-acylation reactions due to the greater reactivity of their carboxylate acyl fragments when compared with their less-reactive carbonate, phosphinic, and phosphate fragments, respectively (Figure 26).[13,16]

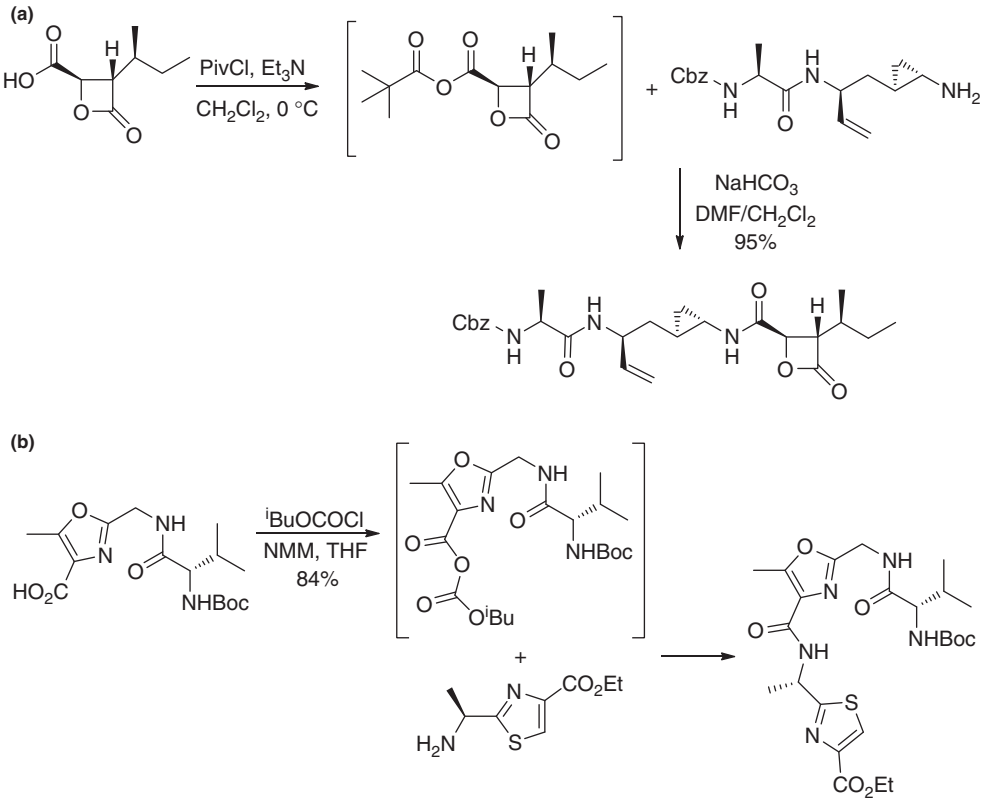


Figure 25 (a) Mixed anhydride for the synthesis of structural analogs of belactosin A[120] and (b) a thiooxazoline intermediate for the synthesis of promothiocin A.[121]

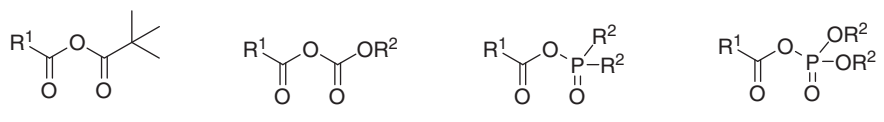


Figure 26 Different types of mixed anhydride acyl donors used for amide bond formation.

6.11.3.6 Esters

The long-term bench stability of many esters makes them an attractive *N*-acyl source, with many different ester derivatives having been shown to react with amines to afford amides under both catalytic and noncatalytic conditions. The term 'activated-ester' is often used to describe an ester that has good leaving group properties (e.g., succinimidyl, pentafluorophenyl (PFP), *p*-nitrophenyl, etc.), which often react with amines to give cleaner amide products than those obtained using more reactive acid chlorides/anhydrides. In practice, the existence of many one-pot procedures that rely on *in situ* activation of acids means that the use of isolated activated esters for *N*-acylation reactions is quite limited. However, in specific cases where *in situ* activation of acids is problematic, activated esters can provide bench-stable alternatives for use in *N*-acylation reactions.

6.11.3.6.1 Alkyl esters

A survey of the literature reveals that simple methyl and ethyl esters are by far the most common class of stable ester donors used in *N*-acylation reactions (Figure 27(a)).[122] This is due to their long-term stability and the ease of removal of either methanol or ethanol byproducts from the amidation reaction, with elevated temperatures or acid catalysts often employed to facilitate amide bond formation. For example, Mandal and coworkers have found that methyl, ethyl, allyl, and benzyl esters of *N*-protected amino acids react with primary or cyclic secondary amines under catalyst- and solvent-free conditions at 40 °C to afford their corresponding amides in good yields.[123] Vinyl esters are often used in catalytic *N*-acylation reactions, with irreversible tautomerization of their enolic leaving groups to their keto forms facilitating amide formation. For example, Pelagalli et al. have shown that isopropenyl acetate can be used to acetylate primary and secondary amines under catalyst and solvent-free conditions at 60 °C (Figure 27(b)).[124] These conditions were found to be chemoselective for primary amines over alcohols, however, acetylation of more poorly nucleophilic anilines did not occur.

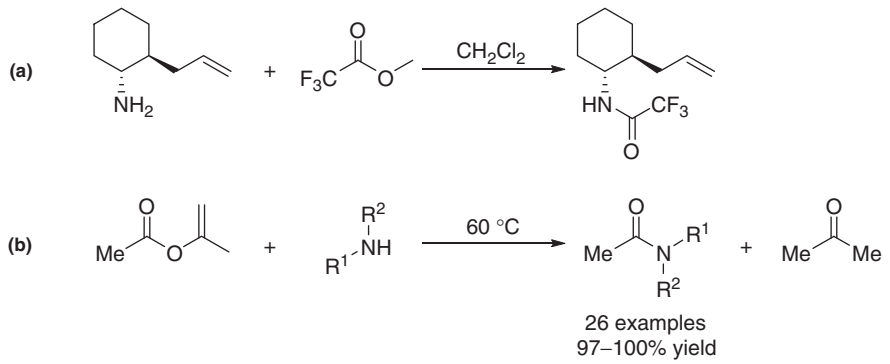


Figure 27 (a) Trifluoroacetylation of an amine intermediate for the synthesis of a PDE9 hypoglycemic inhibitor[122] and (b) acetylation of amines using isopropenyl acetate as an acetyl donor.[124]

Microwave activation has been shown to be an effective method for the aminolysis of esters,[125,126] with a limited number of catalytic methods utilizing esters as acyl sources for the synthesis of amides having also been reported. For example, Yamamoto and coworkers used $Sb(OEt)_3$ as a catalyst for macrolactamization of a tetraamino ester for the synthesis of a series of macrocyclic spermine alkaloids.[127] Porco and coworkers have developed a versatile catalytic ester–amide exchange using a zirconium alkoxide-based catalyst, with a number of alkyl esters found to acylate both primary and secondary amines using 10 mol% $Zr(O^tBu)_4$ as a catalyst in the presence of 10 mol% of either HOAt or HOBt as an additive (Figure 28).[128] Detailed mechanistic studies revealed that the HOAt additive does not form an activated ester *in situ*, but instead undergoes ligand exchange with $Zr(O^tBu)_4$ to form a dynamic interconverting mixture of Zr–OAt species. These Zr–OAt species can dimerize in the presence of an amine to afford metal–amide complexes, with intramolecular H-bonding between the OAt ligand and the amine NH combining to increase the relative nucleophilicity of the amine toward a coordinated ester.

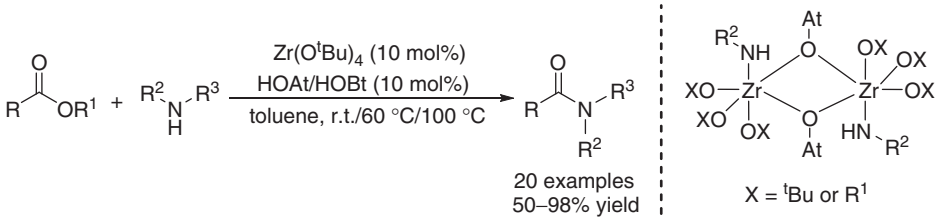


Figure 28 Zirconium alkoxide-catalyzed ester–amide exchange.[128]

Ohshima et al. found that use of 5–10 mol% sodium methoxide catalyzes the *N*-acylation of a number of primary and secondary amines with methyl esters under strictly anhydrous conditions in toluene at 50 °C.[129] The use of 4-trifluoromethylphenol (10–30%) as an additive allowed benzylamine to be *N*-acylated with a range of *N*-Boc-amino acid methyl esters in good yield without racemization of their *α*-stereocenters occurring. Vinyl, benzyl, and ethyl esters have also been used as *N*-acylating agents by Waymouth and coworkers using 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as a catalyst,[130] whereas TBD has been used as a nucleophilic catalyst on an industrial scale using a heterocyclic methyl ester as an acyl donor.[131] Vaidyanathan and coworkers have also reported that the bicyclic amidine DBU catalyzes amidation of ethyl cyanoacetate with a small range of secondary amines.[132] Movassaghi and Schmidt have reported that *N*-heterocyclic carbenes (NHCs) can catalyze amidation of a wide range of primary amino alcohols with methyl esters under mild conditions (Figure 29(a)).[133] The authors propose that the NHC acts as a Brønsted base to promote an initial transesterification reaction, with subsequent O→N acyl transfer forming a secondary amide, which limits its use to the *N*-acylation of alkyl amino alcohol substrates. Yang and Birman reported that a number of primary amines could be acetylated with isopropenyl acetate using 5 mol% 1,2,4-triazole anion as a catalyst at room temperature (Figure 29(b)).[134] Although the acetylation of methyl L-phenylalaninate proceeded with no loss of stereochemistry, the use of methyl D-phenylglycinate resulted in complete racemization. This method could be extended to the use of methyl esters as *N*-acylating agents when the reaction was performed at higher temperature using higher catalyst loadings (20 mol%).

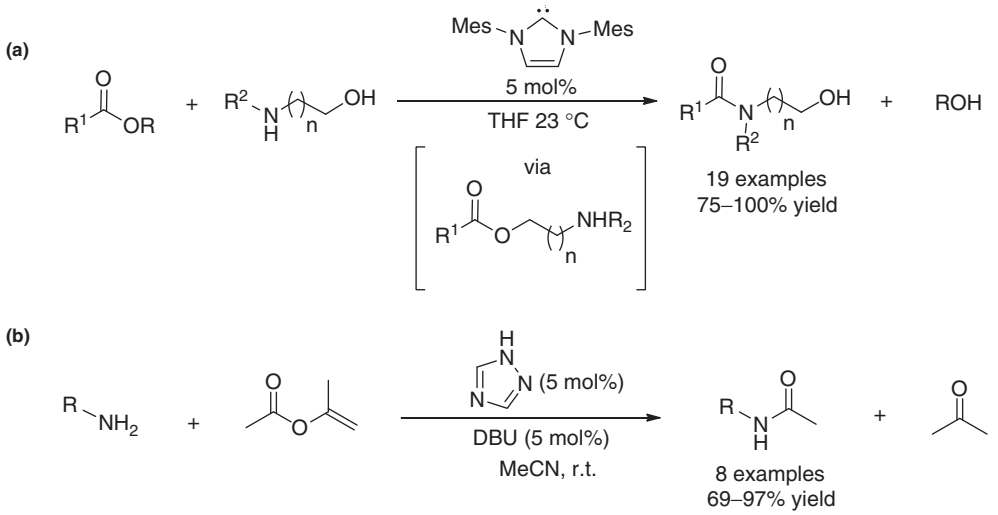


Figure 29 (a) NHC-mediated amidation of esters[133] and (b) acetylation of amines with isopropenyl acetate using 1,2,4-triazole as a catalyst.[134]

Recently, Gnanaprakasam and Milstein reported a conceptually different and highly atom-efficient approach for amide bond formation using esters as acyl donors that employs a dearomatized ruthenium–pincer PNN complex and a 'pseudosymmetric' ester as an *N*-acylating agent (Figure 30(a)).[135] Initial complexation of the ester and amine to the ruthenium metal center results in formation of an amide bond and a metal-bound alkoxide species. This metal-alkoxide species is then thought to be oxidized to a metal-bound aldehyde species, which reacts oxidatively with a second equivalent of amine (via a hemiaminal intermediate) to afford a further equivalent of amide product (Figure 30(b)). This catalytic method was shown to be highly effective for *N*-acylation of a series of primary and secondary amines using 'pseudosymmetric' alkyl esters, forming a range of alkyl amides in high yields with H_2 being liberated as the only byproduct.

The use of enzymes as catalysts for the *N*-acylation of amines using esters as substrate donors is a potentially powerful approach for amide bond formation, with the lipase CAL-B having been employed as a biocatalyst for the ammonolysis of esters to afford primary amides.[136] Representative examples, where this lipase has been used for amide synthesis, include its use for the ammonolysis of triacylglycerols (Figure 31(a)),[137] synthesis of a hindered pyrrole-amide as a drug intermediate (Figure 31(b)),[138] and for the regioselective amidation of diester substrates to selectively afford monoamide esters (Figure 31(c)).[139]

6.11.3.6.2 Activated esters

Various bench-stable activated esters have been synthesized and employed as effective racemization-free *N*-acylating reagents for a wide range of amide bond-forming reactions. Succinimidyl esters are usually bench stable and can be readily prepared from their corresponding carboxylic acids. They have been used for catalyst-free *N*-acylation reactions of primary or secondary amines and for peptide synthesis.[140] One of the advantages of succinimidyl esters over other activated esters for *N*-acylation reactions is that the succinimide byproduct is water soluble and readily removed from the desired amide products, and they have often been used in *N*-acylation reactions where the corresponding acid chlorides or acid anhydrides have proven to be unstable. For example,

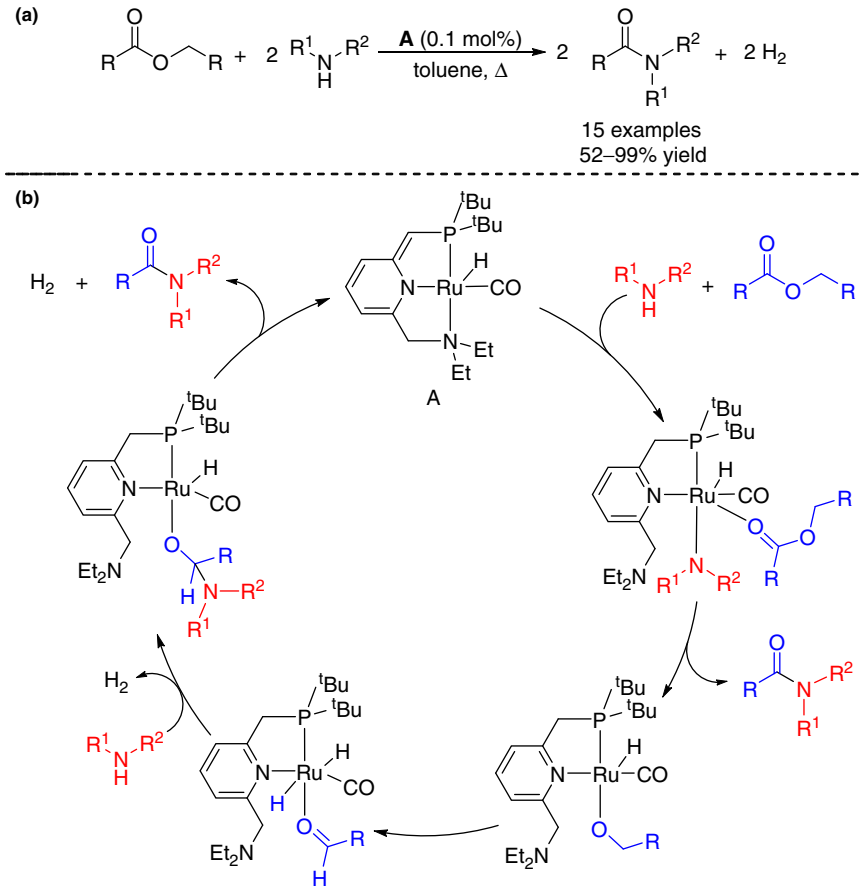


Figure 30 Ru–pincer PNN-catalyzed amide formation from pseudosymmetric esters.[135]

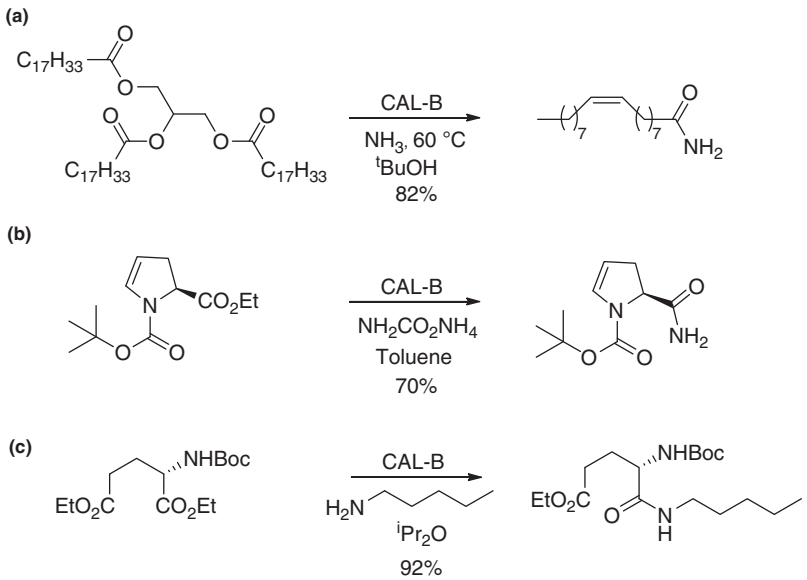


Figure 31 Ammonolysis and amminolysis of esters using CAL-B as a biocatalyst for amide bond formation.

succinimidyl diazoacetate is a stable crystalline solid (unlike its acid chloride) which can be used for the diazoacetylation of primary and secondary amines (Figure 32).[141] Activated succinimidyl esters are widely used as coupling partners in immobilization protocols to form amide bonds between the amino groups of peptides and proteins and the carboxyl groups of polymers, cells, biochips, and other surfaces.[142]

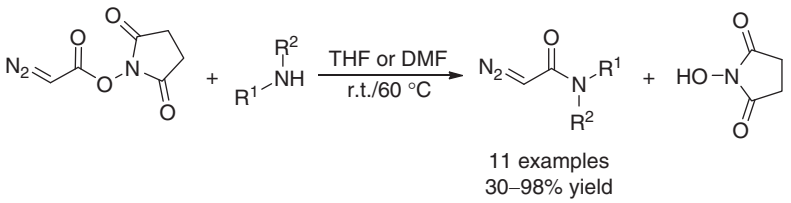


Figure 32 Succinimidyl diazoacetate for the acylation of amines.

p-Nitrophenol (PNP) esters are easily prepared, often crystalline, and have been used for the *N*-acylation of a wide range of both primary and secondary amines (Figure 33(a)). For example, Bundle and coworkers found that reaction of *p*-nitrophenyl diesters with oligosaccharides gave stable amide half esters that could be purified and reacted further to form complex neoglycoproteins.[143] The PNP byproduct produced in these acylation reactions can be difficult to separate from the desired amide, with ion-exchange protocols having been developed to facilitate purification of crude reaction products.[144] PFP esters are often very reactive toward both primary and secondary amines and have been used as coupling partners for a number of challenging amide bond-forming reactions (Figure 33(b)). For example, PFP esters have been used for the synthesis of complex *N*-linked glycopeptides where the corresponding succinimidyl esters were found to be unreactive.[145] However, as with *p*-nitrophenyl esters, the pentafluorophenol byproduct formed in *N*-acylation reactions can sometimes be difficult to separate from the amide product. HOBT (Figure 33(c)) and 1-hydroxy-7-azabenzotriazole (HOAT) esters have been used to facilitate amide and peptide bond

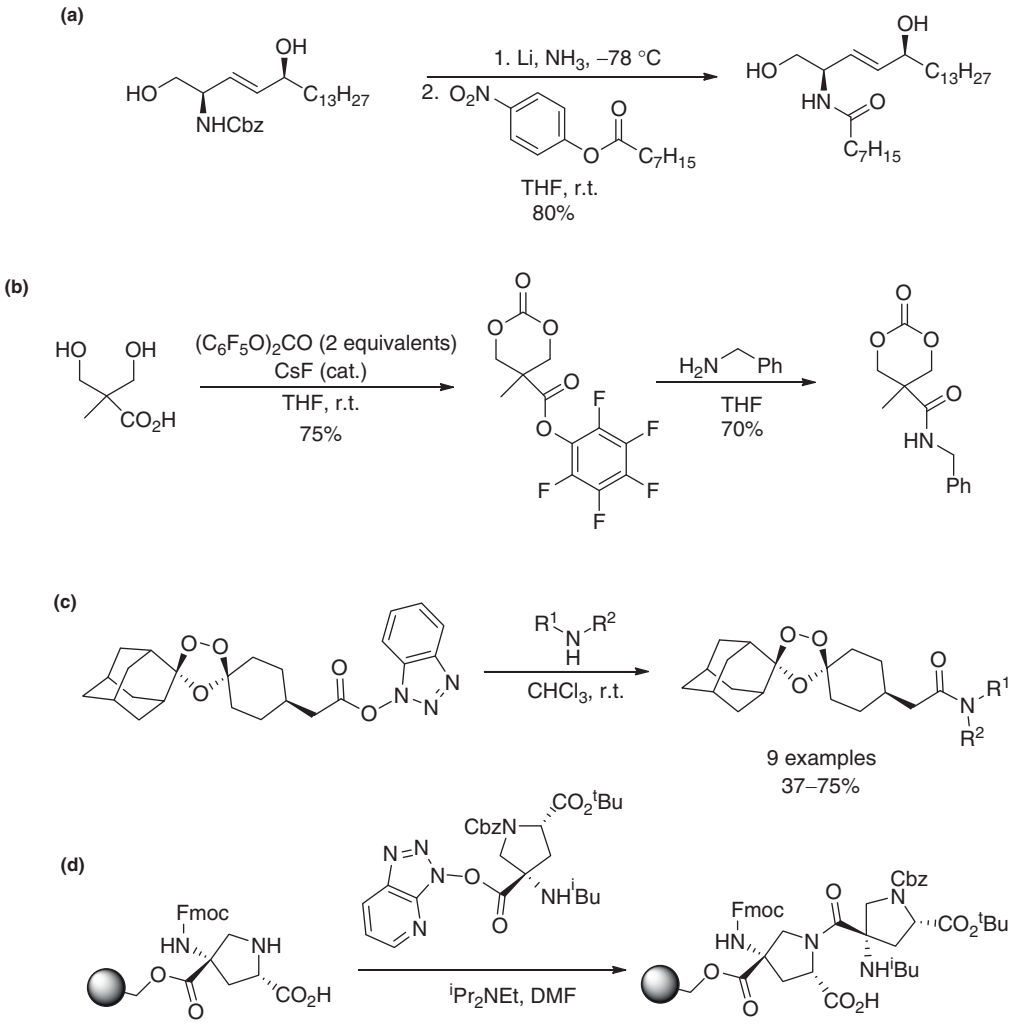


Figure 33 Stable activated esters that are routinely employed for amide bond formation: (a) PNP esters used in the synthesis of sphingenine derivatives[147]; (b) PFP esters for the synthesis of a functionalized cyclic carbonate amide[148]; (c) HOBT esters used to prepare analogs of antimalarial arterolane[149]; and (d) HOAT esters for solid-phase coupling of sterically hindered α,α-disubstituted amino acids.[150]

formation using *in situ* protocols, with HOAT esters generally demonstrating improved reactivity for challenging *N*-acylation reactions (Figure 33(d)).[146]

6.11.4 Carbodiimide-Mediated Coupling Reactions

Carbodimiides are versatile coupling agents for the formation of peptide bonds from their component carboxylic acids and amines[151] that are widely used for the high-throughput synthesis of amidic compounds.[144] Reaction of a carboxylic acid with commercial coupling reagents such as dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), and 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (EDCI) (Figure 34) afford *O*-acylisourea mixed anhydride intermediates that rapidly react with amines to afford amides and urea byproducts. Much research has been carried out into designing new carbodiimide reagents that afford urea byproducts with physical properties that enable their facile separation (precipitation, extraction, immobilization, etc.) from the resultant amide product.[152] DIC has proven to be a particularly versatile coupling agent for the solid-phase synthesis of many peptide sequences.[153] Problems in carbodiimide coupling reactions for peptide synthesis can occur due to racemization occurring (via formation of oxazolone intermediates), or via rearrangement of *O*-acylisourea intermediates into their corresponding *N*-acylurea intermediates.[16] Consequently, protocols have been developed that involve addition of additives (e.g., DMAP, HOBT, PFP, *N*-hydroxysuccinimide, etc.)[154] to rapidly intercept *O*-acylisourea species to afford new activated ester species that are less prone to racemization or rearrangement (Figure 35).[155] Ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma) has recently been introduced as an efficient additive for carbodiimide coupling reactions, which is reported to have a lower risk of explosion than conventional additives, thus enabling its potential use on a large scale.[156] EDCI is a particularly popular coupling agent for the synthesis of structurally complex amides since its urea byproducts are water soluble (Figure 36), whereas its use in the presence of NHS[157] (or sulfo-NHS[158]) has proven popular for bioconjugation of peptides and proteins to biomacromolecules.

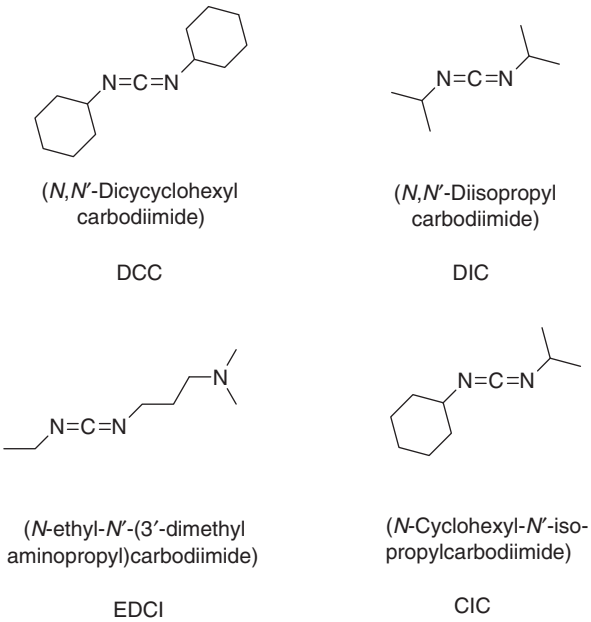


Figure 34 Carbodiimide reagents employed to carry out amide bond formation.

6.11.5 Onium and Pyridinium Peptide Coupling Agents

A bewildering range of coupling agents have been developed to facilitate efficient peptide coupling reactions and address problems associated with poor yields and racemization for the synthesis of 'difficult' peptide sequences. One of the most popular range of peptide coupling reagents in current use are those known as 'onium' salts,[161] which have proven to be particularly effective for the formation of active ester species for peptide bond coupling *in situ*. A number of different phosphonium, phosphate, and phosphinium[162]-derived reagents have been developed for amide bond-forming applications (Figure 37). For example, bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP) has been reported to be an excellent reagent for

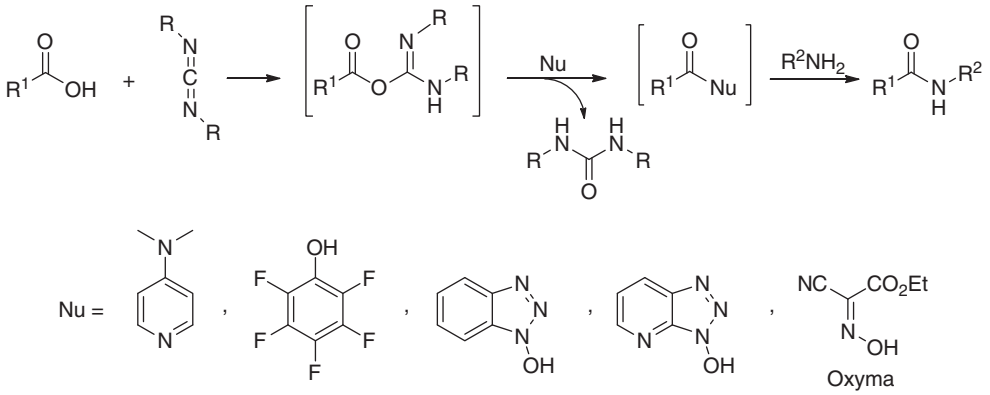


Figure 35 Common additives employed to minimize racemization and improve the yields of carbodiimide-mediated amide bond-forming reactions.

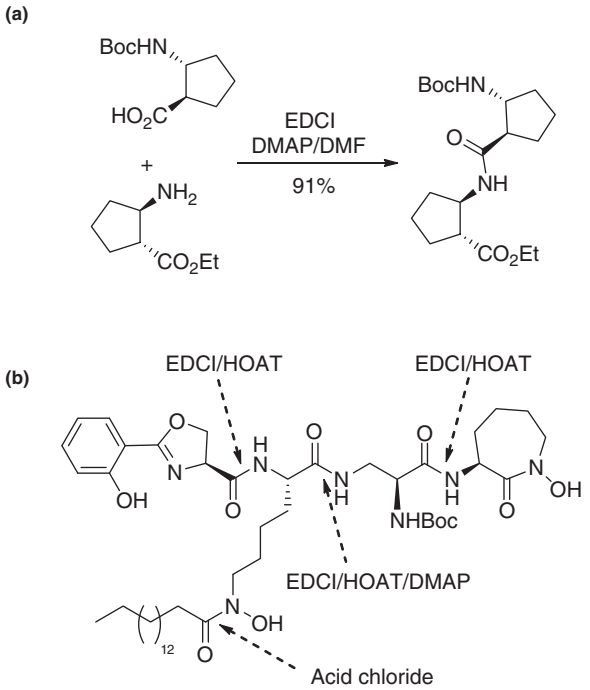


Figure 36 Representative EDCI-mediated amide couplings used to prepare: (a) a foldameric β-dipeptide[159] and (b) mycobactin analogs.[160]

incorporating challenging protected *N*-methyl-amino acid residues.[163] 3-(Diethoxy-phosphoryloxy)-3H-benzo[*d*][1,2,3]triazin-4-one (DEPBT) is adept at preventing racemization during peptide bond formation,[164] whereas (7-azabenzotriazol-1-yloxy)tri-pyrrolidinophosphonium hexafluorophosphate (PyAOP) is particularly useful for carrying out solid-phase peptide synthesis.[165] A mixture of *n*-propanephosphonic anhydride (T3P) and pyridine has recently been reported as a safe, relatively inexpensive coupling agent for racemization-prone peptide bond syntheses, which affords water-soluble byproducts that makes it suitable for use on a large scale.[166] Uronium species (**Figure 38**) such as *O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) react in a similar manner as phosphonium salts to afford well-behaved activated *N*-acyl oxime coupling species. The salts HBTU, *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetra-methyluronium hexafluorophosphate (HATU), bromotri(pyrrolidino) phosphonium hexafluorophosphate (PyBop),[167] benzotriazoloxy-bis(pyrrolidino)carbonium hexafluorophosphate (BBC),[168] bromotris(dimethylamino)-phosphonium hexafluorophosphate (BroP), and *O*-benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) have all been shown to be effective coupling reagents for carrying out sterically demanding peptide bond formation.[154] 2-Chloro-1,3-dimethylimidazolidinium hexafluorophosphate (CIP) is reported to be extremely useful for the coupling of sterically hindered α,α-dimethyl amino acid and *N*-methyl-amino acid residues.[169] 1-[(1-(Cyano-2-ethoxy-2-oxoethylideneaminooxy)dimethylamino-morpholinomethylene)]methanaminium hexafluorophosphate (COMU) has recently been introduced as a reagent that demonstrates improved peptide-coupling properties and greater stability than other 'onium' reagents.[170] Immonium salts such as 5-(1*H*-benzotriazol-1-yloxy)-3,4-dihydro-1-methyl-2*H*-pyrrolium hexachloroantimonate (BDMP) are considered to be more reactive coupling agents than phosphonium/uronium reagents that mediate racemization-free

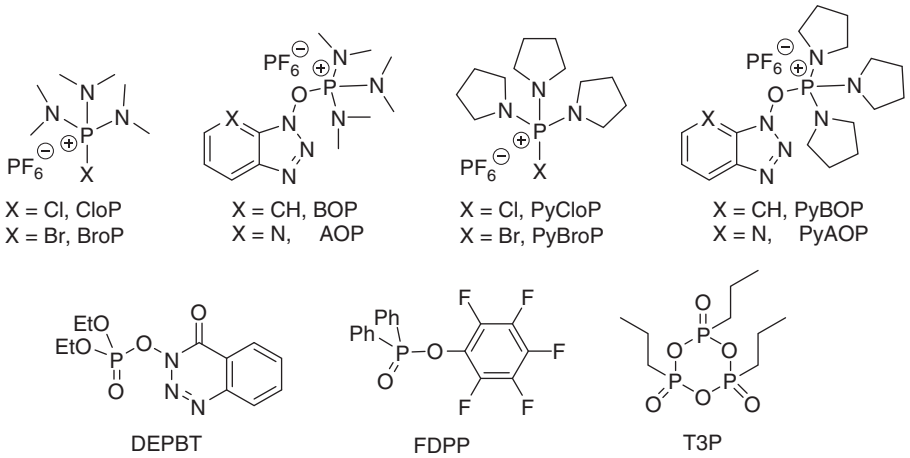


Figure 37 Common phosphorus reagents employed for peptide bond formation. CloP, chlorotris(dimethylamino)phosphonium hexafluorophosphate; BroP, bromotris(dimethylamino)phosphonium hexafluorophosphate; BOP, benzotriazolyl-*N*-oxytrisdimethylaminophosphonium hexafluorophosphate; AOP, (7-Azabenzotriazol-1-yl)oxytris(dimethylamino) phosphonium hexafluorophosphate; PyClop, chlorotri(pyrrolidino) phosphonium hexafluorophosphate; PyBroP, bromotri(pyrrolidino)phosphonium hexafluorophosphate; PyBOP, (benzotriazol-1-yl)-oxy-tripyrrolidin ophosphonium hexafluorophosphate; PyAOP, (7-azabenzotriazole-1-yl)-oxy-tripyrrolidinophosphonium hexafluorophosphate; DEPBT, (Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one; FDPP, pentafluorophenyl diphenyl phosphonate; T3P, *n*-Propanephosphonic anhydride.

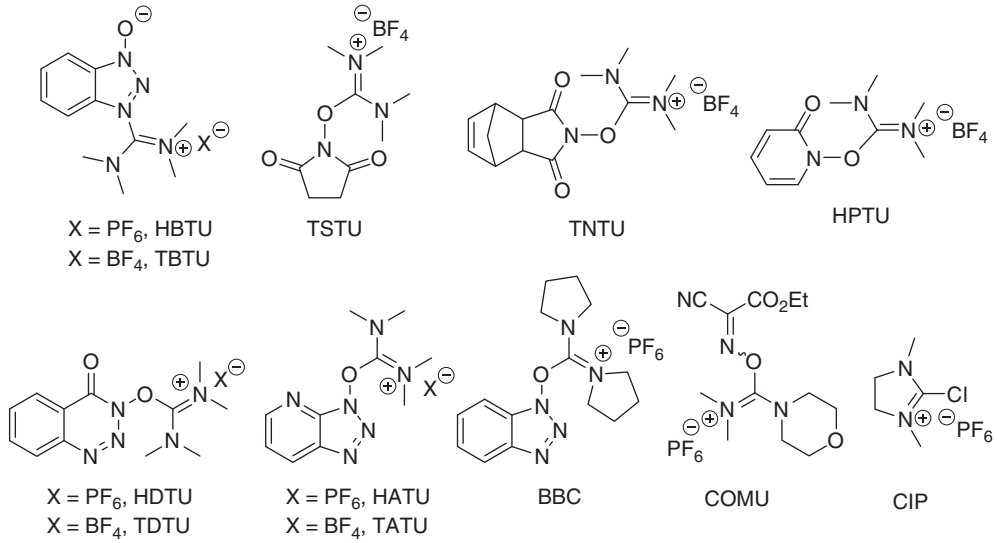


Figure 38 Common uronium and imidazolium reagents used for peptide bond formation. HBTU, *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; TBTU, *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate; HATU, *O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; TSTU, 2-Succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate; TNTU, 2-(5-Norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate; HPTU, 1-((Dimethylamino)(dimethyl iminio)methoxy)-2-hydroxypyridinium tetrafluoroborate; HDTU, *O*-(3,4-Dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; TDTU, 2-(3,4-Dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; HATU, *O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetra-methyluronium hexafluorophosphate; TATU, *O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; BBC, benzotriazoloxy-bis(pyrrolidino) carbonium hexafluorophosphate; COMU, 1-[(1-(Cyano-2-ethoxy-2-oxoethylideneaminooxy)-dimethylamino-morpholinomethylene)]-methanaminium hexafluorophosphate; CIP, 2-Chloro-1,3-dimethylimidazolidinium hexafluorophosphate.

peptide bond-forming reactions in good yield (Figure 39).[171] Triazine-based coupling reagents (Figure 39) such as 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)[172] and polymer-supported variants[173] have been used to prepare highly reactive triazine esters *in situ* that are reported to have improved performance over coupling reagents such as TBTU or HATU.[174] Pyridinium-based coupling reagents such as 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP)[175] or Mukaiyama's reagent[176] also display good activity for peptide bond-forming reactions of sterically hindered nonproteinogenic α-amino acids (Figure 39).

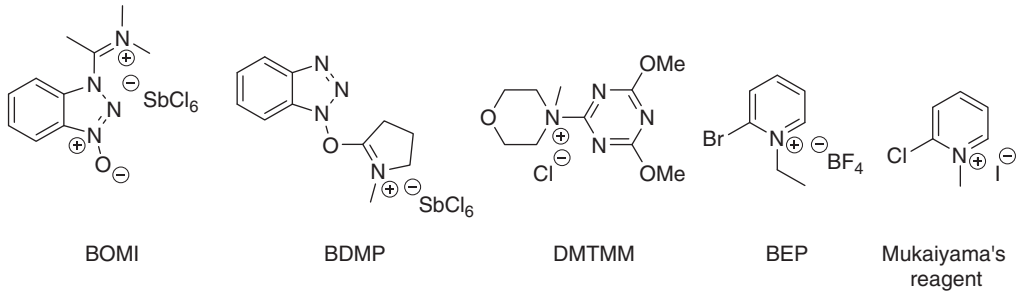


Figure 39 Common iminium, ammonium, and pyridinium coupling agents used for '*in situ*' peptide bond formation.[154] BOMI, benzotriazol-1-yloxy-*N*,*N*-dimethylmethaniminium hexachloroantimonate; BDMP, 5-(1*H*-Benzotriazol-1-yloxy)-3,4-dihydro-1-methyl-2*H*-pyrrolium hexachloroantimonate; DMTMM, 4-(4,6-Dimethoxy[1,3,5] triazin-2-yl)-4-methylmorpholinium chloride; BEP, 2-Bromo-1-ethylpyridinium tetrafluoroborate.

These advanced coupling agents have been developed for carrying out conventional peptide-coupling reactions between suitably protected proteinogenic α-amino acids, however, they have also proven to be extremely useful for carrying out challenging amide bond-forming reactions for the synthesis of advanced chiral intermediates for natural product synthesis (**Figure 40**). This is particularly true for the synthesis of advanced amide intermediates for the synthesis of nonribosomal cyclic peptides, whose synthesis requires construction of multiple amide bonds from a combination of structurally challenging natural and non-proteinogenic α-amino acids (**Figure 41**).

6.11.6 Amide Bond-Forming Reactions for the Synthesis of Peptides and Proteins

Peptides, peptidomimics, and proteins have an enormous range of uses as therapeutic agents and biological tools for biomedical applications,[183] as well as being increasingly important building blocks for biotechnological and materials applications.[184,185] This utility means that peptide bond-forming reactions represent an extremely important subclass of amide bond-forming reactions, with a vast range of conditions and reagents having been developed for their racemization-free synthesis.[186] Peptide synthesis is normally carried out in a stepwise manner whereby activation of the carboxylic acid group of an *N*-protected amino acid derivative (e.g., *N*-Fmoc, *N*-Trt, *N*-Cbz, *N*-BTS, *N*-Alloc, etc.) is followed by its coupling with the amino group of a second amino acid derivative (**Figure 42**).[187,188] The wide range of coupling methods/agents that have been developed are designed to ensure that peptide bond formation occurs in good yield without racemization,[154] with the optimum choice of coupling agents, additives, and side-chain protecting groups[189] employed being highly dependent on the peptide sequence being assembled. A number of different additives (e.g., HOBT, HOAT, Oxyma, etc.) have been developed that facilitate the efficient synthesis of problematic peptide sequences, with coupling protocols available having been designed to minimize formation of unwanted oxazolone, diketopiperazine, *N*-carboxyanhydride, and guanidine side products.[154] However, after reviewing the bewildering array of coupling reagents and conditions that are available for peptide bond formation, an excellent review has recently concluded that the majority of peptide sequences can be prepared using a relatively limited set of commercially available coupling reagents such as DCC/HOBT, HATU, HBTU, and PyBroP.[15] A range of dedicated coupling protocols for the incorporation of sterically hindered α-amino acids, nonproteinogenic α-amino acids, α,α-disubstituted α-amino acids, dehydroalanine-amino acids, and β-/γ-/δ-amino acids into peptidic natural products have also been developed.[190–194] Microwave-enhanced solution and solid-phase peptide synthesis is becoming an increasingly popular approach, particularly for difficult peptide sequences.[6,195–197] The amide bonds of some severely hindered peptide sequences are notoriously difficult to prepare and a novel coupling method has been developed for their formation,[198] including the use of amino-azirines as highly reactive monomers for the synthesis of challenging α-amino-isobutyric (aib)-containing peptides (**Figure 43**).[199]

A range of polymer-supported reagents and additives have also been developed to improve the efficiency of solution-phase peptide synthesis. For example, fluorous-based techniques to facilitate peptide purification are available[200] that employ *N*-fluoro-protected amino acid derivatives [201,202] as building blocks for synthesis, or use fluorous polymers as soluble supports for peptide synthesis.[202,203] Peptide synthesis has also been carried out using coupling reagents in ionic liquids,[204] or via peptide attachment to soluble ionic liquid supports that facilitate peptide purification. Small-to-medium-sized peptide sequences (up to 20–30 amino acids) have been routinely prepared using solution-phase techniques,[187] enabling peptide intermediates to be isolated, purified, deprotected, and coupled together to afford larger peptides (up to 60 amino acids) as required.[205] However, the majority of bespoke peptides (5–60 residues) are prepared using solid-supported techniques that employ variants of Merrifield's original solid-phase method,[206] with tens of thousands of different peptides being produced annually. Briefly, this approach involves stepwise peptide bond formation between suitably activated amino acid monomers and the *N*-terminus of a growing peptide chain whose *C*-terminus is attached to a polymer support using peptide coupling reagents that are suitable for automation. This approach enables large excesses of reagents and activating agents to be used to drive peptide bond-forming reactions to completion and avoids handling problems associated with the poor solubility and aggregation of medium-length peptides.[6,207]

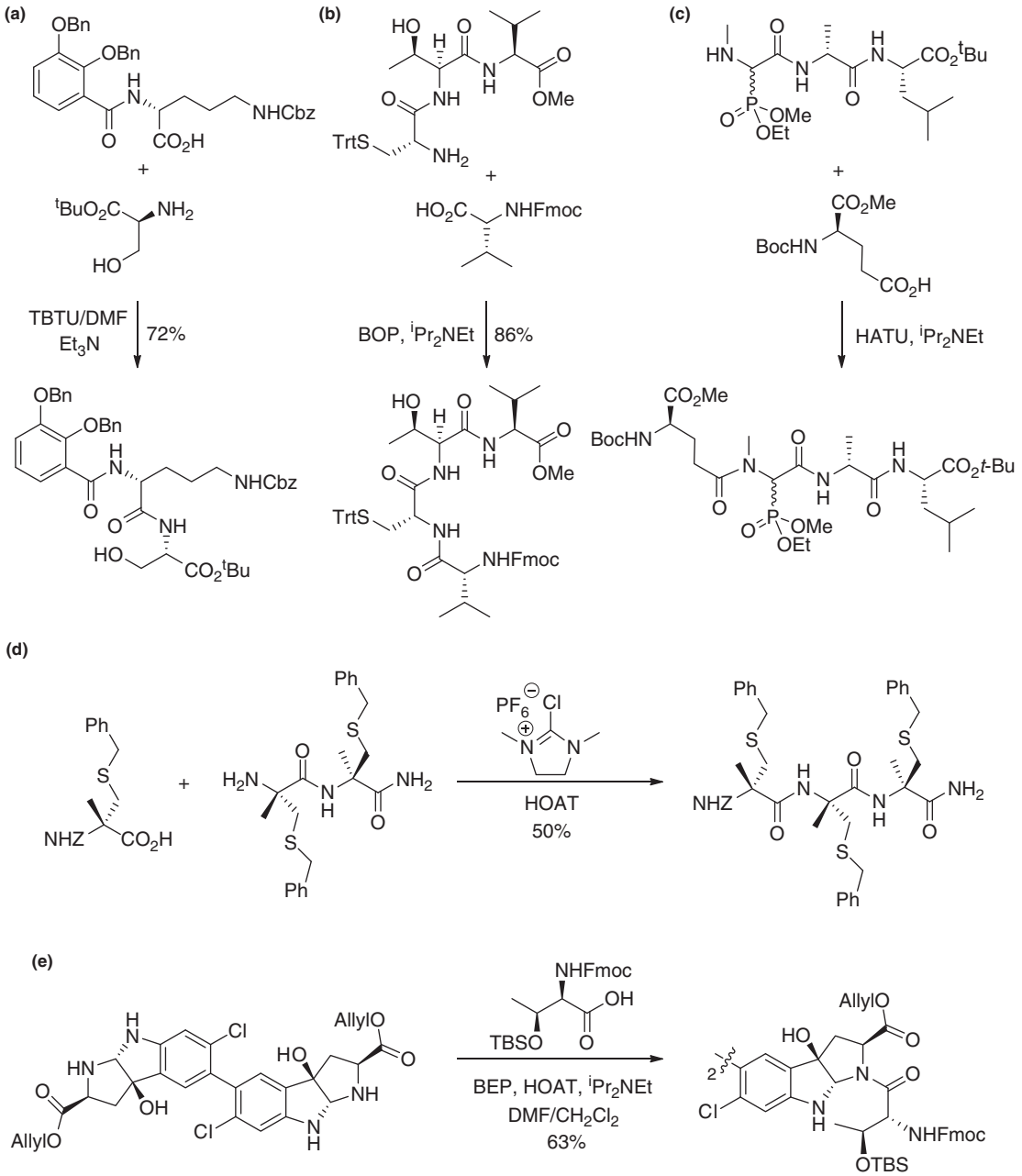


Figure 40 Selected 'onium'-mediated peptide bond-forming reactions: (a) TBTU-mediated amide bond-forming reaction for the synthesis of vanchrobactin[177]; (b) BOP-mediated amide bond-forming reaction for the synthesis of antitumor depsipeptide FR-901,208[178]; (c) HATU-mediated amide bond-forming reaction for the synthesis of mirabazole C[179]; (d) CIP-mediated amide bond-forming reaction for the synthesis of microcystin-LA[180]; and (e) BEP-mediated amide bond-forming reaction for the synthesis of chloptosin.[181]

A significant amount of research has been carried out in improving the efficiency of solid-phase protocols, including studies on the use of different protecting groups (e.g., *N*-FMoc vs. *N*-Boc, *O*-Bn vs. *O*-^{t}Bu),[189,194,208] optimization of the performance of different polymer supports (e.g., Merrifield vs. PEGA),[209–216] the use of different coupling reagents (e.g., phosphonium vs. uronium salts),[154] variation in the point of attachment of the peptide (e.g., *N*-terminus vs. side chain vs. backbone amide),[217] and optimization of the linker/cleavage conditions employed to attach/release peptides to/from solid support.[218] Manual solid-phase peptide synthesis may be performed using inexpensive protocols that employ syringes fitted with filters,[6] or using variations of the polypropylene 'Teabag' technology developed by Houghten and coworkers.[219] A range of commercial peptide synthesizers are available for carrying out automated high-throughput solid-phase synthesis,[220] which have enabled a wide range of natural peptides and peptide drug candidates to be prepared for a wide range of therapeutic applications. For example, solid-phase synthetic techniques have been used to prepare peptide pharmaceuticals[20] such as insulin,[221,222] whereas a combination of

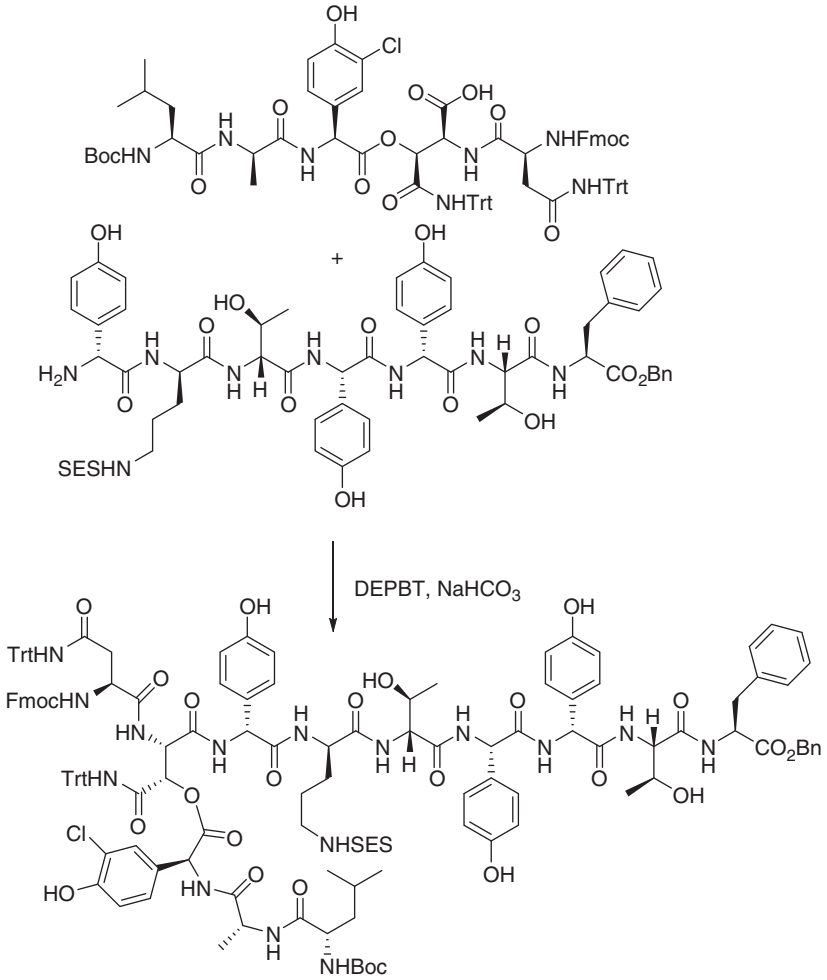


Figure 41 DEPTB-mediated amide bond-coupling reaction for the synthesis of ramoplanin A2.[182]

solution and solid-phase chemistry has been used to produce the T-20 peptide Fuzeon for the treatment of HIV infections on a ton scale (Figure 44).[223] The largest nonribosomal ion-channel peptide, polytheonamide B, that contains 48 D- and L-amino acid residues, has been synthesized via solid-phase assembly of four protected peptide thioester fragments, followed by silver[224] mediated ligation of the peptide fragments and global deprotection.[225] Automated high-throughput synthesis is also used widely to prepare libraries of peptides using 'split and mix'[226] or 'one bead–one compound'[211] techniques for screening against a wide range of biological targets.[227–231] Successful examples where this approach has been employed to identify peptides for biomedical applications include the generation of DNA-binding polyamides containing imidazole and pyrrole amino acids,[232] the discovery of peptides with integrin antagonist activity,[233] identification of hairpin peptides as inhibitors of IgE receptors,[234] isolation of peptide agonists of G-protein-coupled receptors,[235] and peptides containing pyrrolidine bis-cyclic guanidines with antimicrobial activity.[236] Specialized solid-phase strategies for the synthesis of peptides with *C*-terminal end groups,[237] that employ side chain/backbone amide anchoring strategies using specialized resins that allow for nucleophilic cleavage have also been developed.[238] The synthesis of libraries of peptides for screening in proteomic studies, deciphering protein–protein interactions, profiling protease activities, cell adhesion and other drug discovery applications is becoming increasingly popular.[239–243] These microarrays are prepared either via iterative synthesis of peptide fragments on a suitable solid support,[244] or via grafting of peptide sequences onto the surface of chemically reactive surfaces.[245] The SPOT synthesis technique[246–248] developed by Frank et al. has proven to be particularly useful for preparing high-density arrays of peptides (up to 20 amino acids) on cellulose membrane supports[249] for screening in biomedical applications.[250] Amide bond-forming reactions have also been used widely to attach preformed peptides and proteins to the surfaces of biomacromolecules, cells, polymers (e.g., PEG) and inorganic supports, thus creating a wide range of bioconjugates with new catalytic[251] and biomedical applications.[184]

Although the role of amidases and proteases in Nature is to hydrolyze amide bonds, they may also be employed to catalyze the formation of amide bonds in organic solvents under thermodynamic control, which is normally achieved using one of the coupling partners in a large excess, or devising conditions that result in the peptide precipitating from solution.[253] Serine or cysteine protease-catalyzed reactions of amines using activated esters or carbonates as acyl donors under kinetic control can also be

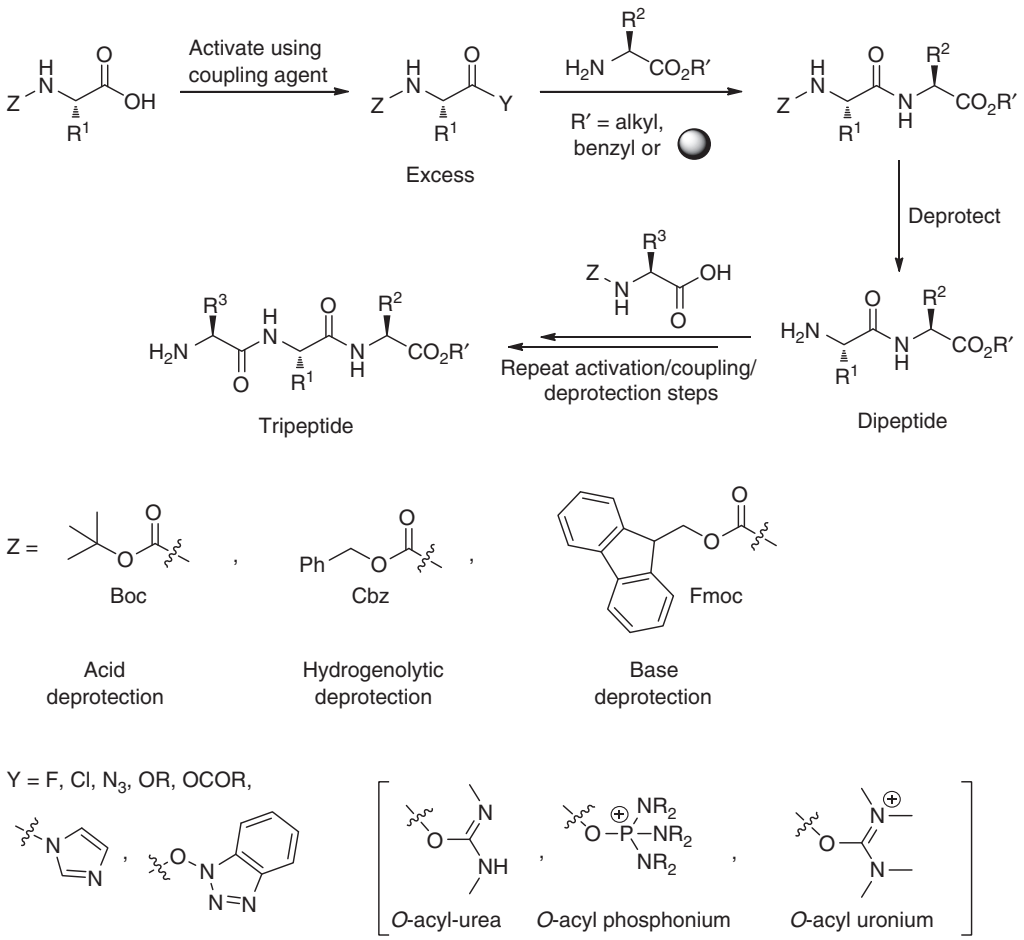


Figure 42 Strategy employed for solution- or solid-phase synthesis of a representative tripeptide.

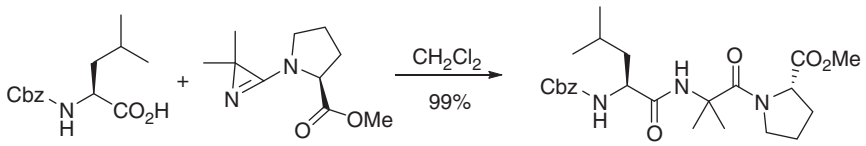


Figure 43 Application of 'azirine/oxazolone' coupling method for peptide bond formation.[199]

used for amide synthesis.[254–256] Proteases have the advantage that they can operate as catalysts at ambient temperature in aqueous media on unprotected amino acids, whereas the use of immobilized enzymes facilitates biocatalyst recycling.[257] However, proteases often display limited specificity profiles, which can severely limit the range of peptide bonds that can be produced using individual enzymes, although chemical modification strategies[258] and molecular biology techniques[259–261] have been employed to improve their specificity profiles. Consequently, it is often necessary to screen a large number of enzymes to identify a biocatalyst with the necessary activity for a particular peptide bond-forming reaction,[138] which is often only worthwhile when a specific peptide is required on a large scale. Proteases such as chymotrypsin, subtilisin, trypsin, and papain have been widely used for the synthesis of peptides and peptide isosteres,[262] particularly for the synthesis of dipeptides and tripeptides.[263] For example, alcalase is a stable, inexpensive protease that has been shown to employ a wide range of acyl donors for the *N*-acylation of both D- and L-amino acids and other amines.[256] Trypsin and chymotrypsin have also been used to catalyze incorporation of sterically demanding α,α-disubstituted-fluoroalkyl amino acids into peptides using reactive 4-guanidinophenyl esters as acyl donors.[264] The use of proteases for peptide synthesis has been extensively reviewed,[265–267] with solid-phase approaches having been used to prepare peptide targets that are difficult to synthesize in solution phase due to competing hydrolytic pathways.[268] These solid-phase systems have the advantage that a large excess of acyl donors can be used to drive peptide bond-forming reactions to completion, with the solid support serving to suppress ionization of the free amino group, and improve solvation of hydrophilic acyl donors.

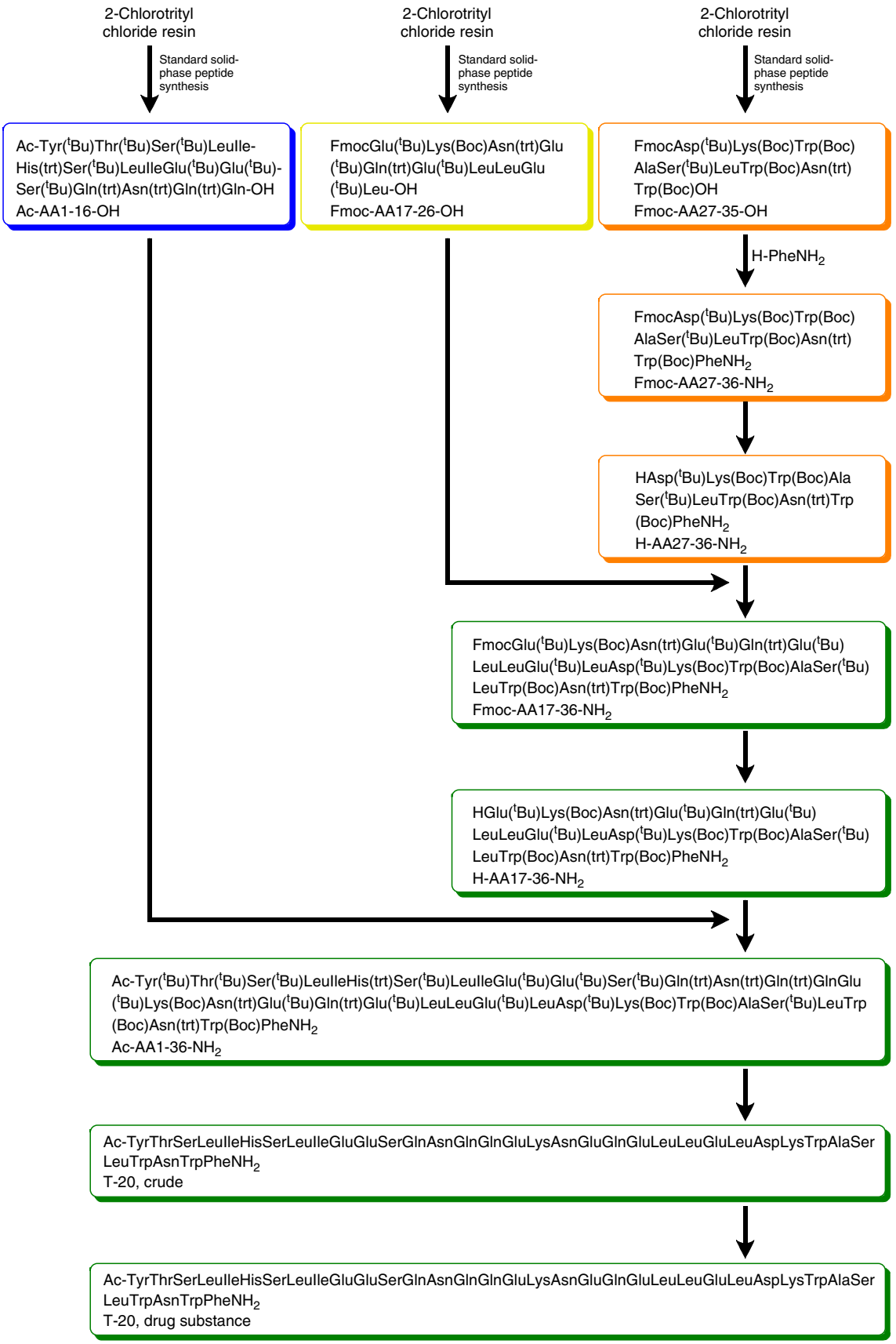


Figure 44 Synthesis of the T20 fusion peptide inhibitor Fuzeon using a combination of solid-phase and solution-phase coupling.[252]

Proteases have also been used for the synthesis of oligopeptides,[270] with different proteases that exhibit different specificity profiles being used to catalyze consecutive peptide bond-forming reactions using ester donors.[271] For example, Gill et al. reported on a convergent synthesis of the highly functionalized 'delicious' octapeptide Lys–Gly–Asp–Glu–Glu–Ser–Leu–Ala–NH_2 with an overall yield of 39% (**Figure 45**).[269] An alternative strategy is to prepare two individual peptide sequences on polymer support and then use a protease to splice the two peptide fragments together in solution phase.[272] For example, an engineered subtilisin has been used to complete the synthesis of a mutant ribonuclease A by effectively catalyzing the sequential ligation of six separate esterified peptide residues.[273] The broad specificity profile of many proteases means that they may also be used to catalyze the *N*-acylation of natural and unnatural amino acids with activated ester donors to afford peptide isosteres.[274,275] Proteases with broad specificity profiles such as clostripain[276] have been employed for the synthesis of nonpeptidic carboxylic acid amides from the coupling of simple primary amines with activated acyl donors.[277] For example, chymotrypsin was used to couple unprotected L-Tyr and L-Arg together to prepare the potent analgesic Kyotorphin (L-Tyr–L-Arg) on a kilogram scale,[278] whereas industrial processes have also been developed that enable thermolysin to catalyze stereoselective coupling of the L-enantiomer of (*rac*)-phenylglycine methyl ester with *N*-Cbz-L-Asp to afford *N*-carbobenzoxy-L-Asp-L-Phe-OMe as a precursor to the sweetener aspartame.[279] Penicillin acylase has also been employed to *N*-acylate 6-aminopenicillanic acid with phenylglycine methyl ester/amide to afford ampicillin on a ton scale.[280]

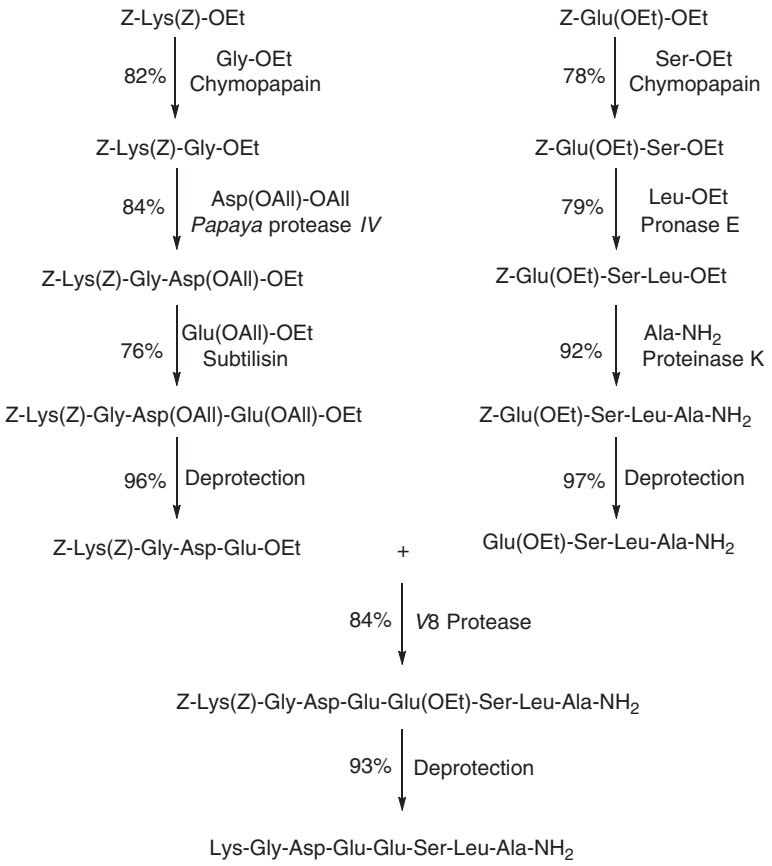


Figure 45 Solution- and solid-phase synthesis of an octapeptide.[269]

The chemical synthesis of larger peptides and proteins using conventional solution and solid-phase stepwise peptide coupling approaches is complicated by difficulties associated with incomplete coupling and deprotection reactions, accumulation of peptide byproducts, and problems caused by peptide aggregation/precipitation. Consequently, large peptides and proteins are normally synthesized chemically via a convergent approach involving solid-phase synthesis of medium-sized peptide fragments that are then coupled together using solution-phase peptide bond-forming reactions.[281] One such approach involves silver-mediated coupling of partially protected peptide thioesters with the terminal α-amino groups of a second peptide fragment in the presence of HOBt,[224] which has been used for the synthesis of 23 kDa MUC2 glycoprotein.[282] Interestingly, Wong and coworkers have recently developed efficient buffer conditions for the direct coupling of peptide thioesters with unprotected peptides to afford larger peptides containing a wide range of α-amino acids at their ligation junctions.[283] Rapid developments in the field of native chemical ligation chemistry[4,284] are being exploited to construct amide bonds between different types of medium-sized peptide fragments to afford fully functioning synthetic proteins.[285–287] The most commonly employed amide bond-forming ligation technique involves use of an

intermolecular transthioesterification reaction of an unprotected synthetic peptide-α-thioester[288] with the sulfhydryl group of an *N*-terminal cysteine residue of a second peptide fragment. The resulting thioester bond rapidly rearranges via an intramolecular S→N acyl migration reaction to afford an amide bond (Figure 46(a)).[289,290] Consequently, efficient methods have been developed for the solid-phase synthesis of peptide thioesters as ligation partners,[215,291–294] as well as a number of new reagents, coupling partners, and protocols for carrying out these types of regioselective and racemization-free ligation reactions.[295,296] A number of glycopeptides and glycoproteins have been prepared using this approach,[297–299] with larger proteins constructed via sequential ligation of multiple peptide fragments.[300] Desulfurization approaches that enable structural modification of thiol-containing amino acids at the ligation site have also been developed for incorporating amino acids other than cysteine at the ligation site.[301] The full potential of these types of native chemical ligation strategies has recently been demonstrated for the synthesis of nonglycosylated forms of the medicinally important 166-amino acid long-protein hormone, erythropoietin (EPO) (Figure 47).[302,303] Other notable applications include the synthesis of 'mirror-image' proteins derived from D-amino acid monomers[304] and K48-linked tetraubiquitin protein that contains 304 amino acids.[305] The potential of native chemical ligation has been expanded further using recombinant methods that can be used to genetically encode *N*-terminal cysteine residues into peptide sequences, and the development of elegant intein splicing techniques for the construction of specific peptide sequences.[306] Other widely employed native ligation methods include the use of Staudinger ligation reactions of peptide *N*-terminal acyl azides with peptide phosphinothioesters, which afford unstable iminophosphorane intermediates that rearrange to afford amide bonds (Figure 46(b)).[307,308] Reaction between a *C*-terminal α-keto-acid and an *N*-terminal peptide hydroxylamine has also been used for the efficient formation of peptide bonds (Figure 46(c)),[309] including the construction of a human glucagon-like peptide.[310]

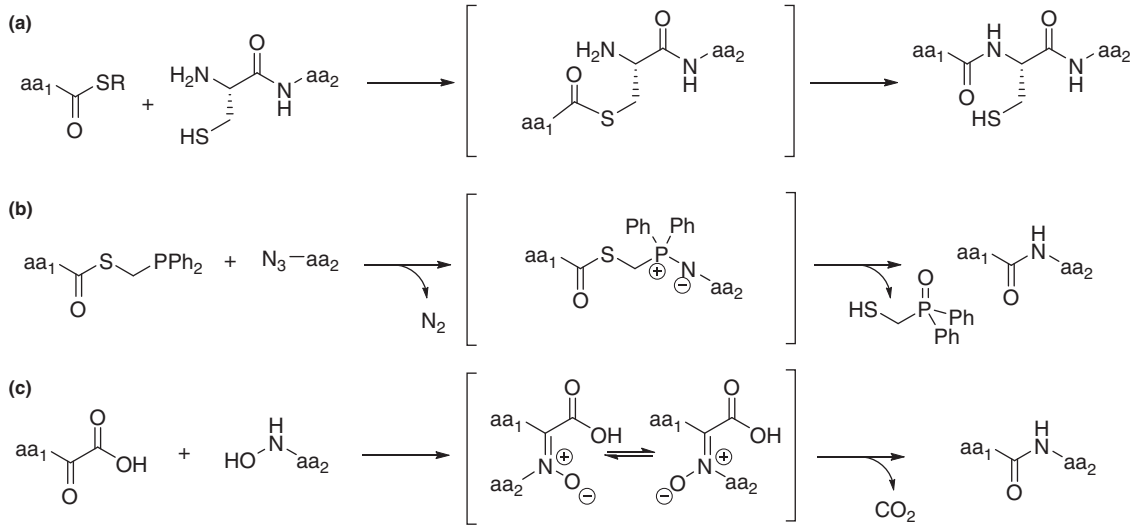


Figure 46 Native chemical ligation amide bond-forming reactions for the synthesis of proteins.

Recombinant DNA technology may also be used for the ribosomal synthesis of larger peptides and proteins using host organisms such as *Escherichia coli*[311,312] or *Pichia pastoris* for heterologous protein expression, with a range of molecular biology techniques available that enable amino acid sequences to be varied to afford mutant proteins as required.[313] Recent advances include the use of yeast (e.g., *P. pastoris*),[313,314] mammalian[315] and plant cells, and cell-free expression systems[316] to produce posttranslationally modified recombinant proteins. These approaches can be used to generate pharmaceutical proteins containing the correct glycosylation patterns and intramolecular disulfide bonds required for activity, many of which have undergone proteolytic cleavage to afford fully functioning proteins.[221] Similarly, exciting developments on the biotechnological use of nonribosomal peptide synthetases[317,318] are being exploited for the construction of cyclic peptides[319,320] that contain non-proteinogenic amino acids.[321,322] The broad specificity profile of the ribosome has also been exploited for the synthesis of nonnatural peptides using *E. coli* that employ a reprogrammed genetic code that enables unnatural amino acids to be incorporated into peptide sequences.[323–325]

6.11.7 Macrolactamization Approaches

The lactam moiety is found as a structural motif within numerous natural products and biologically active compounds, whilst lactams are also useful as versatile synthetic building blocks and as monomers for polymerization.[326–329] Intramolecular *N*-acylation strategies are extremely useful for the synthesis of β-, γ-, and δ-lactams, with intramolecular variants of many

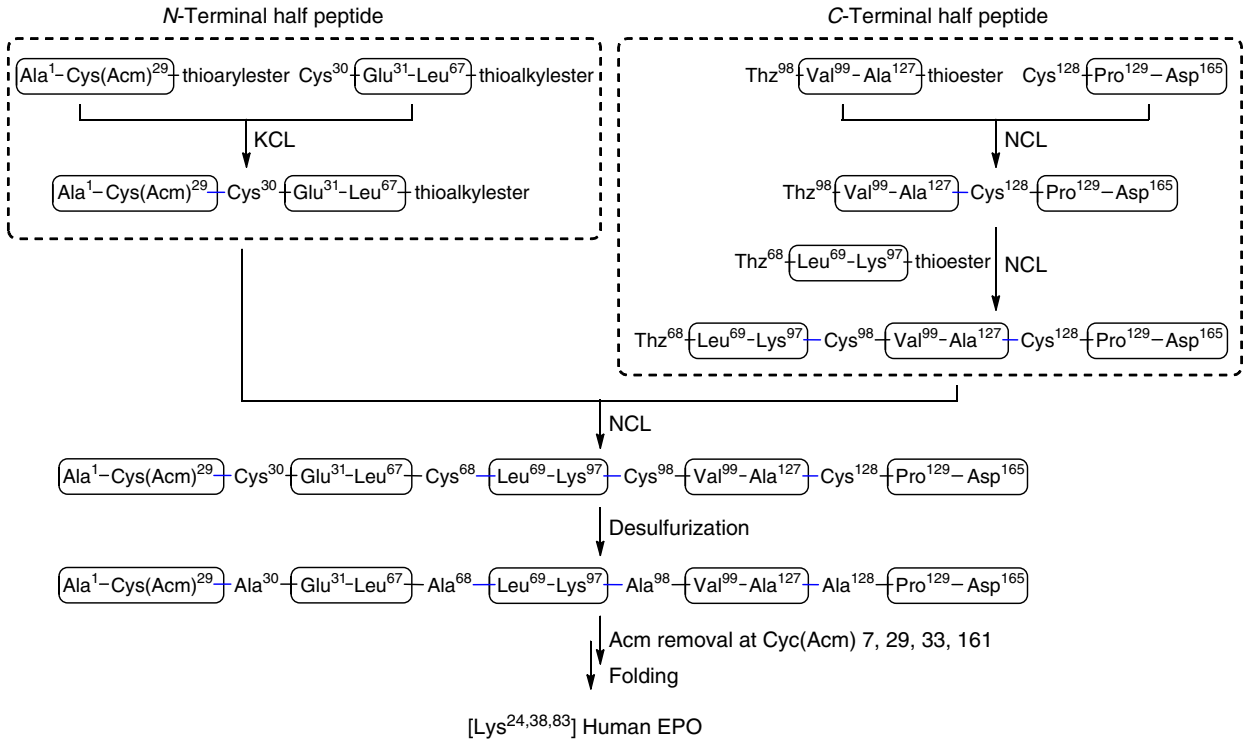


Figure 47 Convergent strategy for the total chemical synthesis of [Lys][24,38,83] human EPO. NCL, native chemical ligation; KCL, kinetically controlled ligation; Acm, acetamidomethyl; Thz, (*R*)-1,3-Thiazolidine-4-carboxylic acid.[303]

intermolecular amide bond-forming processes having been demonstrated. The intramolecular cyclization of β-amino acids into β-lactams is an attractive strategy for the synthesis of highly substituted β-lactam derivatives (Figure 48).[330] β-Amino acids are readily converted into their corresponding β-lactam derivatives through activation of their carboxyl group with a coupling reagent, whereas unactivated β-amino esters have also been cyclized in the presence of a strong base (e.g., LDA or a Grignard reagent).

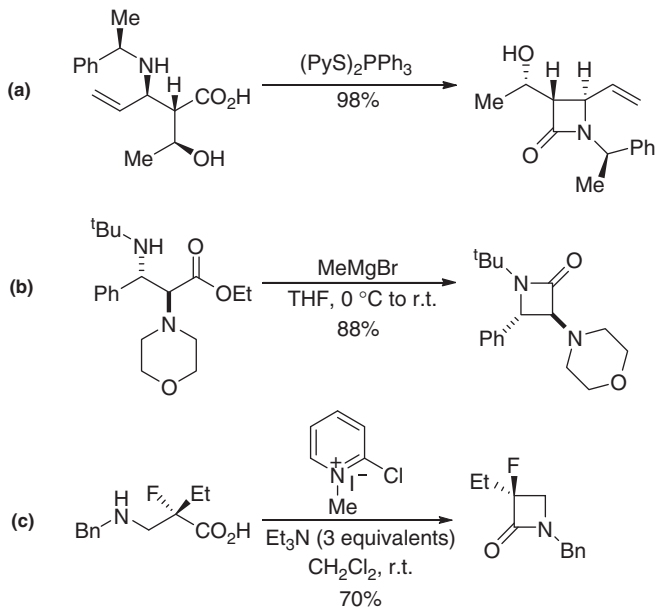


Figure 48 Intramolecular *N*-acylation reactions to afford β-lactams: (a) pyridyl disulfide/triphenylphosphine-mediated cyclization reaction of a β-amino acid derivative for the formal synthesis of thienamycin[331]; (b) synthesis of a protected α-amino β-lactam via cyclization of a magnesium amide onto an ethyl ester[332]; and (c) synthesis of an α-fluoro-β-lactam containing a quaternary stereocenter substituent via activation with a 2-chloro-*N*-methyl-pyridinium coupling agent.[333]

Intramolecular *N*-acylation to form both γ- and δ-lactams is a highly facile process that has been carried out under a wide range of conditions, with cyclization of an amino acid substrate normally requiring activation of the carboxylate group, whereas cyclization of γ- and δ-amino esters to afford their corresponding lactams often occurs spontaneously (Figure 49).

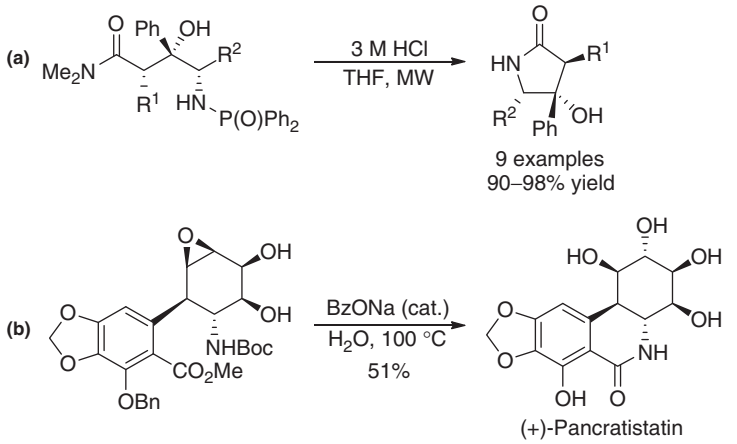


Figure 49 (a) Deprotection–cyclization of a γ-amino acid derivative to afford a highly substituted γ-lactam[334] and (b) tandem epoxide opening/deprotection/lactamization sequence used for the synthesis of (+)-pancratistatin.[335]

Larger ring lactams (>6 members) have a number of biological and material applications,[326] however, they cannot be easily synthesized through simple intramolecular *N*-acylation reactions of their corresponding amino acid derivatives. This is because the spatial arrangement of their amino and carboxylate groups prevents cyclization from occurring in most cases, unless there is a specific conformational bias present that favors lactamization. However, the problem of carrying out medium-ring lactamization cyclization reactions has been addressed indirectly by van Maarseveen and coworkers using an intramolecular Staudinger reaction to facilitate ring closure (Figure 50).[336] First, the amino group of an amino acid is converted into its corresponding azide derivative, before a thio-phosphane auxiliary is introduced as its borane complex to prevent unwanted side reactions and premature cyclization from occurring. Removal of the borane of the resultant intermediate with 1,4-diazabicyclo[2.2.2]octane (DABCO) liberates a phosphane, which then undergoes facile Staudinger ligation to afford carbocyclic and heterocyclic medium-ring lactams in acceptable yields.

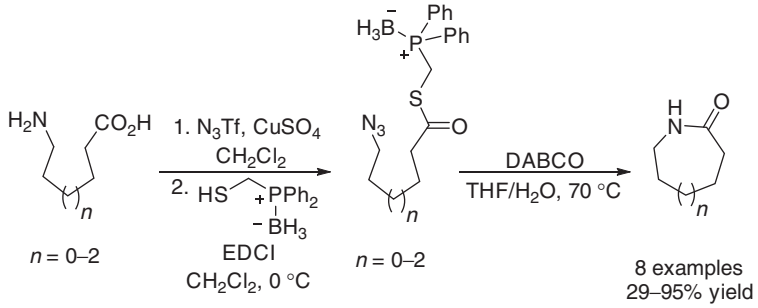


Figure 50 Synthesis of 7–9-membered lactams through Staudinger ligation.[336]

A wide range of intramolecular cyclization approaches have also been developed to enable efficient macrolactamization of linear peptides in solution phase and on solid support, using conventional activating reagents to facilitate ring closure (Figure 51).[337–341] Lactam formation is normally achieved under high dilution using syringe-pump techniques to minimize competing oligomerization pathways, or via side-chain attachment of the cyclization substrate onto a polymer support to achieve 'pseudodilution' conditions. Cyclization of larger peptides (>7 amino acids) generally proceeds in good yields, however, smaller cyclic peptides (<7 amino acids) are normally more difficult to prepare, with cyclization success highly dependent on the nature of their component α-amino acids. Approaches that have been developed to promote intramolecular peptide bond formation include the use of chelating metal ions (e.g., Na^+, Li^+, Ag^+, and Cs^+),[342,343] and the action of isolated thioesterases on polymer-supported peptides.[319] The ability of coordinating transition metals (Ni(II), Cu(II), Pd(II)) to simultaneously dimerize two acylic peptides in a 'head-to-tail' fashion to afford 12–18-membered cyclic peptides is particularly noteworthy.[344] Houghten and coworkers have employed imidazole as a nucleophilic catalyst to mediate the head-to-tail cyclization of peptide thioesters to afford cyclic peptides containing 5–11 amino acids,[345] whereas treatment of peptide thioacids with Sanger's reagent (1-fluoro-2,4-difluorobenzene) has been used for cyclization of penta- and hexapeptides.[346] Yudin and coworkers have developed an

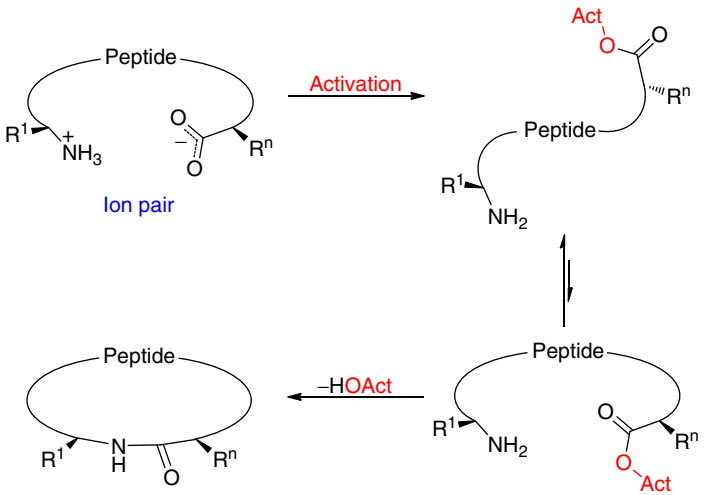


Figure 51 Macrolactamization reaction of an acyclic peptide substrate.[347]

ingenious ligation approach employing *tert*-butylisonitrile and an aziridine aldehyde to facilitate macrocyclization of linear tripeptides to afford cyclic peptides that contain reactive aziridine groups that can be derivatized as required.[347] Many cyclic peptide natural products have been prepared via intramolecular peptide bond-forming reactions using conventional coupling agents (Figure 52), with the full power of 'onium' coupling agents having been demonstrated for the synthesis of the cyclic peptides didemnin A[348] and cyclosporin O (Figure 53).[349] Thiol-based native chemical ligation approaches have also been used to cyclize acyclic peptides in good yield,[350,351] which is particularly useful for mediating peptide bond macrocyclization between the *N*- and *C*-termini of large peptide sequences for the synthesis of circular peptides/proteins (>15 α-amino acids).[352]

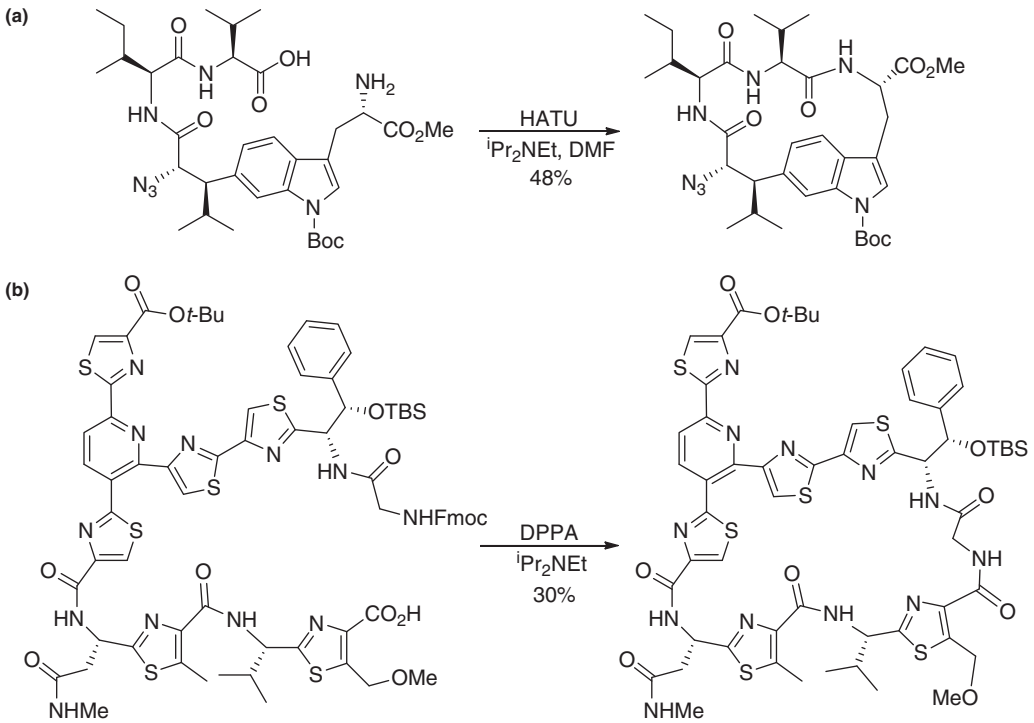


Figure 52 Macrolactamization reactions used for the synthesis of: (a) (–)-stephanotic acid methyl ester[353] and (b) antibiotic GE2270 A.[354]

6.11.8 Nitriles, Thiocarboxylic Acids, Thioesters, Trihaloketones, and α-Keto-acids

The hydrolysis of nitriles to give primary amides has been widely investigated and there are many efficient catalysts for this process,[355] however, there are only a limited number of reports of amidation reactions of nitriles with primary and secondary

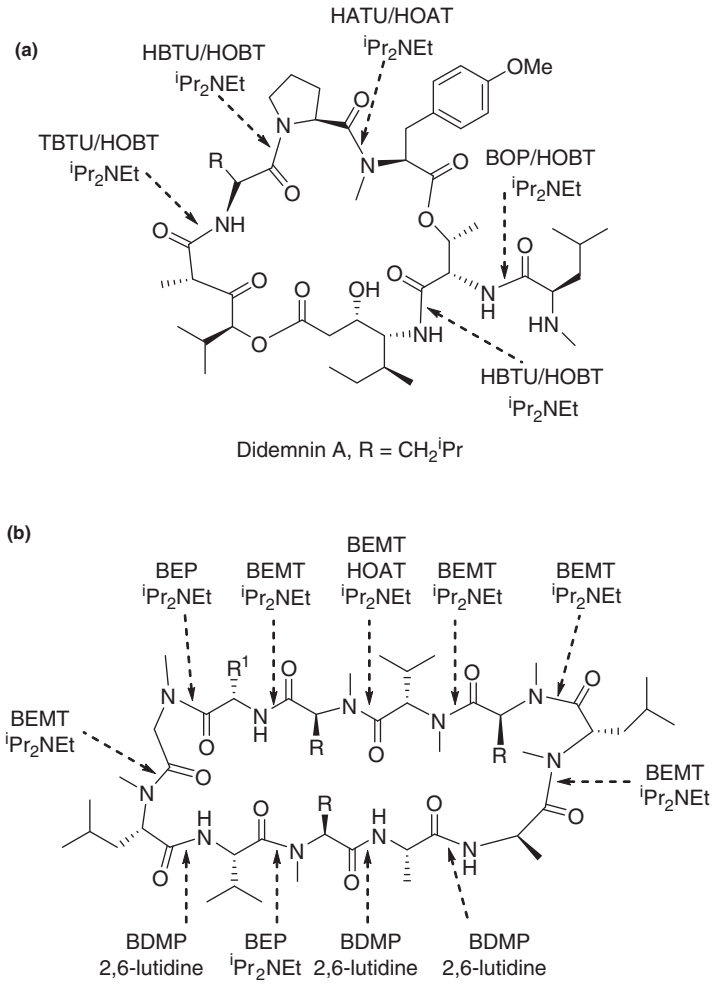


Figure 53 A range of 'onium' coupling reagents employed for preparation of the cyclic peptides: (a) didemnin A[348] and (b) cyclosporin O.[349]

amines. For example, de Vries and coworkers have employed a platinum complex to catalyze reaction of simple nitriles with amines at high temperature (160 °C) to afford secondary and tertiary amides in good yields (Figure 54(a)).[356] Williams and coworkers showed that iron nitrate nonahydrate catalyzes the amidation of nitriles under solvent-free conditions at 125 °C (Figure 54(b)).[357] This method was used to synthesize a number of amides from amines using an excess of nitrile, although the use of anilines and sterically demanding primary amines was not tolerated.

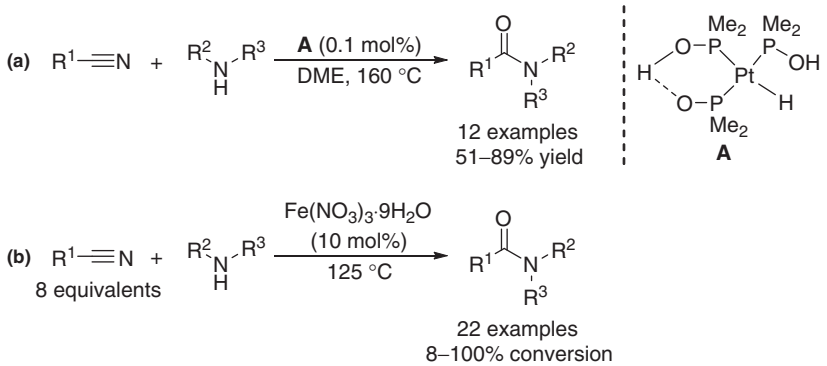


Figure 54 Metal-catalyzed amidation of nitriles with amines using a (a) platinium complex **A**[356] and (b) iron nitrate nonahydrate.[357]

Thioacids have been shown to acylate amines in aqueous solution under oxidative conditions (e.g., $[Fe(CN)_6]^{3+}$), with oxidative dimerization shown to occur to afford dimeric $(RCOS)_2$ species *in situ* that then act as acylating agents to facilitate amide

bond formation.[358] Danishefsky and Wang have reported a useful protocol for the synthesis of peptide bonds from condensation of thioacids and amines that proceeds under extremely mild conditions in the presence of the additive HOBT (**Figure 55(a)**).[359] Treatment of thioacids and amines with $CuSO_4{\cdot}5H_2O$ generates a catalytic copper sulfide species in methanol that mediates rapid and racemization-free peptide bond formation,[360] thus complementing earlier reports of silver(I)-mediated peptide bond-forming reactions in the presence of *N*-hydroxysuccinimide (*vide supra*).[361] Xian and coworkers have shown that *in situ* activation of thioacids with an orgononitrite reagent affords highly reactive *S*-nitrosothio acid intermediates that react with amines to afford amides in good yield (**Figure 55(b)**).[362] Danishefsky and coworkers have employed thioacids in a chemical ligation strategy that employs a sterically hindered isonitrile to generate a reactive intermediate that is intercepted by an amine to afford either secondary or tertiary amide bonds (**Figure 55(c)**).[363] This method was subsequently extended for the chemical ligation of peptides and glycopeptides,[359] and has been used for the macrolactamization of acyclic peptide precursors to afford synthetic seco-cyclosporins.[364] Liebeskind and coworkers reacted thioacids with bis(trimethylsilyl) acetamide (BSA) to afford *O*-silylthionoesters, which rearrange via a silatropic switch mechanism to afford sterically demanding secondary and tertiary amides, and peptides (**Figure 55(d)**).[365] Thioesters are versatile *N*-acylating agents for amino groups in aqueous environments, which have been widely used in native chemical ligation and intein splicing protocols for the synthesis of large peptides and proteins (*vide supra*).[7] Metal-free amidation reactions of peptidyl thiol esters with α-amino acid esters have also been carried out in the presence of BSA for the synthesis of simple *N*-protected peptides with this method, demonstrating good functional group compatibility (**Figure 56(a)**).[366] The enhanced reactivity of thioesters toward amine nucleophiles, relative to their corresponding carboxylate esters has also been exploited to prepare complex amide intermediates for natural product synthesis (**Figure 56(b)**).[367]

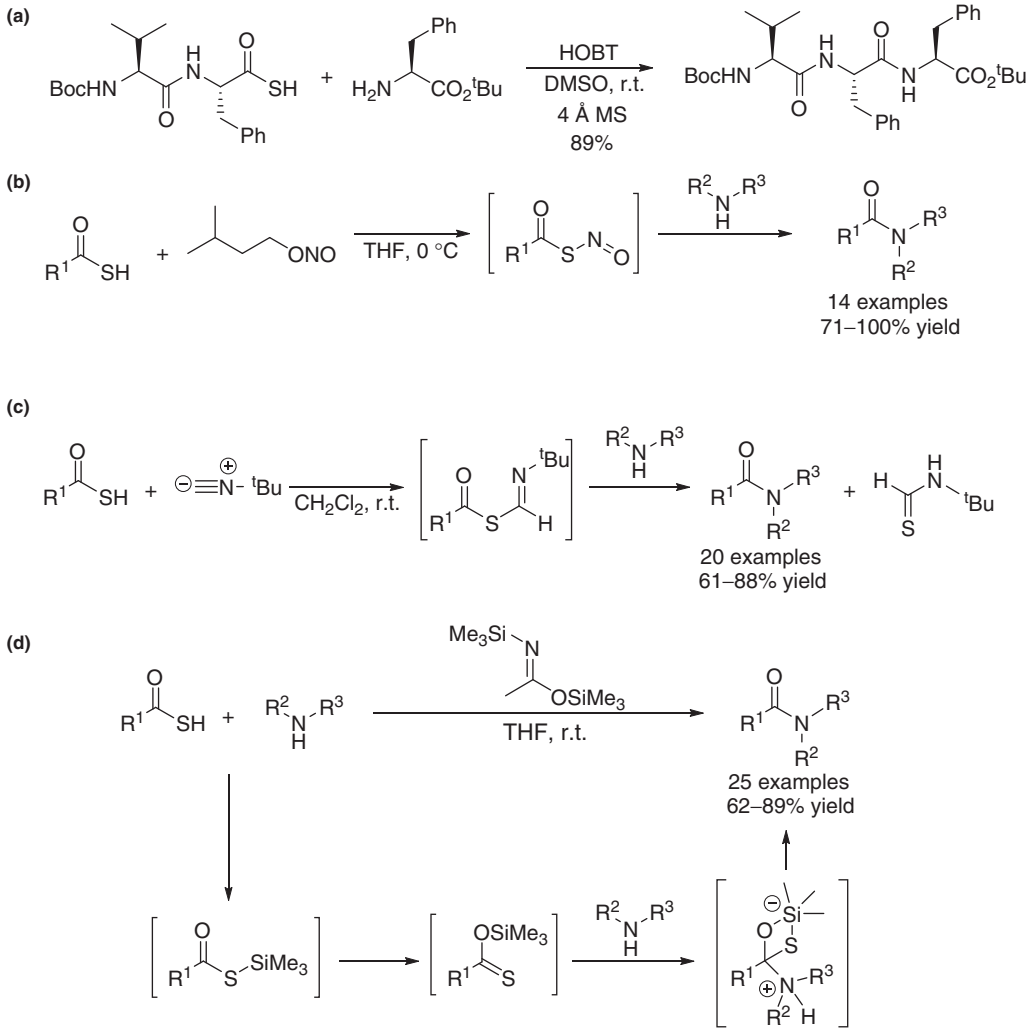


Figure 55 (a) Amide bond formation via direct reaction of a thioacid with an amine[359]; (b) amide bond formation using an organonitrite as a coupling agent[362]; (c) amide bond formation using *tert*-butylisonitrile as a coupling agent[363]; and (d) amide bond formation using BSA as a coupling agent.[365]

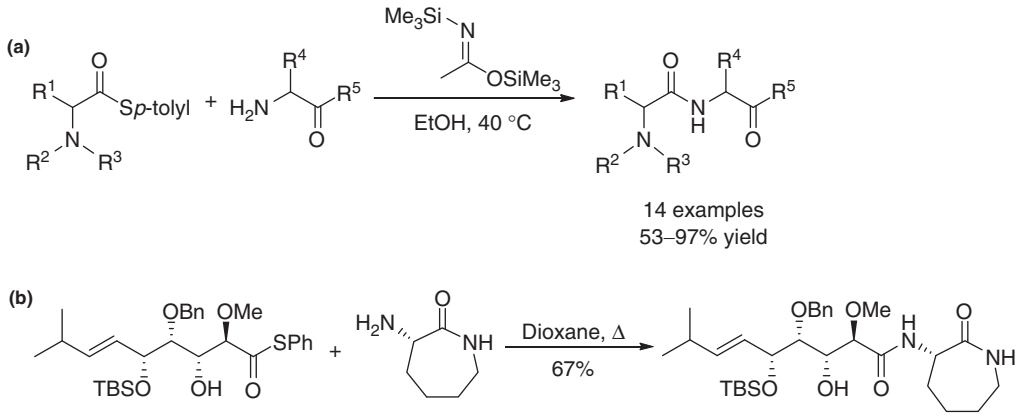


Figure 56 (a) Use of BSA as a coupling agent for thioesters and amines[366] and (b) amide bond formation between a thioester and an amine for the formation of an *N*-acyl-lactam intermediate used in the synthesis of bengamide A.[367]

Trihalomethylketones have been used as *N*-acylating agents, whereby attack of an amine at the ketone functional group affords an unstable hemiaminal intermediate that then decomposes via elimination of a stable trihalomethyl anion to afford an amide bond. For example, Baran et al. used excess trichloroacetylpyrrole to *bis*-acylate, an advanced diamine intermediate for their synthesis of the axenillamines (**Figure 57(a)**).[368] Alternatively, treatment of a range of methyl ketones (or alcohols) with a mixture of iodine and ammonia results in a tandem Lieben–Haller–Bauer reaction that generates triiodomethylketone intermediates *in situ* that react with ammonia to afford primary amides (**Figure 57(b)**).[369]

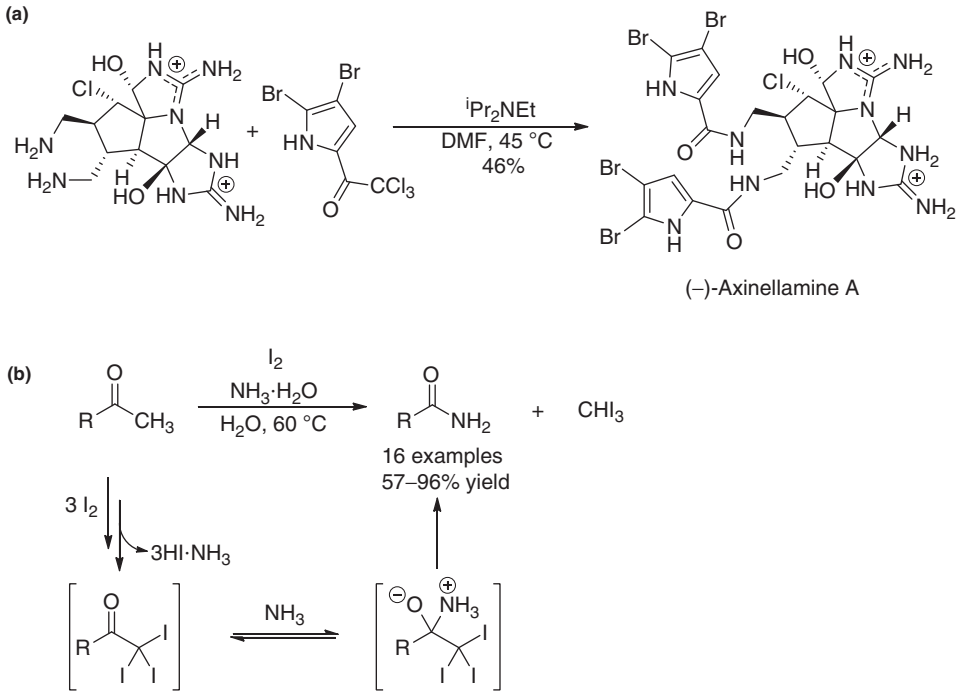


Figure 57 (a) Reaction of a diamine with a trichloroketone for amide bond formation[368] and (b) a 'one-pot' method for the conversion of methyl ketones into primary amides.[369]

Bode et al. have developed a native chemical ligation strategy for amide bond formation using the reaction of α-keto-acids (or isoxazolidines) with hydroxylamines and *N*-methoxyhydroxylamines, which has proven useful for the synthesis of peptides and proteins (*vide infra*) (**Figures 58(a)** and **(b)**).[309] These chemoselective amide bond-forming reactions occur under very mild conditions via stirring the two reagents in a 1:1 water/*tert*-butanol solvent at room temperature to form a range of secondary amides in excellent yield. Mechanistically, the hydroxylamine nucleophile condenses with the α-keto-acid to form an unstable nitrone intermediate, which then decarboxylates to afford an amide bond.[370] The synthetic versatility of this method has recently been extended to the reaction of *N*-acyltrifluoroborate salts with *O*-benzoyl hydroxylamines (**Figure 58(c)**).[371] Arora et al.

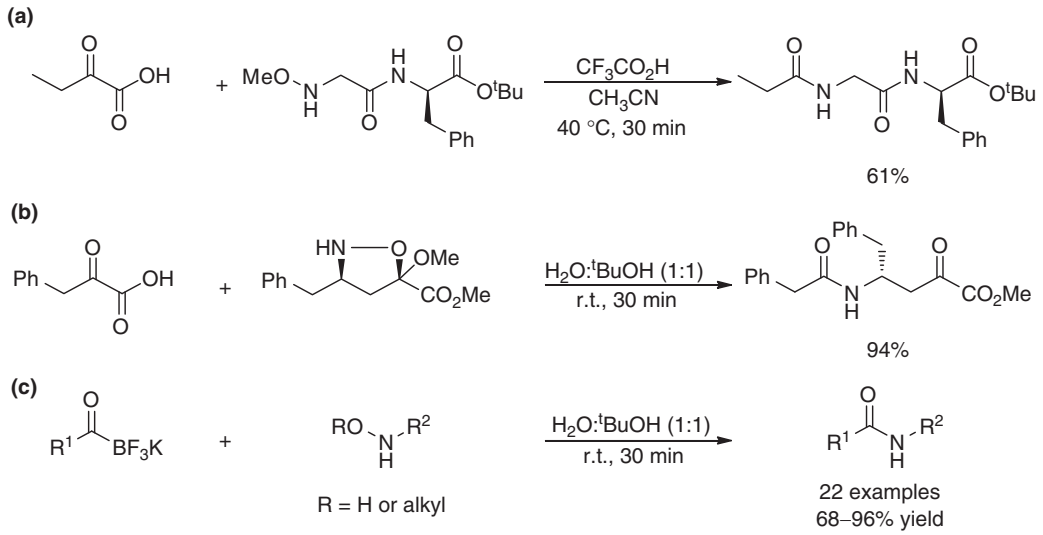


Figure 58 (a) Reaction of an α-keto-acid with an *N*-alkoxyamine to afford an amide bond[309]; (b) reaction of an α-keto-acid with an isoxazolidine for amide bond formation[309]; and (c) ligation of acyltrifluoroborates and hydroxylamine derivatives to afford amides.[371]

have also used *O*-benzoyl hydroxylamines for ligation with α-ketophosphonic acids, chemoselectively forming a number of secondary amides in good yields under mild conditions.[372]

6.11.9 Redox Amidation Reactions

Oxidative amidation of aldehydes and alcohols to afford amides using a catalyst and a stoichiometric oxidant is a rapidly emerging area of research that aims to improve the atom efficiency and practicality of amidation reactions. The use of an aldehyde as a masked *N*-acyl donor that avoids the problems associated with carboxylic acids is an attractive one, with many reactions involving oxidation of hemiaminal intermediates that are generated *in situ* from reaction of an amine with an aldehyde donor (Figure 59(a)). One-pot reactions that employ alcohols as *N*-acylation donors generally involve metal-catalyzed catalytic oxidation into their corresponding aldehydes *in situ*, which then undergo oxidative coupling reactions with an amine to afford an amide bond (Figure 59(b)).

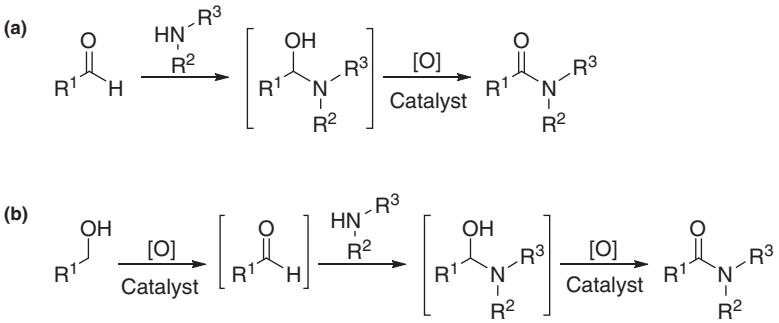


Figure 59 Catalytic oxidative amidation reactions using an aldehyde or an alcohol as masked acyl donors.

A wide range of metal-based catalytic systems have been developed to catalyze oxidative amide bond-forming reactions from aldehydes and amines using a stoichiometric amount of oxidant to facilitate coupling. Efficient metal-based catalytic systems that operate under relatively mild conditions include the use of CuI, $AgIO_3$, and *tert*-butyl hydroperoxide (TBHP),[373] $PdCl_2$–xantophos and hydrogen peroxide under acidic conditions,[374] and the use of heterobimetallic lanthanide/sodium phenoxides.[375] The use of iron(II) sulfate as an inexpensive and effective catalyst for the TBHP-mediated oxidative amidation of aldehydes with amine hydrochloride salts has been shown to be particularly effective, affording a wide range of secondary and tertiary amides under mild conditions (Figure 60).[376]

Palladium-catalyzed one-pot conversion of aldehydes into primary amides in the presence of hydroxylamine hydrochloride and Cs_2CO_3 in the absence of external oxidants has also been reported.[377] Homoleptic lanthanide amido catalysts have been developed for the oxidative coupling of aldehydes and amines that are thought to proceed via Tishchenko-like coupling

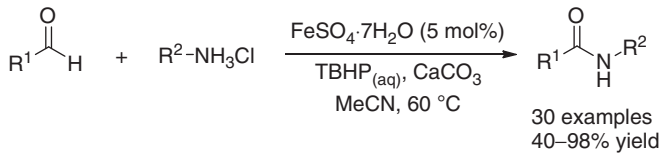


Figure 60 Iron sulfate-catalyzed oxidative amidation reactions using an aldehyde donor.[376]

processes.[378] Williams and coworkers found that treatment of an aldehyde with hydroxylamine and $NiCl_2{\cdot}6H_2O$ in the presence of an amine results in formation of amides in good yield. These reactions were proposed to proceed via nucleophilic attack of an amine at an activated nickel metal complex derived from 2 equivalents of aldoximine, which is generated *in situ* from reaction of the aldehyde and hydroxylamine (Figure 61).[379]

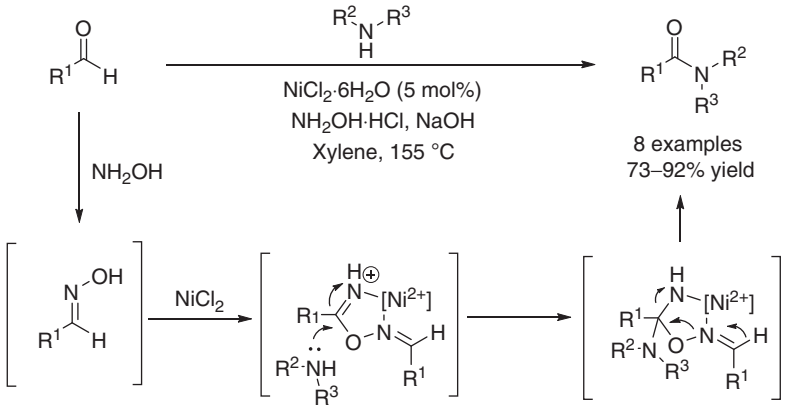


Figure 61 Nickel-catalyzed conversion of aldoximines into amides.[379]

A number of NHC-catalyzed redox acylations of amines using α-functionalized aldehydes have also been reported, using cocatalysts to overcome the problem associated with competing imine formation.[380] Vora and Rovis demonstrated that α,α-dichloroaldehydes, α,β-epoxyaldehydes, α,β-aziridinoaldehydes, and α,β-unsaturated aldehydes could all be used as acyl equivalents for NHC redox catalysis. These reactions employed either HOAT or imidazole as a cocatalyst and were shown to proceed under mild conditions to form a range of functionalized secondary and tertiary amides in good yield (Figure 62(a)).[381] An *N*-acyl azolium species is generated via addition of the NHC catalyst to the aldehyde, which undergoes acyl transfer with the cocatalyst to form an activated carboxylate intermediate that then undergoes nucleophilic attack by the amine. Independently, Bode and Sohn found that electron-deficient formyl cyclopropanes, α-chloroaldehydes, and α,β-unsaturated aldehydes undergo NHC-catalyzed redox acylation with simple primary amines in the presence of imidazole as an additive (Figure 62(b)).[382] Mechanistic studies revealed that an *N*-acyl imidazole species is formed under the reaction conditions which is likely to function as the active *N*-acylating agent. Bode and coworkers subsequently found that α-hydroxyenones could be used as masked *N*-acylating agents for both primary and secondary amines using an NHC and 1,2,4-triazole as a cocatalyst (Figure 62(c)).[383] Addition of NHC to an α-hydroxyenone promotes a retro-benzoin reaction that releases acetone, with the resulting Breslow intermediate then undergoing an imidazole-mediated redox amidation reaction. In 2012, Yamada and coworkers employed an NHC catalyst in conjunction with *N*-chlorosuccinimide (NCS) as an oxidant in the presence of HOBT to form secondary and tertiary amides from unfunctionalized aldehydes.[384] Heterocyclic carbene-catalyzed oxidative amidations of various aldehydes into their corresponding hexafluoroisopropyl esters using 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone as a sacrificial oxidant have also been described, with the resultant active esters then functioning as acyl donors to react further with amines (Figure 62(d)).[385]

Reddy et al. have reported a metal-free variant of the oxidative amidation reactions of aldehydes and alcohols using TBHP that proceeds in the presence of a catalytic amount of KI, forming amides in water in good yield. This method can also be used for the racemization-free *N*-acylation of α-amino-esters in acetonitrile (Figure 63(a)).[386] Aldehyde donors generally afford better yields of amides than alcohols, with these *N*-acylation reactions proposed to proceed via iodine-mediated oxidation of hemiaminal intermediates. A related one-pot synthesis of amides has been described involving treatment of an amine with NCS to afford an *N*-chloroamine that then reacts with an aldehyde in the presence of $Cu(OAc)_2$ and TBHP via a radical-based mechanism (Figure 63(b)).[387] Ekoue-Kovi and Wolf have described an attractive 'catalyst-free' oxidative amination of aldehydes with amines via the simple action of TBHP in acetonitrile at reflux for the synthesis of a range of tertiary amides in good yield (Figure 63(c)).[388]

Wan and coworkers have reported that treatment of aromatic aldehydes with tetrabutylammonium iodide (Bu_4NI) and TBHP in dimethylformamide at 90 °C under oxidative conditions results in formation of a range of tertiary amides in acceptable-to-good yields. They proposed that their oxidative amidation reactions proceed via a free-radical mechanism involving reaction of the

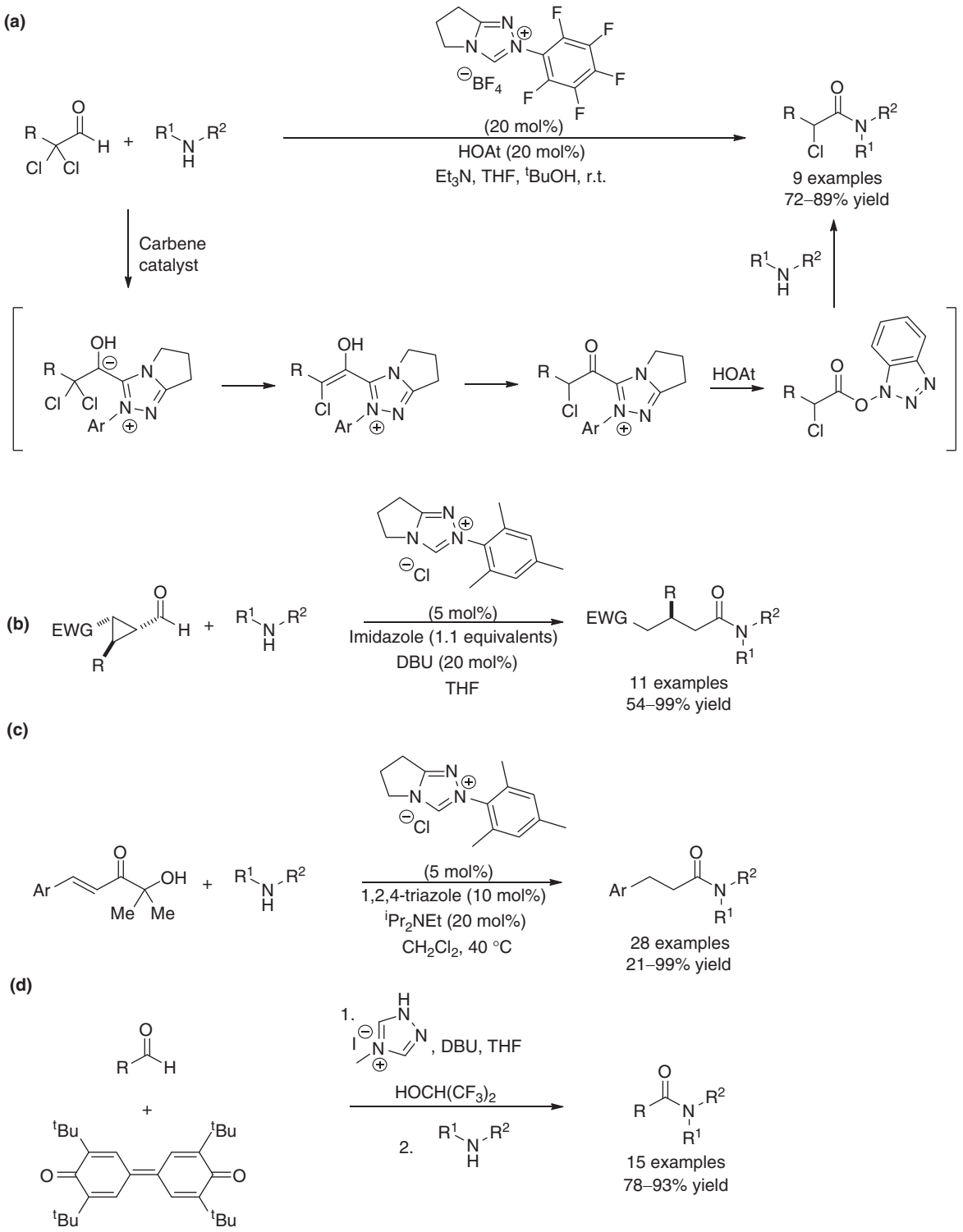


Figure 62 NHC-mediated protocols for the catalytic redox *N*-acylation of amines.[381–385]

aldehyde and dimethylformamide with *tert*-butoxide radicals (or TBHP radicals) to afford acyl radical and aminyl radical species, respectively, which then cross-couple to afford an amide bond (Figure 64(a)). A number of control experiments were carried out to discount alternative oxidative mechanisms, with a range of electron-deficient and electron-rich aromatic and heteroaromatic aldehydes having been coupled to secondary amines to afford tertiary amides in moderate-to-good yields.[389] The potential of this approach has been demonstrated further by Barbas and coworkers, who employed *N*-hydroxysuccinimide in the presence of Bu_4NI

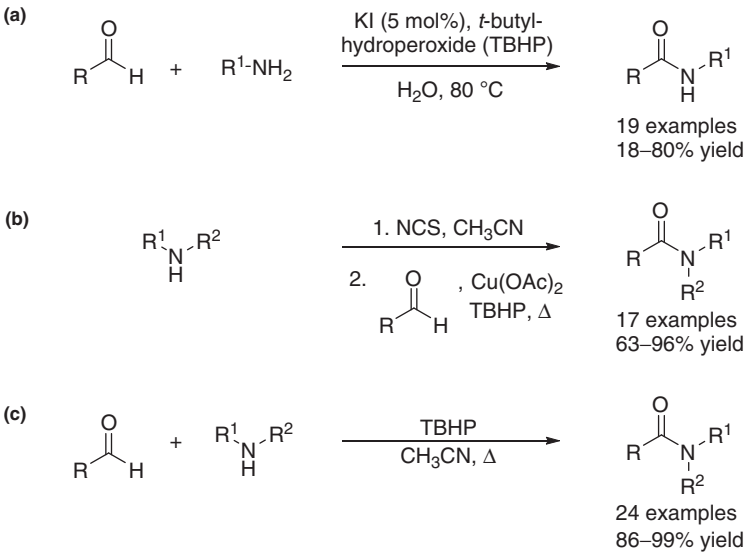


Figure 63 TBHP-mediated protocols for the redox *N*-acylation of amines.[386–388]

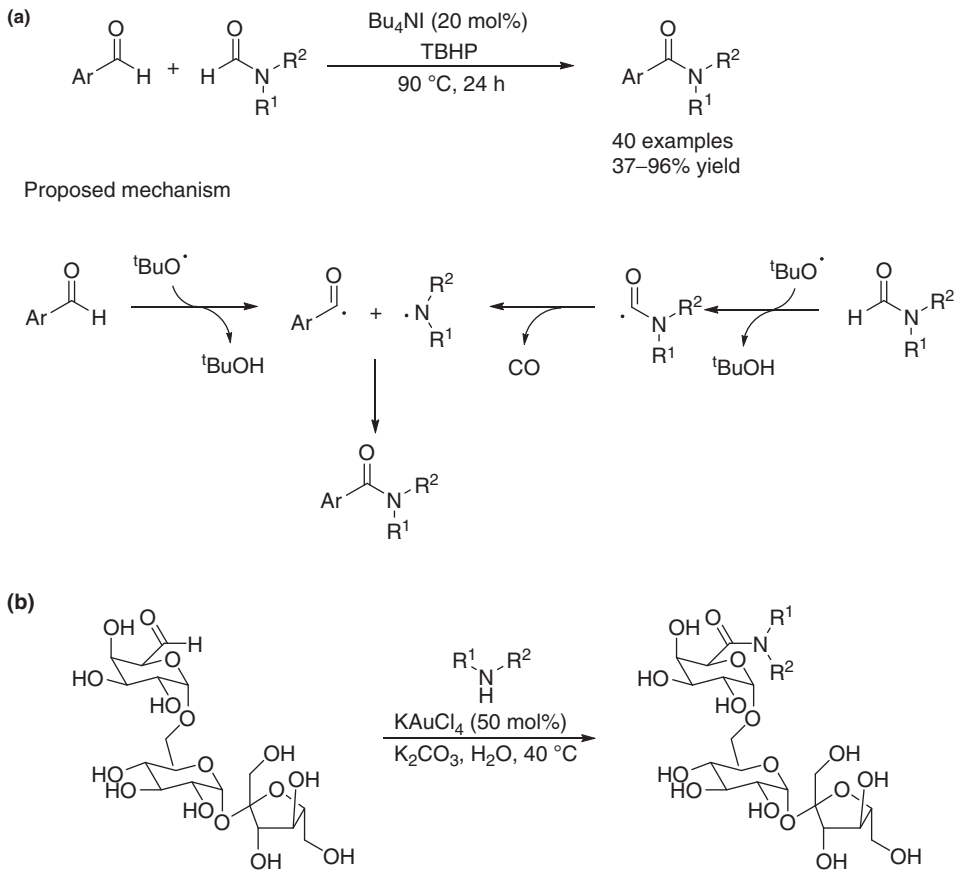


Figure 64 (a) A free radical-mediated protocol for the redox *N*-acylation of amines[389] and (b) *N*-acylation of a complex-unprotected sugar aldehyde.[393]

and TBHP in ethyl acetate to prepare NHS esters *in situ*, which could be intercepted by amines to afford their corresponding amides in good yield.[390] Other protocols that are proposed to proceed via free-radical intermediates using aldehyde donors have also been developed, including catalytic systems such as $FeCl_3$/TBHP,[391] and the use of diacetoxyiodobenzene in the ionic liquid $BMIMBF_4$.[392] An efficient gold(III)-catalyzed amide bond-forming protocol that employs aldehydes and amines in aqueous medium using oxygen as a sacrificial oxidant has also been reported, including the chemoselective *N*-acylation of unprotected

sugar substrates under ambient conditions (Figure 64(b)).[393] Oxone has also been reported to be an effective oxidant for the amidation of aldehydes with anilines to furnish amides in a one-pot process under mechanical milling conditions.[394]

In 2007, Milstein and coworkers reported a significant breakthrough for amide bond formation involving the catalytic amidation of primary amines using alcohols as masked acyl donors, with molecular hydrogen as the only byproduct (Figure 65).[395] A ruthenium–pincer complex (0.1 mol%) catalyzes the reaction without the need for any other additives, with the ruthenium–pincer complex undergoing aromatization/dearomatization during the catalytic cycle. Addition of the alcohol aromatizes the pyridine fragment of the complex, with subsequent β-hydride elimination releasing an aldehyde and forming a *trans*-ruthenium dihydride complex. Elimination of molecular hydrogen regenerates a dearomatized catalyst, which then undergoes a second catalytic cycle to oxidize the hemiaminal, formed from condensation of the aldehyde and amine into the desired amide product. Since this seminal publication, a significant number of other catalytic systems have been reported for the same reaction, with the groups of Madsen[396] and Hong[397] both utilizing NHC–ruthenium complexes in the presence of base, and Williams and coworkers developing a catalytic system using commercially available $[Ru(p\text{-cymene})Cl_2]_2$, dppb, Cs_2CO_3, and a sacrificial ketone as hydrogen acceptor.[398] In all cases, these reactions proceeded well for the formation of secondary amides using alcohols and primary amines, with cyclic secondary amines generally affording their corresponding tertiary amides in lower yields. Phosphine-free[399] NHC ruthenium-based catalytic systems have also been shown to display good activity for these types of oxidative amidation processes.[400] Other heterogeneous metal-based systems for the amidation of amines using alcohol donors include heterogeneous alumina-supported silver clusters,[401] and gold, gold/iron, nickel, or cobalt nanoparticles.[402] Related ruthenium-based catalytic systems have also been developed that employ alcohols for the *N*-acylation of azides as masked amine donors.[403]

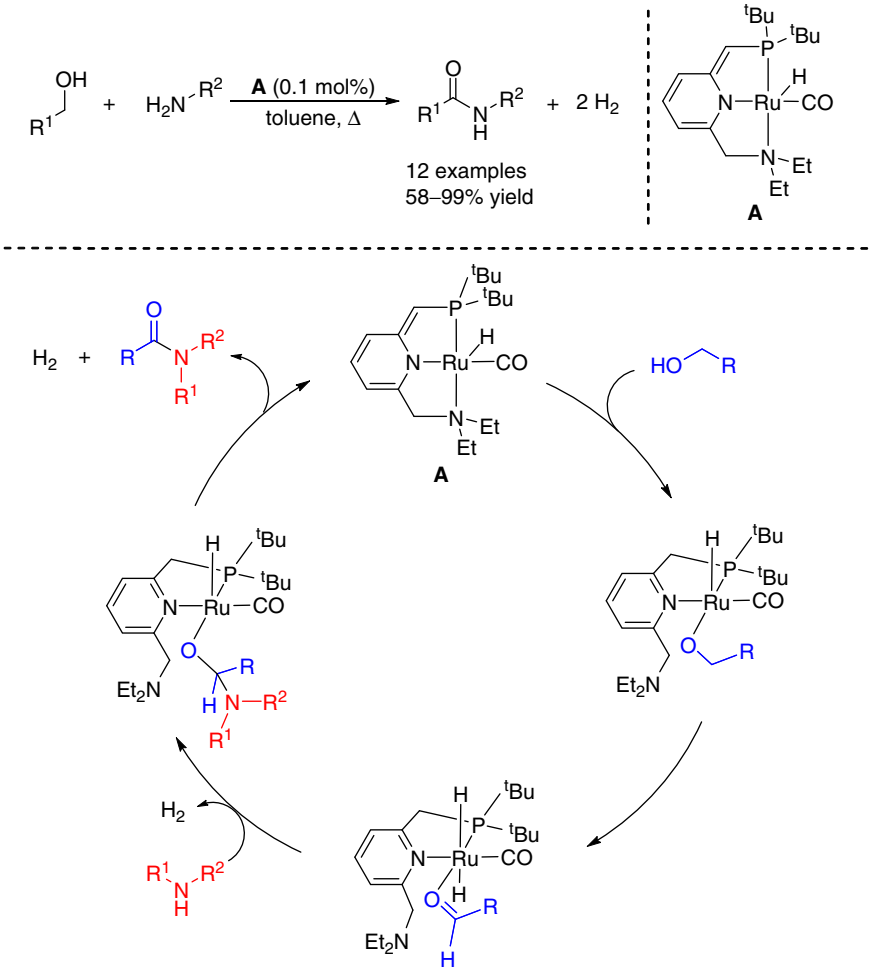


Figure 65 Oxidative amidation of alcohols catalyzed by a Ru–pincer complex.[395]

Grützmacher and coworkers found that primary amides could be synthesized from alcohols under mild conditions using 0.1 mol% of a rhodium amido complex and ammonia as the nitrogen source.[404] Mizuno and coworkers demonstrated that heterogeneous $Ru(OH)_x/Al_2O_3$ catalyzes the oxidation of primary amines into primary amides in the presence of water and air at

high temperature (130–160 °C).[405] They have also shown that manganese oxide-based octahedral molecular sieves (KMn_8O_{16}; OMS-2) are effective heterogeneous catalysts for oxidative primary amide bond formation, with the catalytic cycle thought to proceed through both hemiaminal and nitrile intermediates,[406] whereas Shimizu et al. have employed γ-alumina-supported silver clusters as recyclable catalysts.[407] Che and coworkers have synthesized secondary amides from amines using alkynes as masked acyl sources under oxidative conditions that employed a manganese porphyrin catalyst and Oxone® as oxidant (Figure 66).[408] This method was applied to the synthesis of small peptide sequences, with the *N*-terminal α-amino group being chemoselectively acylated in the presence of unprotected amino acid side chains. Related methodology involving the uncatalyzed reaction of ω-bromo-alkynes with secondary amines in water at 120 °C has also been shown to afford a range of tertiary amides in good yield.[409]

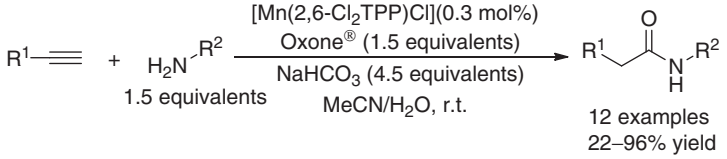


Figure 66 Oxidative amide synthesis from alkynes. 2,6-Cl_2TPP, *meso*-tetrakis(2,6-dichlorophenyl)porphyrin.[408]

In 2010, Johnston and coworkers reported a conceptually new method of oxidative amide bond formation from amines and α-bromo nitroalkanes using an equivalent of *N*-iodosuccinimide (NIS) and K_2CO_3 in water.[410] Mechanistic studies suggest umpolung reactivity of the reagents, with *N*-iodosuccinimide activating the amine toward nucleophilic attack of the nitronate fragment followed by hydrolysis of the resulting intermediate to afford an amide. This method was used to prepare secondary amides in good yields from primary alkyl amines and various α-bromo nitroalkanes containing other synthetically useful functional groups (Figure 67(a)). Impressively, this method has also been used to prepare dipeptides from an enantiopure α-aryl glycine derivative and esters of all 20 naturally occurring α-amino acids (Figure 67(b)) without epimerization of their potentially labile α-stereocenters.

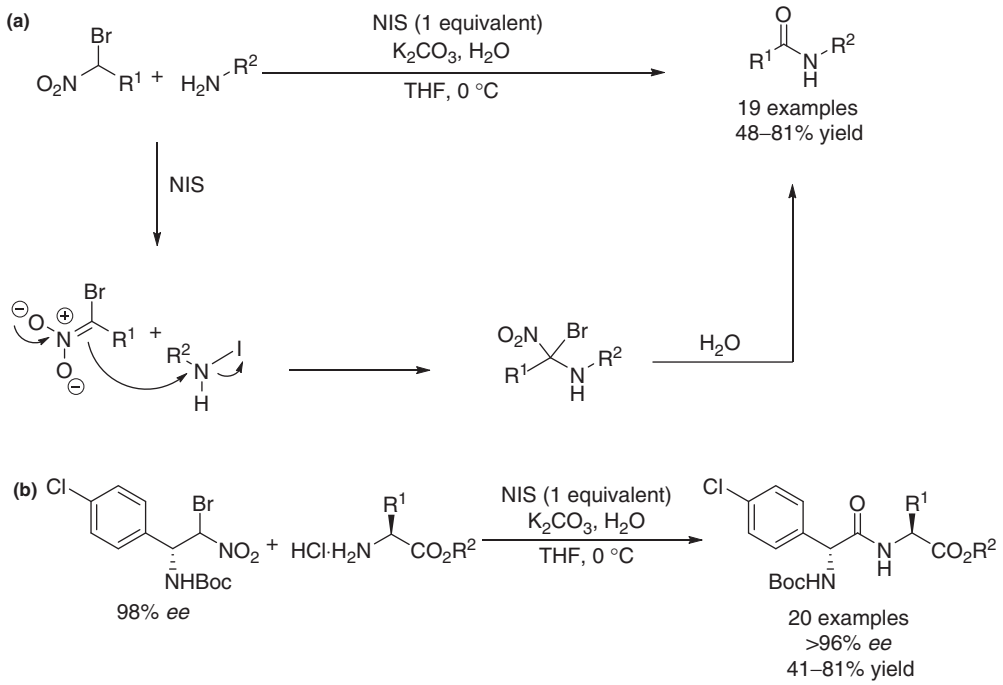


Figure 67 Oxidative amidation using α-bromo nitroalkanes as acyl equivalents.[410]

6.11.10 *N*-Acylation Reactions for the Kinetic Resolution of (*rac*)-Amines

The inherent nucleophilicity and reactivity of amines makes the development of stereoselective *N*-acylation protocols for the kinetic resolution of (*rac*)-amines a challenging goal.[73,411–413] One strategy is to use an enantiopure stoichiometric acylating reagents that contains a stereodirecting group contained within its leaving group. This approach ideally involves selective reaction of one

enantiomer of a (*rac*)-amine with 0.5 equivalent of a chiral acylating reagent to afford a chiral amide product in high enantiomeric excess (*ee*), which is then separated from unreacted amine of the opposite configuration. A number of chiral *N*-acylating agents have been developed that proceed with excellent selectivity (*s*) values, with selected reagents affording amines in good *ee* at approximately 50% conversion.[411] For example, Ie and Fu demonstrated that 0.5 equivalent of a *N*-acetyl chiral planar ferrocene DMAP reagent could be used for the *N*-acylation of a series of arylalkylamines to afford chiral amides in up to 78% *ee*. Increasing the ratio of (*rac*)-amine to catalyst to 8:1 enabled stereoeselective amide bond formation in up to 91% *ee* (**Figure 68 (a)**).[414] A series of enantiopure 3-(diacylamino)-quinazolin-4(3*H*)-ones containing an N–N axis of chirality have also been used for the kinetic resolution of (*rac*)-amines, with the chemo- and stereoselectivity of these protocols determined by the conformation of the acyl groups of the chiral acylating reagent. For example, kinetic resolution of a (*rac*)-α-amino ester derivative using 0.5 equivalent of chiral reagent resulted in selective benzoylation of its (*S*)-enantiomer to afford amide in 94% *ee* and unreacted (*R*)-amine in 92% *ee* (**Figure 68(b)**).[415] Mioskowski and coworkers have employed a chiral disulfonamide as a reagent for the enantioselective *N*-acylation of a range of (*rac*)-amines in DMPU at −20 °C, affording chiral amides with good levels of stereocontrol (**Figure 68(c)**).[416] A chiral benzimidazole has been used for the enantioselective benzoylation of a series of α-amino esters in THF at −10 °C, affording (*R*)-*N*-benzoylamides in 89–91% *ee* at approximately 50% conversion (**Figure 68(d)**).[417] Bode and coworkers have recently employed a recyclable polymer-supported acylating reagent derived from chiral hydroxamic acids for the kinetic resolution of a wide range of *N*-heterocycles that contain secondary amino groups in good-to-excellent *ee* (**Figure 68(e)**).[418]

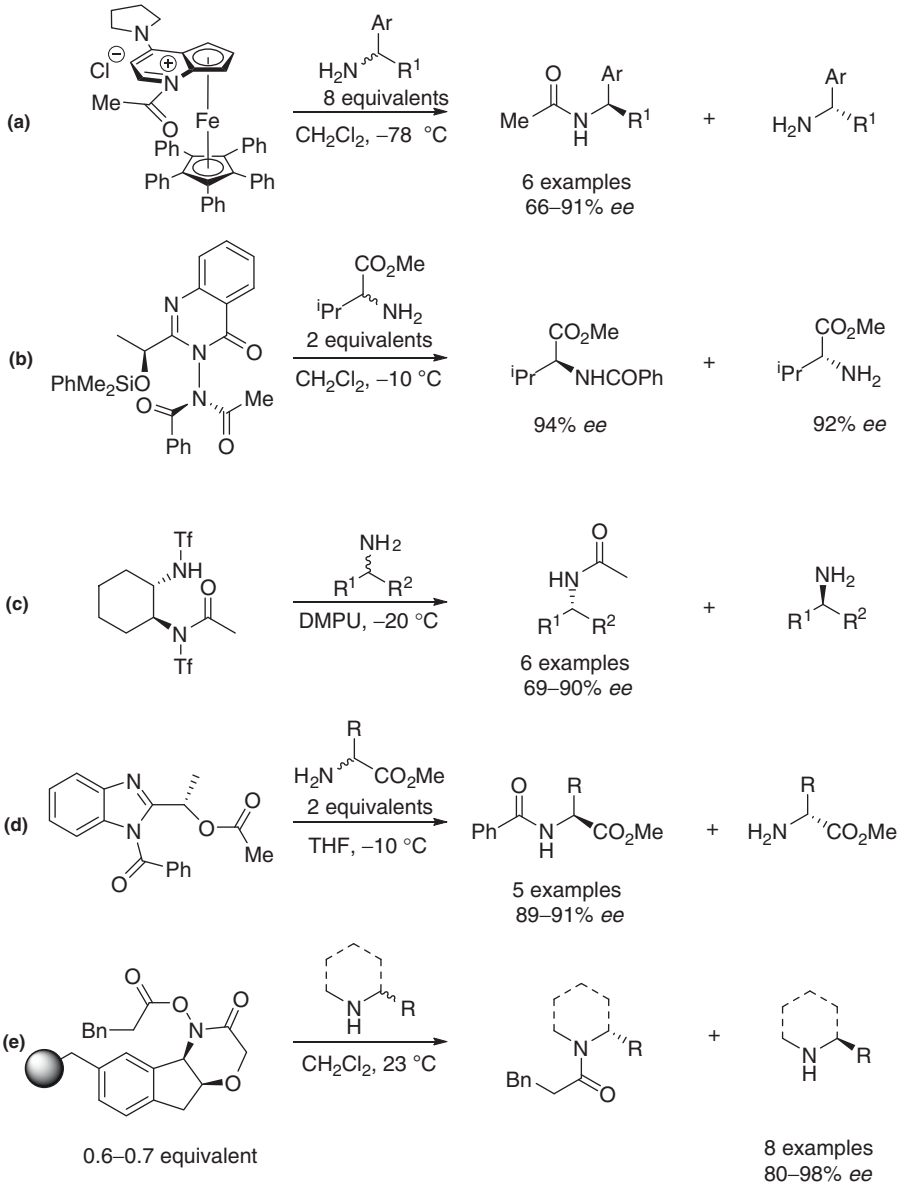


Figure 68 Kinetic resolution of (*rac*)-amines using acylating agents that contain a stereodirecting leaving group.[414–418]

Kinetic resolution strategies involving stereoselective derivatization of a (*rac*)-amine with chiral acylating agents that afford diastereomeric amide products have also been developed. An impressive example of this approach involves reaction of (*rac*)-secondary amines with (*S*)-naproxen chloride, resulting in the selective *N*-acylation of its (*S*)-enantiomer to afford an (*S,S*)-amide in 87% *de* (Figure 69).[419]

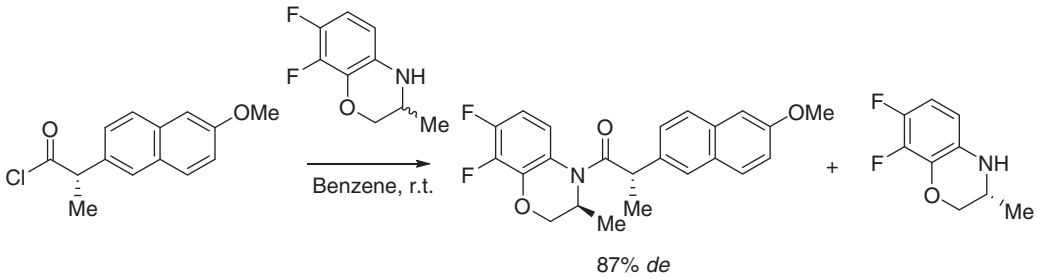


Figure 69 Kinetic resolution of a (*rac*)-amine using a chiral acylating agent to afford a diastereomeric amide.[419]

The development of catalytic processes for the kinetic resolution of (*rac*)-amines using achiral *N*-acylating reagents remains a significant challenge. Consequently, for good levels of enantiocontrol to be obtained, it is essential that the acyl donor reacts with the catalyst at a significantly faster rate than its direct reaction with the amine substrate. For example, Fu and coworkers found that an *O*-acylated azlactone reacts more rapidly with chiral ferrocene DMAP analogs than it does with aromatic amines, allowing for effective kinetic resolution with *s* values between 11 and 27 for a range of aromatic secondary amines (Figure 70).[420] This method was subsequently extended to the kinetic resolution of indolines using a variant of the chiral ferrocene DMAP catalyst in the presence of lithium bromide and 18-crown-6.[421]

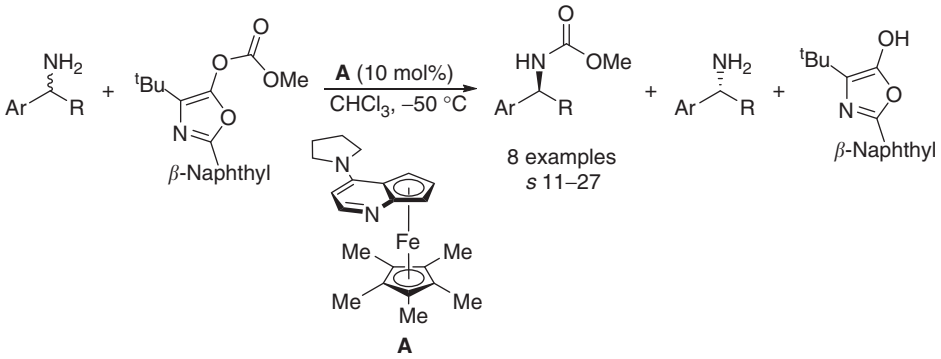


Figure 70 Kinetic resolution of (*rac*)-amines using chiral ferrocene DMAP catalyst and *O*-acyl-azlactone.[420]

Seidel and coworkers have reported a dual organocatalytic approach for the kinetic resolution of arylalkylamines that relies on a combination of DMAP, a chiral thiourea catalyst and 0.5 equivalent of benzoic anhydride for stereocontrol (Figure 71). A number of enantiomerically enriched amides were formed in up to 49% conversion with high *s* factors obtained in most cases. It is proposed that asymmetric induction occurs via formation of an activated chiral ion pair *in situ*, in which the chiral thiourea catalyst is complexed to the benzoate counterion of an *N*-acylpyridinium catalytic intermediate.[422]

Bode and coworkers have used an achiral NHC catalyst and a chiral hydroxamic acid cocatalyst for the kinetic resolution of (*rac*)-secondary amines using a hydroxyenone as an acyl donor. It is proposed that the achiral carbene catalyst serves to transform hydroxyenone into an acyl azolium intermediate via a retro-benzoin reaction followed by an internal redox reaction. The acyl azolium intermediate then transfers its acyl unit to the hydroxamic acid cocatalyst to afford an *O*-acyl intermediate that is responsible for inducing stereocontrol in these *N*-acylation reactions. This novel catalytic protocol proved successful for the kinetic resolution of a range of racemic piperidines, piperazines, morpholines, tetrahydroisoquinolines, and azepanes with synthetically useful *s* values ranging 8–74 (Figure 72).[423]

There have been numerous reports of lipases employing esters and carbonates as acyl donors for the enantioselective *N*-acylation of ammonia, primary and secondary amines, anilines, and hydroxylamines.[253] Ester ammonolysis and aminolysis reactions are essentially irreversible in organic or ionic liquid solvents under anhydrous conditions that serve to minimize unwanted hydrolysis of enzyme–acyl intermediates.[424] The activity of immobilized lipases (adsorbed or covalently bonded) in organic solvents is generally greater than for free enzyme, as the enzyme is protected from deactivation and more uniformly dispersed over the surface of the solid support. A wide range of enzymes are commercially available as potential biocatalysts for the kinetic resolution of (*rac*)-amines, with many protocols having been devised that afford chiral amides (and/or their unreacted antipodal amine) in very high *ee* (Figure 73).[253,425] CAL-B has proven to be particularly useful for the synthesis of a wide

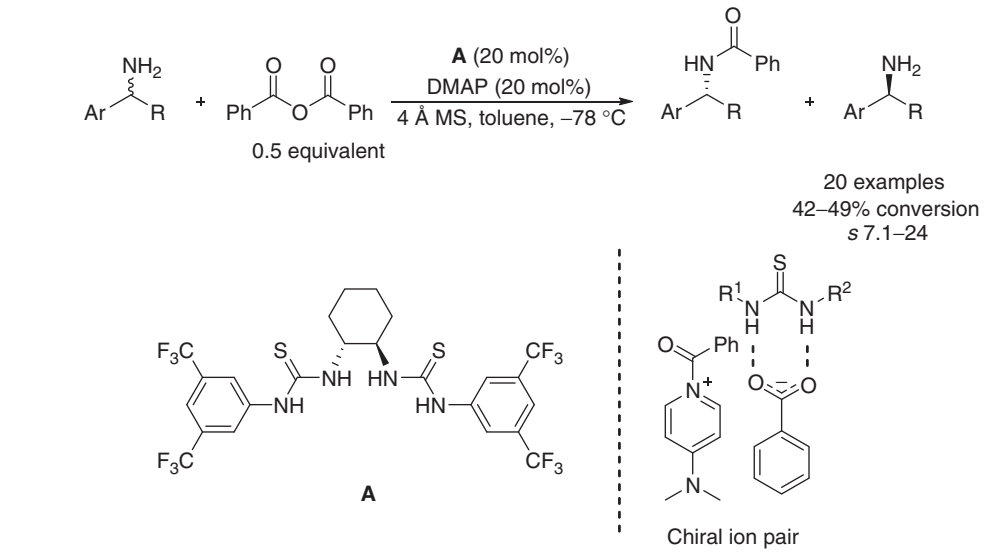


Figure 71 Tandem organocatalytic *N*-acylation of (*rac*)-secondary amines using DMAP and a chiral thiourea catalyst.[422]

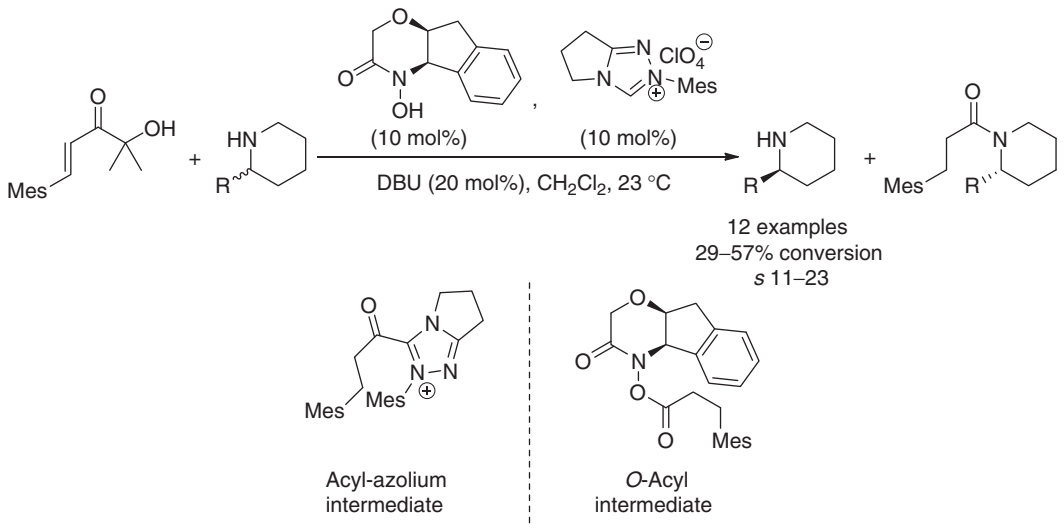


Figure 72 Tandem organocatalytic *N*-acylation of (*rac*)-secondary cyclic amines using hydroxyenone as an acyl donor.[423]

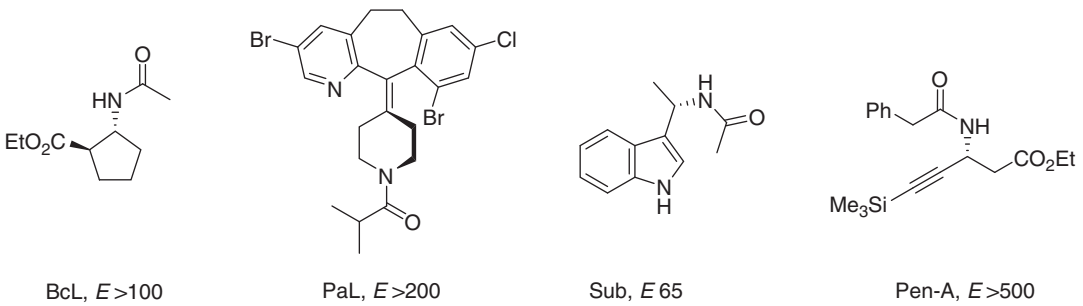


Figure 73 A representative range of chiral amides prepared in high enantioselectivity via lipase-catalyzed *N*-acylation of their parent (*rac*)-amines using esters or acids as acyl donors.[429–432] BcL, *Burkholderia cepacia* lipase; PaL, *Pseudomonas aeruginosa* lipase; Sub, subtilisin; Pen A, penicillin acylase.

range of amides, whose *N*-acylation reactions often proceed with excellent levels of enantioselectivity (Figures 74(a) and (b)).[426] Desymmetrization reactions of prochiral diesters have also been carried out using a CAL-B-mediated reaction of dimethyl 3-substituted-glutarates with ammonia or amines to give (*S*)-amido esters in 90–99% *ee* (Figure 74(c)).[427,428]

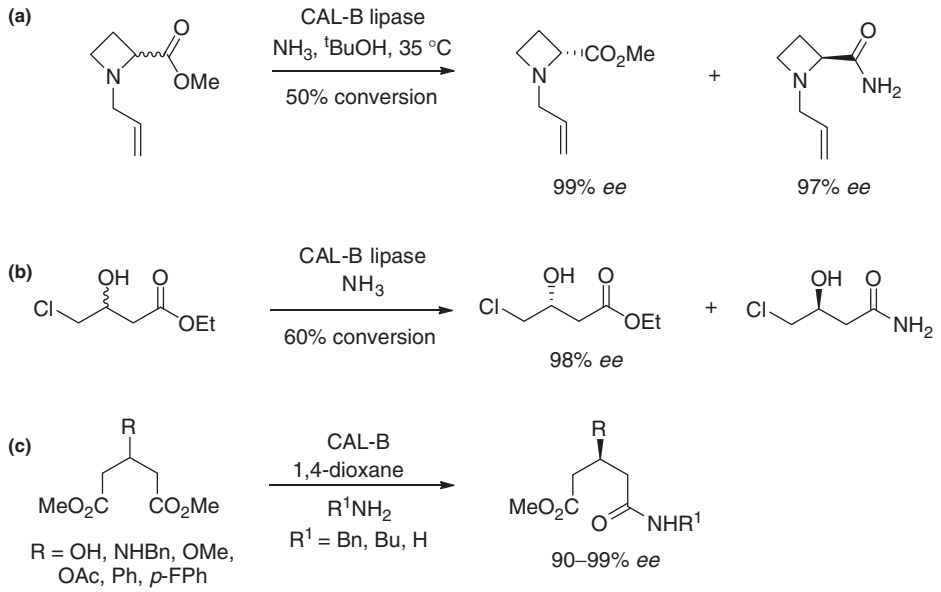


Figure 74 CAL-B used as a biocatalyst for (a) kinetic resolution of *N*-alkyl-azetidine esters[433]; (b) kinetic resolution of ω-chloro-β-hydroxy esters[434]; and (c) desymmetrization of glutarate diesters.[435]

Sheldon and coworkers have employed CAL-B as a biocatalyst for the enantioselective *N*-acylation of amines using heteroatom acyl donors to afford chiral amides, which were then separated from their antipodal amines. The amide products could subsequently be deprotected using Novozyme-435 (immobilized CAL-B) in water to afford the enantiomeric amines (Figure 75(a)).[436] Gotor and coworkers have reported an intriguing protocol that employs CAL-B for the 'one-pot' *N*-acylation of a (*rac*)-amine with a (*rac*)-ester to simultaneously afford a chiral alcohol and chiral amide in good *ee*.[437] For example, CAL-B catalyzed *N*-acylation of

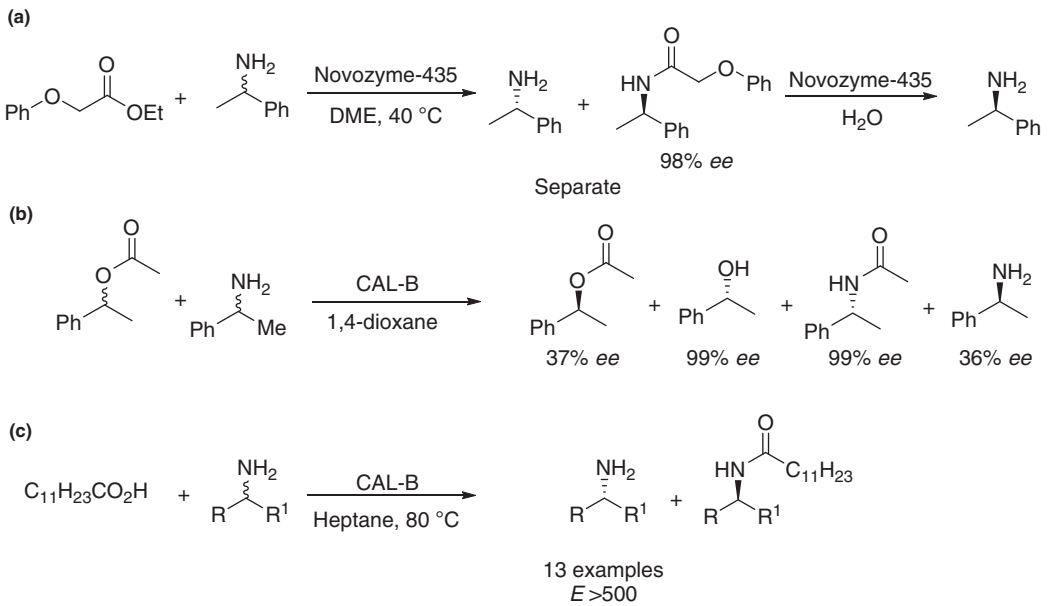


Figure 75 (a) Acylation/deacylation strategy using CAL-B for the production of both enantiomers of a chiral amine[436]; (b) enzymatic 'one-pot' protocol for the simultaneous kinetic resolution of a (*rac*)-alcohol using a (*rac*)-amine[437]; and (c) CAL-B-mediated enantioselective *N*-acylation reactions of chiral amines using long-chain fatty acids as acyl donors.[438]

(*rac*)-1-phenylethylamine with (*rac*)-1-phenylethylacetate enabling isolation of both (*S*)-1-phenylethanol and (*R*)-*N*-(1-phenylethyl)acetamide in 99% *ee* at 27% conversion (Figure 75(b)). The thermostability of CAL-B has also been exploited for the kinetic resolution of chiral primary amines at 80 °C with excellent enantioselectivity in a relatively short period of time (Figure 75(c)).[438]

Effective protocols for the dynamic kinetic resolution (DKR) of amines have been developed by coupling an enantioselective lipase-catalyzed acylation reaction with a transition metal-catalyzed racemization event.[439] Paetzold and Bäckvall reported that treatment of a range of (*rac*)-amines with a ruthenium catalyst and *Candida antartica* lipase resulted in DKR occurring to afford a range of chiral amides in high yields and high *ee*. In these type of DKR processes, the transition metal catalyst racemizes the amine stereocenter via reversible formation of an imine species, with the lipase then selecting one of the amine enantiomers for *N*-acylation (Figure 76(a)).[440] For example, a DKR protocol was devised using a Shvo-like ruthenium catalyst to racemize a primary amine (via an imine intermediate), with CAL-B being used to selectively acylate one of the enantiomers with isopropyl acetate to afford a chiral amide as an intermediate for the synthesis of serotonin reuptake inhibitor norsertraline (Figure 76(b)).[441] Park and coworkers have shown that a recyclable palladium nanocatalyst can be used for the DKR of 11 primary amines using Novozym-435 as an acylation catalyst in 85–99% yield and 97–99% *ee*.[442] Iridium catalysts have been recommended as particularly effective racemization catalysts for carrying out DKR reactions using lipases and mixed carbonate acyl donors on a large scale.[443]

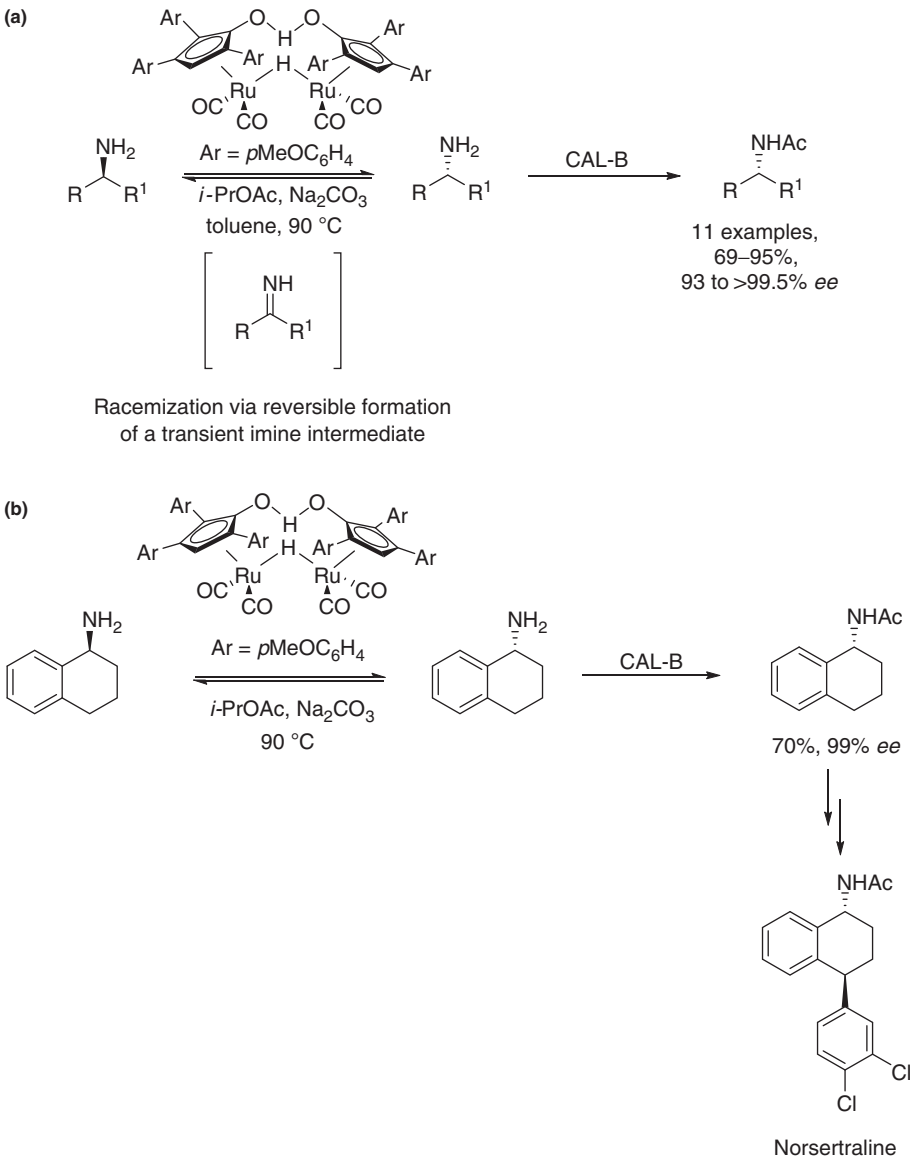


Figure 76 DKR for the synthesis of chiral amides and the drug Norsertraline.[440,441]

A range of other ingenious methods have also been developed to racemize amine substrates *in situ* to enable DKR protocols for the synthesis of chiral amines. Ammonolysis of D,L-phenylglycine methyl ester catalyzed by Novozyme 435 at 40 °C in *tert*-butyl alcohol in combination with pyridoxal-catalyzed racemization (via Schiff base formation) of the unconverted ester at −20 °C gave D-phenylglycine amide with 88% *ee* at 85% conversion.[444] Alcalase has also been used for the DKR of (*rac*)-α-amino esters in 2-methyl-2-propanol/water (19:l) using pyridoxal-5-phosphate as a catalyst for racemization *in situ*.[445] Effective protocols for the DKR of (*rac*)-*N*-Boc-amino acid thioesters using DBU as a base for racemization in the presence of alcalase have proven effective for the synthesis of chiral amides.[446] An alternative racemization process using alkylsulfanyl radicals for reversible hydrogen atom abstraction at the stereogenic center of a chiral amine has also been developed for use in DKR protocols using CAL-B (**Figure 77(a)**).[447] Ramstrom and coworkers have shown that a lipase from *Burkholderia cepacia* can be used for the DKR of α-amino-nitriles to afford chiral amides, with racemization occurring via a lipase-mediated reversible *retro*-Strecker/Strecker reaction (**Figure 77(b)**).[448] *Candida cylindracea* encapsulated in porous silica glass has been employed as a recyclable biocatalyst to catalyze the DKR of (*rac*)-ethyl 2-chloropropionate via an *N*-acylation strategy using polymer-supported triphenylphosphonium chloride to facilitate racemization (**Figure 77(c)**).[449]

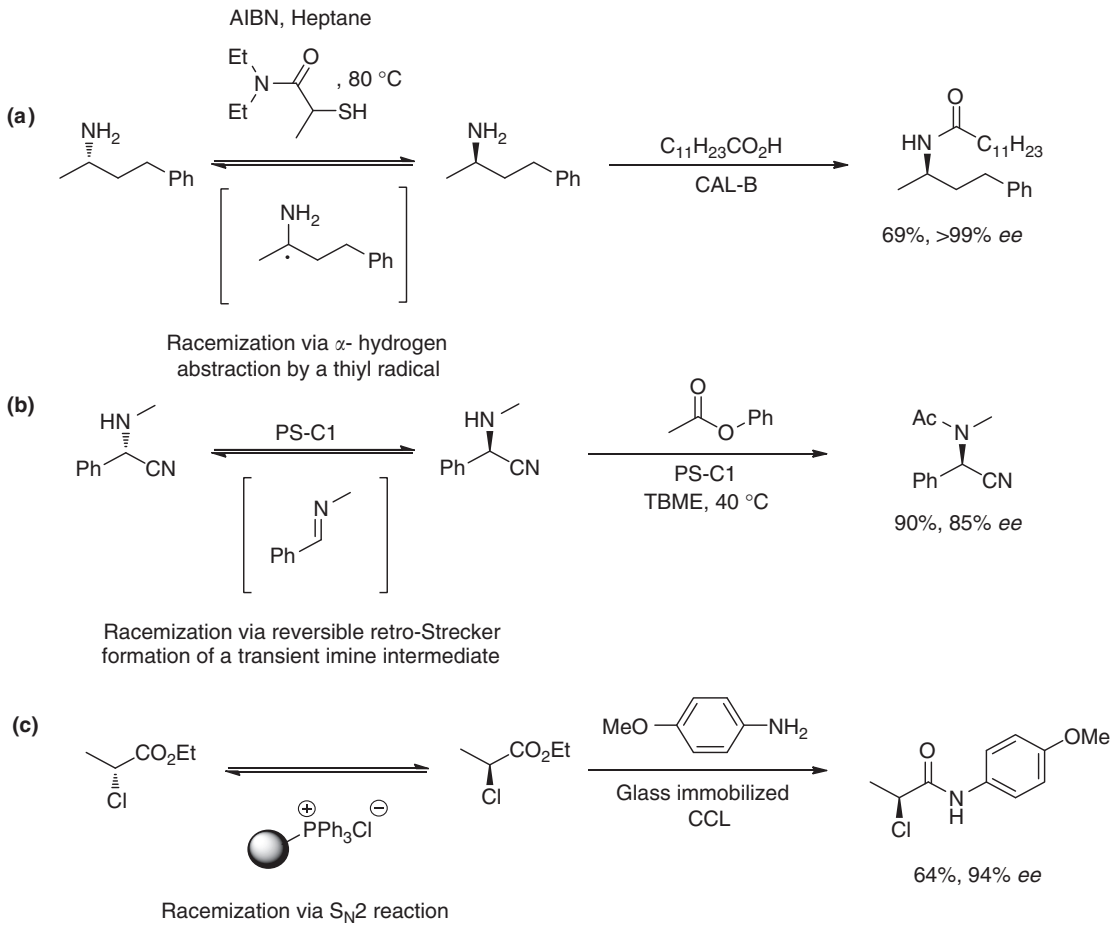


Figure 77 A range of different racemization strategies used for the DKR of (*rac*)-amines using lipases to catalyze enantioselective *N*-acylation reactions. CCL, *Candida cyclindracea* lipase; PS-C1, *Burkholderia cepacia* lipase.[447–449]

6.11.11 Conclusion

The importance of the amide bond has resulted in the development of many excellent synthetic protocols for their formation through *N*-acylation reactions of amines. Problems relating to chemo- and regioselectivity, weakly nucleophilic amines, sterically demanding substrates, and racemization of adjacent stereocenters have been overcome in many cases, with modern techniques allowing for the synthesis of structurally complex amides/peptides that would have been impossible just 20 years ago. No area highlights these achievements better than the synthesis of peptides, where the synthesis of polypeptides containing anywhere from

2–100 amino acid residues is now routinely possible on a multigram scale. However, it is interesting to note that although many techniques exist for carrying out *N*-acylation reactions, the vast majority of small-molecule amides that are synthesized on an industrial scale make use of acyl chlorides, acid anhydrides, or carboxylic acids as acyl donors, with relatively few large-scale protocols employing coupling reagents or catalytic protocols for amide bond-forming reactions. The chemical syntheses of peptides on scale relies on the use of coupling reagents that generate stoichiometric amounts of byproducts using protocols that are both expensive and wasteful. Therefore, the development of catalytic and cost-effective *N*-acylation reactions that are racemization-free and significantly reduce the amount of waste generated is the biggest immediate challenge in this field. Consequently, much current research is focused on the development of catalytic procedures for the formation of small-molecule amides from amines and simple, unactivated carboxylate derivatives, although many of these methods currently require harsh reaction conditions and have limited substrate scopes. Therefore, further developments in catalytic *N*-acylation reactions are required to enable amide bond-forming reactions to occur under milder conditions at lower catalyst loadings, with improved scope for *N*-acylation of challenging electron-deficient amines and sterically demanding secondary amines. Finally, the identification of robust catalytic amide bond-forming method that was capable of using unprotected α-amino acids as monomers for the rapid racemization-free synthesis of polypeptides would represent a major breakthrough in chemical synthesis that would have the potential to make major contributions to the many areas of science that rely on access to peptide-derived materials.

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6.12 Inorganic Acid Derivatives

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Glossary

Phosphitylation This process entails the formation of a phosphite triester from P(III) reagents. Further oxidation to the P(V) form constitutes a phosphorylation process.

Phosphonates Entities in which one of the P–O bonds of a phosphate is replaced with a P–C bond [C-$PO(OR)_2$] are called phosphonates and if replaced with a P–H bond [H-$PO(OR)_2$] it forms an *H*-phosphonate.

Phosphoramidates The monoamides of phosphate diesters or monoesters are classified as phosphoramidates, having the general formula $(RO)_2P(O)NR_2$.

Phosphoramidites The monoamides of phosphite diesters are classified as phosphoramidites, having the general formula $(RO)_2PNR_2$.

Phosphorochloridites/Phosphorochloridates/Phosphorodichloridates Organic phosphorus compounds with the general formula $(RO)_2PCl$ are classified as phosphorochloridites, the oxidized versions phosphorochloridate have the formula $(RO)_2P(O)Cl$, and the dichloride species $(RO)P(O)Cl_2$ are phosphorodichloridates.

Phosphorodiamidates The diamides of phosphate diesters or monoesters are classified as phosphoradimidates, having the general formula $(NR_2)_2P(O)OR$.

Pyrophosphates Pyrophosphates are anhydrides of phosphoric acid or phosphoric esters; they could also be the anions, that is, salts of esters of pyrophosphoric acid.

6.12.1 Introduction

Organophosphates $[(RO)_3P(=O)]$ and their derivatives are ubiquitous in nature and possess unique physical and chemical properties that contribute to their fundamental importance in a number of essential biological processes, including cellular signal transduction,[1] lipid metabolism,[2] and transmembrane signaling (Figure 1).[3,4] In two seminal reviews, Westheimer (1987) and Blackburn (2010) provide keen insight into the significance of phosphates and highlight an extensive list of their assorted functions in biological systems.[5] In light of this impressive biochemical utility, it comes as no surprise that the isolation, characterization, and synthesis of phosphate-based small molecules – and their carbon-, nitrogen-, and sulfur-containing analogs – have continued to hold the interest of the scientific community for over a century.[6]

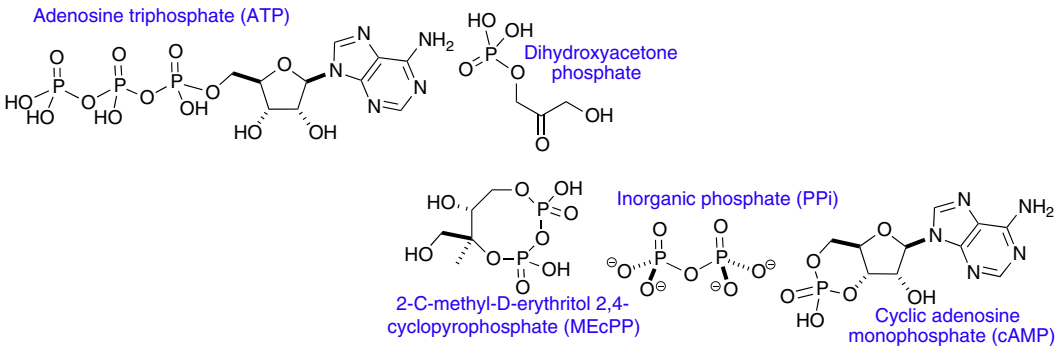


Figure 1 Phosphate-containing biomolecules.

A variety of phosphate-containing natural products have shown great potential as medicinal leads and small molecule affecters of biological systems, three of which – the potent and selective phosphatase inhibitors fostriecin[7] and calyculin A,[8] as well as the cytotoxic marine natural product enigmazole A[9] – are shown below (Figure 2). In addition to those naturally occurring, a number of synthetic phosphate esters have shown to be medicinally important as Food and Drug Administration (FDA)-approved drugs and prodrugs, including cyanocobalamin and hydroxocobalamin (synthetic forms of vitamin B_{12} for the treatment of vitamin B_{12} deficiency), fosphenytoin (a prodrug for the treatment of epileptic seizures), amifostine (a drug used to reduce the undesired side effects of certain chemotherapy agents and radiation treatment), fludarabine (a purine analog, used as a chemotherapy drug in the treatment of B-cell chronic lymphocytic leukemia), and fosamprenavir (a prodrug of the protease inhibitor and antiretroviral drug amprenavir) (Figure 2).[10] Taken collectively, the rich history of globally important and pharmaceutically relevant phosphate-containing bioactive compounds has justified their selection as valuable synthetic targets.

From the seminal discovery of elemental phosphorus in 1669[11] to recent advances in the synthesis and uses of its derivatives, the illustrious and storied history of phosphates and the corresponding phosphorylation methods developed to access them continue to be useful entities in the arsenal of the organic toolbox. Although several aspects of phosphate chemistry resemble that of their carbon-based counterparts, a number of notable differences set phosphates apart in terms of utility and reactivity. Among many salient features, the unique leaving group properties of tetravalent phosphates have enabled the development of several asymmetric and stereospecific phosphate displacement reactions. This leaving group ability, governed by the pK_a profile[12] of phosphoric acid and its derivatives, and its notable tunability result in remarkable and seemingly unconventional reactivity patterns that can allow phosphates to act as both leaving groups and temporary protecting groups. In addition, the complex and varied nature of substitution at phosphorus provides opportunities for orthogonal and selective cleavage profiles using acid, base, or reductive conditions (Figure 3).[13]

The aforementioned properties of phosphates have served as a cornerstone for their application in a number of important synthetic processes, ranging from oligonucleotide assembly to phosphate tether-mediated natural product construction.[14] In particular, the ambiphilic nature of phosphates – their ability to act as both electrophiles/latent leaving groups, as well as tetravalent nucleophiles – have helped established their roles as synthetically useful intermediates in asymmetric, allylic substitution,[15] reductive cyclizations,[16] phosphate extension reactions/iodolactonization,[17] transition metal-mediated cross-coupling reactions,[18] and temporary tether-mediated, one-pot sequential processes (Figure 4).[19] Phosphates can also be used as a source of organolithium compounds,[20] as precursors for alkenes via dehydration,[21] and as stereodirecting groups in oligosaccharide synthesis.[22] As a whole, this impressive biological and synthetic utility has driven efforts toward the development of new phosphorylation reactions that allow for the efficient introduction of phosphorus to a diverse set of substrates.

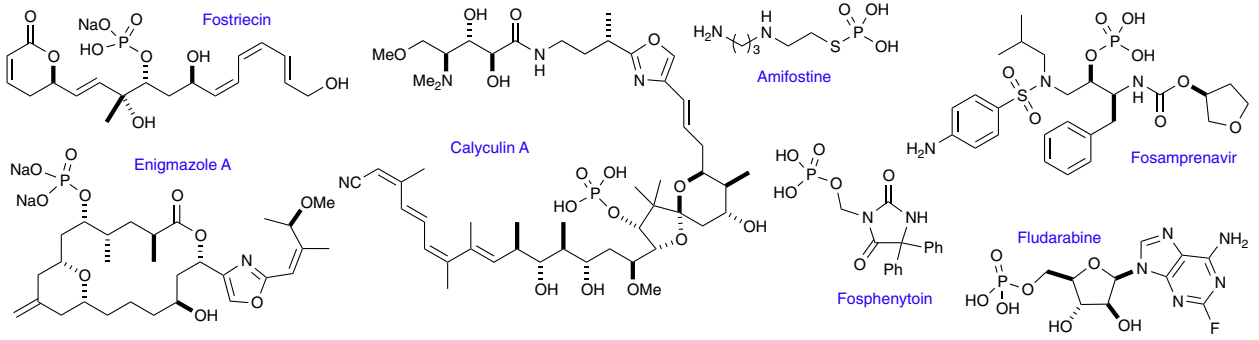


Figure 2 Natural and synthetic bioactive phosphate compounds, phosphate drugs, and prodrugs.

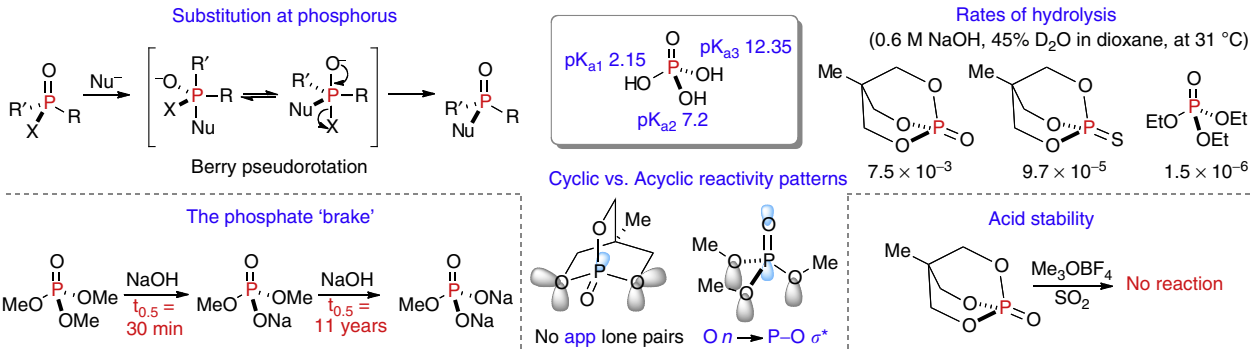


Figure 3 Characteristic reactivity of phosphates.

In this regard, the role of phosphorus(V) [P(V)] and phosphorus(III) [P(III)] phosphorylating reagents will be the main focus of this chapter. Examples from recent literature involving direct phosphorylation of protic substances (alcohols, amines, and thiols), as well as other newly developed methods of organophosphate synthesis, will be discussed in the context of the fundamentals of phosphorylation presented in the previous chapter which shares the same name.[23] It should be noted that there are a large number of phosphorus-containing organic molecules, in particular those that contain C–P bonds, that is, phosphonates, which have been reviewed extensively[24] and, as such, will not be covered in this chapter (outside the area of generating phosphates). In addition, new advances in oligonucleotide synthesis will be summarized, with a special emphasis on phosphorothiolate/phosphorothioate oligonucleotides, and recently reported methods of novel phosphorylation strategies, including both catalytic and asymmetric versions, as well as their use in natural product synthesis, will also be presented. Finally, as several reviews devoted to the removal of phosphate protecting groups have been reported,[25] and as deprotection strategies will be discussed in nearly every section of this chapter, only a small portion of this work will be delegated to the analysis of recent advancements with respect to this field.

6.12.2 Phosphorus(V) Reagents

Phosphorus(V) reagents containing a single phosphoryl P–O bond are versatile reagents for phosphorylation of nucleophiles, due to a number of significant attributes including the stability of P(V) reagents to oxidation, the electrophilicity of the hard phosphorus center (which can be readily attenuated), and the ability of P(V) reagents to facilitate di- and tripodal coupling manifolds. In general, phosphoryl-containing P(V) compounds have a stable tetrahedral geometry, and the formation of a thermodynamically stable P–O bond[26] is often the driving force for most phosphorylation reactions involving free alcohols.

At the foundation of P(V) chemistry lie mechanistic aspects of substitution at phosphorus, and although a detailed mechanistic discussion of this substitution is not the purpose of this review, it is noteworthy to highlight certain features of this process, as a number of the syntheses of phosphates involve phosphorus transfer (**Figure 5**). Though the exact details of this process have, historically, been under debate,[27] it is generally accepted that the nucleophilic substitution at phosphorus – with P(III)- and P(V)-substrates – proceeds through a pentavalent transition state, whose nature and lifetime primarily depends upon the steric and electronic qualities of the attacking nucleophile and groups attached to the central phosphorus, as well as the corresponding reaction conditions (solvation, pH, and the presence of activators in solution).[28]

Although a large number of nucleophilic substitutions at phosphorus occur with inversion of *P*-stereochemistry, a simple in-line S_N2-type displacement cannot be applied generally to all phosphorus-based systems as the exact mechanism of phosphate substitution is relatively complex (**Figure 5**).[28d,f–h,k] Geometries of nucleophilic attack and leaving group elimination, as well as substituent stereoelectronic effects and pseudorotation in the transition state, have important implications for phosphorus stereochemistry (retention vs. inversion), as well as chemo- and regioselective product formation, for different *P*-containing systems.[28]

6.12.2.1 Halophosphates

Since the discovery of phosphoric acid by Scheele in the 1770s,[11] a number of chlorinated phosphate reagents (halophosphates) have emerged as efficient tools for phosphorylation. In 1810, John Davy generated phosphorus pentachloride (PCl_5) by burning phosphorus in the presence of chlorine gas, and phosphorus oxychloride ($POCl_3$) was first reported by Charles Wurtz in the late 1840s.[11] Centuries after these seminal discoveries, $POCl_3$ and its mono- and dichloridate analogs (phosphorochloridates and phosphorodichloridates, respectively; see Section 6.12.2.1.3) represent the most conventional means of generating phosphate mono-, di-, and triesters from the corresponding alcohols. The incorporation of acid scavengers (primarily nonnucleophilic bases such as trialkylamines, pyridine and 4-dimethylaminopyridine (DMAP), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), activators (including imidazole and its derivatives), and catalysts (both Lewis-acid and transition-metal in nature) helps to compensate

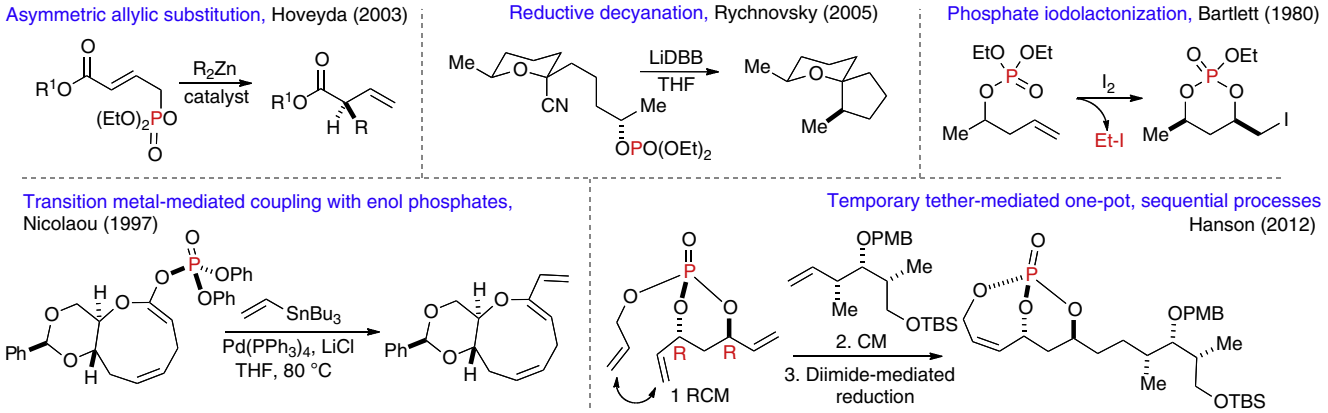


Figure 4 Synthetic utility of phosphates.

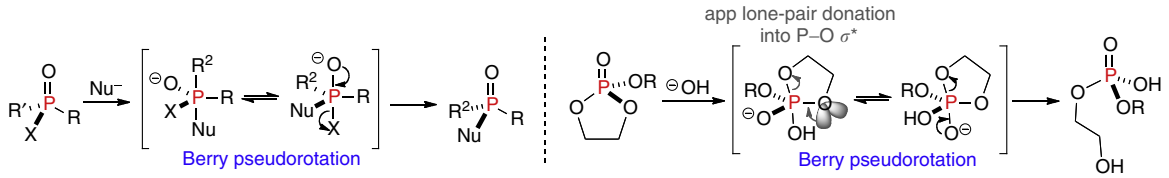


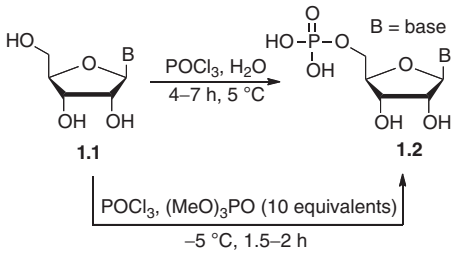
Figure 5 Substitution at phosphorus.

for the lower reactivity of P(V) halophosphates, when compared with those of type P(III), and serve to increase yields while decreasing reaction times, as highlighted in detail in the previous edition of this book chapter.[23,29]

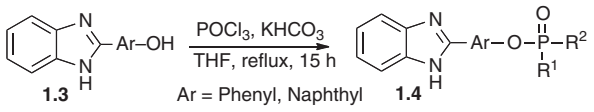
6.12.2.1.1 Phosphorus oxychloride

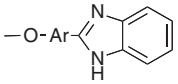
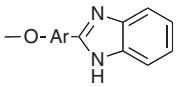
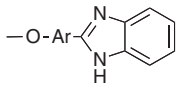
Since its discovery, $POCl_3$ has become one of the most widely used phosphorylating reagents for alcohols because of its ready availability, low cost, and convenience of handling. It is most commonly used to generate symmetrically substituted phosphotriesters of type $(RO)_3PO$, although phosphate monoesters and diesters can be readily prepared from their corresponding alcohols via the treatment of $POCl_3$ with 1 or 2 equivalents of alcohol and equal equivalents of a nonnucleophilic base or acid scavenger, followed by hydrolysis of the resultant phosphochloridate.[30] However, because of the reactivity profile of $POCl_3$, excessive substitution – resulting in deleterious di- or triester formation – is often unavoidable with a number of nucleophilic substrates. Thus, as controlled addition to $POCl_3$ can be a difficult process, much effort has been devoted to resolving these selectivity issues, primarily due to the synthetic utility and importance of the monophosphorylated and diphosphorylated intermediates in carbohydrate chemistry,[31] natural product synthesis,[14] and the synthesis of biologically relevant molecules.[32]

In general, manipulation of common reaction conditions, including the stoichiometric addition of the nucleophile and facilitating base, as well as solvent and temperature, is used to achieve mono- and disubstitution of $POCl_3$ in good to excellent yields (per substrate).[29] In 1967, Yoshikawa et al. demonstrated selective monophosphorylation of nucleosides **1.1** with $POCl_3$, accelerated by a small amount of water, to furnish the corresponding nucleoside 5′-monophosphates **1.2** in excellent yields (Scheme 1).[33] However, relatively long reaction times were required to reach completion. Thus, Yoshikawa et al. extended this method to incorporate superstoichiometric amounts of trialkyl phosphate additives, which allowed for a dramatic decrease in reaction times without a sacrifice in yield or selectivity.[29f] Recently, in 2009, Pareek et al. reported the controlled addition of a phenolic species **1.3** to $POCl_3$ to generate mono-, di-, and trisubstituted phosphate aryloxy esters **1.4** through simple variation of the stoichiometric addition of substrate and base (Scheme 1).[34]



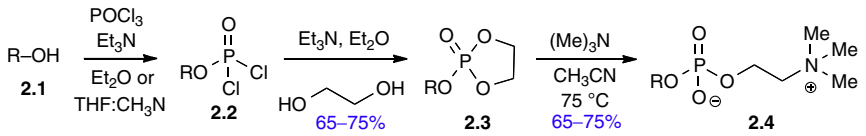
Nucleoside or Nucleotide	Yield (%) no additive	Yield (%) with $(MeO)_3PO$
Inosine	88	92
Guanosine	87	90
Adenosine	90	90



equivalent $KHCO_3$	equivalent **1.3**	R^1	R^2
1	1	Cl	Cl
2	2	Cl	
3	3		

Scheme 1

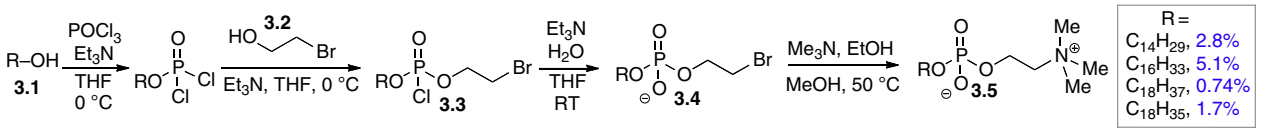
Another commonly utilized method for the formation of phosphate monoesters with $POCl_3$ involves the use of trialkylamines – in most cases, triethylamine (Et_3N) – as acid scavengers.[23] In an impressive 2-pot, 3-step synthesis of a number of *N*-alkyl phosphorylcholines (**2.4**), Johnson and coworkers attained monophosphorylation of alcohols **2.1** with stoichiometric amounts of $POCl_3$ and triethylamine, in an anhydrous ether (Et_2O) or tetrahydrofuran (THF)-acetonitrile (CH_3CN) at 0 °C, to generate dichlorophosphate **2.2**, which was then reacted with ethylene glycol to provide monocyclic phosphates **2.3** in 65–75% yield over two steps (Scheme 2).[35] Subsequent nucleophilic ring opening with trimethylamine (Me_3N) in CH_3CN, at 75 °C afforded *N*-alkyl phosphorylcholines **2.4** in good yield.



R	Phosphorylation solvent	Yield (%) over 3 steps
$C_{18}H_{37}$	E_2O	50
$C_{18}H_{37}O(CH_2)_2$	THF:CH_3CN	45
$C_{18}H_{37}S(CH_2)_3$	Et_2O	45

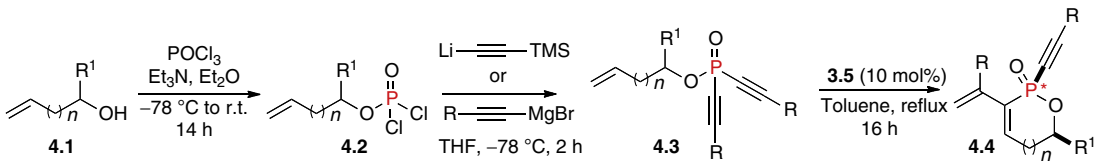
Scheme 2

In 2009, Parrill and coworkers reported a protocol involving two sequential monosubstitutions of chlorophosphates – as a one-pot protocol – for the synthesis of a number of lysophosphatidylcholine (LPC) analogs (**3.5**), which, upon screening, could provide substrate structure–activity relationships for the LPC-hydrolytic enzyme autotaxin (Scheme 3).[36] Alcohols **3.1** and **3.2** were added sequentially to a solution of triethylamine and $POCl_3$ in THF. Hydrolysis of monochlorophosphate **3.3** with a solution of Et_3N in water to form free phosphate **3.4** and nucleophilic displacement of bromide with Me_3N in EtOH/MeOH afforded zwitterionic LCP-analogs **3.5** (albeit in low yield over four steps).

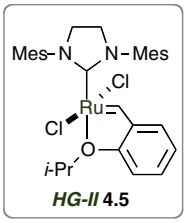


Scheme 3

In 2010, Gouverneur and coworkers reported monosubstitution of $POCl_3$ with secondary alcohols **4.1** to furnish phosphorodichloridates **4.2** in moderate to good yields (Scheme 4).[37] Successive acetylation, to afford **4.3**, followed by diastereoselective ring-closing enyne metathesis with second-generation Hoveyda-Grubbs catalyst (HG-II) allowed for the formation of phosphonates **4.4** in good to excellent yields.



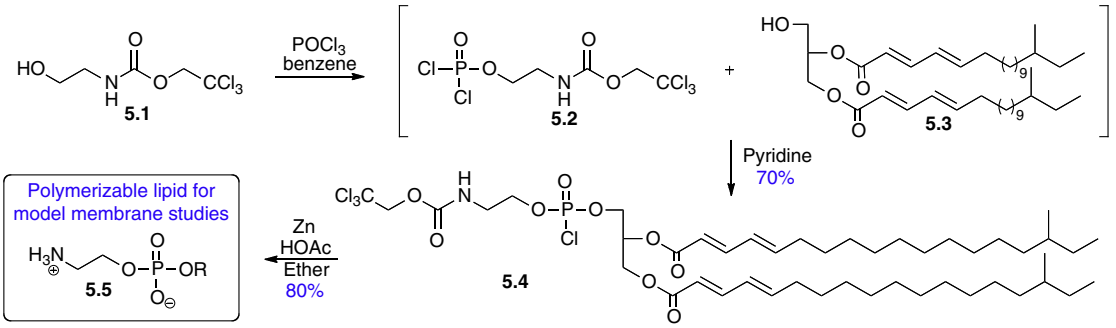
R^1	*n*	R	Yield (%) **4.2**	Yield (%) **4.3**	Yield (%) **4.4**	*dr* **4.4**
Me	1	H	72	56	86	18:1
Me	2	H	46	55	79	3:1
Me	1	Me	72	83	n.d	
Me	2	Me	46	65	0	



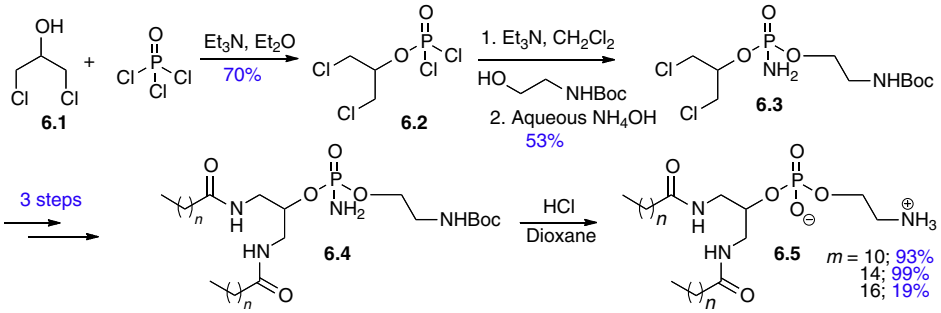
Scheme 4

En route to polymerizable phospholipids, O'Brien and coworkers reported on the monophosphorylation of carbamate **5.1** with freshly distilled $POCl_3$ in benzene (Scheme 5).[38] Coupling of dichlorophosphate **5.2** with **5.3**, in the presence of pyridine, afforded the corresponding phosphorochloridate (**5.4**) in excellent yield. Most notably, the authors mention that **5.4** was stable for 1 month when stored in benzene at 0 °C. Finally, Troc-amide deprotection with activated zinc and acetic acid afforded phosphate diester **5.5** in 80% yield.

In 2010, Zumbuehl and coworkers reported on the monosubstitution of $POCl_3$ with achiral dichloroalcohol **6.1**, in the presence of triethylamine, to yield phosphorodichloridate **6.2** in 70% yield (Scheme 6).[39] Coupling with Boc-protected



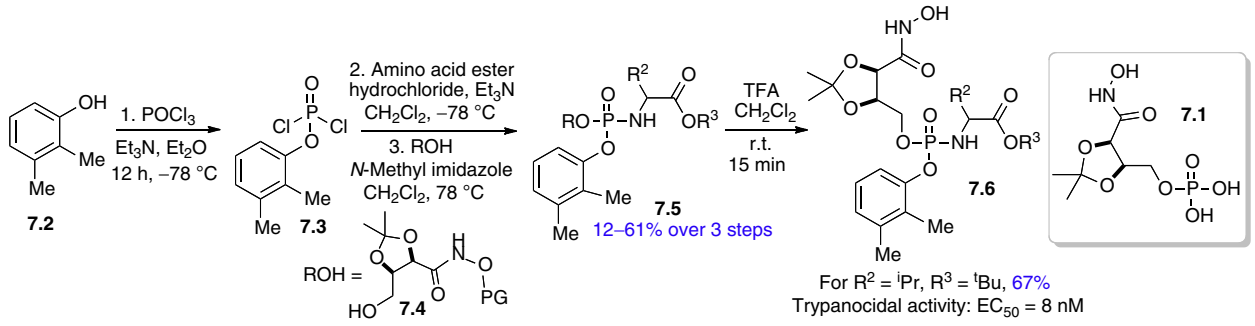
Scheme 5



Scheme 6

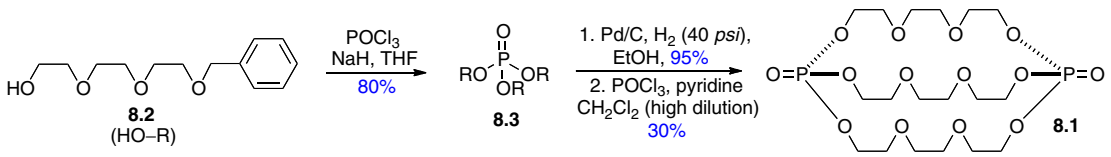
aminoethanol and subsequent treatment with aqueous ammonium hydroxide furnished asymmetric phosphoramidate **6.3** in 53% yield over two steps. Transformation of **6.3** to **6.4** was achieved via nucleophilic displacement of the chloride groups with NaN_3, reduction of the resultant azides to amines, and successive acylation with the corresponding acyl chlorides. Finally, simultaneous phosphoramidate hydrolysis and Boc-deprotection with HCl afforded elaborated zwitterionic phosphate diester **6.5**.

In 2010, Gilbert and coworkers reported on the formation of unsymmetric phosphoramidate prodrugs of phosphate monoester **7.1**, which has shown medicinal potential in the treatment against human African typanosomiasis, via a sequential, three-step monosubstitution of $POCl_3$ (Scheme 7).[40] Addition of Et_3N to a cooled (−78 °C) solution of phenol **7.2** and $POCl_3$ (1:1) produced phosphodichloridate **7.3**, which was coupled, without further purification, with a number of amino acid esters, in the presence of triethylamine, at equally low temperatures. The sequential addition of complex alcohol **7.4** provided phosphoramidates **7.5** that, on distal *N*-hydroxy acetamide deprotection, generated aryl phosphoramidates prodrugs **7.6**, which represent a new class of potent trypanocidal compounds.



Scheme 7

In 1994, Spreer and coworkers synthesized bis(phosphotriester) macrobicyclic polyether cryptand **8.1** (phosphocrypt), a member of a notable class of phase transfer catalysts and ion transporting reagents, via the formation of its symmetrical acyclic precursor (Scheme 8).[41] In a typical protocol to access phosphates of this type, an excess of polyethylene glycol (PEG) **8.2**, generated by the nucleophilic addition of a triethyl glycol alkoxide to benzyl chloride, was treated with $POCl_3$ in anhydrous THF



Scheme 8

to furnish symmetric phosphate triester **8.3**. Subsequent debenzylation with H_2, Pd/C and a second treatment with $POCl_3$, in the presence of pyridine, at high dilution, afforded cryptand **8.1** in modest yield.

6.12.2.1.2 Cyclic phosphodiesters with $POCl_3$

In 1955, Tener and Khorana observed that cyclic 2′,3′-phosphorylated ribonucleotides react much faster with water and alcohols than the comparable acyclic phospholipids.[42] Several years later, Westheimer[43] and Ramirez[44] observed extremely high relative rates of hydrolysis of five-membered cyclic phosphates with respect to their acyclic phosphate triester analogs, thus sparking enhanced interest in the synthesis and study of these unique heterocycles (**Figure 6**).

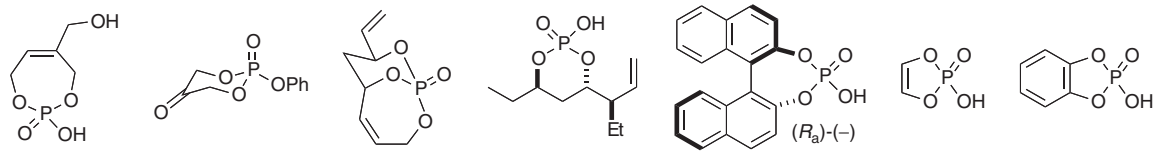
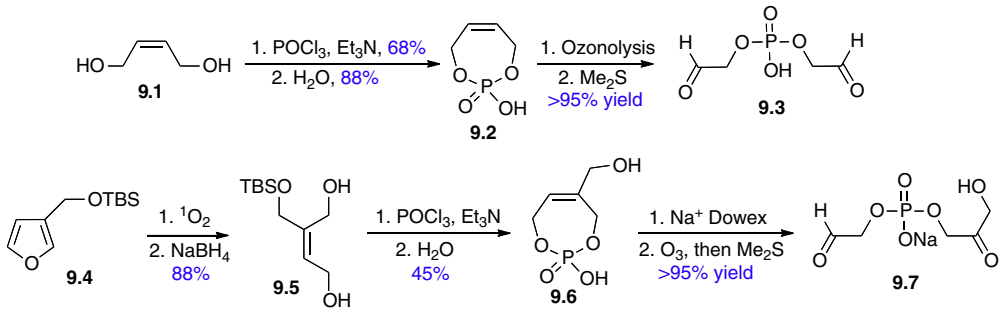


Figure 6 Cyclic phosphates.

Historically, the most convenient way to synthesize cyclic phosphodiesters entails the use of $POCl_3$.[42,45] In 1994, Sutherland and coworkers were able to accomplish the synthesis of bis(glycoaldehyde) phosphodiester **9.3** and glycoaldehyde-triose-mixed phosphodiester **9.7** by employing a two-step phosporylation/ozonolysis protocol (**Scheme 9**).[46] In their study, (*Z*)-2-butene-1,4-diol (**9.1**) was treated with $POCl_3$, in the presence of Et_3N, followed by hydrolysis, to yield the corresponding cyclophosphodiester **9.2**. Ozonolysis in MeOH, followed by reductive workup with Me_2S furnished the bis(glycoaldehyde) phosphodiester **9.3**. Unsymmetric phosphodiester **9.7** was also synthesized utilizing a similar protocol, wherein TBS-protected furan **9.4** was transformed into the cyclic phosphate **9.6** in good overall yield.

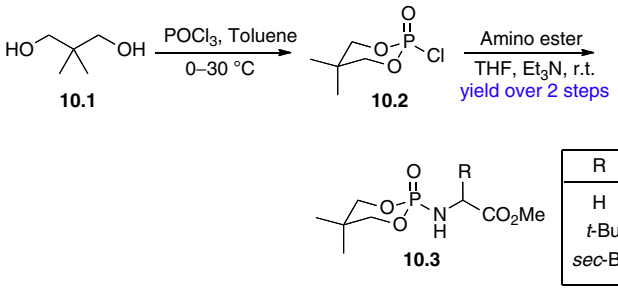


Scheme 9

In 2008, Raju and coworkers synthesized antimicrobial 5,5′-dimethyl-2-oxido-[1,3,2]-dioxaphos-phorinane-2-yl-amino carboxylates **10.3** through a two-step process, starting from the reaction of diol **10.1** with $POCl_3$ and proceeding through intermediate monochloride **10.2** [(2-chloro-5,5-dimethyl [1,3,2]dioxaphosphorinane-2-oxide], which was subjected to reactions with different amino esters to afford **10.3** (**Scheme 10**).[47]

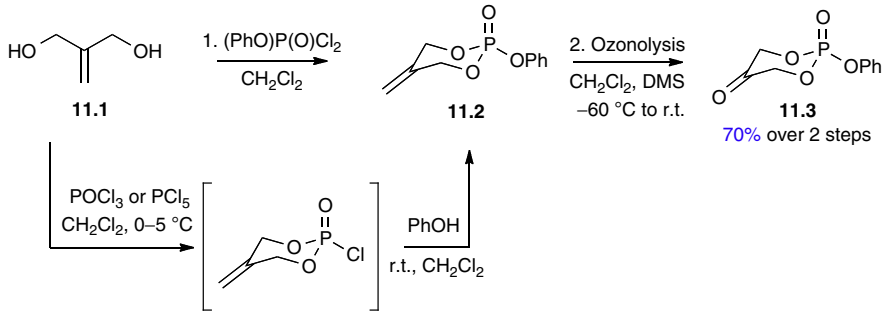
In 2002, Goswami and coworkers reported the phosphorylation of 2-methylenepropane-1,3-diol (**11.1**) with $POCl_3$, PCl_5, and a phosphochloridate [$(PhO)P(O)Cl_2$], in dry CH_2Cl_2, to afford cyclic phosphate **11.2**, which was subjected to ozonolysis to provide six-membered cyclic dihydroxyacetone phosphate (CDHAP) **11.3** in good yield over two steps (**Scheme 11**).[45] Intermediate **11.3** was then utilized in the synthesis of a number of keto-sugars and their analogs.

In 2005, Hanson and coworkers[48] utilized a ring-closing metathesis (RCM)-mediated desymmetrization of the C_2-symmetric 1,3-*anti*-diol diene **12.1** to enable the formation of the unique bicyclo[4.3.1]phosphate (S,S,S_P)-**12.3** via a diastereoselective RCM of phosphate triester **12.2** using [$(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$; *G-II cat*] (**Scheme 12**).[49]

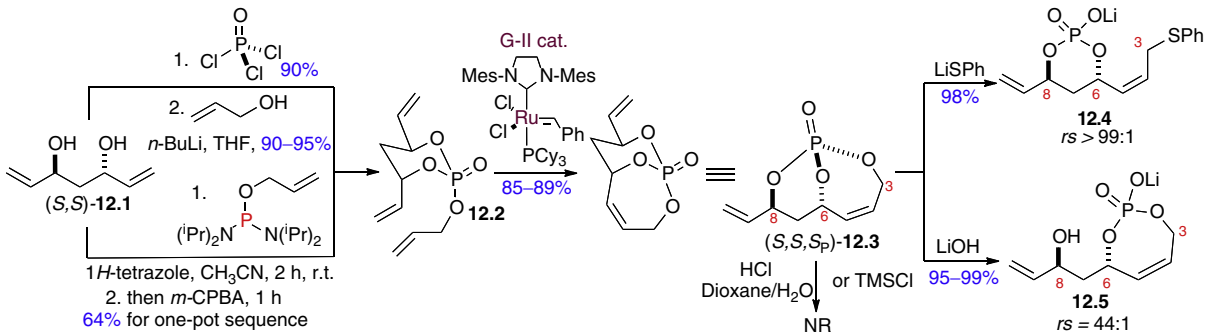


R	Yield (%)	R	Yield (%)
H	68	CH_3	64
t-Bu	57	Benzyl	68
sec-Bu	62	Phenyl	71

Scheme 10



Scheme 11

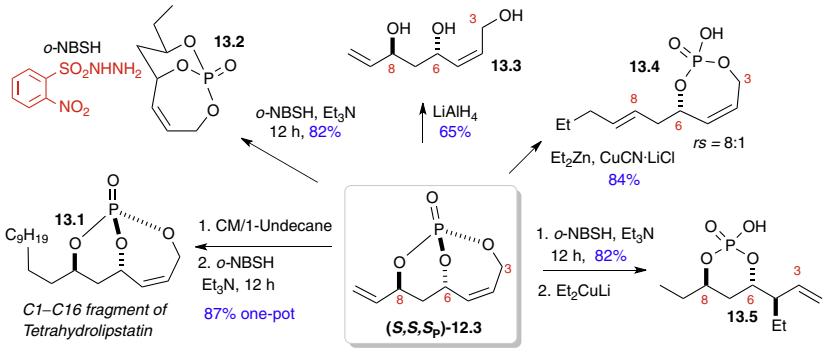


Scheme 12

The inherent properties of phosphate, as well as the overall stability of its [4.3.1]-bicyclic variant (particularly stability to acid-promoted hydrolysis), have led to the development of a number of synthetically useful transformations of the bicyclic phosphate template (S,S,S_P)-**12.3**, (or its enantiomeric (R,R,R_P)-counterpart) (Scheme 13). In particular, a chemoselective hydrogenation of the exocyclic olefin (**13.2**), a diastereoselective cuprate addition (**13.4** and **13.5**), and successful cross-metathesis of type I and type II olefins with the exocyclic double bond (as in example **13.1**), along with a variety of other transformations, have allowed for the generation of other mono- and bicyclic phosphates.[50] Most notably, the coupling of orthogonal transformations in a multistep, one-pot, sequential RCM/CM/H_2 process[19] has allowed for the facile generation of advanced intermediates *en route* to the total synthesis of natural products.[14]

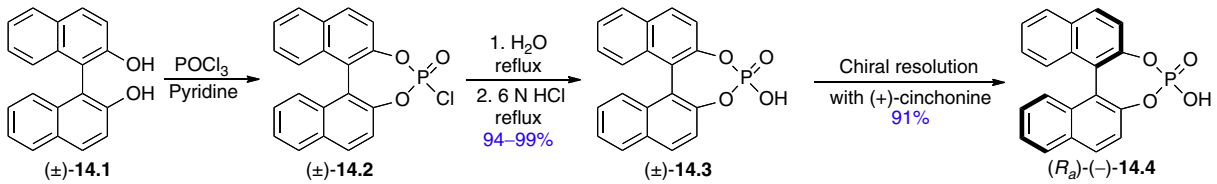
Utilization of phosphoric acid-derived catalysts, which possess centers of axial chirality, has emerged as a useful tool to affect several asymmetric processes.[51] Historically, the phosphorylation of racemic binaphthols and related systems,[52] followed by classical resolution with optically pure amines, such as brucine and cinchonine, provide an ammonium phosphate intermediate, which upon conversion to the free acid has been used to generate a number of chiral, nonracemic phosphoric acid derivatives for this purpose.

In 1971, Jacques and Fouquey reported the first synthesis of enantiomeric (*S*)-(+)- and (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (**14.4**), and a multigram synthesis of enantiomerically pure **14.4** was reported in 1989.[53,54] Synthesis began with the phosphorylation of [1,1′-binaphthalene]-2,2′-diol (**14.1**) with $POCl_3$, followed by hydrolysis, to afford cyclic phosphoric



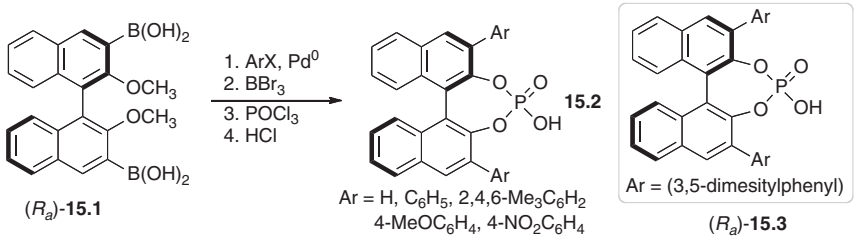
Scheme 13

acid derivative **14.3**, which upon classical resolution with (−)- or (+)-cinchonine furnished chiral, nonracemic binaphthol phosphoric acid **14.4** in excellent yield (Scheme 14).



Scheme 14

In 2004, Akiyama and coworkers reported the synthesis of chiral binaphthol phosphoric acid derivatives **15.2** to catalyze enantioselective, Mannich-type reactions via a Suzuki coupling reaction with chiral (2,2′-dimethoxy-[1,1′-binaphthalene]-3,3′-diyl)diboronic acid (**15.1**) and a variety of aromatic halides, followed by phosphorylation and hydrolysis (Scheme 15).[55] In the same year, Terada and coworkers utilized another phosphoric acid-derived binaphthol catalyst **15.3** for asymmetric aza-Friedel–Crafts alkylation of furan.[56]

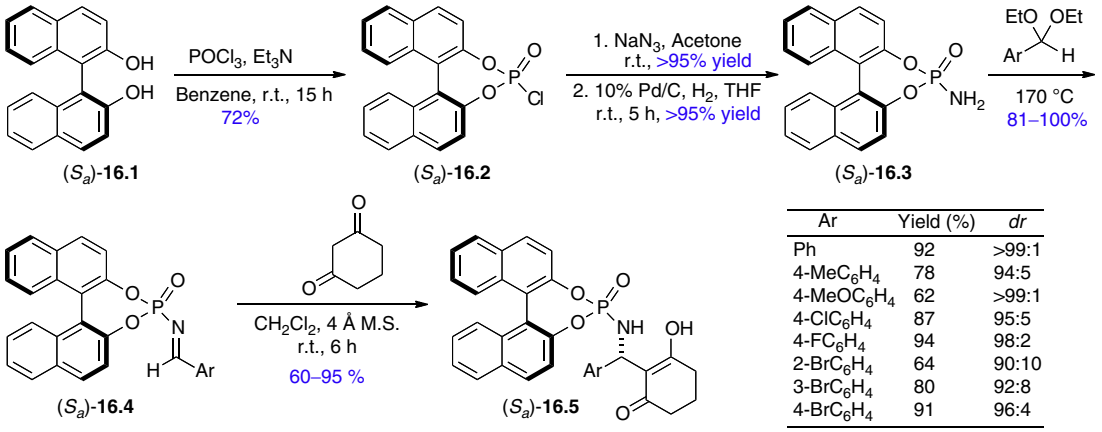


Scheme 15

In 2010, Pan, Li, and coworkers reacted (*S*)-[1,1′-binaphthalene]-2,2′-diol (**16.1**) with $POCl_3$ to generate the phosphoryl chloride **16.2**, which was treated with sodium azide and reduced (H_2, Pd/C) to afford phosphoramide **16.3** (Scheme 16).[57] Using this method, the authors prepared a variety of *N*-phosphoryl imines **16.4** by condensing **16.3** with acetals in good yields. Asymmetric addition of 1,3-cyclohexanedione to imines **16.4** was achieved in excellent yields and diastereoselectivities to furnish chiral, nonracemic phosphoramides **16.5** in good to excellent yield.

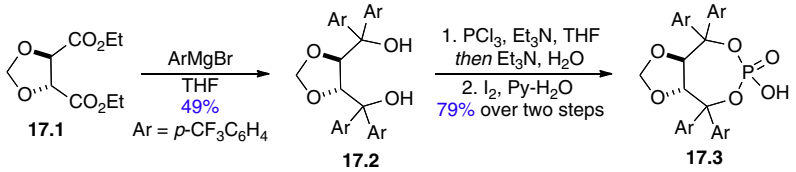
In 2005, Akiyama and coworkers synthesized a novel cyclic dialkyl phosphate **17.3** via the phosphorylation of *α,α,α,α*-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) derivative **17.2**, which was prepared through an aryl-Grignard reaction with methylidene-protected (+)-diethyl tartrate (**17.1**) (Scheme 17).[58] TADDOL-derivative **17.3** was then utilized as a chiral Brønsted acid to catalyze the Mannich-type reaction of ketene silyl acetals with aldimines to obtain the corresponding *β*-amino acid esters with high enantioselectivity.

In 2010, Wenzel and coworkers performed an oxidative coupling of phenols to obtain racemic, biaryl derivatives (±)-**18.1** (Scheme 18).[59] Subsequent treatment with $POCl_3$, followed by hydrolysis, furnished phosphorylated biaryl system (±)-**18.2**, which was then subjected to classical resolution using cinchonidine and hydrolyzed with an aqueous acid to afford chiral, nonracemic phosphate (S_a)-(+)-**18.3**. Alkylation with Me_2SO_4, followed by reductive phosphate removal with Red-Al, afforded chiral nonracemic diols (S_a)-(+)-**18.4**, which were further applied in asymmetric catalysis for hydrophosphonylation of imines and Friedel–Crafts alkylation of indoles.

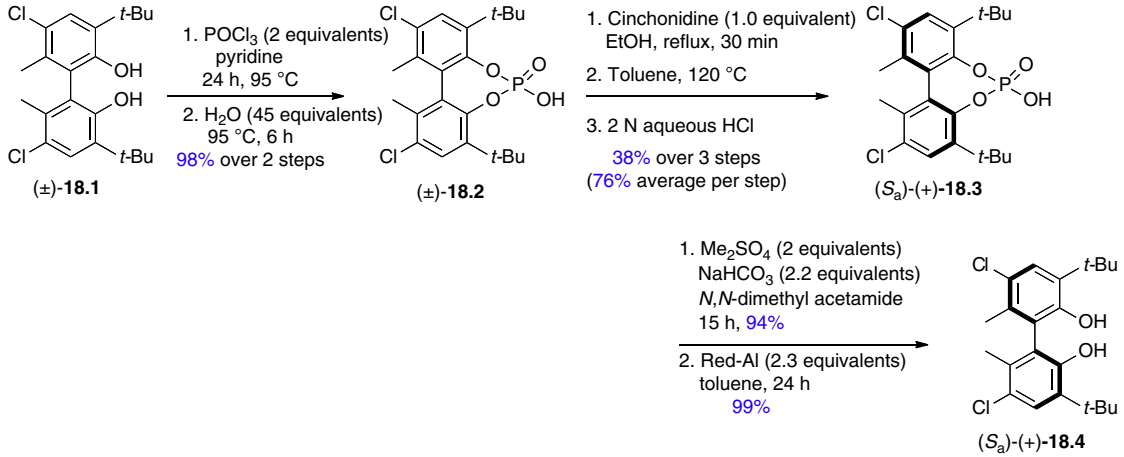


Ar	Yield (%)	*dr*
Ph	92	>99:1
4-MeC_6H_4	78	94:5
4-$MeOC_6H_4$	62	>99:1
4-ClC_6H_4	87	95:5
4-FC_6H_4	94	98:2
2-BrC_6H_4	64	90:10
3-BrC_6H_4	80	92:8
4-BrC_6H_4	91	96:4

Scheme 16



Scheme 17

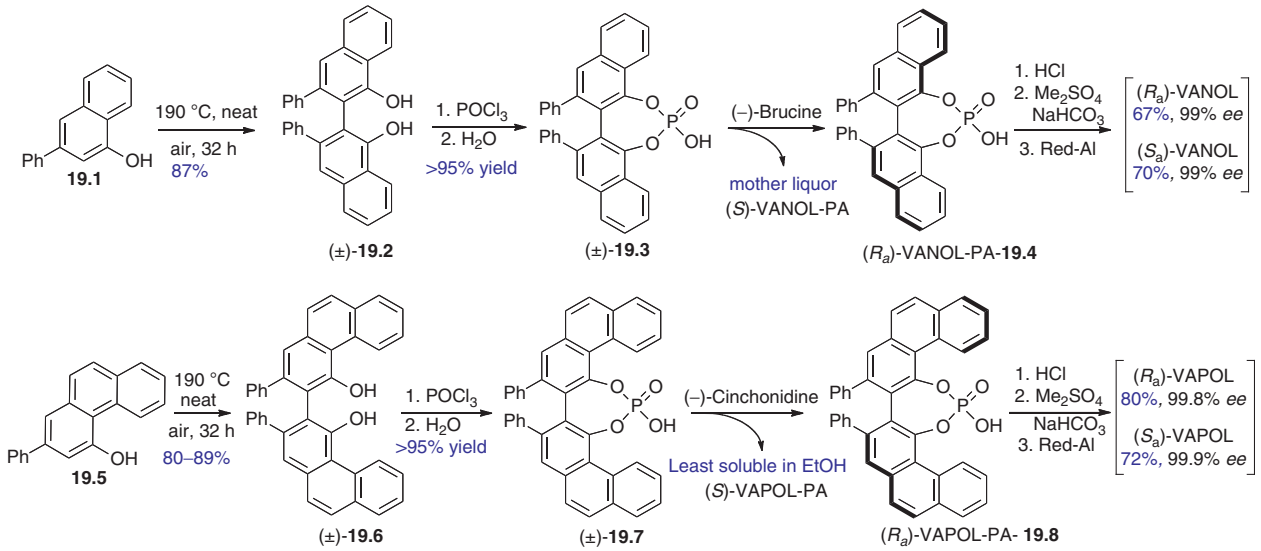


Scheme 18

In 1996, Wulff and coworkers developed a new class of vaulted, C_2-symmetric biaryl ligands, VANOL (3,3′-diphenyl-2,2′-bi-1-naphthol) and VAPOL [2,2′-diphenyl-(4-biphenanthrol)], in which the conjugated π-aromatic fused-ring systems of the ligand serve to define the chiral pocket (Scheme 19).[60] The aromatic ring systems of VANOL and VAPOL curve around the active nascent site, in comparison with BINOL whose two aromatic systems are parallel to each other and, thus, are linearly arranged. The distinctive orientation of the aromatic fused ring systems in VANOL and VAPOL make them useful alternatives for reactions where BINOL fails to yield the desired result. In fact, VANOL and VAPOL have proven to be superior to the BINOL system in a number of catalytic asymmetric transformations.[61]

Both the enantiomers (R_a- and S_a-) of ligands (VANOL and VAPOL) were synthesized via chiral resolution of racemic VANOL-PA (**19.3**) and VAPOL-PA (**19.7**) with (−)-brucine and (−)-cinchonidine, respectively, followed by reductive deprotection of optically pure phosphate esters **19.4** and **19.8**. The oxidative coupling of both monomers **19.1** and **19.5**, utilizing air as an oxidant, followed by phosphorylation and subsequent hydrolysis, provided the racemic phosphates **19.3** and **19.7** in excellent yield.

In 2007, Antilla and coworkers utilized the aforementioned vaulted biaryl phosphoric acids in a highly enantioselective process to catalyze reduction of α-imino esters.[62] They also utilized VAPOL-PA and VANOL-PA to desymmetrize meso-aziridines[63] and



Scheme 19

carry out Brønsted acid-catalyzed imine amidation.[64] Additional biaryl and related phosphoric acid systems have been used for catalytic and asymmetric chemical transformation and are shown below (Figure 7).[65]

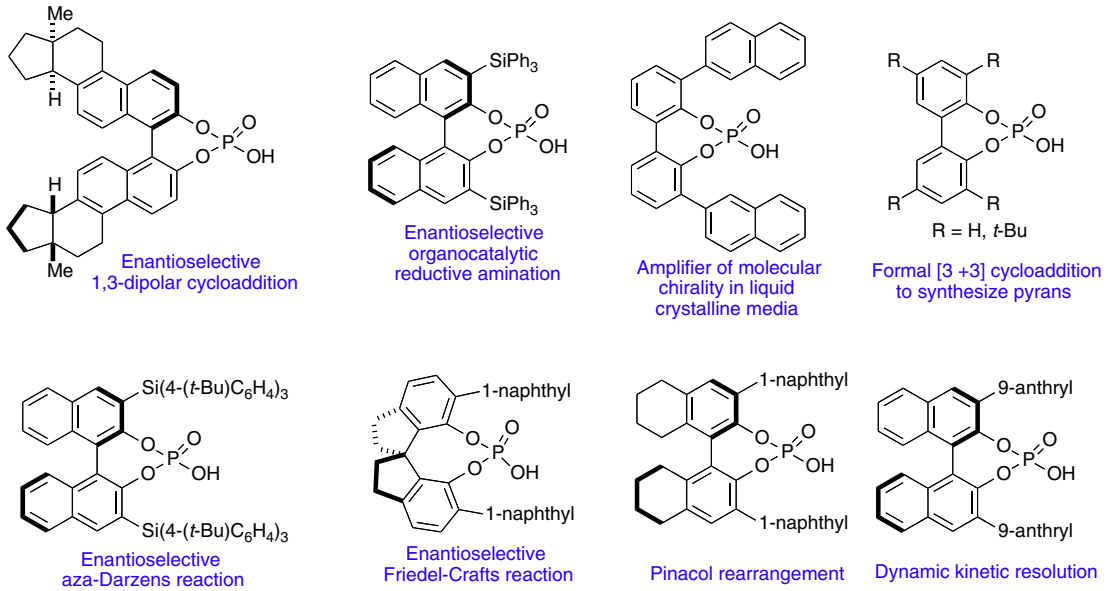
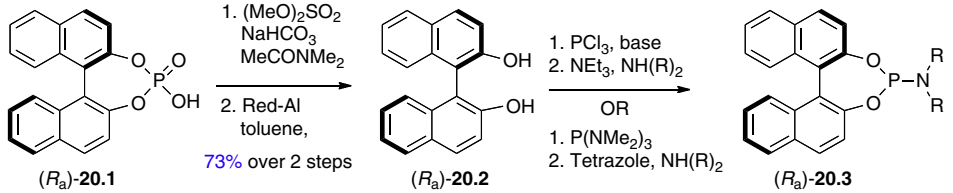


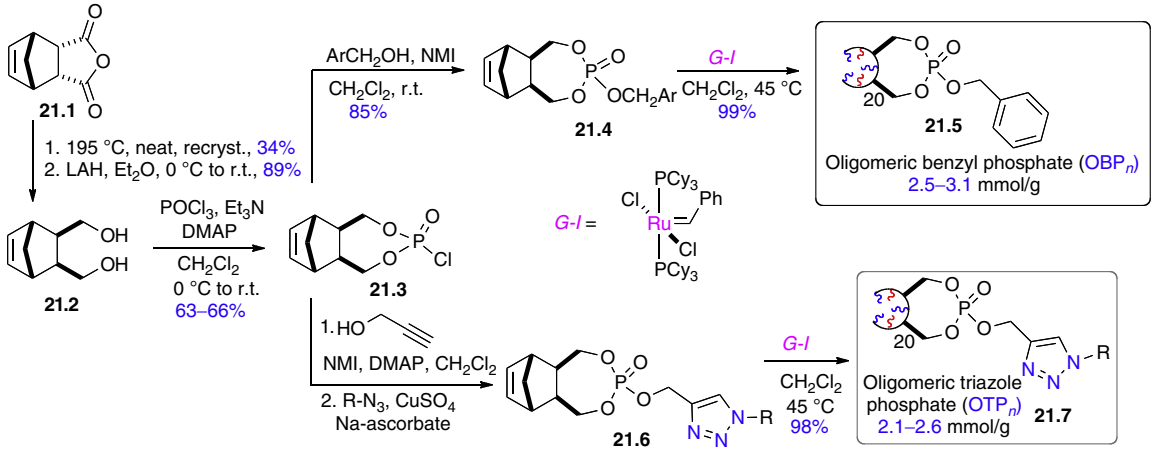
Figure 7 Biaryl phosphoric acid catalysts.

In addition to their application in enantioslective processes, chiral biaryl phosphoric acid derivatives **20.1** have been employed to synthesize chiral phosphoramidites **20.3,** which were also utilized as catalysts in asymmetric processes (Scheme 20).[66] Chiral, nonracemic phosphoramidites **20.3** were synthesized from chiral nonracemic biaryl diol **20.2**[67] via treatment with PCl_3 or $P(NMe_2)_3$, in the presence of trialkylamine activators and appropriate dialkyl amine.

In 2010, Hanson and coworkers reported two high-load, ring-opening metathesis polymerization (ROMP)-derived reagents, oligomeric benzylphosphate **21.5** (OBP) and oligomeric triazole phosphate **21.7** (OTP), as efficient benzylating and triazolating agents (Scheme 21).[68] Both syntheses were accomplished via thermal isomerization of inexpensive *endo*-carbic anhydride (**21.1**), which was carried out on large scale, using sequential recrystallizations in toluene, to yield *exo*-carbic anhydride in up to 84:1 diastereomeric ratio. This *exo*-carbic anhydride was used for the preparation of norbornenyl-tagged monochlorophosphate (OPC) **21.3**. Both OBP and OTP reagents were derived from a central OPC monomer, where simple phosphorylation of a variety of benzyl alcohols and subsequent ROMP with $[(PCy_3)_2Cl_2Ru(=CHPh)]$ rapidly generates the desired OBP oligomer **21.5**.[69]



Scheme 20



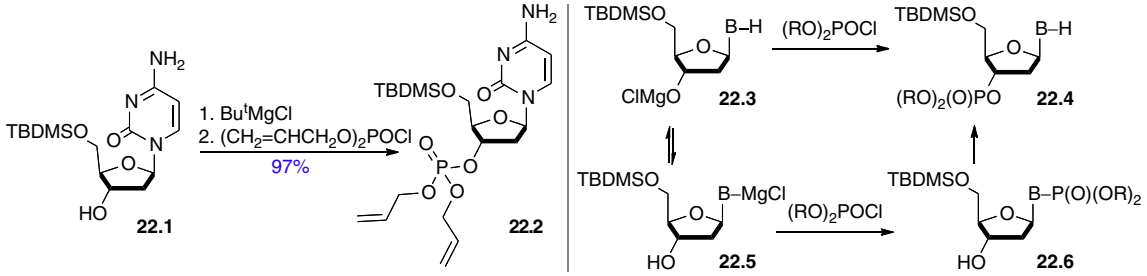
Scheme 21

Alternatively, phosphorylation of propargyl alcohol, followed by a Huisgen [3+2] 'click' reaction with a variety of alkyl/aryl azides and ROM polymerization, provided access to a suite of oligomeric OTP reagents **21.7**.

6.12.2.1.3 Phosphorochloridates and related compounds

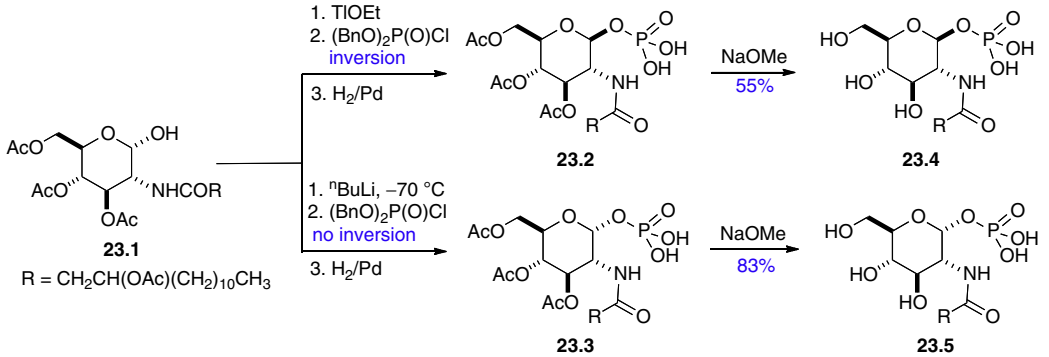
Phosphorochloridates $[(RO)_2P(O)Cl]$ and phosphorodichloridates $[(RO)P(O)Cl_2]$ serve as widely used phosphorylating reagents in the generation of protected, organic soluble phosphate triesters, which, upon hydrolysis/deprotection, can afford the desired phosphate mono- or diesters. In the previous installment of this book chapter,[23] Hayakawa provides a detailed account of several phosphorylation strategies, which utilize phosphorochloridates and phosphorodichloridates, most of which involve the activation of the nucleophilic substrate with organometallic reagents, KO^tBu, TlOEt, RLi, ^{t}BuMgCl, and $Al(OR)_3$, in the presence of facilitating amines, pyridine, DBU, and *N*-alkylazoles.[70] Since then, a number of interesting strategies involving the use of phosphorochloridates and phosphorodichloridates have been reported, and although alkoxide activation of alcohol nucleophiles is still common, many strategies have been developed which address the synthesis of phosphates and phosphate esters under more mild reaction conditions.

In 1993, Hayakawa, Noyori, and coworker described the facile and chemoselective *O*-phosphorylation of *N*-unprotected nucleosides via metal alkoxide formation (Scheme 22).[71] *N*-unprotected nucleosides **22.1**, when reacted with an equimolar amount of an organometallic base, such as an alkyllithium, KO^tBu, ^{t}BuMgCl, $LiAl[N(CH_3)_2]_4$, $Al[N(CH_3)_2]_3$, $(^iBu)_2AlH$ etc., followed by addition of phosphorochloridate or *p*-nitrophenyl phosphate, provided *O*-phosphorylated nucleotides **22.2**. It was shown that magnesium alkoxides resulted in the best chemoselectivity, generalizability, and operational simplicity and that



Scheme 22

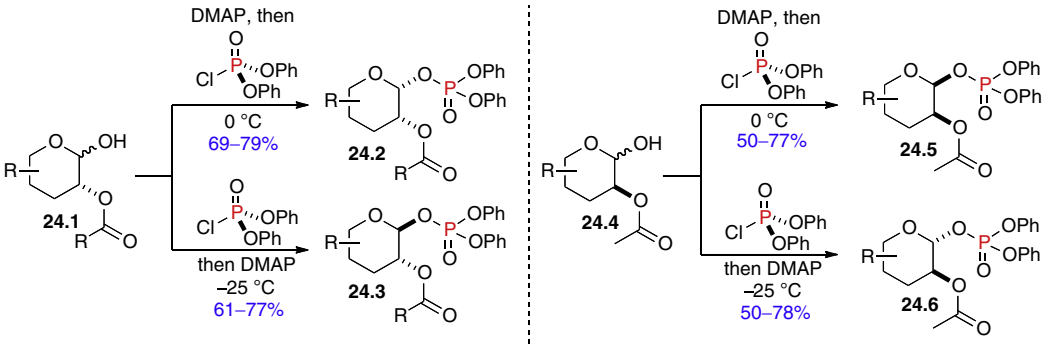
addition of ^{t}BuMgCl strongly affected the product distribution, selectively generating *O*-phosphorylated nucleotides with improved reactivity and yield. As such, high-quality Grignard reagent was crucial for the reaction to proceed. Unfortunately, selectivity issues limited the scope of this method, as the reaction of *N*-unprotected cytosinyl nucleoside and phosphorochloridate or *p*-nitrophenyl phosphate, in the presence of ^{t}BuLi, led to a mixture of products. Thus, it was proposed that the mechanism to *O*-phosphorylated product **22.4** heavily depends on the structure of the reacting nucleoside and the amount of the activator employed. In particular, the competitive deprotonation of the nucleoside base, to generate anion **22.5**, in equilibrium with the formation of the desired *O*-alkoxide **22.3**, could lead to complex mixtures of the desired product and *B*-phosphorylated nucleoside **22.6**. The general mechanism described for the process is shown below (Scheme 23).



Scheme 23

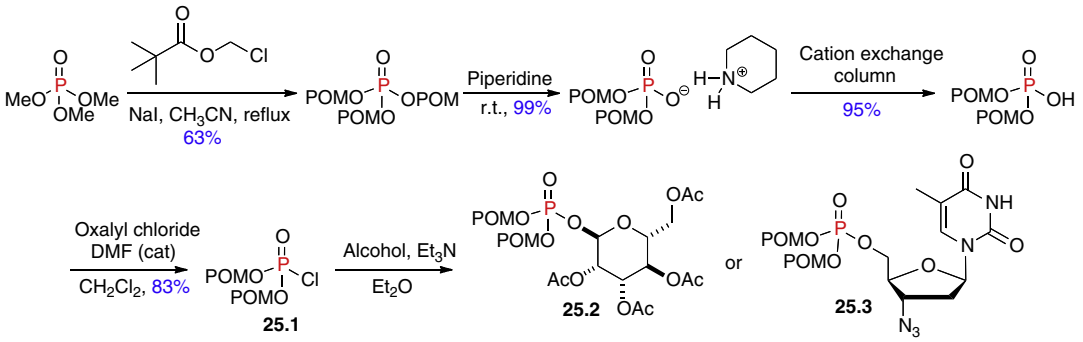
In sensitive systems such as carbohydrates, which contain anomeric hydroxyl groups, the stereochemistry of the phosphorylated product has been shown to vary with the activator and reaction conditions employed. In 1982, Inage and coworkers demonstrated that the use of *n*-butyllithium, at low temperature (−70 °C), for the phosphorylation 1α-hydroxylaminosugar **23.1** with dibenzyl phosphorochloridate to generate α-phosphate **23.3** with retention of configuration at the anomeric carbon (Scheme 23).[70e] Five years later, Hayakawa and coworkers reported the same phosphorylation using TlOEt in CH_3CN to afford the β-glycosyl phosphate **23.2** through inversion of the anomeric center.[70f] The authors also found a significant solvent effect, as phosphorylation of the thallium alkoxide of glucopyranose in CH_3CN proceeds with retention to yield the α-anomer whereas β-anomer predominates in benzene.

Despite the fact that an enormous number of studies on the use of phosphorochloridates as phosphorylating reagents have been reported and reviewed,[23] interest in the development of new reagents and conditions – particularly those which are milder – to increase selectivity, generalizability, and efficiency still exists. In 1992, Sabesan and Neira demonstrated that all four diastereomers can be synthesized by employing diphenyl chlorophosphate and DMAP under either thermodynamic or kinetic conditions (Scheme 24).[72] Under thermodynamic control (0 °C and warmer), the sequential addition of DMAP followed by diphenylphosphochloridate provided diphenyl *cis*-glycosyl phosphates **24.2** and **24.5** as the predominant diastereomer. In contrast, at low temperatures (kinetic control) glycosyl phosphate triesters having 1,2-*trans* stereochemistry **24.3** and **24.6** were obtained, with the addition of diphenylphosphochloridate, followed by DMAP.



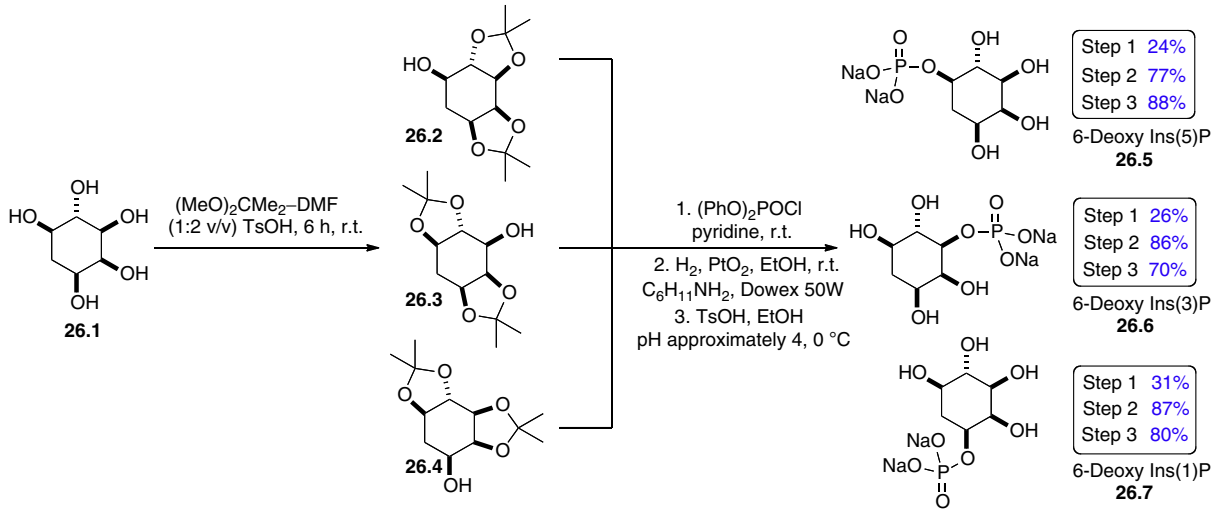
Scheme 24

In 2004, Cole and coworkers described an efficient method for the synthesis of phosphorylated prodrugs, which involves the preparation of various *bis*-pivaloyloxymethyl (POM) phosphate triesters **25.2** and **25.3** in moderate to good yields by utilizing bis (POM) phosphoryl chloride **25.1** under mild conditions employing Et_3N as the acid scavenger and H_2O as the solvent (Scheme 25).[73]



Scheme 25

In 2006, Ogawa and coworkers synthesized some biologically interesting phosphate and polyphosphate analogs from (+)-*epi*- and (−)-*vibo*-quercitols.[74] Di-*O*-isopropylidene derivatives of (+)-*epi*-quercitol **26.2**, **26.3**, and **26.4** were readily prepared from (+)-*epi*-quercitol **26.1** via acetal protection with dimethoxypropane in DMF (Scheme 26). These (+)-*epi*-quercitol derivatives were then treated with $(PhO)_2POCl$ in pyridine, followed by reduction and deprotection to provide 6-deoxy Ins(5)P **26.5**, 6-deoxy Ins(3)P **26.6**, and 6-deoxy Ins(1)P **26.7**.



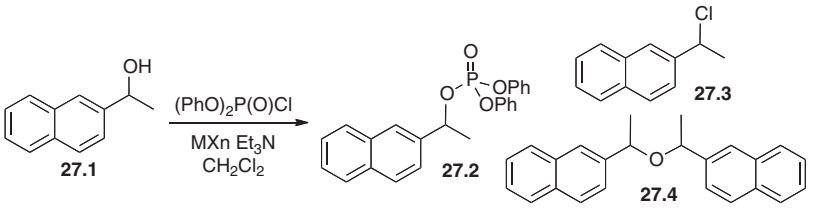
Scheme 26

In 2002, Jones and coworkers studied phosphorylation utilizing phosphochloridates with a number of Lewis acids, and observed that $Cu(OTf)_2$, $Y(OTf)_3$, and $TiCl_4$ show the highest conversion of starting alcohol **27.1** to the corresponding triester **27.2** (Scheme 27).[75] The most promising catalyst, $TiCl_4$, was selected and the condition was optimized, allowing access to a number of phosphotriesters **27.5** in excellent yield. Addition of 2,2′-dipyridyl (DIPY) had beneficial effects; however, a precise rationale for this improvement – whether the ligand had accelerating effects or simply increased solubility of the cationic species – was unclear.

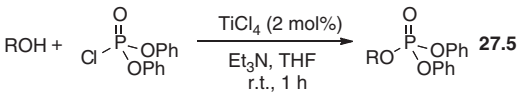
In 2003, the same group (Jones and coworkers) evaluated several inorganic esters as phosphate transfer catalysts. Among these, Ti(*t*-BuO)$_4$ was found to be the most effective catalyst, providing excellent yields of the desired phosphate esters, and catalyst loading could be reduced to as little as 5 mol% for a majority of simple substrates, with no loss in the yield of product (Scheme 28).[76] Most notably, this method was significantly more versatile than using $TiCl_4$ and was suitable for the phosphorylation of more complex carbohydrates and molecules of biological interest, such as **28.1** and **28.3**, without the need for alcohol activation by organolithiates, which have been found to be incompatible with a number of sensitive systems (Scheme 28).

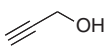
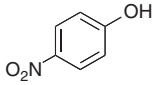
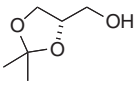
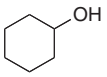
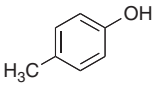
In 2003, Ranu and coworkers illustrated the utilization of $InCl_3$ in a simple and an efficient procedure to catalyze the reaction of dialkyl chlorophosphate **29.1** and several simple alcohols to yield the corresponding phosphate triesters **29.2** (Scheme 29).[77] Importantly, this report shows the versatility of $InCl_3$ with respect to the phosphorylation of a wide range of alcohols and highlights its ability to serve as an alternative catalyst to the more common Ti(IV) species.

In 2010, Chen and coworkers examined 14 oxidometallic species namely $TiO(acac)_2$, $TiOCl_2$, $ZrOCl_2$, $HfOCl_2$, $VO(OTf)_2$, VCl_3, $VOCl_3$, $VO(O\text{-}i\text{-}Pr)_3$, $WOCl_4$, WO_2Cl_2, MoO_2Cl_2, $MoOCl_4$, $MoO_2(acac)_2$, $MoCl_5$, MoO_2Cl_2, and $MoOCl_4$ in the catalytic phosphorylation of alcohols with phosphorochloridate **29.3** (Scheme 29).[78] In particular, oxidomolybdenum tetrachloride

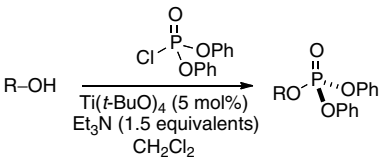


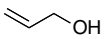
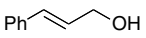
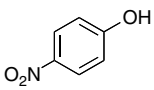
Catalyst	Conversion (%)			
	27.1	27.2	27.3	27.4
$Cu(OTf)_2$	15	0	0	85
+ DIPY	90	7	0	3
$Y(OTf)_3$	61	27	9	3
+ DIPY	65	31	3	1
$TiCl_4$	55	17	26	2
+ DIPY	64	26	6	4

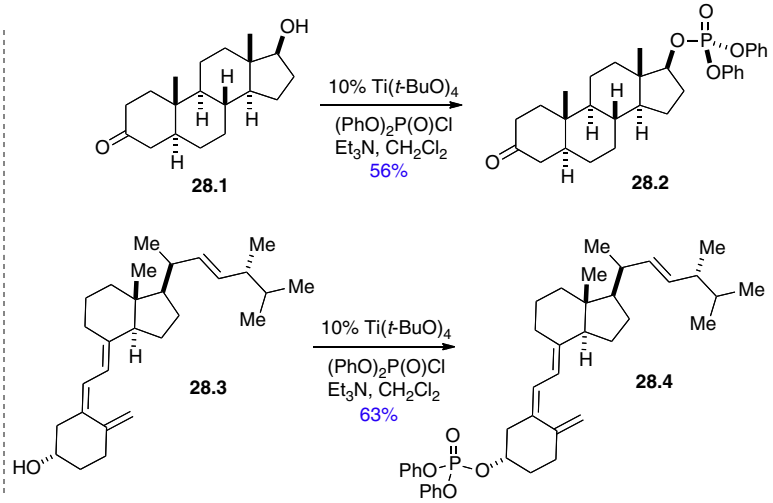


ROH	Yield (%)	ROH	Yield (%)	ROH	Yield (%)
	97		90		98
	84		97		95

Scheme 27



R–OH	Yield (%)
	97
	66
	97
	86



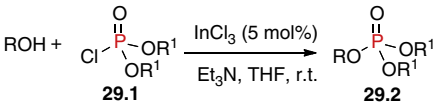
Scheme 28

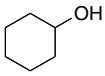
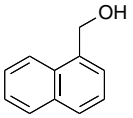
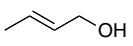
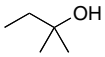
($MoOCl_4$) was found to be the most efficient catalyst for the phosphorylation of a range of primary, secondary, and tertiary alcohols, which have been accomplished in excellent yields.

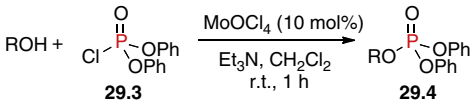
Additionally, phosphorochloridates are heavily used in the phosphorylation of allylic alcohols to provide key substrates for allylic substitution reactions. In 1991, Yamamoto touted the superiority of phosphate leaving groups in a seminal copper-mediated *anti*-S_N2' displacement reaction of allylic phosphate **30.2** (Scheme 30).[79] In 2003, Hoveyda[15] (see Figure 4) and Feringa[80] (Scheme 30) reported catalytic, asymmetric variants of this protocol. Feringa and coworkers achieved an efficient desymmetrization of *meso*-(bis)allylic phosphate **30.5**, which is derived from *meso*-alcohol **30.4** and *n*-BuLi and $(EtO)_2P(O)Cl$, to synthesize bis-allylic phosphate **30.5** in high yield.

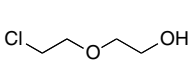
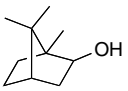
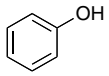
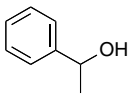
In 2006, Hanson and coworkers reported the utilization of phosphorodichloridates in the synthesis of cyclic phosphates **30.10** and **30.13** by sequential coupling with allylic alkoxide followed by RCM with $[(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh]$[49] (Scheme 30). These cyclic phosphates further subjected to *anti*-S_N2' Cu-mediated allylic phosphate displacement, in a substrate-controlled process, to provide *syn*-(*E*)-phosphate **30.11** and homoallylic alcohol *anti*-(*E*)-**30.14** in good yield.[50b,81]

In addition to the commonly used phosphorochloridates and phosphorodichloridates, a number of phosphoroiodates, phosphorobromidates, and phosphorofluoridates have been used as phosphorylating reagents. Although phosphorofluoridates have used as mechanistic probes or potent inhibitors of enzymatic reactions, they have relatively poor reactivity, rendering them less useful in synthetic chemistry.[82] Despite this, in 1970, Von Tigerstrom and Smith used (methoxytrityl)deoxyribonucleoside phosphorofluoridate **31.1** (Scheme 31) to react with the (methoxytrityl)deoxyribonucleoside **31.2** in the

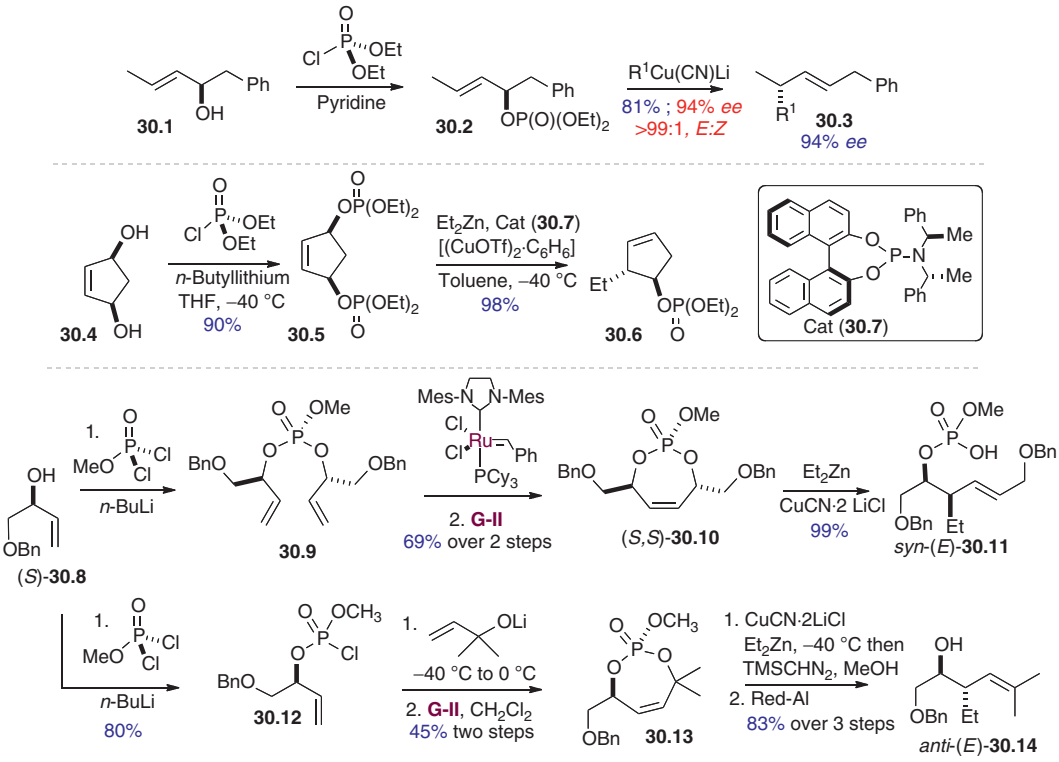


ROH	R^1	Yield (%)	ROH	R^1	Yield (%)
n-$C_{10}H_{21}OH$	Ph	80		Et	76
	Et	85		Et	73
	Ph	79		Et	80

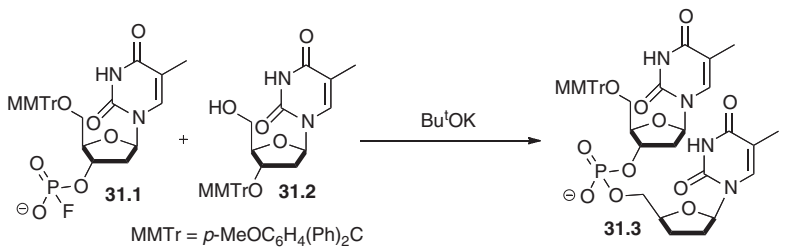


ROH	Yield (%)	ROH	Yield (%)
	97		90
	98		92
	95		90

Scheme 29



Scheme 30

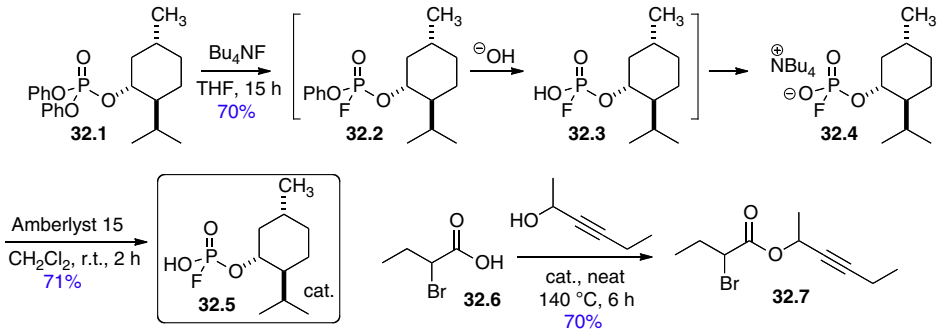


Scheme 31

oligodeoxyribonucleotide synthesis.[83] It was also observed that slow phosphorylation of alcohols does occur in the presence activators such as *n*-BuLi, CsF, DBU,[84] and *N*-methylimidazole.[85]

In 2011, Murai and coworkers prepared trialkyl phosphate **32.1**, which was subjected to fluorinative hydrolysis with Bu_4NF providing phosphorofluoridic acid ammonium salt monoesters **32.4** (Scheme 32).[86] The salt **32.4** was converted to the corresponding phosphoric acids **32.5** and was utilized to catalyze the condensation of α-bromobutanoic acid and 3-hexyne-2-ol.

While fluorophosphates show utility, bromophosphates and iodophosphates are generally regarded as too unstable to isolate. Although Timperley has reported the isolation of a dialkyl iodophosphates with electronegative fluoroester group on the phosphorus,[87] *in situ* generation of these reagents, proceeding from the corresponding phosphite and halogen, carbon tetrahalides, or trihalomethanes, is required in most cases (see Section 6.12.3.2 on Phosphite for detail).

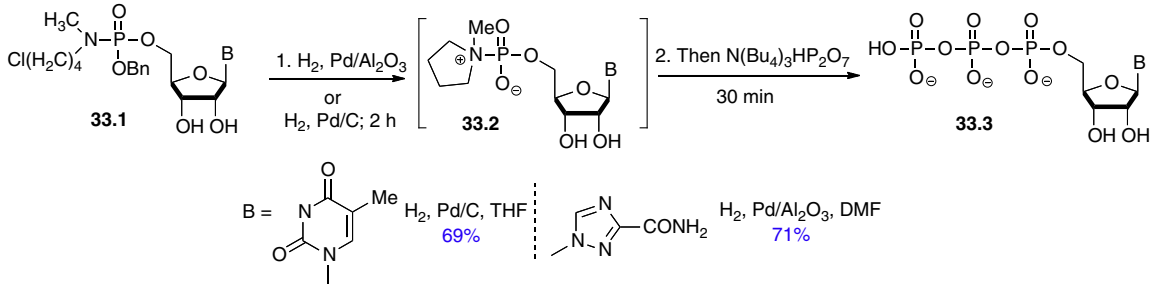


Scheme 32

6.12.2.2 Phosphoramidates and Related Compounds

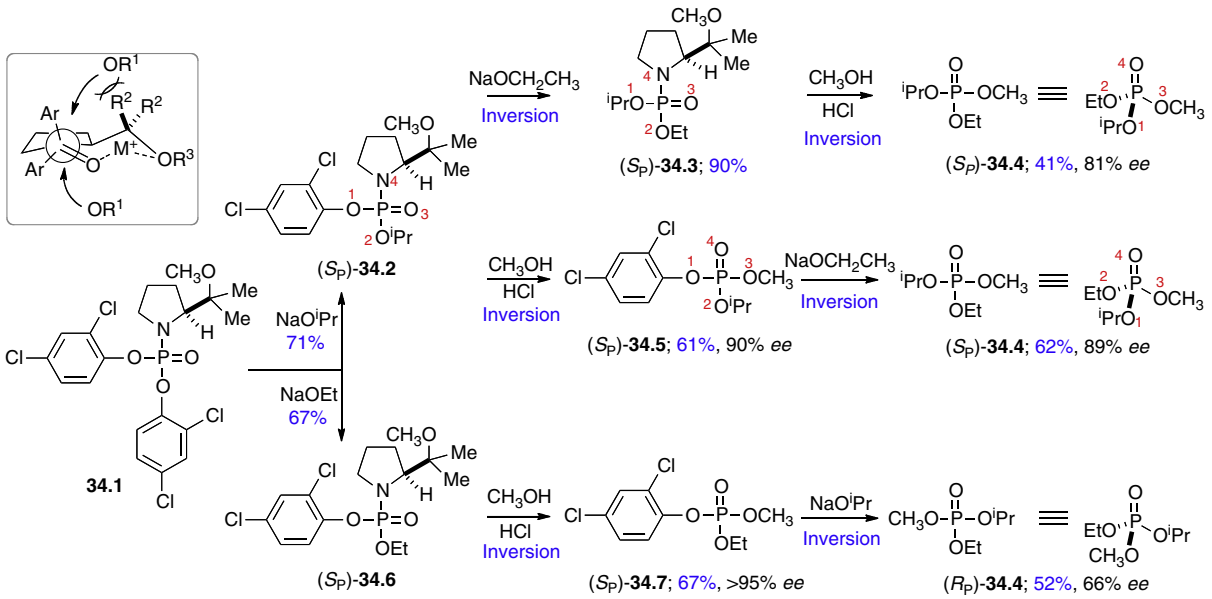
Phosphoramidates are the aliphatic amides of phosphoric acid and are widely employed in the synthesis of differentially protected phosphate esters as more stable alternatives to halophosphates.[88] They have been used as prodrug moieties to enhance water solubility[89] and to enhance the therapeutic potential of a parent drug.[90] In addition, they can be exploited to synthesize phosphate monoester prodrugs[91] by hydrolysis of the phosphoramide bond. In 2002, Banait and Gryaznov reviewed oligonucleotide phosphoramidates with bridging nitrogen as DNA and RNA analogs.[92] In 2004, a review by Venkatachalam et al. discussed rational drug design of multifunctional phosphoramidate-substituted nucleoside analogs,[93] and in 2010, Gryaznov and coworkers highlighted oligonucleotide N3′→P5′ phosphoramidates and thiophosphoramidates as potential therapeutic agents.[94]

Phosphoramidate chemistry has been applied in the synthesis of nucleoside triphosphates, though not to the same extent as their phosphoramidite [P(III)] counterparts. Although phosphoramidates can be quite stable, the condensation of phosphoramidates and pyrophosphates (phosphate anhydrides) to produce polyphosphates is known and was discussed in detail in Hayakawa's 1991 review.[23] In 2004, Broch and coworker used highly reactive pyrrolidinium phosphoramidate zwitterions (intermediate **33.2**), generated *in situ* by reductive cyclization, which coupled efficiently with $N(Bu_4)_3HP_2O_7$, to provide nucleoside triphosphate **33.3** (Scheme 33).[95]



Scheme 33

In 1990, Nakayama and coworkers introduced a general and highly enantioselective method for the synthesis of chiral phosphate triesters (S_P)-and (R_P)-**34.4** utilizing bis(2,4-dichlorophenyl) phosphoramidates **34.1** bearing a 2-substituted pyrrolidine as a chiral auxiliary (Scheme 34).[96] Chiral phosphoroamidate **34.1** was treated with alkoxides to replace the 2,4-dichlorophenyl group with the corresponding alkoxide to provide (S_P)-**34.2** and (S_P)-**34.6**. Treatment of (S_P)-**34.2** with ethoxide,

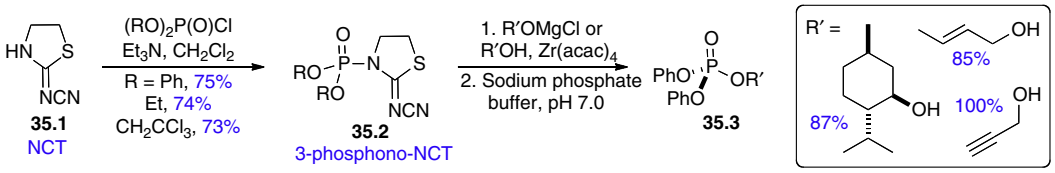


Scheme 34

followed by methanolysis, furnished phosphate triester (S_P)-**34.4** in modest yield and good enantioselectivity (inversion, 81% *ee*). However, when the order of methanolysis and ethoxide addition were reversed, higher optical yields and stereoselectivity was obtained. Alternatively, by changing the sequence of alkoxide addition, phosphates (R_P)-**34.4** were obtained from the same starting material (**34.1**). The authors attributed stereoselectivity to the chelation of a metal spectator ion by the phosphoryl and proline-substituent oxygens, which acts to facilitate nucleophilic substitution at the phosphorus atom by creating a rigid intermediate that biases the approach of the nucleophile. Other methods for the synthesis of chiral phosphates, which include utilization of chiral auxiliaries derived from L-proline,[97] D-glucose,[98] and (−)-ephedrine,[99] have also been reported.

It should be noted that, in the context of the previously described work by Nakayama, both ethoxide addition and methanolysis proceeded with inversion of the stereochemistry at phosphorus, though the stereochemical descriptor remained the same, as the substituent priorities change per intermediate.[96] Though stereochemical designation of phosphate esters has been the source of some confusion, Cahn–Ingold–Prelog priority rules indicate that, in phosphate triesters, P=O is treated as a P–O with assignment of least priority, as 'contributions by d-orbitals to bonds of quadriligant atoms are [to be] neglected.'[100] As such, group priority is listed, along with stereochemical descriptor, for each intermediate, *vide infra* (Scheme 34).

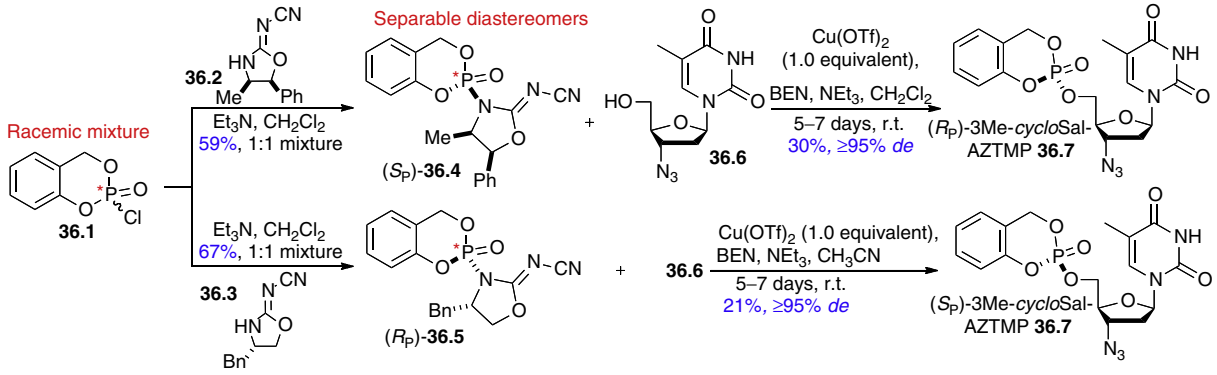
In 2002, Tanaka and coworkers developed new phosphorylating agents, 3-phosphono-2-(*N*-cyanoimino)-thiazolidine derivatives (3-phosphono-NCTs, **35.2**), from the coupling of a number of phosphorochloridates with NCT **35.1**.[101] Utilizing **35.2**, the authors report the facile phosphorylation of various primary and secondary alcohols in good to excellent yields. Importantly, these reagents are stable crystalline compounds, and the NCT eliminated during phosphorylation process can be recovered for reuse (Scheme 35).



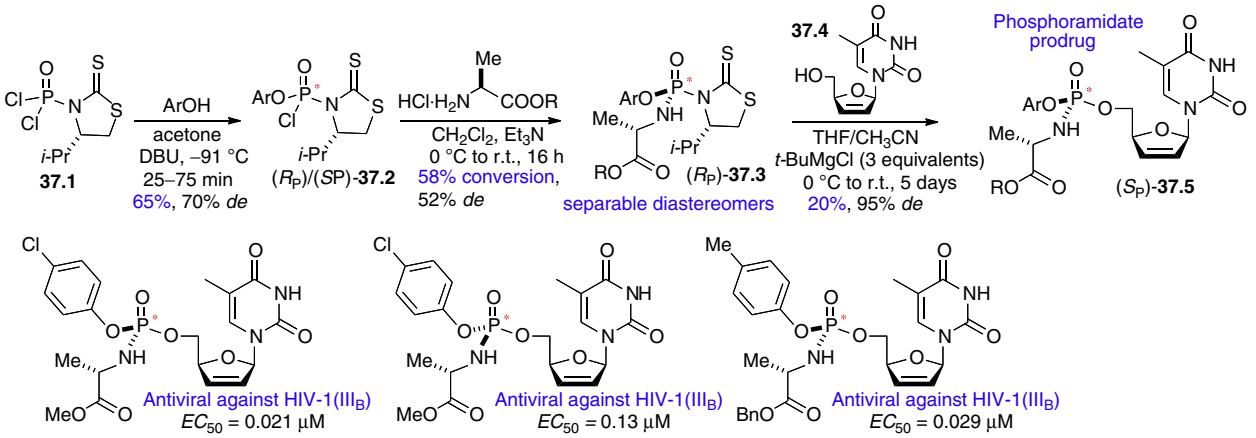
Scheme 35

In 2011, Meier and coworkers developed a diastereoselective synthesis of cycloSaligenyl-phosphotriesters (cycloSal) **36.7** via the use of chiral auxiliaries (Scheme 36).[102] CycloSal-compounds **36.4** and **36.5** were obtained from chiral auxiliaries **36.2** and **36.3**, respectively, as 1:1 diastereomeric mixtures that were separable by column chromatography. Isomerically pure **36.4** and **36.5** were then coupled with nucleoside **36.6** to provide the corresponding cycloSal-pronucleotides in high diastereoselectivity, albeit in a relatively low yield.

In 2011, Meier and coworkers also completed the diastereoselective synthesis of phosphoramidate prodrugs from diastereomerically pure phosphorodiamidates **37.3** (Scheme 37). Addition of aryl alcohols and various amino acid esters to dichlorophosphoroamidate **37.1** led to the formation of phosphoramides **37.3**, as a separable mixture of diastereomers (in moderate *de* for both steps).[103] Subsequent addition of nucleoside **37.4** generated the corresponding phosphoramide prodrugs (**37.5**) with



Scheme 36



Scheme 37

excellent diastereoselectivity. Utilizing this method, the authors were able to synthesize eight diastereomerically pure arylphosphoramidate prodrugs, several of which showed potent antiviral (HIV) activity.

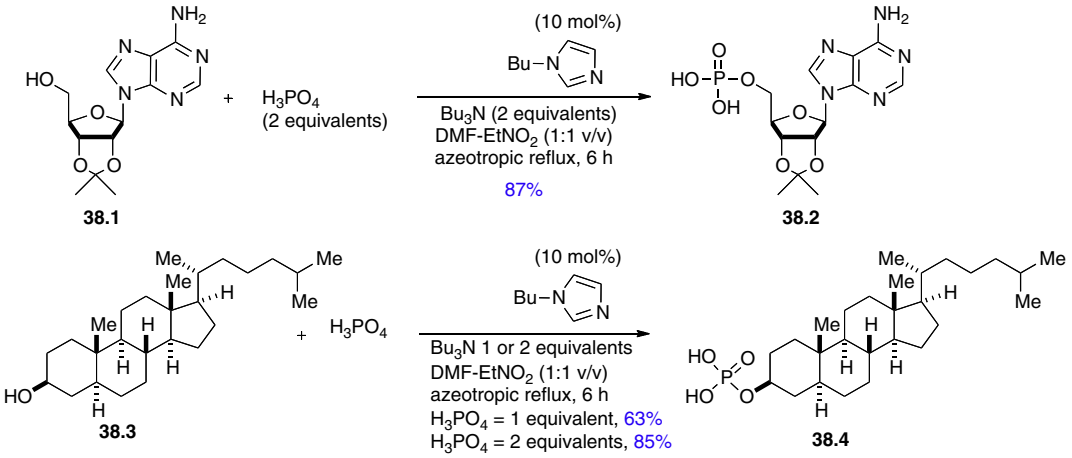
Additionally, several groups have utilized *N*-phosphorooxazolidinones for catalytic phosphorylation of alcohols, *vide infra*. The oxazolidinones are discussed in detail in the section devoted to catalytic and asymmetric phosphorylation (Section 6.12.4).

6.12.2.3 Phosphoric Acid

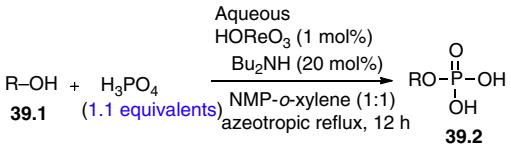
The catalytic condensation of equimolar phosphoric acid (H_3PO_4) with alcohols is an attractive tool for the synthesis of phosphoric acid monoesters with respect to green chemistry, as well as an industrial process, as the sole byproduct of the reaction is water. However, because of the increased acidity/decreased nucleophilicity of phosphates with respect to their carboxylic acid analogs, esterification of phosphoric acid can be a relatively difficult process. However, in 1966, Honjo group reported the noncatalytic synthesis of 2′,3′-*O*-isopropylidene ribonucleoside 5′-monophosphates from the corresponding ribonucleosides, utilizing 5 equivalents of H_3PO_4 in the presence of 10 equivalents of tributylamine (Bu_3N) under refluxing conditions in dimethylformamide.[104] In 2005, Ishihara and coworkers reported the synthesis of phosphate monoesters **38.2** and **38.4** with phosphoric acid (1 or 2 equivalents) and alcohol **38.1** and **38.3** (1 equivalent) in the presence of tributylamine (Scheme 38).[105] In addition, nucleophilic bases such as *N*-alkylimidazole and 4-(*N*,*N*-dialkylamino) pyridine promoted both reactions to provide the desired products in good yields.

Two years later, Ishihara and coworkers reported the first catalytic direct condensation of nearly equimolar mixture of phosphoric acid and alcohols **39.1** employing oxorhenium complexes for the synthesis of phosphoric acid monoesters (Scheme 39).[106] Highest yields were obtained using perrhenic acid ($HOReO_3$) as the active catalyst, and addition of dibutylamine (Bu_2NH) allowed for the stabilization of the catalytic species (as the amine salt), as well as the stabilization of acid-sensitive substrates and products via acid scavenging.

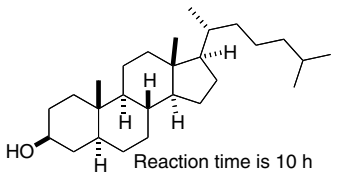
Although the protocol discussed above is catalytic and high yielding, use of expensive oxorhenium complexes, as well as purification problems were notable drawbacks that limited the potential utility of the method. Thus, in the same year, the same



Scheme 38

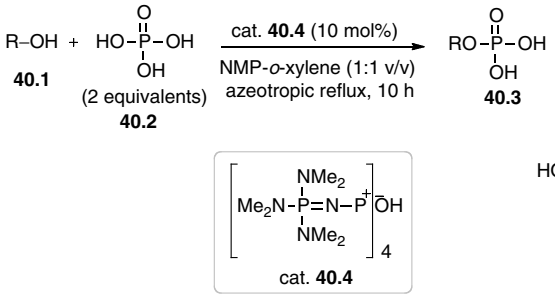


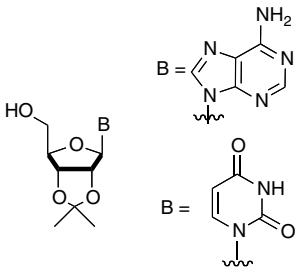
Cat. (10 mol%)	Yield (%)	Cat. (10 mol%)	Yield (%)
Aqueous $(HO)ReO_3$	97	CH_3ReO_3	12
$(TMSO)ReO_3$	94	ReO_3	35
Re_2O_7	81	ReO_2	8

ROH	Yield (%)
n-$C_{18}H_{37}OH$	98
(*Z*)-*n*-$C_8H_{17}CH{=}CH(CH_2)_8OH$	100
(*Z*)-*n*-$C_8H_{17}CH{=}CH(CH_2)_8OH$ (100 mmol scale)	96
 Reaction time is 10 h	95

Scheme 39

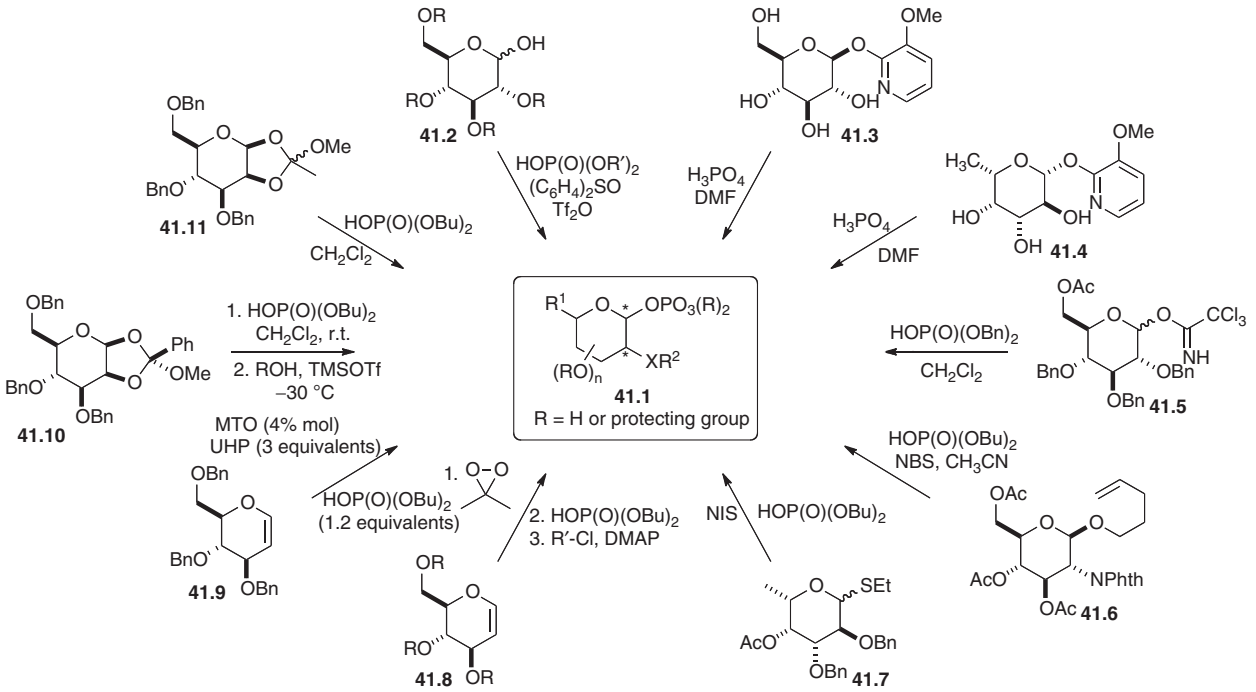
group (Ishihara) reported a metal-free phosphazenium cation-catalyzed direct dehydrative condensation of phosphoric acid with alcohols **40.1** to synthesize phosphate monoesters **40.3** (Scheme 40).[107]



Alcohol	Yield (%)
	72%
	83%

Scheme 40

In oligosaccharide synthesis, stereospecific formation of glycosidic linkages and the C2 hydroxy group is a significant challenge. In this regard, anomerically controlled addition of phosphoric acid to carbohydrate hemiacetals to furnish glycosyl-1-phosphates **41.1** (Scheme 41) has appeared as a widely used method.[108] In 2000, Gin and Garcia reported a dehydrative coupling of carbohydrate hemiacetals **41.2** and dialkyl phosphates, using dibenzothiophene-5-oxide and triflic anhydride, to provide direct access to glycosyl-1-phosphates **41.1** with good control over anomeric selectivity.[109] In addition, Hanessian et al. reported 2-(1,2-*trans*-glycopyranosyloxy)-3-methoxypyridines (MOP glycosides **41.3** and **41.4**) as useful substrates for the synthesis of the corresponding 1,2-*cis*-1-phosphates in good yield and excellent stereoselectivity.[110] Other glycosyl donor species in anomeric



Scheme 41

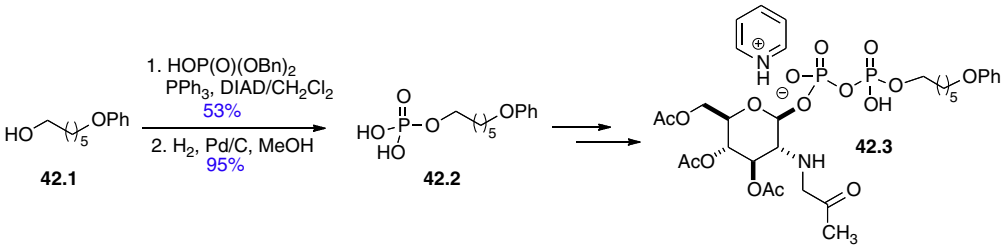
phosphate synthesis include trichloroacetimidate **41.5**,[111] glucosamine *n*-pentenyl glycoside **41.6**,[112] and fucosyl thioglycoside **41.7**.[113] Alternatively, in a three-step, 'one-pot' procedure developed by Seeberger and coworkers, glycal **41.8** was converted into a 1,2-anhydrosugar by epoxidation with dimethyldioxirane.[114] Sequential epoxide opening with a phosphoric acid and acylation of the generated C2 hydroxyl group led to the glycosyl phosphate product. In this method, a strong solvent-dependent ratio of α- and β-glycosyl phosphates formation was observed.

In 2004, Goti and workers described a catalytic oxidation–phosphorylation procedure of glycals **41.9** in which methyltrioxorhenium (MTO) was used as the catalyst, urea hydrogen peroxide (UHP) as the stoichiometric oxidant, and dibutyl phosphate as the nucleophile (Scheme 41).[115] Proper selection of solvent and addition of nitrogen ligands such as pyridine or immidazole provide the diasteroselectivity at C2. Tribenzylmannosyl 1,2-orthoacetate **41.10** and **41.11** was also used as the substrate in a highly effective protocol toward C2 acyl glycosyl phosphates.[116] This method has been successfully applied in the synthesis of the immunodominant epitope trirhamnoside of group B *Streptococcus*.

6.12.2.3.1 Mitsunobu reactions with phosphate nucleophiles

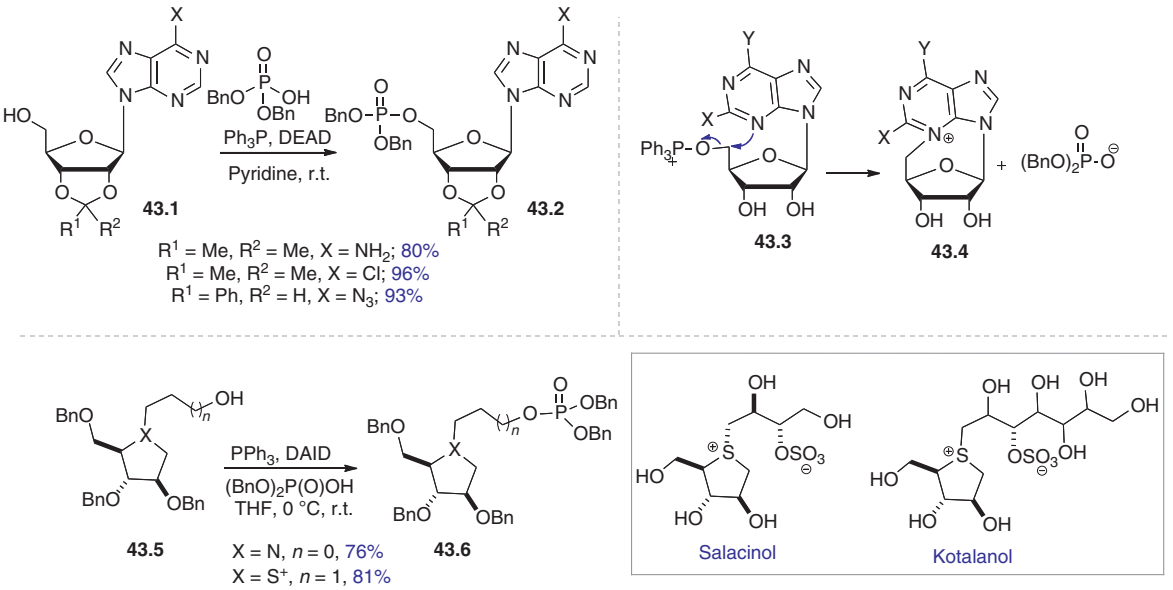
First reported by Mitsunobu and coworkers in 1969,[117] the Mitsunobu reaction employing phosphates as a nucleophile has served as a powerful tool for phosphate installation in total synthesis, particularly in phosphorylated carbohydrate synthesis. From 1992 to 1994, Campbell and coworkers further developed this method with respect to phosphonate nucleophiles *en route* to peptidylphosphonate ester synthesis under alcohol-limiting conditions.[118]

In 2010, Brockhausen and coworkers described the synthesis of a series of GlcNAc-pyrophosphate-lipid analogs to study the enzymes involved in the biosynthesis of *O*-antigens.[119] The Mitsunobu reaction with alcohol **42.1** and dibenzyl phosphate, followed by debenzylation with H_2 and Pd/C, afforded dihydrogen phosphate **42.2**, which was further subjected to a series of reactions to synthesize *O*-acetylated glycoside **42.3** (Scheme 42).



Scheme 42

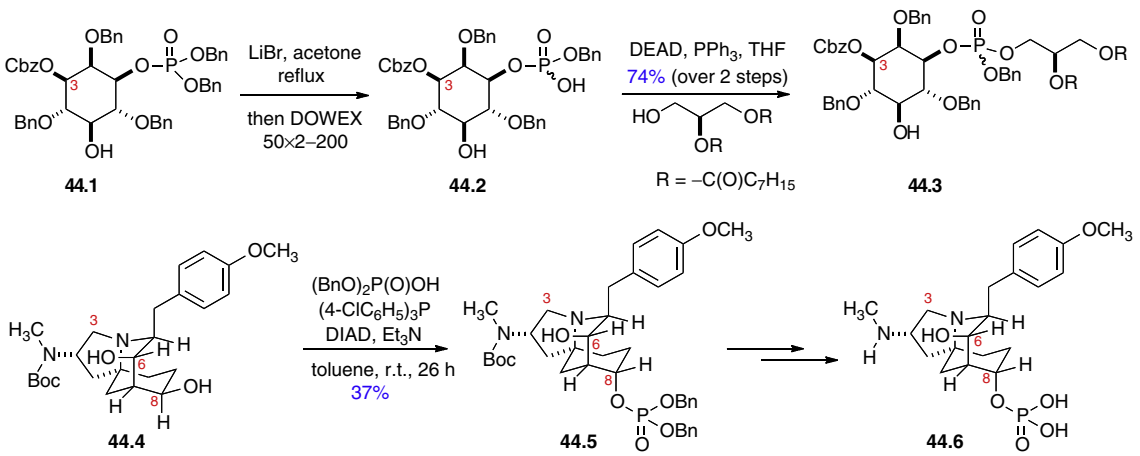
In 1995, Saddy and coworkers reported successful phosphorylation of 2′,3′-*O*-protected adenosine derivatives **43.1** via the Mitsunobu reaction, where nucleosides **43.1** were coupled with phosphoric acid diesters, in the presence of anhydrous pyridine, to afford 5′-phosphate derivatives **43.2** in good to excellent yields (Scheme 43).[120] Surprisingly, it was noted that when 2′,3′-positions of the substrate purine nucleosides **43.3** were not protected, intramolecular nucleophilic attack by the purine base to 5′-carbon was observed to furnish **43.4** as a major product.



Scheme 43

Bhat and coworkers reported additional examples of the Mitsunobu reaction in synthesizing phosphate prototype compounds of the naturally occurring glycosidase inhibitor salacinol. Phosphorylation of *N*- and *S*-hydroxyalkyl derivatives of 2,3,5-tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-arabinitol and 1,4-anhydro-2,3,5-tri-*O*-benzyl-1-thio-D-arabinitol **43.5** was accomplished via the Mitsunobu reaction with dibenzyl phosphate, to afford the corresponding phosphate derivatives **43.6** in good yield (Scheme 43).[121]

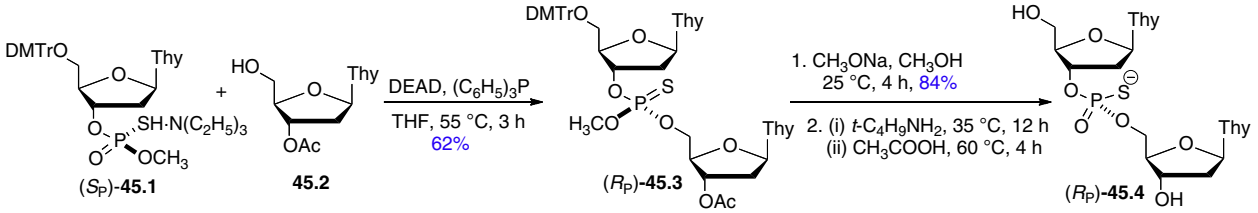
In 2008, Miller and coworkers described the first enantioselective synthesis of an *ent*-phosphatidylinositol 5-phosphate (PI5P) analog, employing asymmetric phosphorylation, selective monodebenzylation, and subsequent Mitsunobu reaction to afford the key intermediate **44.3**.[122] Notably, the yield of this step was dependent on the selective protection of C3 hydroxyl group and higher yields were obtained with benzyloxycarbonyl group (Scheme 44).



Scheme 44

In addition to its use in carbohydrate chemistry, the Mitsunobu reaction with phosphates has also been applied in the total synthesis of natural products. In 2000, Sorenson and coworkers accomplished the total synthesis of immunosuppressant FR901483 (**44.6**; Scheme 44) enantioselectively employing a selective Mitsunobu reaction.[123] Interestingly, starting from **44.4**, installation of the phosphate group via Mitsunobu reaction occurred selectively with inversion at C8, albeit in moderate yields, to afford the key intermediate **44.5** (Scheme 44), which was later converted to the natural product **44.6** over two steps.

In 2006, Hayakawa and coworkers reported the synthesis of pure phosphate/phosphorothioates(PO/PS)-chimeric oligodeoxyribonucleotides by employing the Mitsunobu reaction to couple phosphorothioate (S_P)-**45.1** and 5′-*O*-free thymidine partner **45.2** to afford (R_P)-dithymidine phosphorothiate **45.3** (Scheme 45).[124] Subsequent alcohol and phosphorothiate deprotection then afforded phosphorothioate diester **45.4** in two steps.



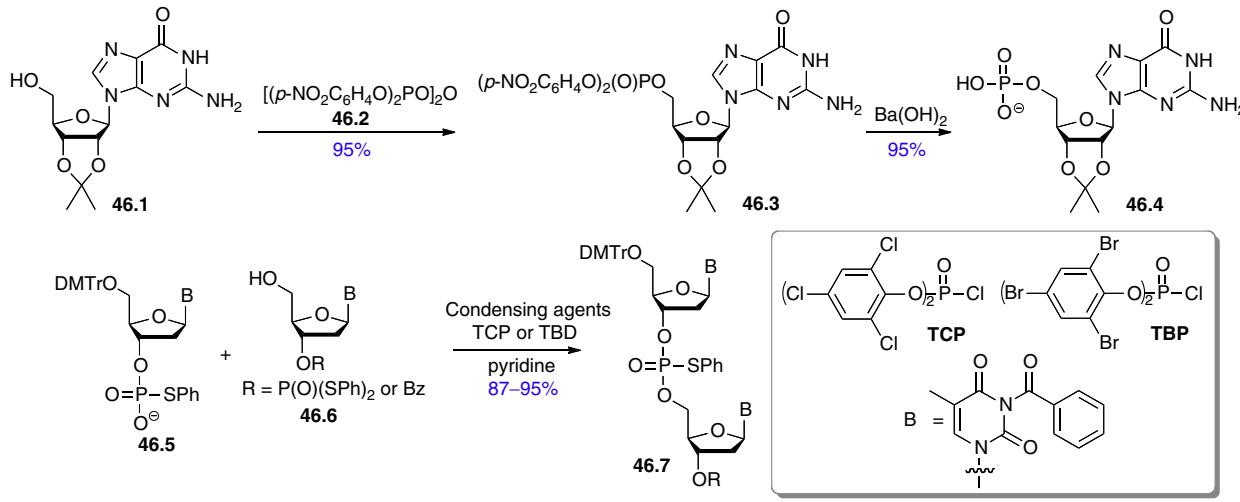
Scheme 45

6.12.2.4 Pyrophosphates

The term pyrophosphate refers to chemical compounds that encompass the esters, salts, and anions of pyrophosphoric acid. Most notably, free pyrophosphoric acid (phosphoric anhydride, PP_i) serves as a source of inorganic phosphate in the body (see Figure 1) and is stable under standard basic conditions. As discussed in the previous book chapter,[23] pyrophosphoric acids can be employed as phosphorylating agents (most commonly to generate di- and triphosphate-containing intermediates), and though phosphorylation with pyrophosphates was not a highly utilized method in the past, new 'biomimetic' developments in this field have led to a dramatic increase in their use, especially in the synthesis of inositol derivatives, *vide infra*.

In 1993, Berridge published a review in *Nature* that summarized the calcium signaling pathways involving inositol trisphosphate.[1a] This discovery initiated renewed interest in the use of pyrophosphate in chemical biology and, in particular, inositol phosphate pyrophosphate/polyphosphate chemistry. Phosphorylation with pyrophosphates is now one of the most widely employed methods in carbohydrate chemistry, and a variety of different strategies have been developed for utilizing pyrophosphates in phosphorylation.

In a seminal publication in 1957, Chambers and coworkers reported the synthesis of guanosine 5′-phosphate **46.4** via the use of tetra-*p*-nitrophenyl pyrophosphate (**46.2**) (Scheme 46).[125] Early approaches to phosphorylation with pyrophosphates include the utilization of sterically hindered diaryl phosphorochloridates – namely, bis(2,4,6-trichlorophenyl) phosphorochloridate (TCP) and bis(2,4,6-tribromophenyl) phosphorochloridate (TBP) – as condensing agents, which, when allowed to react with phosphodiester component **46.5**, in the presence of pyridine, generates a more reactive unsymmetric pyrophosphate. This higher energy



Scheme 46

intermediate then smoothly couples with protected nucleoside **46.6** to afford the desired product **46.7**, in the presence of an activating agent such as an appropriate azole.[126]

Recently developed pyrophosphate-based methods usually involve the generation of the alkoxide with a suitable base (generally, organolithium bases, lithium diisopropylamide (LDA),[127] lithium hexamethyldisilazide (LiHMDS),[128] OR $LiN(TMS)_2$[129]), subsequent attack of the alkoxide on the pyrophosphate, followed by leaving group elimination, to furnish the desired phosphate. Notably, benzyl pyrophosphates have found extensive use in the generation of phosphates due to the ease of benzyl deprotection with catalytic hydrogenation. In 1998, Werner and coworkers reported the synthesis of LY-307853 (the phosphate prodrug of the FDA-approved antifungal drug LY-303366) via the use of tetrabenzyl pyrophosphate (TBPP) with LiOH in DMF, to furnish the prodrug in excellent yield (96%).[130]

In 2008, Kline and coworkers synthesized three sets of 4-deoxy-L-arabinose analogs, as potential inhibitors of Gram-negative bacterial resistance, utilizing a phosphorylation protocol with TBPP (Scheme 47).[131] 4-Azido **47.1** was converted to its alkoxide and phosphorylated with TBPP, which, upon a modified Staudinger phosphorylation of the azide with trimethyl phosphine, subsequent benzyl deprotection with H_2 and Pd/C in MeOH and treatment with Et_3N, furnished α-anomer **47.2** (Scheme 47).

In 2004, Finney and coworkers employed TBPP and LDA in the phosphorylation of **47.3** to furnish **47.4** in excellent overall yields (Scheme 47).[132] In 2008, Fairbanks and coworkers reported the phosphorylation of inositol derivatives **47.5** utilizing TBPP and LDA to afford *cis*-products **47.6**, exclusively, in good yield.[133] Subsequent benzyl deprotection and addition of Et_3N in MeOH produced the desired ammonium phosphate salts (**47.7**) in 89–93% yield over two steps.

In 2011, Fukase, Fujimoto, and coworkers reported the synthesis of a number of proinflammatory *Helicobacter pylori* lipopolysaccharides via the phosphorylation of common intermediate **48.1** (Scheme 48).[134] Deprotonation of **48.1** with LiHMDS, followed by coupling with TBPP in THF at −78 °C and simultaneous benzyl and *p*-methoxybenzyl (MPM) deprotection, yielded α-anomer **48.2** in good overall yield.

In 1987, Watanabe and coworkers published a protocol for the diphosphorylation of *myo*-inositol derivatives (**49.2**, **49.4**, and **49.6**), utilizing *n*BuLi and LDA in coordination with TBPP, to afford phosphate triesters **49.3**, **49.5**, and **49.7** in good yield (Scheme 49).[135] Interestingly, the authors noted that monophosporylation of the diols was not observed, though equimolar amounts of lithium salt was used. Instead, diphosphorylation products were isolated in addition to unreacted starting material, and complete diphosphorylation was accomplished using excess lithium salt. The authors also found that phosphorylation of acetyl- and phosphate-protected inositol derivatives **49.4** and **49.6** proceeded in good yields with milder base, LDA, which allowed for phosphorylation in the presence of acetate-protecting groups.

In 2007, Percy and coworkers were able to access a conformationally locked difluorinated pentopyranose analog **50.2** from cyclooctenone **50.1** (Scheme 50).[136] Initial attemps at chemoselective phosphorylation of the pseudoanomeric hydroxyl group using *n*-BuLi resulted in poor conversion and selectivity toward the desired monophosphorylated product **50.3**. Alkoxide formation with sodium hexamethyldisilazide (NaHMDS), in the presence of Na-selective 15-crown-5 provided higher but still not satisfactory yield and selectivity. However, acetyl protection of the C4 hydroxy group to **50.5**, followed by phosphorylation with NaHMDS (15-crown-5 additive), generated desired phosphate triester **50.6** in a modest but acceptable 64% yield. Subsequent acetate and benzyl deprotection and salt formation with Et_3N in $MeOH/H_2O$ generated difluorinated pentapyranose phosphate **50.7** in good yield.

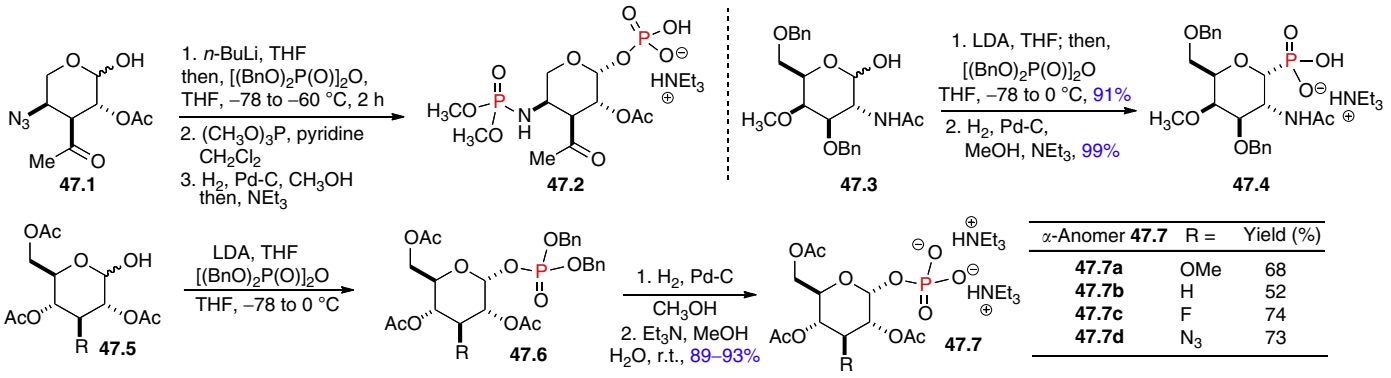
In 2005, Schlewer and coworkers published a TBPP-mediated phosphorylation protocol in the synthesis of *myo*-inositol trisphosphate derivative **51.2**, which was found to be an effective second messenger full agonist of an endogenous D-*myo*-inositol 1,4,5-tris(phosphate) G-protein-coupled receptor (Scheme 51).[137] Alkoxide formation of **51.1** with NaH and successive coupling with TBPP, in THF, followed by 5-min benzyl deprotection with $Pd(OH)_2$ under microwave (μW), generated trisphosphorylated product **51.2** (Scheme 51).

In 1996, Frost and Migaud synthesized 2-deoxy-myo-inositol 1-phosphate (dMIP) **52.2** a possible inhibitor of 1-phosphate synthase (Scheme 52).[138] Phosphorylation of 2-deoxymyo-inositol (**52.1**) with NaH, in refluxing THF, and TBPP afforded fully protected dMIP, which, upon hydrogenolysis, was smoothly converted to the desired dMIP **52.2**.

Six years later, Raboisson and coworkers reported the synthesis of cyclic phosphate **53.5** and bisphosphate **53.3** via a *t*BuOK/TBPP reaction protocol (Scheme 53).[70c] Stereospecific reduction of **53.1** with $NaHB(OAc)_3$ and K-selectride afforded *trans*-diol **53.2** and *cis*-diol **53.4**, respectively. Phosphorylation with TBPP, in the presence of *t*BuOK, followed by *N*-methyl-*N*-phenyl amine- and benzyl-deprotection, furnished diphosphorylated product **53.3** from *trans* 1,3-diol **53.2** and cyclic phosphate **53.5** from *cis*-diol **53.4**, where spatial proximity of the 1,3-diols allowed for rapid cyclization of the phosphorylated intermediate.

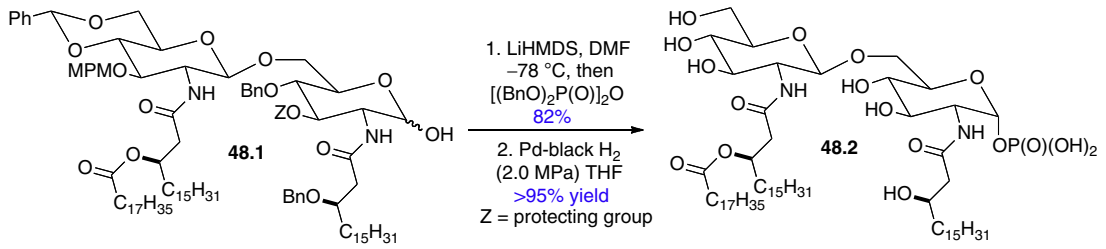
In 2010, Kuo and coworkers were able to convert quinolinones **54.1** and **54.4** to the phosphorylated derivatives, such as **54.3**, to improve the hydrophilicity of quinolinones in pursuit of new platelet aggregation inhibitors (Scheme 54).[139] Monophosphorylation was achieved utilizing TBPP $[(BnO)_2P(O)]_2O$, NaH in THF, to yield enol phosphate **54.2**, which was converted to monosodium phosphate salt **54.3** for biological screening. Although this protocol was efficient for the synthesis of **54.3** and several derivatives thereof, an attempt to use the same strategy on selenophone-containing **54.4** was unsuccessful, as hydrogenation resulted in the removal of the phosphate and ring opening of the selenophene, to afford the alkyl-containing quinolinone **54.6**.[140]

In the same year, Kuo and coworkers also accomplished the diphosphorylation of the quinolinone derivatives, such as **55.1** (Scheme 55).[141] Deprotonation of **55.1** with NaH and subsequent trapping of the phenoxide and enolate with TBPP furnished intermediate bis-phosphate **55.2**. Enol phosphate hydrolysis with MeOH (to **55.3**), followed by debenzylation and treatment with $NaHCO_3$ afforded disodium phosphate salt **55.4** in moderate yield.

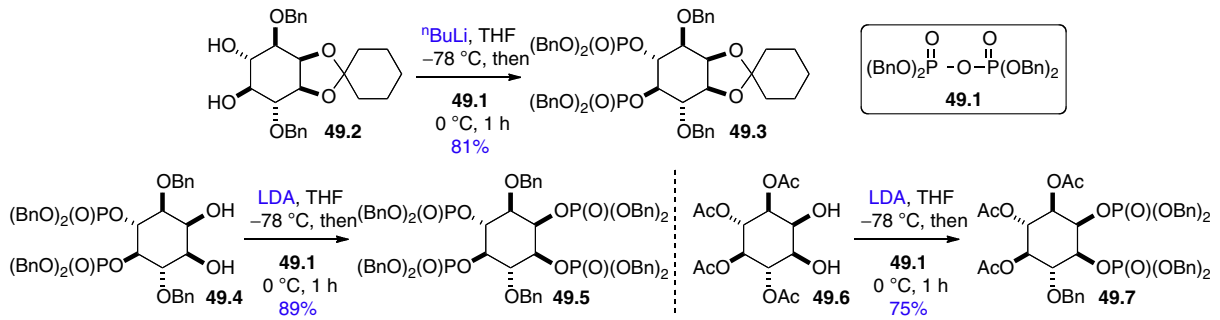


α-Anomer **47.7**	R =	Yield (%)
47.7a	OMe	68
47.7b	H	52
47.7c	F	74
47.7d	N_3	73

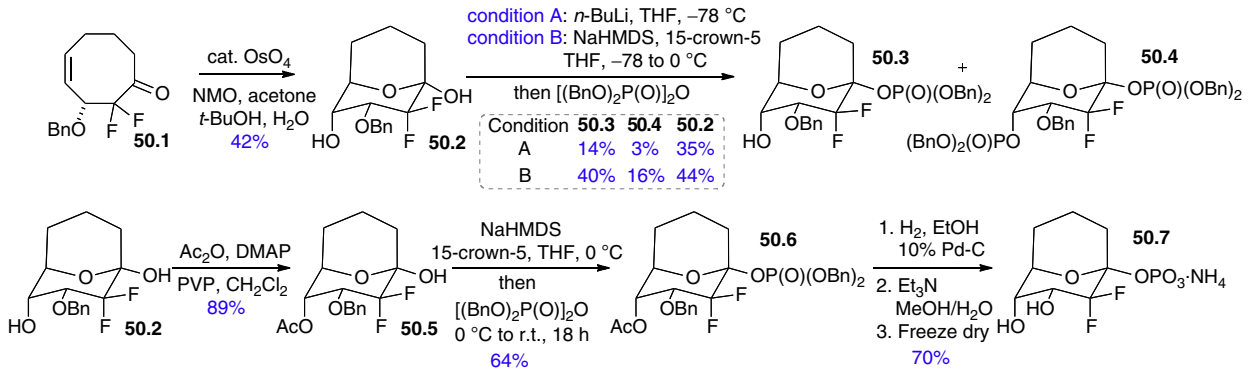
Scheme 47



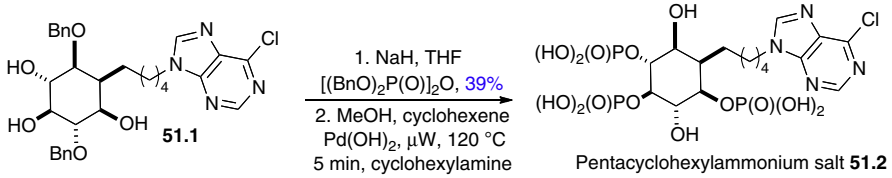
Scheme 48



Scheme 49



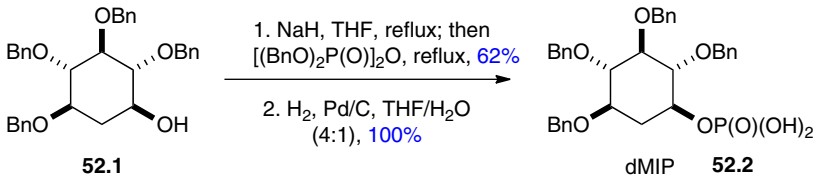
Scheme 50



Scheme 51

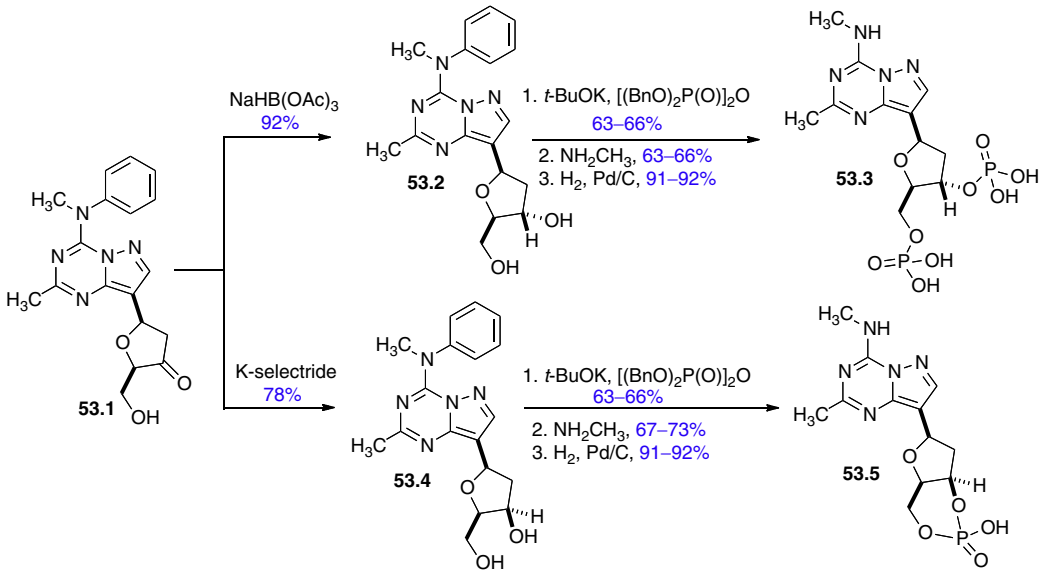
In 2012, O'Neill applied the same method described above to access phosphorylated bisaryl quinoline prodrugs targeting *Plasmodium falciparum* type II NADH:ubiquinone oxidoreductase (PfNDH2) (Scheme 56).[142] Enolate formation of **56.1** by treatment with NaH, followed by *O*-phosphorylation with TBPP and debenzylation, afforded enol phosphate **56.2** in good overall yield.

In addition to the previously discussed methods, a number of recent phosphorylation strategies involve the use of pyrophosphates and facilitating transition metal additives that allow for the elimination of strong bases or oxidants within the phosphorylation protocol. In 2005, Watanabe utilized nBu$_2$SnO to achieve regioselective phosphorylation of 1,2-cyclohexylidene-*myo*-inositol



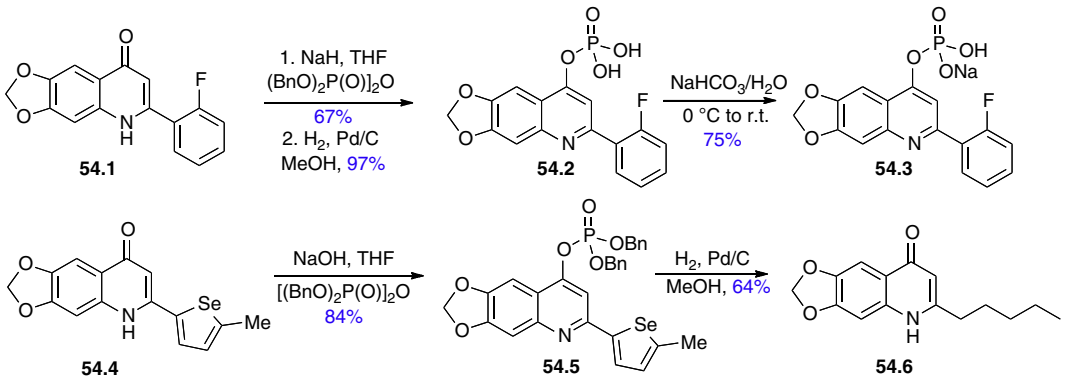
52.1 dMIP 52.2

Scheme 52



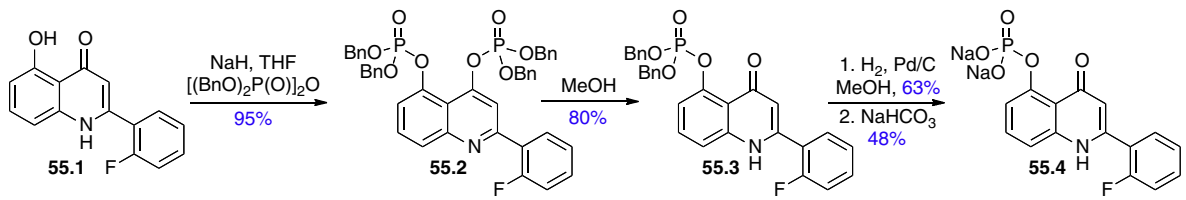
53.1 53.2 53.3 53.4 53.5

Scheme 53



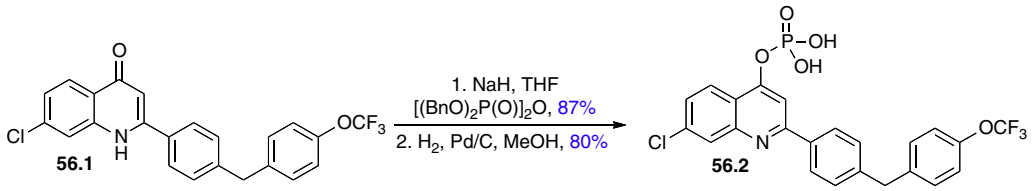
54.1 54.2 54.3 54.4 54.5 54.6

Scheme 54



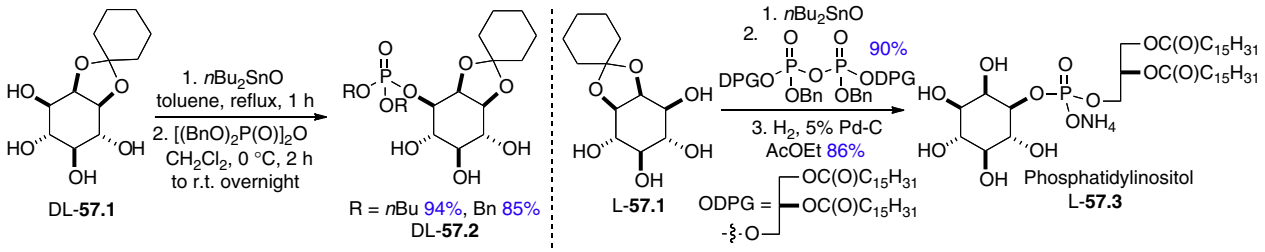
55.1 55.2 55.3 55.4

Scheme 55



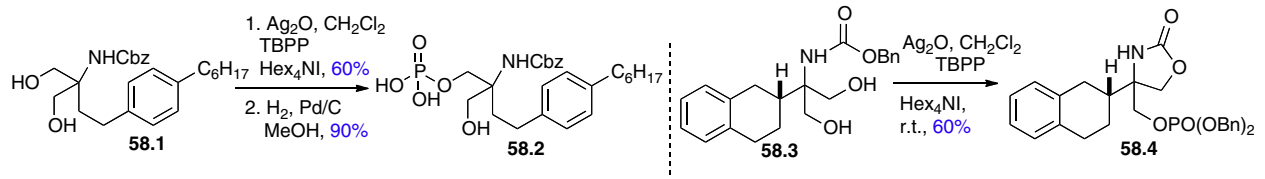
Scheme 56

57.1, furnishing the 3-phosphate moieties **57.2** and **57.3** in 85–90% yields (Scheme 57).[143] Addition of nBu$_2$SnO to DL-**57.1** in refluxing toluene to form the corresponding stannylene, followed by treatment with TBPP or [(BnO)$_2$P(O)]$_2$O in CH_2Cl_2 afforded phosphorylated product DL-**57.2**. Importantly, the authors noted that the use of alternative phosphorylating reagents (phosphorochloridates and phosphorobromidates) were inefficient, as they resulted in low yield or a mixture of multiphosphorylated products. In an impressive application of this method, the authors were able to accomplish a concise synthesis of phosphatidylinositol (PI) **57.3** with the natural configuration from inositol L-**57.1** in high overall yield.



Scheme 57

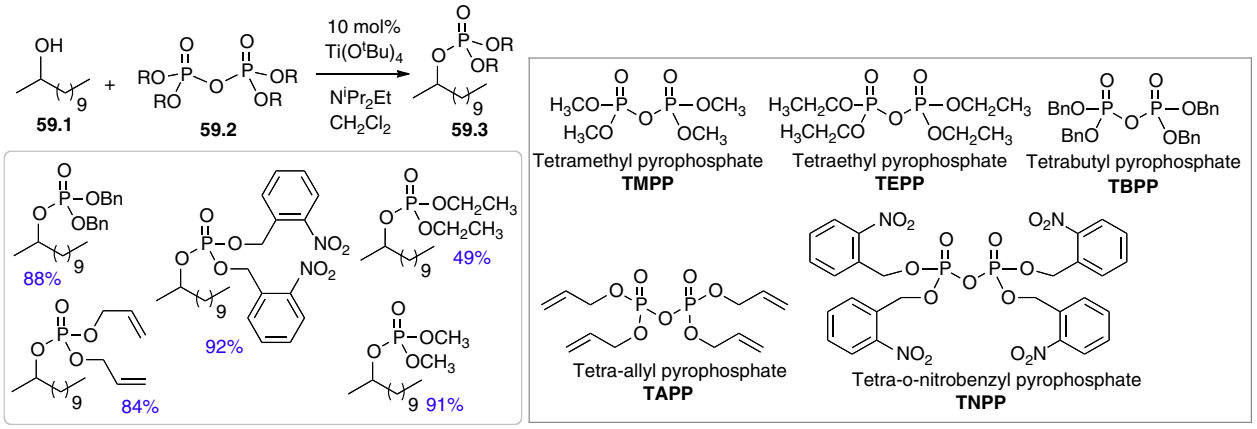
In 2005, Takeda and coworkers reported Ag-mediated direct monophosphorylation of 1,3-diols, which was later applied to the synthesis of FTY720-phosphate, a sphingosine-derived immunosuppressant.[144] In this protocol, diol-**58.1** was treated with Ag_2O, TBPP, and Hex_4NI in CH_2Cl_2 at room temperature to synthesize monophosphorylated product **58.2** (Scheme 58). In the development of this method, studies have shown a general preference for the phosphorylation of primary and phenolic alcohols over secondary and aliphatic hydroxy groups, and the authors noted that the proximity of the two hydroxyl groups to one another had a direct effect on the yield of the phosphorylation step, due to a decrease in effective chelation of the silver between the two hydroxyl moieties. In 2010, Ma and coworkers further demonstrated the utility of this method, by applying it towards the synthesis of orally active tetralin sphingosine 1-phosphate agonist prodrugs (Scheme 58).[145]



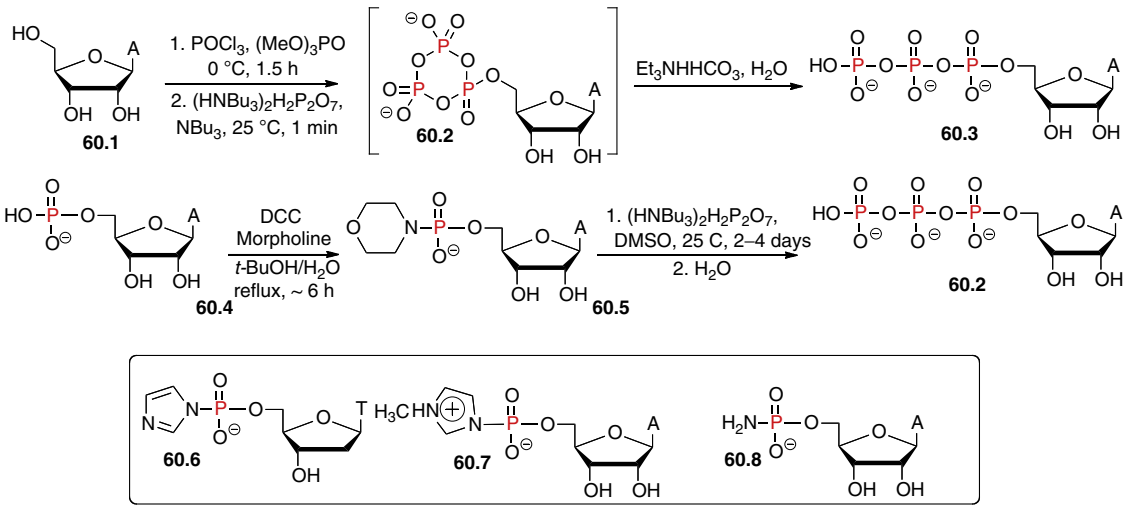
Scheme 58

In 2012, Sculimbrene and coworkers developed a Lewis acid-catalyzed phosphorylation protocol utilizing a variety of pyrophosphate tetraesters **59.2** (Scheme 59).[146] A range of Lewis acids including Ti(O^{i}Pr)$_4$, Ti(O^{t}Bu)$_4$, Sc(OTf)$_3$, and Bi(OTf)$_3$ were investigated. Ti(O^{t}Bu)$_4$ was proved to be the most effective catalyst for both primary and secondary alcohols utilizing TBPP. Other tetrasubstituted pyrophosphates were tested and were all demonstrated to be effective under such condition.

The marriage of $POCl_3$ and pyrophosphate-based reagents is also widely used in the synthesis of nucleoside triphosphates, as shown in a 2000 review by Burgess and Cook.[147] In an extension of a previous work by Yoshikawa et al. (Scheme 60),[29f] Ludwig demonstrated that the resultant chlorophosphate intermediate formed by the treatment of nucleosides **60.1** with $POCl_3$, in the presence of trialkyl phosphate esters as accelerators, can be further treated with bis(tributylammonium)pyrophosphate $(HNBu_3)_2H_2P_2O_7$ to yield nucleoside triphosphates **60.3** through the trimetaphosphate intermediate **60.2**.[148] Similarly, strategies involving the treatment of phosphoramidate **60.5**, or other activated nucleoside phosphate intermediates such as **60.6–60.8** with pyrophosphate salts have also been utilized to access nucleoside triphosphates **60.2**, and were also covered in the same review.[147]



Scheme 59

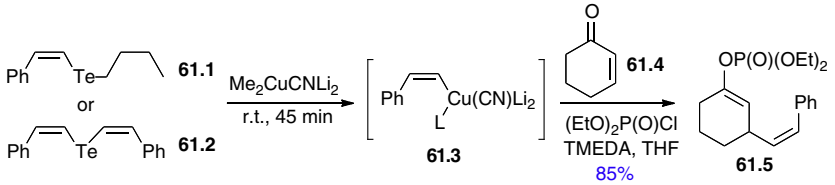


Scheme 60

6.12.2.5 Enol Phosphates (Vinyl Phosphates)

The chemistry and properties of enol phosphates were first reviewed in 1961.[149] Enol phosphates have since emerged as versatile intermediates in organic synthesis, as they can be easily elaborated into valuable building blocks.[150,151] The most common method to generate enol phosphates involves the treatment of ketones/aldehydes with an appropriate base to allow for the trapping of the resulting enolate intermediate with dialkyl phosphorochloridates.[152] In the previous book chapter, the authors primarily highlight the use of vinyl phosphates (enol phosphates) – in particular, iminoether type enol phosphates generated *in situ* by dicyclohexylcarbodiimide (DCC)-mediated coupling of phosphoric mono- and diphosphate esters with free alcohols – to afford new phosphate diesters and triesters.[23] However, recent advances in the synthetic utility of enol phosphates[150,151] have prompted efforts devoted to the development of methods for their installation and further diversification.

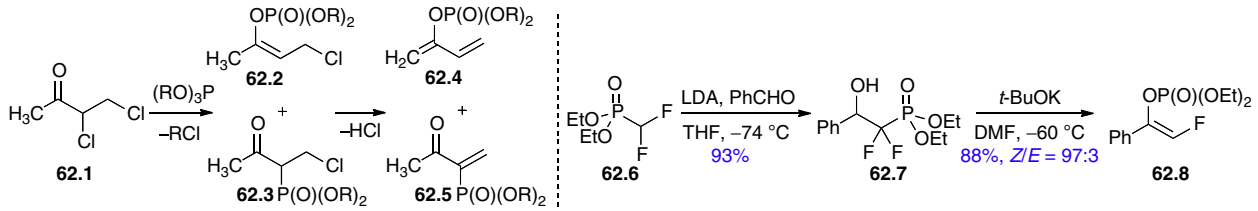
In 2000, Comasseto and coworkers reported the formation of *Z*-vinylic cyanocuprates **61.3** via transmetalation reaction between *Z*-vinylic tellurides **61.1** and **61.2** and higher order cyanocuprates (Scheme 61).[153] Subsequent conjugate addition of the



Scheme 61

cuprates to enones **61.4**, followed by trapping of the resultant enolate via *O*-phosporylation, produced enol phosphates **61.5** in excellent yield. Trapping was also demonstrated with silyl enol ethers and enol triflates.

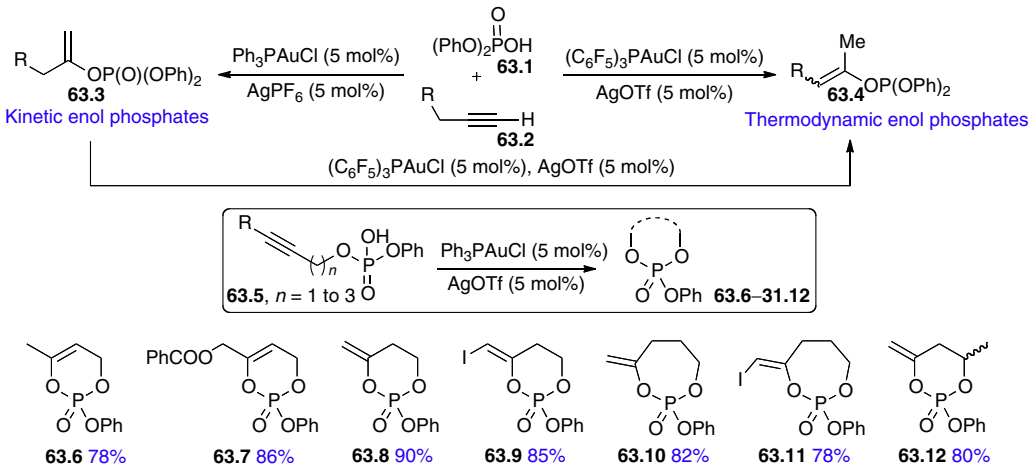
Enol phosphates can also be prepared through use of the Perkow reaction, in which a phosphite reacts with α-halo carbonyl compounds, followed by a rearrangement, to unveil the vinyl phosphate group (see Section 6.12.3.2 on Phosphite).[149,154] Similarly, utilizing 3,4-dichlorobutanone **62.1** with trialkyl phosphites results in a mixture of dialkyl enol phosphate **62.4** (by the intermediate **62.2**, which is the product of the Perkow reaction) as the major product and phosphonate esters **62.5** (by the intermediate **62.3**, product of Michaelis–Arbuzov reaction) on elimination of HCl (**Scheme 62**).[155]



Scheme 62

In 2009, Beier and coworkers utilized the phosphorus–Brook rearrangement of difluorophosphonate **62.7** in the synthesis of (*Z*)-fluoroenol phosphate **62.8** (**Scheme 62**).[156] Aldol coupling of difluoromethylphosphonate **62.6** and benzaldehyde, in the presence of LDA, generated intermediate **62.7**, which, upon alkoxide formation with *t*BuOK, underwent a [1,4]-phosphorus–Brook rearrangement to yield (*Z*)-fluoro-enol phosphate **62.8** in excellent yield and selectivity.

In 2010, Lee, Kim, and coworkers developed a catalytic hydrophosphoryloxylation of alkynes using diphenyl phosphate [$(PhO)_2P(O)OH$], where ligand-specific Au(I)-catalysis resulted in selective formation of either the kinetic or thermodynamic enol phosphate (**Scheme 63**).[157] Conversion of kinetic enol phosphates **63.3** (generated by the reaction of phosphate **63.1** with alkyne **63.2**) to thermodynamic enol phosphates **63.4** was accomplished by utilizing $(C_6F_5)_3PAuCl$, in the presence of AgOTf. In 2011, the same group synthesized alkynyl hydrogen phosphates **63.5** by the treatment of alkynols with phosphorodichloridates.[158] These alkynyl hydrogen phosphates underwent 6-*endo-dig*, 6-*exo-dig*, or 7-*exo-dig* cyclizations in the presence of Au(I) catalyst to furnish six- andseven-membered cyclic enol phosphates **63.6–63.12** in good to excellent yield.

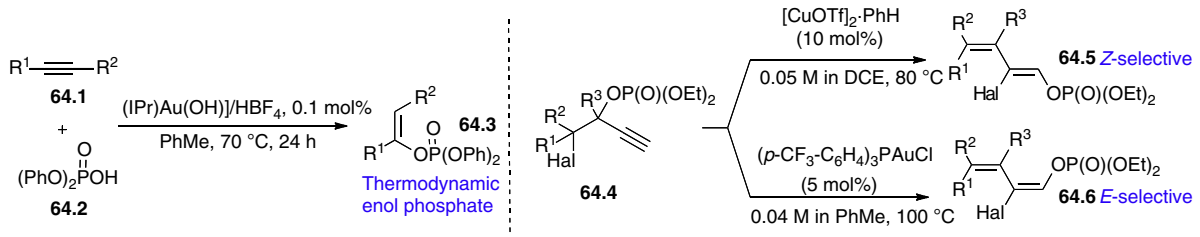


Scheme 63

In 2012, Nolan and coworkers reported Ag-free synthesis of thermodynamic alkenyl enol phosphates **64.3** from alkyne **64.1** and diphenylphosphate diesters **64.2** (**Scheme 64**).[159] The addition of diphenyl phosphate to the actived alkynes furnished *trans*-addition products in a regio- and stereoselective manner, using *in situ*-generated cationic Au(I) complexes formed from the mixing of precatalyst [Au-(IPr)(OH)] and HBF_4.

In 2012, Gevorgyan and coworkers reported the use of Cu- or Au-catalysis in a selective migratory cascade reaction with α-halogen-substituted propargylic phosphates **64.4** to generate highly functionalized 1,3-dienes.[160] Occurring through either of the two catalytic pathways (Cu- or Au-mediated), this stereodivergent method allowed the generation of both (*Z*)-**64.5** and the (*E*)-1,3-dienes **64.6** from propargylic phosphates **64.4**.

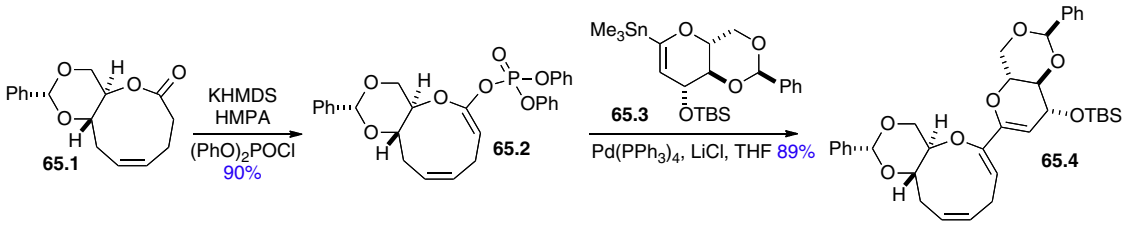
As previously mentioned, the synthesis of enol phosphates has gained prominence due to their application in a wide range of cross-coupling reactions (such as Stille, Suzuki-Miyaura, Negishi, Kumada, Sonogashira, and Mizoroki-Heck reactions) *en route* to complex synthesis.[159] In particular, the Pd-catalyzed synthesis of *N*- and *O*-heterocycles from enol phosphate precursors has



Scheme 64

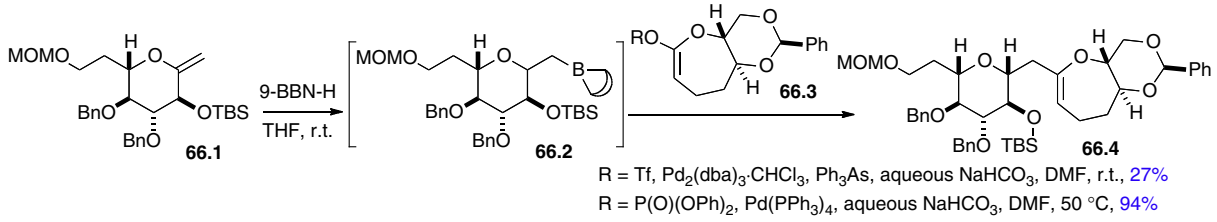
emerged as a significant faction in the realm of Pd-couplings and was highlighted in a recent review.[151] In addition, enol phosphates are more stable than their enol triflate counterparts, which tend to be expensive and corrosive, and more robust than their silyl ether analogs, which are, in general, more sensitive to a variety of reaction conditions. Thus, enol phosphates have emerged as useful alternatives to traditional protecting/trapping groups in reactions that incorporate the use/generation of carbon enolates.

In 1997, Nicolaou and coworkers published the synthesis of nine-membered lactone-derived enol phosphate **65.2** en route to the synthesis of functionalized cyclic enol ethers (Scheme 65).[18] Enol phosphate **65.2** was synthesized from lactone **65.1** utilizing KHMDS, HMPA and $(PhO)_2POCl$. Subsequent Stille coupling with stannane **65.3** provided cyclic enol ether **65.4** in 89% yield. In addition, a series of lactone-derived enol phosphates and their application in the Stille coupling have been demonstrated with vinylstannanes to provide the corresponding dienes, where, in contrast, the use of vinyltriflate technology has suffered from failure or low yield.



Scheme 65

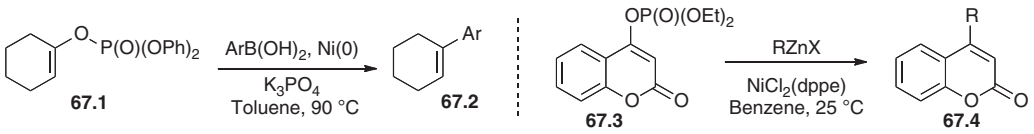
In 1999, Sasaki and coworkers demonstrated that enol phosphates [R=P(O)(OPh)$_2$] were superior to enol triflates (R=SO_2CF_3) in the Suzuki–Miyaura coupling between alkylborane **66.2** (synthesized from hydroboration of alkene **66.1**) and the enolic compound **66.3***en route* to the enol ether subunit **66.4**.[161] Utilizing the same conditions in the Suzuki–Miyaura coupling of a variety of medium-sized cyclic enol phosphates (six- to nine-membered), the authors completed the synthesis of the ABCD-ring fragment of the natural product CTX3C (Scheme 66).



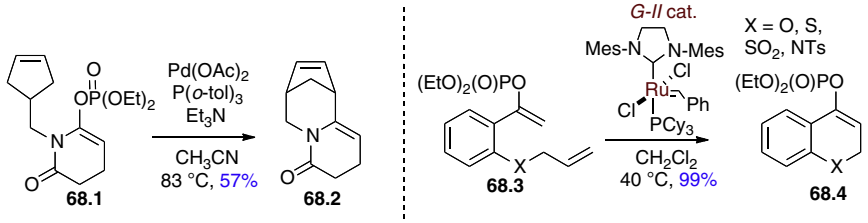
Scheme 66

In 1999, Yang and Nan reported the first utilization of cyclohexenylphosphate **67.1** in the nickel(0)-catalyzed Suzuki cross-coupling reaction with various arylboronic acids to furnish coupled products **67.2** (Scheme 67).[162] In 2001, Yang and Wu described the Ni-catalyzed Negishi cross-couplings of 4-diethylphosphonooxycoumarins **67.3** with a variety of organozinc reagents to generate 4-substituted coumarins **67.4** at room temperature.[163] The yields are generally high for arylzinc halides, although alkylzinc bromides produced product in only moderate yields.

In 2000, Coe and coworkers developed an intramolecular Heck cyclization on enol phosphate **68.1** to construct the tricyclic skeleton of compound **68.2** in their total synthesis of (±)-cytisine (Scheme 68).[164] While both enol triflate and phosphate underwent cyclization, the phosphate-activated intermediates were found to be more robust.



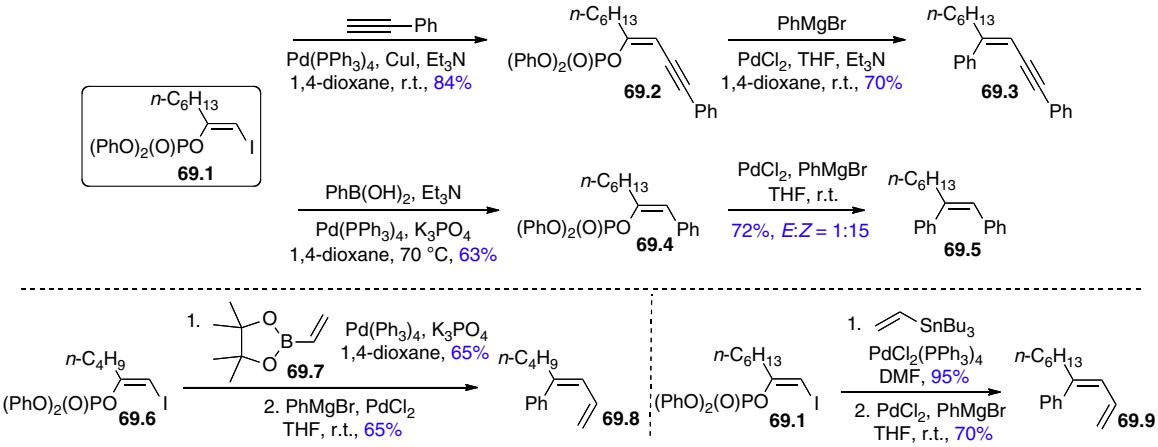
Scheme 67



Scheme 68

In 2003, Hanson and coworkers demonstrated the first RCM of an enolphosphate using the Grubbs second generation catalyst $[(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh]$[49] and showed facile generation of a variety of cyclic enol phosphates **68.4**.[165]

In 2011, Kim, Lee, and coworkers demonstrated an impressive regio- and stereoselective synthesis of trisubstituted alkenes via different Pd-catalyzed consecutive cross-coupling reaction sequences, as shown in **Scheme 69**.[157] Bisfunctional (*Z*)-alkenyl iodophosphates **69.1**, prepared via a previously reported Au-catalyzed reaction, were coupled in a Sonogashira/Kumada reaction sequence with ethynylbenzene and PhMgBr, through intermediate **69.2**, to yield (*Z*)-3-en-1-yne product **69.3**. Similarly, product **69.5** was synthesized through a Suzuki/Kumada reaction sequence involving intermediate **69.4**. Treatment of **69.6** with vinylboronic acid pinacol ester **69.7**, followed by coupling with PhMgBr to furnish an alternative Suzuki/Kumada sequence leading to (*Z*)-1,3-diene **69.8**. At last, the authors showed a Stille/Kumada sequence to generate the (*Z*)-1,3-diene **69.9** from (*Z*)-alkenyl iodophosphates **69.1**.



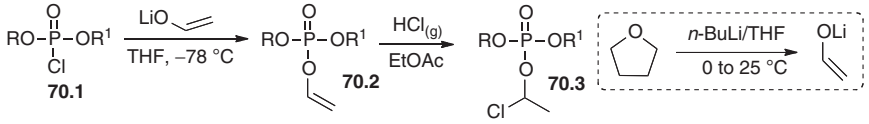
Scheme 69

In 2005, Kumpulainen reported a useful, proficient, and straightforward method for the preparation of various 1-chloroethyl phosphates **70.3** and phosphoramidates (**Scheme 70**).[166] These were synthesized from the enol phosphates **70.2** (formed via the coupling of *in situ* generated allyl lithium species with phosphorochloridate **70.1**) by treating with HCl in EtOAc.

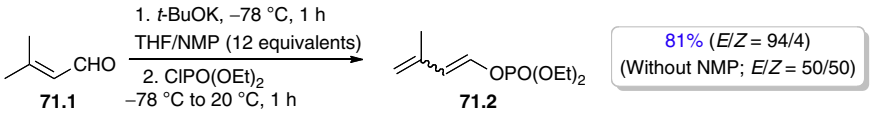
In 2008, Gager and coworkers demonstrated the first stereoselective method of preparation of (*E*)-dienol phosphates **71.2** from unsaturated aldehydes, such as **71.1**, via the stereoselective enolization of conjugated alkenals by ^{t}BuOK in the presence of *N*-methylpyrrolidinone (**Scheme 71**).[167]

6.12.2.6 Miscellaneous

As the synthesis of organophosphates is a broad and diverse area of science, an extremely large number of unique methods and interesting technologies to access a wide array of phosphate-containing substrates have been established. However, as the purpose



Scheme 70

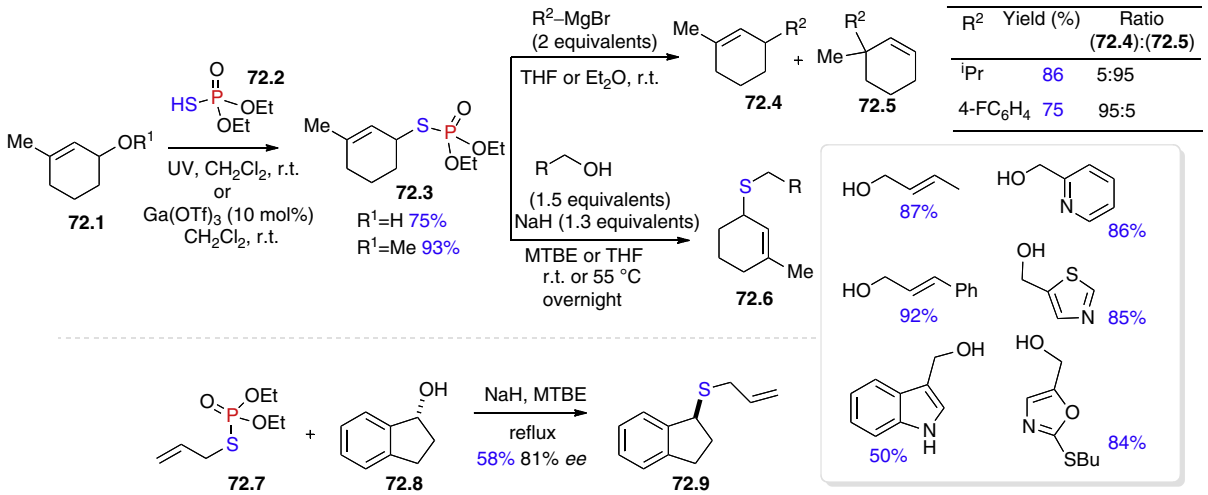


Scheme 71

of this chapter is to highlight the recent advances in these developments and not to serve as a complete listing of every available preparation, there are a certain number of substrates and transformations which are useful for the generation of phosphates and phosphate derivatives that, unfortunately, will not be covered in this review. Thus, for a detailed, historical perspective on the use of phosphoric-arenesulfonic anhydrides, acyl phosphates, phosphoryl phenoxides, and triphenylphosphonium salts of phosphoric acid ester in the synthesis of phosphates, please see the previous book chapter (Comprehensive Organic Synthesis I: Chapter 2.8 Inorganic Acid Derivatives) with which this review shares its name.[23]

6.12.2.6.1 Thiophosphates

Thiophosphates have been utilized as important synthetic tools in many synthetic strategies, due to their synthetic utility (particularly, alkylating ability) as well as biological significance.[168] In 2010, Jimmy Wu and coworkers reported the synthesis of allylic phosphothioate **72.3** as a key intermediate for transition-metal-free allylic displacement reactions, employing photochemically promoted substitution of alcohols **72.1** with phosphothioric acids **72.2**, which can be synthesized in multigram scale with diethyl phosphite and S_8 (Scheme 72).[169] However, this transformation was limited to γ,γ-disubstituted allylic alcohols, such as **72.1**. Primary, secondary, and tertiary aliphatic alcohols and benzyl alcohols did not participate. Despite this limitation, the alkylation reaction (Grignard addition) was shown to be broadly applicable to a wide range of nucleophiles and tolerant of both electron-withdrawing and donating groups as well as vinylic substrates. Moreover, both primary and secondary alkyl Grignard reagents also participate in the substitution reaction. Interestingly, aromatic and alkenyl neucleophiles underwent the S_N2-type displacement to provide **72.5** selectively; whereas, secondary aliphatic Grignard reagents provide the S_N2'-type displacement product **72.4** as the major product.

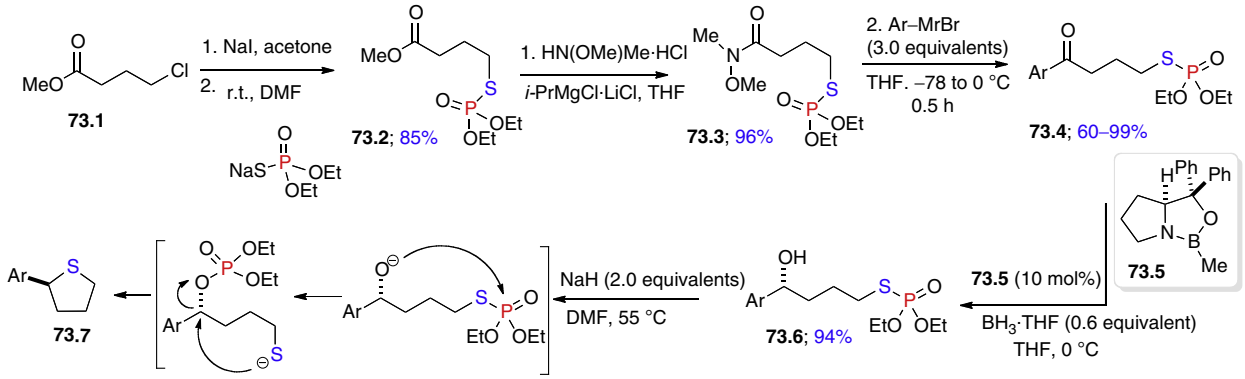


Scheme 72

In that same year, Wu and coworkers further developed a $Ga(OTf)_3$-catalyzed direct substitution protocol, used to generate **72.3** that possessed a greater substrate scope to include a larger variety of alcohol starting materials.[170] However, although tertiary alcohols were smoothly converted to their corresponding thiophosphates, allylic or aromatic substitution is required for the reaction to proceed with secondary and primary alcohols. Analogously, the coupling of phosphorothioate ester **72.3** with an appropriate alkoxide, generated by treatment with NaH in THF, furnished thioethers **72.6** in excellent yields (Scheme 72). Most notably, this protocol is compatible with substrates containing a series of potentially sensitive functionalities, including nitriles,

esters, and unprotected indole nitrogens, as well as a wide range of nitrogen-, oxygen-, and sulfur-containing heterocycles. Wu and coworkers further illustrated the application of phosphothioate in the synthesis of chiral, nonracemic thioethers **72.9** (Scheme 72) with an overall inversion of stereochemistry from **72.7**.[171]

In 2012, Wu and coworkers reported another application of thiophosphates in the synthesis of tetrahydrothiophenes **73.8** (Scheme 73).[172] Thiophosphate **73.2** was obtained from an iodoester intermediate, which was obtained from the corresponding choloroester **73.1** via the alkylation of a phosphorothioic acid precursor. Weinreb amide formation, followed by Grignard addition, afforded keto thioesters **73.4** in good to excellent yields. Asymmetric reduction of **73.4** with Corey–Bakshi–Shibata catalyst **73.5** provided the cyclization precursor **73.6**, which, upon treatment with NaH, afforded tetrahydrothiophenes **73.7** in excellent yields.

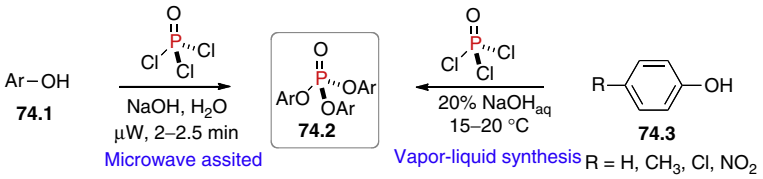


Scheme 73

6.12.2.6.2 Triaryl phosphates

Triaryl phosphates [$(ArO)_3PO$] have important applications in several different industrial processes, namely in the production of plasticizers for cellulose acetate, polyvinylchloride and vinyl polymers, lubricating oil additives, flame retardants, and hydraulic acids.[173] In the 1970s, the most common preparation of triaryl phosphates was the coupling of $POCl_3$ with phenols, at high temperatures (160–250 °C), in the presence of a Lewis acid catalyst (Mg, Ca, Al or $MgCl_2$, $CaCl_2$, or $AlCl_3$).[174] To avoid the need for higher temperatures (which are necessary for successive displacement of the chlorine atoms of $POCl_3$), in the 1980s an approach was introduced involving phase transfer catalysis at room temperature, which employed tricaprylmethylammonium chloride and PEGs.[175] In 1994, Sagar and coworkers reported a simple method to synthesize triaryl phosphates with polymer-supported phenoxide and $POCl_3$, and in 1997, Cajaiba da Silva developed a 'one-pot' synthesis of sodium phenoxides with $POCl_3$.[176]

In 2000, Sagar and coworkers reported a facile and environmentally friendly, microwave-assisted method for the synthesis of triaryl phosphates **74.2** (Scheme 74).[177] Phenols **74.1** were treated with NaOH and $POCl_3$, in the presence of a small amount of water, under microwave conditions for 2–2.5 min, to provide triaryl phosphates **74.2** in 87–90% yields. In addition to the decreased reaction times, the use of solvent- and catalyst-free conditions, as well as compatibility with normal atmospheric conditions (i.e., no need for inert gas), have established this method as an attractive means of generating triaryl phosphates.



Ar	Time (minutes)	Yield (%)
C_6H_5	2.0	90
o-MeC_6H_4	2.5	88
m-MeC_6H_4	2.5	87
p-MeC_6H_4	2.5	88
p-ClC_6H_4	2.5	89

R	Yield (%)
H	95
Me	90
Cl	92
NO_2	90

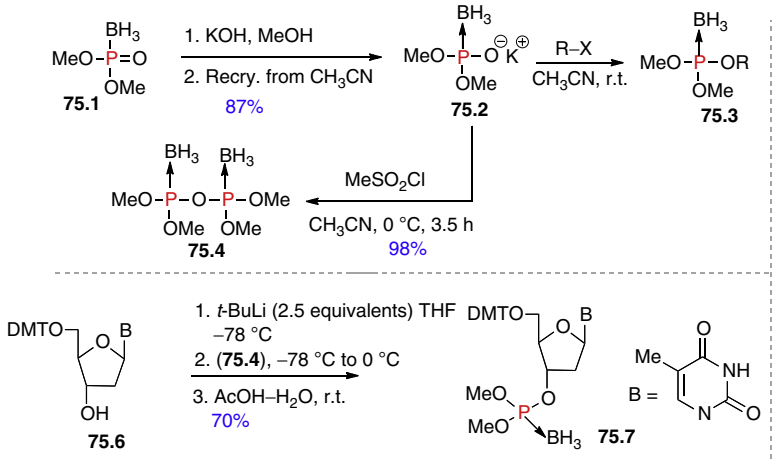
Scheme 74

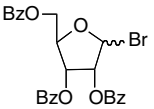
In 2005, Ilia and coworkers reported another efficient and 'green' method of synthesizing triaryl phosphates **74.2** via vapor–liquid condensation of $POCl_3$ with hydroxyaryl compounds **74.3**, while avoiding the use of organic solvents and complex purification procedures (Scheme 74).[178] $POCl_3$ was heated and carried by a stream of nitrogen into a solution containing 20% aqueous sodium hydroxide and aryl alcohols **74.3** to furnish the corresponding triaryl phosphates in excellent yields. Triaryl phosphates **74.2** were obtained as solid products and were separated by filtration, purified, and dried under vacuum.

6.12.2.6.3 Boranophosphates

Isoelectronic with conventional phosphates, boranophosphates $[(RO)_2P(O)BH_3]$ have high chemical and enzymatic stability when compared with all oxygen-containing phosphotriesters and *H*-phosphonate diesters and, as such, they have become important intermediates in biochemical and molecular biological investigations.[179] In light of this, the syntheses of a variety of boranophosphates have been reported as interest in their properties and synthetic utility continues to grow.

In 1997, Imamoto and coworkers demonstrated a simple method of synthesizing boranophosphates by the coupling of alcohols with different boranophosphorylating reagents, such as simple dimethylboranophosphate diester **75.2**, which can be easily generated via the hydrolysis of trimethyl boranophosphate **75.1** with KOH in MeOH, followed by recrystallization from CH_3CN (Scheme 75).[180] Reaction of **75.2** with alkyl halides and chlorosilane has showed that applicability of these reagents to build the corresponding boranophosphates via facile S_N2 reactions, and the coupling of **75.2** with acid chlorides, provided the carboxylic and boranophosphoric mixed anhydrides in good yields.



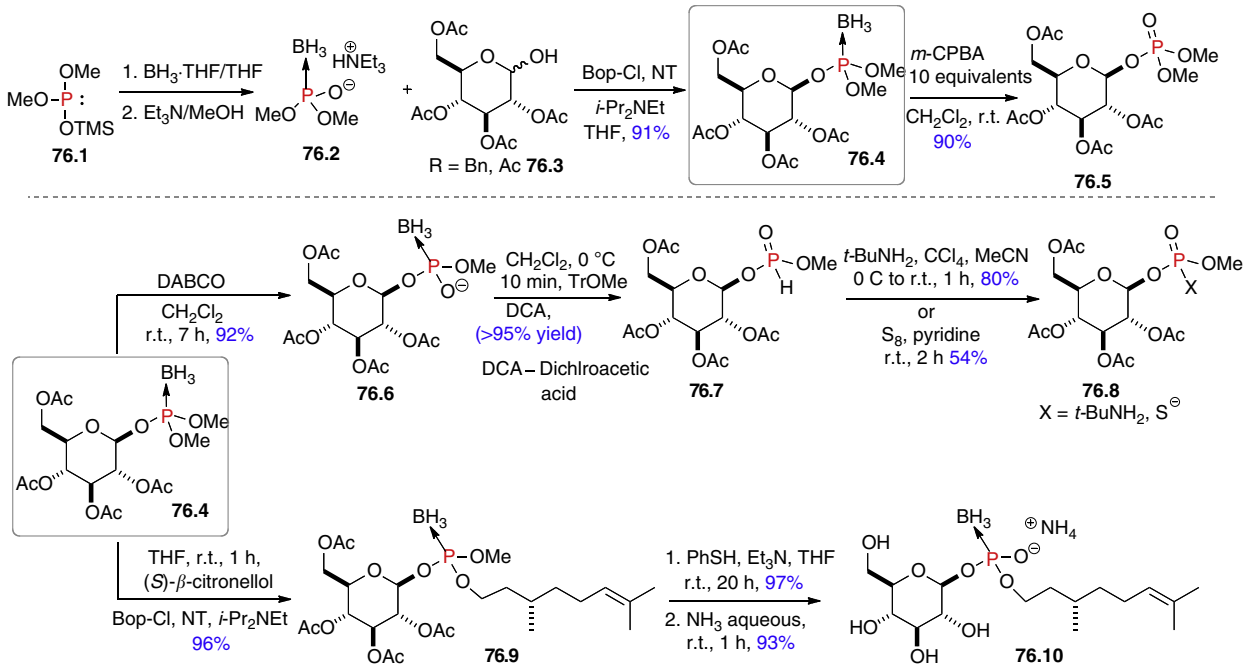
R–X	Time (h)	Yield (%)
$MeOCH_2Cl$	0.5	69
p-$BrC_6H_4COCH_2Br$	15	66
	24	71
t-$BuMe_2SiCl$	1	79
MeCOCl	0.2	74
PhCOCl	1	87

Scheme 75

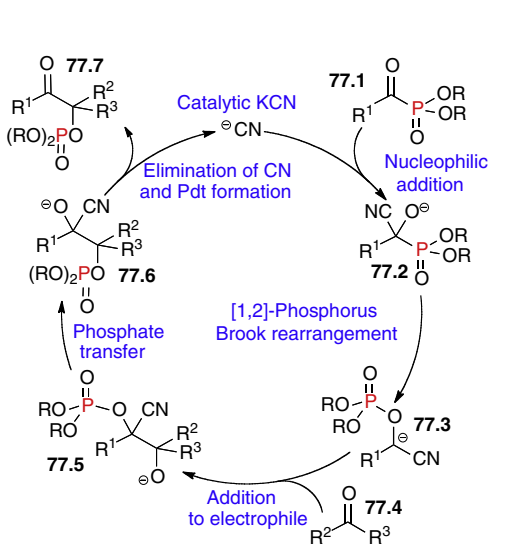
In 2008, Wada and coworkers also reported the synthesis of glycosyl boranophosphates **76.4** and their application in the synthesis of phosphate-containing glycosyl analogs via the use of simple boranophosphate **76.2**, which could be derived from trimethylsilyl phosphite[181] **76.1** (Scheme 76).[182] Boronophosphorylation of sugars **76.3** was accomplished by coupling with triethylammonium dimethyl boranophosphate (**76.2**), in the presence of condensing reagent bis(2-oxo-3-oxazolidinyl)phosphonic chloride (BOP–Cl), activator 3-nitro-1, 2, 4-triazole, and base *i*-Pr_2NEt. The resulting boranophosphates **76.4** were then oxidized with *m*-CPBA to provide the corresponding phosphorylated sugars **76.5** in high yields. In addition, demethylation of boranophosphates **76.4** with DABCO and subsequent treatment with *in situ*-generated trityl (Tr) cation furnished *H*-phosphonate diesters **76.7** in very good yields, highlighting this functionality's unique ability to act as chemically stable precursors to their sensitive *H*-phosphonate diester family members. In application of this feasibility, the authors transformed glycosyl boranophosphates **76.4** into a variety of *P*-substituted analogs **76.10** (Scheme 76). Condensation of β-citronellol with **76.4** provided modified boranophosphate **76.9**, which, upon demethylation with PhS^- and deacetylated with aqueous ammonia, afforded the glycosyl phosphate analog **76.10** in high overall yield.

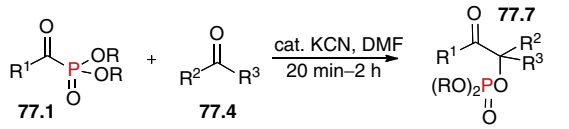
6.12.2.6.4 Phosphorus–Brook rearrangements

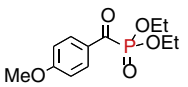
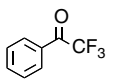
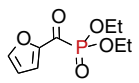
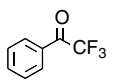
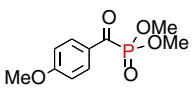
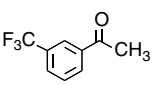
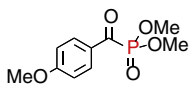
Following the seminal work of Hall, Stephens, and Drysdale (1957),[183] and Wadsworth and Emmons (1961),[184] and Brook (who described the mechanism of the silyl rearrangment in 1974),[185] the phosphorus–Brook rearrangement has emerged as a powerful method to generate diversely functionalized phosphate-containing intermediates.[186] Building on some of their earlier work in benzoin-type coupling reactions, in 2009, Demir and coworkers reported the first catalytic, intermolecular aldehyde–ketone coupling via a [1,2]-phosphorus–Brook rearrangement of acyl phosphonates (Scheme 77).[187] Utilizing a catalytic amount of KCN, in DMF, the authors efficiently coupled acyl phosphonates **77.1** with ketones **77.4** to provide α-keto-phosphates in moderate to excellent yields. The proposed mechanistic cycle involves tetrahedral alkoxide formation resulting from the nucleophilic addition of cyanide to acyl phosphate **77.1**, followed by a [1,2]-phosphorus–Brook rearrangement to yield stabilized carbanion **77.3**,



Scheme 76





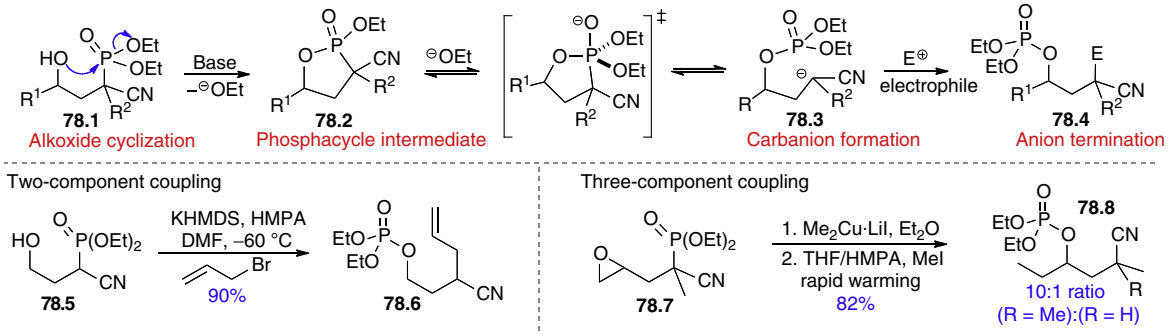
Entry	Phosphonate	Ketone	Yield[a] (%)
1			95
2			83
3[b]			78
4[c]			54

[a]Isolated yields. [b]THF used as solvent. [c]$Cu(OTf)_2$ (10 mol%) used.

Scheme 77

which, on addition to an electrophile (ketone 77.4), [1,4]-phosphate transfer (77.5 to 77.6), and elimination of cyanide, affords the desired product 77.7. Importantly, yields were found to be dependent on the sterics and electronics of both the acyl phosphonate and starting ketone, where electron-rich acyl phosphonates and electron-deficient ketones reacted to afford the highest amount of the desired product. In addition, the difficult conversion of ketones with enolizable hydrogens to the desired product was also demonstrated, though success was achieved in modest yield.

In 2012, Smith and Sokolsky reported a [1,4]-phosphorus–Brook rearrangement using α-cyanodiethylphosphonates for both two- and three-component couplings with appropriate electrophiles to yield phosphate-, as well as cyclopropane-, containing intermediates, in what they term 'anion relay chemistry' (Scheme 78).[188] In accordance with previous work by Singh,[189] Merschaert,[190] and Ghirardelli,[191] they propose a mechanism similar to the silicon-mediated [1,4] Brook rearrangement, in which the generated alkoxide of 78.1 cyclizes to form a five-membered monocyclic phosphonate intermediate 78.2. Following ring opening



Scheme 78

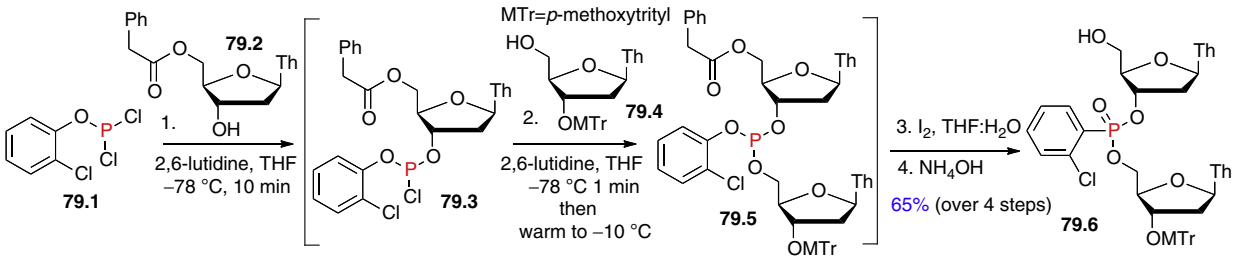
and C–P bond cleavage, the stabilized carbanion **78.3** is quenched with an electrophile and the cascade is terminated to yield the final product **78.4**. This method was applied to the two-component coupling of phosphonate **78.5** with allyl bromide, in the presence of KHMDS and HMPA, to yield allylated **78.6** as the sole product in 90% yield. With this success in hand, the researchers extended the method to the three-component coupling of epoxide **78.7** and MeLi (as a model electrophile). Epoxide opening with methylcuprate and subsequent addition of the cuprate to a solution of THF/HMPA and MeLi at −40 °C, followed by rapid warming to 40 °C, generated phosphate **78.8** in 82% yield as a 10:1 mixture of α-methyl and α-protonated products.

6.12.3 Phosphorus(III) Reagents

The synthesis of phosphates through the manipulation and subsequent oxidation of trivalent phosphorus reagents [P(III)] is an alternative pathway to the use of phosphorus(V). P(III) reagents, such as phosphorochloridites, phosphoramidites, and phosphites, have a trigonal pyramidal structure, with an electron lone pair on the *P* atom, which renders P(III) compounds more reactive than their pentavalent counterparts and less stable due to susceptibility to hydrolysis and oxidation.[192,193] Thus, the P(III)-coupling reagents make it possible to access phosphites under mild conditions, manipulate the resulting P(III) intermediate via oxidation or sulfurization, and ultimately furnish the phosphate products. Phosphorylation reactions with P(III) reagents were last reviewed in 1991.[23] In addition, Michalski published a review on the applications of P(III) reagents in the synthesis of biophosphates and their analogs in 2004.[192]

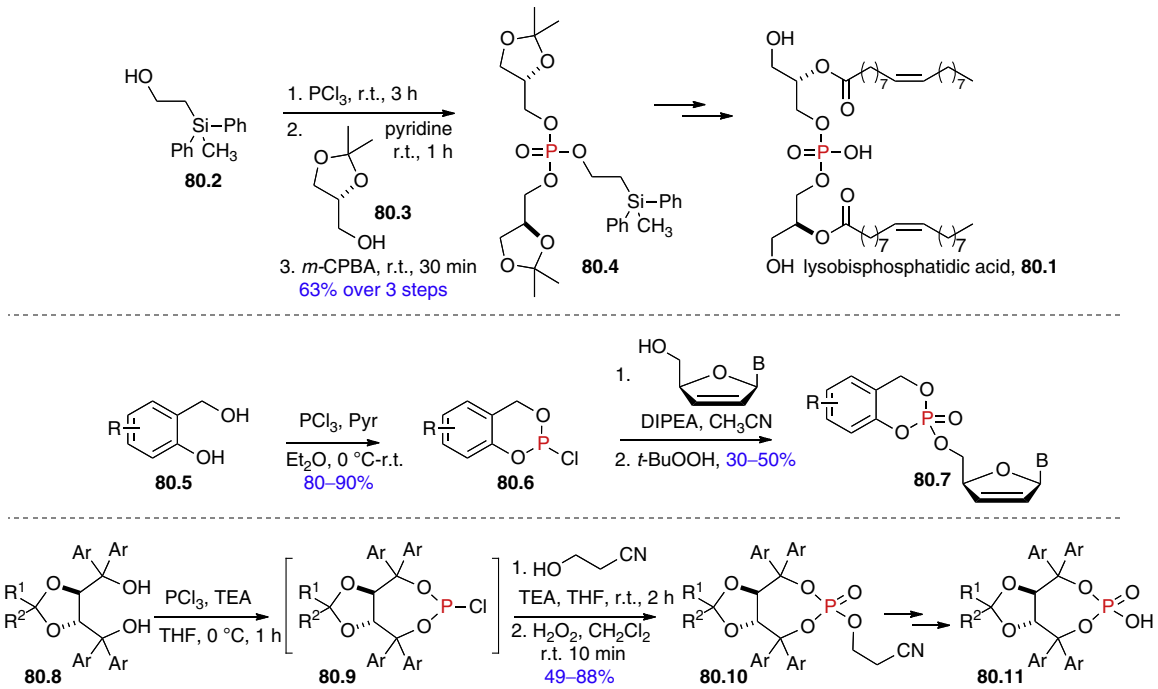
6.12.3.1 Phosphorochloridites

Phosphorus trichloride (PCl_3) is a toxic and highly reactive reagent, which, on hydrolysis generates phosphorous acid (H_3PO_3) and hydrochloric acid, exothermically.[23] It readily reacts with alcohols, in the presence of base, to produce phosphite triesters. Importantly, in 1975, Lundsford demonstrated that mono-, di-, and trisubstituted phosphites could be generated in a stepwise fashion via simple modification of stoichiometry (alcohol, base, and PCl_3) and temperature (Scheme 79).[194] In this example, monoalkylated compound **79.1** was treated with a 5′-protected 3′-OH nucleoside **79.2** in the presence of 2,6-lutidine in THF at −78 °C for 10 min. Sequential addition of a 3′-protected 5′-OH nucleoside **79.4** at −78 °C, with warming to −10 °C, provided the differentially substituted trialkyl phosphite **79.5**, which was oxidized and deprotected to afford the dinucleotide product **79.6** in 65% yield.



Scheme 79

In 2000, Matile and coworkers reported the construction of synthetic lysobisphosphatidic acids **80.1** via the reaction of PCl_3 and alcohol **80.2** (Scheme 80).[195] Subsequent treatment with alcohol **80.3**, followed by oxidation with *m*-CPBA, furnished phosphotriester **80.4** in 63% yield over three steps. The same phosphate installation strategy was also applied in the total



Scheme 80

synthesis of several natural products, two of which, fostriecin and calyculin A, are discussed in a subsequent section (see Section 6.12.6).

Similarly, phosphotriesters can be synthesized through a disubstituted phosphite intermediate, which are most significant with respect to protocols used to generate cyclic phosphorus-containing compounds (Scheme 80). In 2006, Meier and coworkers synthesized the disubstituted phosphite monochloride intermediate **80.6** from diol **80.5** and PCl_3.[196] Successive reaction with a nucleoside yielded cycloSal-d4TMP pronucleotides **80.7**, which bear esterase-cleavable sites. In 2006, Charétte and Voituriez condensed TADDOL (**80.8**) with PCl_3 to form phosphite monochloride intermediate **80.9**.[197] A third coupling with 2-cyanoethanol, followed by oxidation with H_2O_2, afforded phosphate **80.10**, which was later used in the synthesis of the chiral, nonracemic Brønsted acid catalyst **80.11**.

Monosubstituted or disubstituted intermediates obtained from couplings with PCl_3 can also be hydrolyzed and tautomerized to produce *H*-phosphonates (Figure 8), which can be readily transformed into phosphates with analogous oxidation, thus providing another viable P(III)-mediated route to phosphate monoesters or diesters (see Section 6.12.3.4 on *H*-phosphonates for more examples).[198]

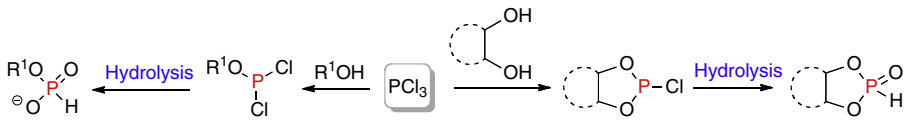
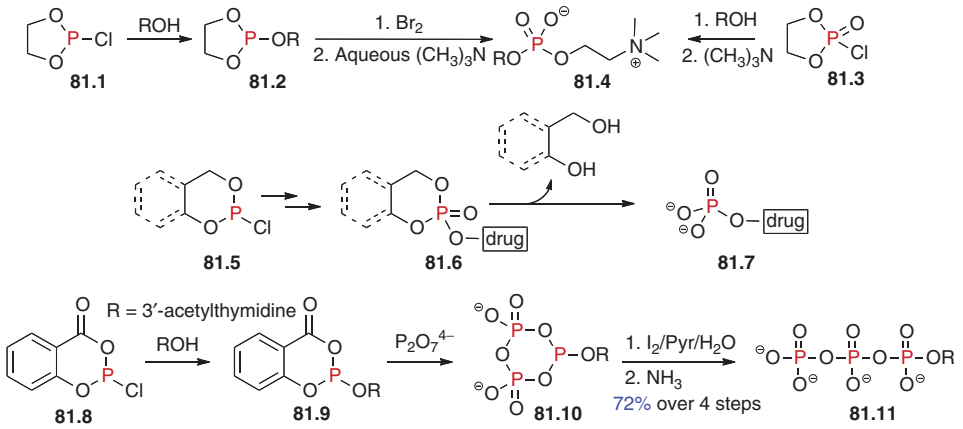


Figure 8 Hydrolysis of PCl_3 derivatives to H-phosphonates.

Similarly, dialkyl chlorophosphites are more stable than PCl_3 and are readily converted to phosphates on condensation with an alcohol, followed by oxidation.[199] In particular, cyclic chlorophosphites have been shown to be synthetically useful in the synthesis of a number of interesting intermediates. For example, commercially available 2-chloro-1,3,2-dioxaphospholane (**81.1**) can readily react with an alcohol to form phosphite **81.2**, which can then be oxidized with Br_2 and treated with aqueous Me_3N to yield ring opened zwitterionic phosphate **81.4**.[200] Ultimately, this approach, in addition to the use of 2-chloro-1,3,2-dioxaphospholane 2-oxide (**81.3**), provides quick access to bioactive phosphatidylcholines **81.4**, and has been employed in several synthetic routes to access phosphates of this type.

The cyclic chlorophosphites **81.5**, which can be prepared from diols such as substituted 2-(hydroxymethyl)phenol shown below, have proven useful in the synthesis of intermediate phosphates **81.6** *en route* to a variety of phosphate-containing prodrugs **81.7** (Scheme 81).[201] The Ludwig–Eckstein phosphorylation method, which proceeds via 2-chloro-4*H*-1,3,2-benzodioxaphosphorine-4-one (**81.8**), is widely used in the formation of triphosphates **81.11**.[202] Addition of an alcohol to cyclic chlorophosphite

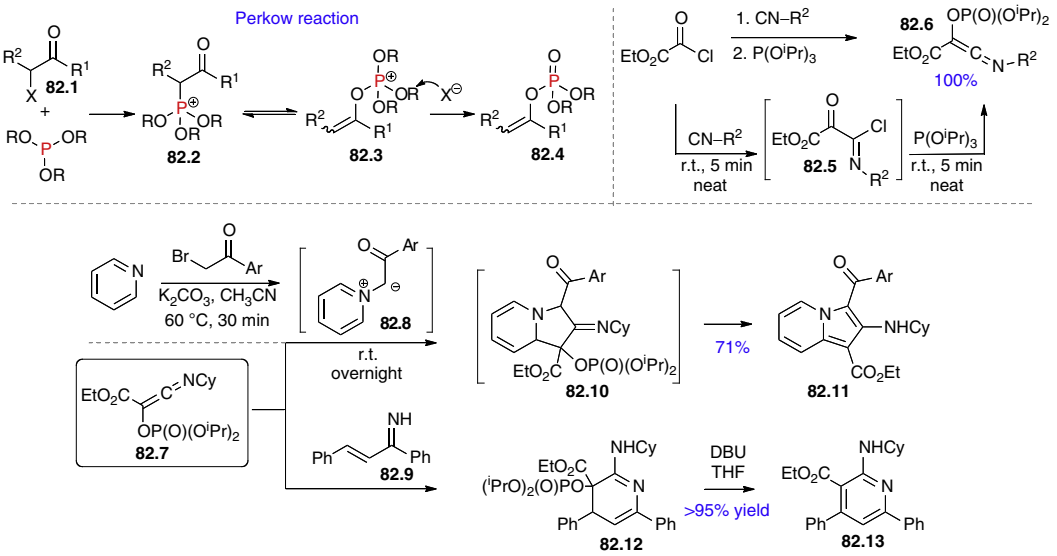


Scheme 81

81.8 yields the corresponding phosphite **81.9**, which, upon double displacement with pyrophosphate and subsequent oxidation, affords triphosphate **81.11**.

6.12.3.2 Phosphite

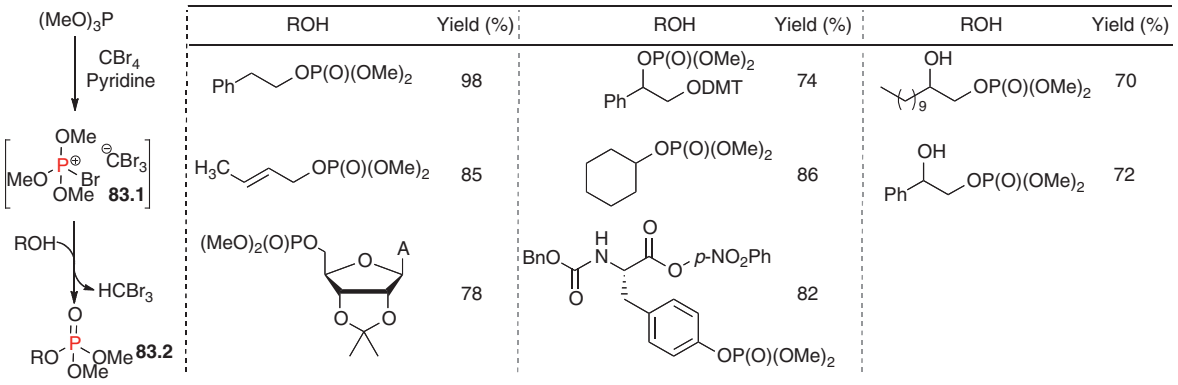
The nucleophicility of phosphites [$(RO)_3P$] has been exploited in a variety of named reactions, including the Michaelis–Arbuzov reaction for the synthesis of phosphonates[203] and the Perkow reaction, in which a phosphite reacts with α-halo carbonyl compound **82.1** to afford enol phosphates **82.4** (Scheme 82).[149,154] Modifications of the Perkow reaction have been well studied,[204] and in 2009, Coffinier, Kaim, and Grimaud developed an isocyanide-based, two-step, three-component protocol for ketene imine formation.[204] In this Perkow-type reaction, isocyanides were added to acyl chlorides, and the resulting imidoyl chloride intermediates **82.5** reacted with phosphites to form the ketene imines **82.6**. In 2010, the same group utilized ketene imines in 1,3-dipolar cycloadditions with pyridinium ylide **82.8** to synthesize indolizine derivative **82.11**,[205] and in 2011, a hetero-Diels Alder reaction with azadiene **82.9** was used to form multisubstituted pyridines such as **82.13**.[206]



Scheme 82

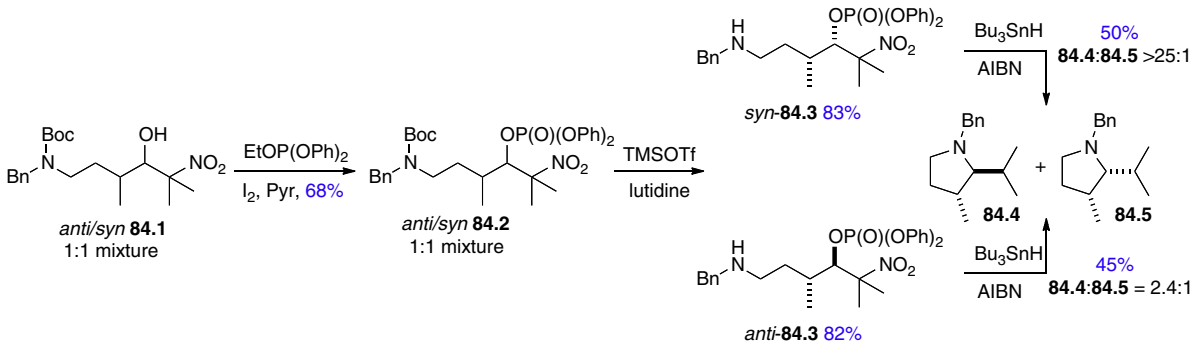
In 1995, Corcoran and Oza reported the addition of trimethyl phosphite to a carbon tetrahalide to form an alkoxy trimethoxyphosphonium salt intermediate **83.1**, which underwent selective demethylation by alcohols (Scheme 83).[207] Although a mixture of mono-, di-, and trisubstituted phosphate esters could be formed, altered conditions (CBr_4, pyridine) allowed for the isolation of the dimethylphosphate esters **83.2**, exclusively.

Trialkyl phosphites can react with Br_2 to form alkyl bromophosphates, which serve as useful and mild phosphorylation reagents[208] that can dually function to convert hydroxyl groups to bromides[209] or aldehydes to 1,1-dibromoalkanes.[210] In 2002,



Scheme 83

Crich and coworkers phosphorylate alcohol **84.1** using ethyl diphenyl phosphite, in the presence of iodine and pyridine, to afford phosphate **84.2** as a 1:1 mixture of diastereomers (Scheme 84).[211] *Anti*- and *syn*-**84.2** were separated and deprotected to yield *anti*- and *syn*-**84.3**, which underwent diastereoselective cyclization to form pyrrolidines **84.4** and **84.5**.

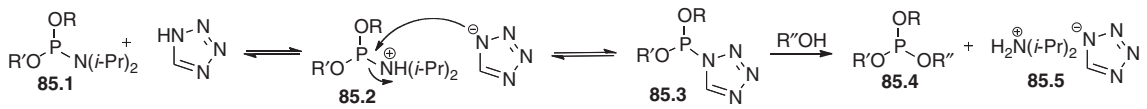


Scheme 84

6.12.3.3 Phosphoramidites

In general, phosphoramidites are more stable than their phosphorochloridite counterparts and, in most cases, are relatively easy to prepare, store, and separate via chromatography, though a variety of phosphoramidites with orthogonal phosphorous-protecting groups are already commercially available.[212,213] Phosphoramidites have been extensively used as metal ligands in asymmetric catalysis.[66,214] In addition, the phosphoramidite-coupling reaction of activated phosphoramidites with alcohols (phosphitylation) readily provides the trialkyl phosphite intermediates, which, when followed by oxidation, yields the corresponding phosphate (the entire process constitutes phosphorylation).

Phosphitylation usually requires activation of phosphoramidites by mild acids such as 1*H*-tetrazole, the use of which was first reported by Caruthers and Beaucage in a phosphoramidite-mediated approach to oligonucleotide synthesis in 1981.[212] Since then, tetrazole and tetrazole-derived acids are still the most commonly used activators in phosphoramidite phosphorylation. Seminal mechanistic work carried out by Dahl[215] and coworkers, and later by Nurminen[216] et al. indicated that 1*H*-tetrazole plays a dual role as both an acid, to protonate nitrogen of the phosphoramidite **85.1**, and as a nucleophile, to displace the protonated amidite **85.2**, thus forming a highly reactive tetrazolide **85.3** (Scheme 85). Subsequent nucleophilic attack on tetrazolide intermediate **85.3** by an alcohol furnishes the phosphite **85.4** along with one equivalent of both tetrazole and the amine, which react together to form a salt. In 2008, Page and coworkers provided additional mechanistic insight into the saccharin/*N*-methylimidazole salt-catalyzed phosphitylation step in CH_3CN using ^{31}P NMR.[217]



Scheme 85

In addition to tetrazole, a number of other phosphoramidite activators have also been reported, including *N*-methylanilinium trifluoroacetate,[218] 5-ethylthiotetrazole,[219] 5-(4-nitrophenyl)tetrazole,[220] 1*H*-1,2,4-triazole,[221] 4,5-dicyanoimidazole,[222] bromo-4,5-dicyanoimidazole,[223] triazole/imidazole,[224] various carboxylic acids,[225] 5-phenyltetrazole,[220] arylsulfonyl-tetrazoles,[226] pyridinium trifluoroacetate (PyTFA),[227] imidazolium triflate,[228] 2,4-dinitrophenol,[229] benzimidazolium triflate,[230] and diisopropylammonium tetrazolide (Figure 9).[231]

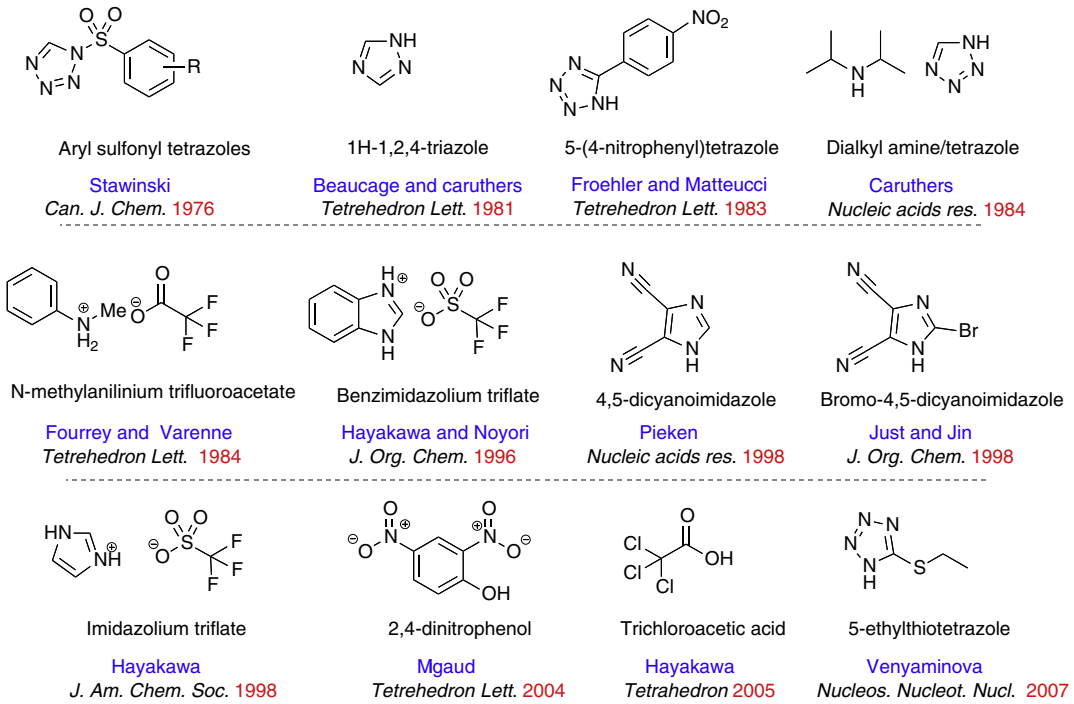


Figure 9 Common phosphoramidite activators.

Oxidation of the trialkyl phosphite intermediates to generate the corresponding phosphates can be achieved via the use of appropriate oxidizing agents. Although simple peroxides (H_2O_2,[232] *m*-CPBA,[233] and *t*-BuOOH[234]) are frequently used, several other efficient oxidants have also been employed, including I_2,[235] O_3,[236] dioxiranes,[237] and singlet oxygen,[238] in addition to protocols which incorporate photooxidation to access phosphates (Figure 10).[239,240]

The phosphoramidite approach to phosphate synthesis has attracted very extensive attention due to its ability to deliver the desired products in high yield, under mild reaction conditions, while avoiding a large amount of byproduct formation. In particular, these strategies are quite synthetically advantageous in the synthesis of natural products and other sensitive, complex polyols. In this regard, Beaucage and Iyer, in 1992 and 1993, reviewed the utilization of phosphoramidites in oligonucleotide synthesis, much of which will be covered later in this chapter (see Section 6.12.5),[241] and, in 2010, Nifantiev published a review on using amides of trivalent phosphorus acids as phosphorylating reagents for proton-donating nucleophiles.[213]

In 2006, Shiozaki and coworkers reported the use of phosphoramidite chemistry *en route* to the synthesis of glucose derivatives **86.6** of E5564 (an antisepsis drug candidate) related compounds with antagonistic activities (Scheme 86).[242] The highlighted steps below incorporate two phosphitylation steps, utilizing 1*H*-tetrazole as an activator and H_2O_2 as the subsequent oxidant of the C4-hydroxy group of **86.1** (to generate **86.3** in 87% yield) and anomeric hydroxy of **86.4** with diallyl diisopropylphosphoramidate to furnish the diphosphorylated disaccharide **86.5** in 86% yield. Global deallylation with catalytic Pd(0) afforded the bis-monophosphate product **86.6** in good overall yield.

In the synthesis of *Helicobacter pylori* lipopolysaccharide partial structures, Fukase treated disaccharide **87.1** with sequential additions of LiHMDS and $[(BnO)_2P(O)]_2O$ (**87.2**) to form the dibenzyl phosphate **87.3**, which, upon hydrogenolysis, afforded phosphoric acid **87.4** (Scheme 87).[134] Alternatively, phosphitylation of **87.1** with phosphoramidite **87.5**, followed by oxidation (DMDO) and hydrogenolysis, furnished product **87.7** in good overall yield.

In 2006, Potter and coworkers developed a highly efficient route to synthesize the anticancer agent Ins(1,3,4,5,6)P_5 (**88.6**) (Scheme 88).[243] In this method, *myo*-inositol was treated with trimethyl orthobenzoate to form *myo*-inositol orthobenzoate **88.1**, which, upon acid hydrolysis with TFA, generated 2-*O*-benzoyl-*myo*-inositol (**88.2**). Phosphate installation was accomplished via the use of *N*,*N*,-diethyl-1,5-dihydro-2,4,3-benzodioxaphosphepin-3-amine (**88.3**), in the presence of 5-phenyl tetrazole (activator) and using *m*-CPBA as the subsequent oxidant. Pd-catalyzed hydrogenolysis, followed by benzoate ester removal, afforded the final product **88.6** in excellent overall yield.

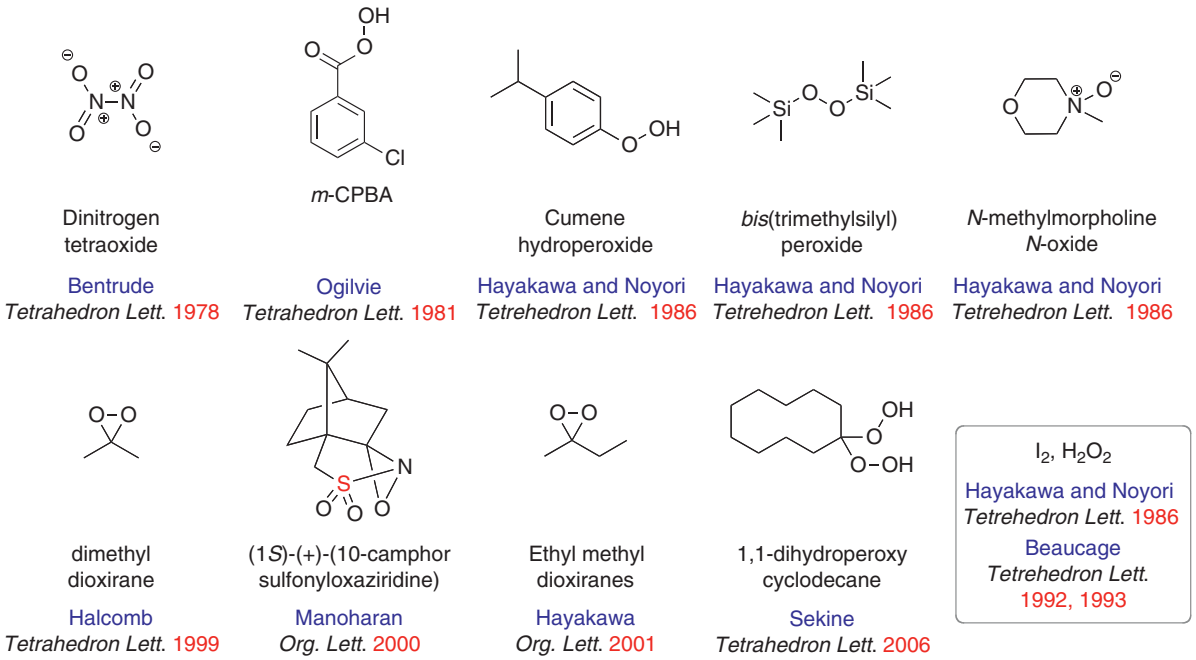
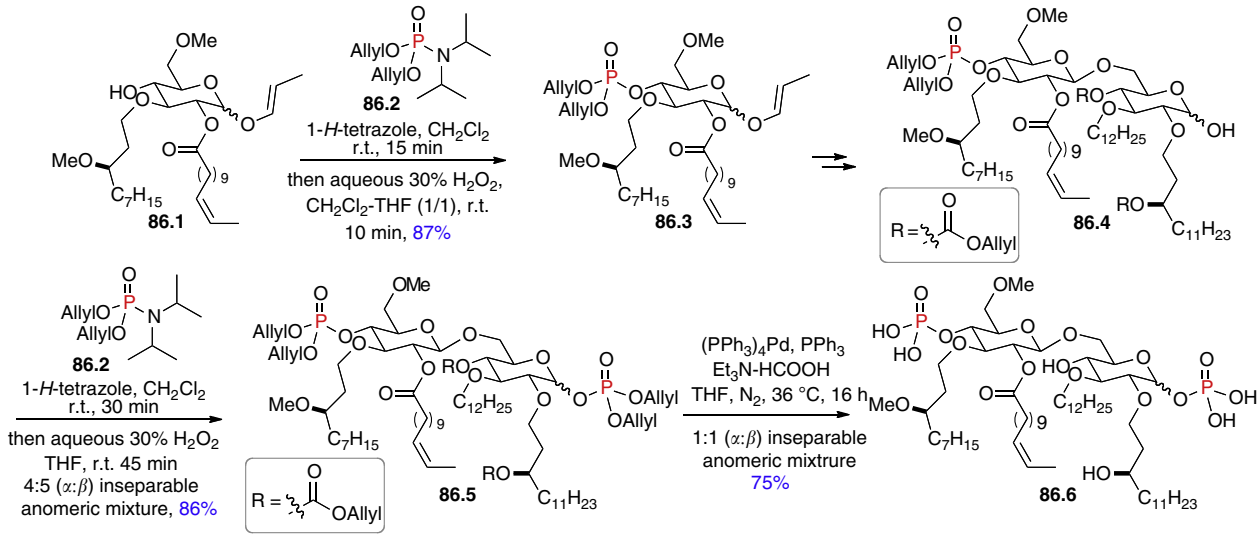


Figure 10 Common phosphoramidite oxidants.

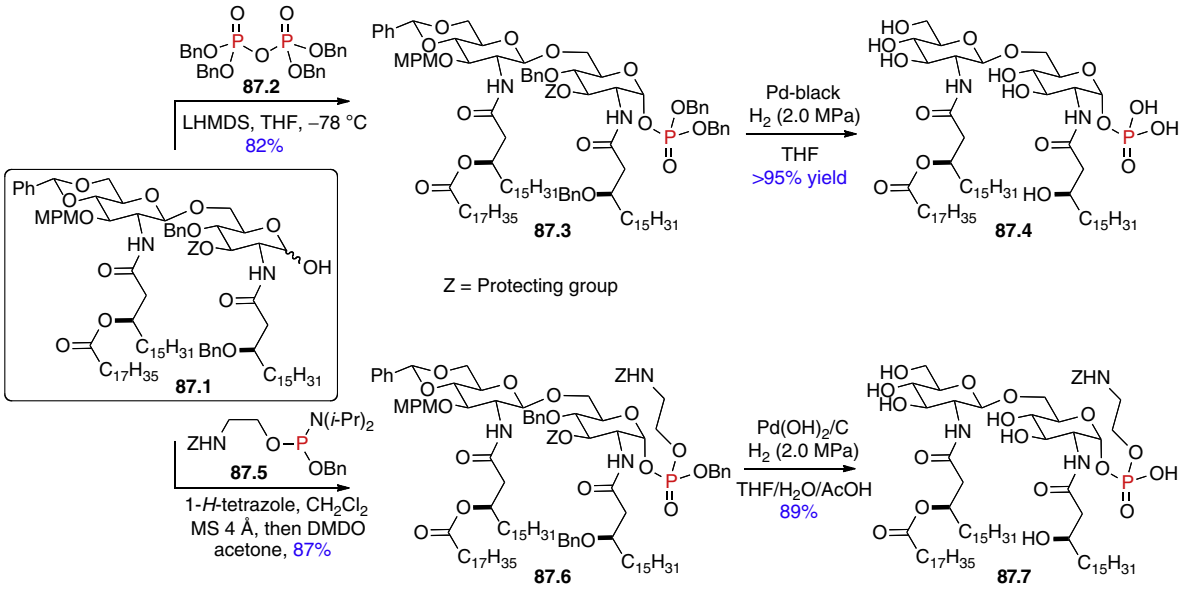


Scheme 86

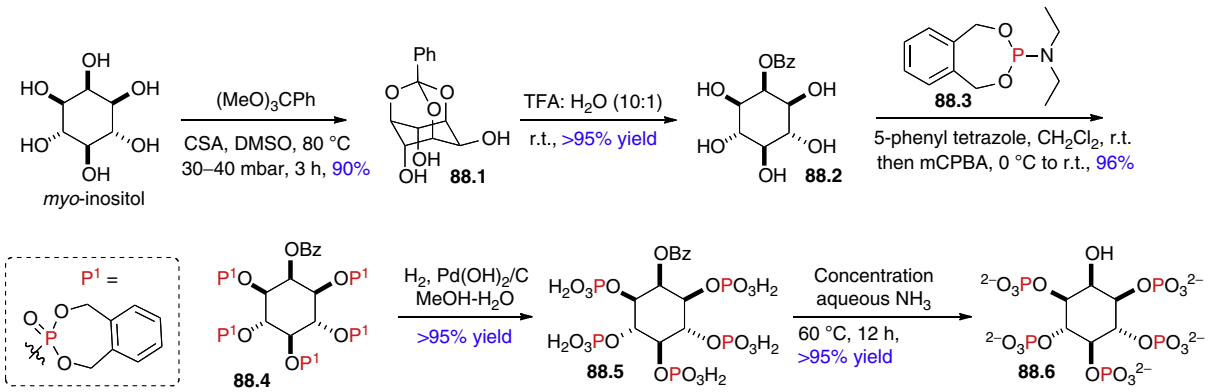
In 2006, Prestwich and coworkers completed the asymmetric total synthesis of phosphatidylinositol-3-methylenephosphate (**89.5**), a metabolically stabilized analog of phosphatidylinositol-3-phosphate (a spatial regulator of vesicular trafficking and other vital cellular processes) (Scheme 89).[244] Alkylation of differentially protected myo-inositol **89.1**, obtained in six steps from *myo*-inositol, with triflate **89.2** afforded phosphonate **89.3** in 64% yield. Following TBDPS-deprotection, the resulting free hydroxyl group was coupled with phosphoramidite **89.4**, in the presence of 1*H*-tetrazole. Successive oxidation with *n*-BuNIO$_4$ and global deprotection with TMSBr provided the phosphonate–phosphate product **89.5** in moderate yield.

In 2009, Prestwich and coworkers described a scalable route for the synthesis of diphosphoinositol pentakisphosphate **90.8** via phosphoramidite-mediated phosphorylation (Scheme 90).[245] A seven-step protection protocol allowed for the generation of monoprotected **90.3**, which, upon phosphitylation with phosphoramidite **90.4**, oxidation with *m*-CPBA, and removal of PMB-protecting group, produced pentakisphosphate **90.5** in nearly quantitative yield. A second phosphitylation/oxidation with phosphoramidite **90.6** furnished hexakisphosphate **90.7**, which was smoothly converted to 5-PP-Ins(1,2,3,4,6)P5 sodium **90.8** via 2-cyanoethyl deprotection, pyrophosphate formation, and global debenzylation (isolated as sodium salt after four steps).

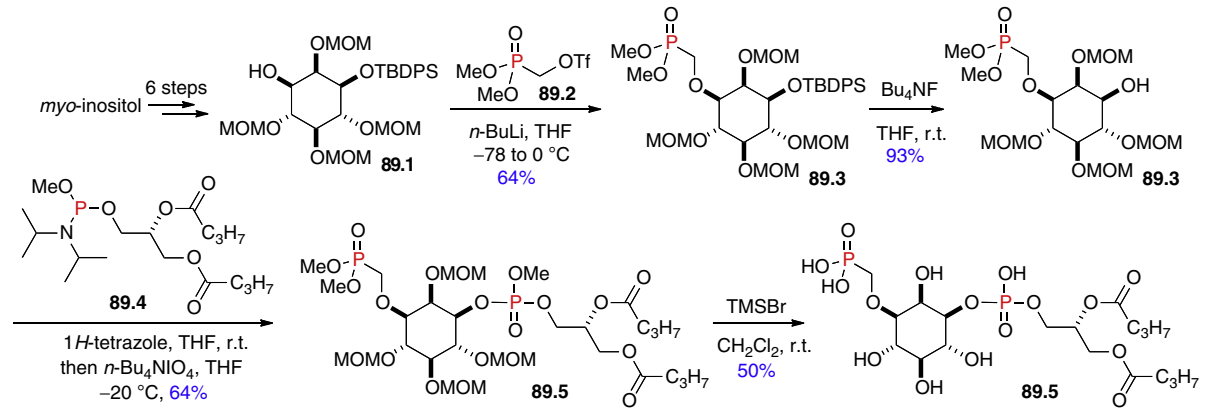
In 2006, Miller and coworkers reported the synthesis of several phosphatidic acid derivatives as lysophosphatidic acid receptor ligands via the exploitation of phosphoramidite chemistry (Scheme 91).[246] Dibenzyl-*N*,*N*-diisopropyl phosphoramidite coupling with **91.1**, in the presence of 1*H*-tetrazole, followed by oxidation with H_2O_2, generated phosphate **91.2** in 68% yield. Simple



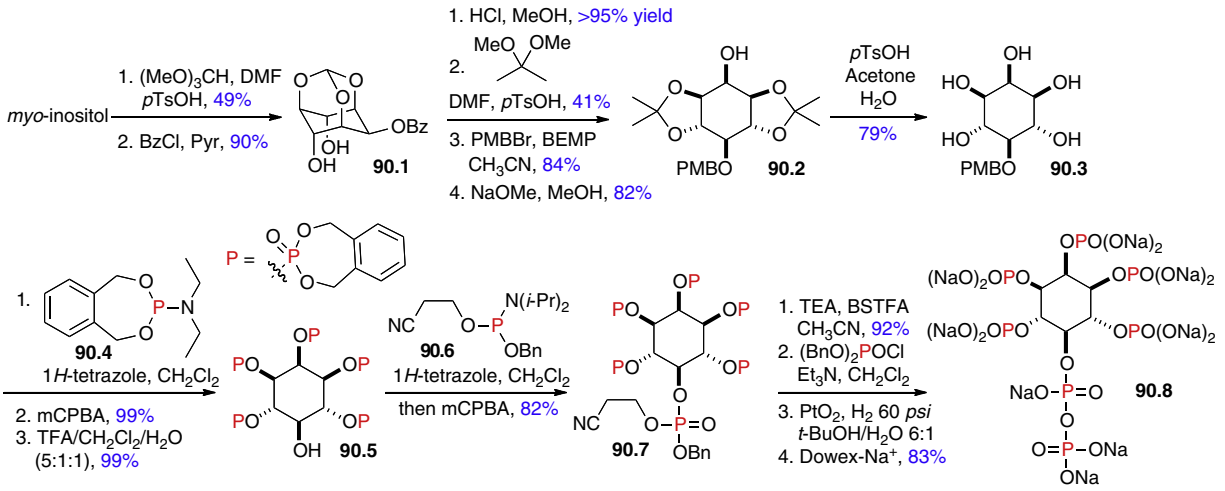
Scheme 87



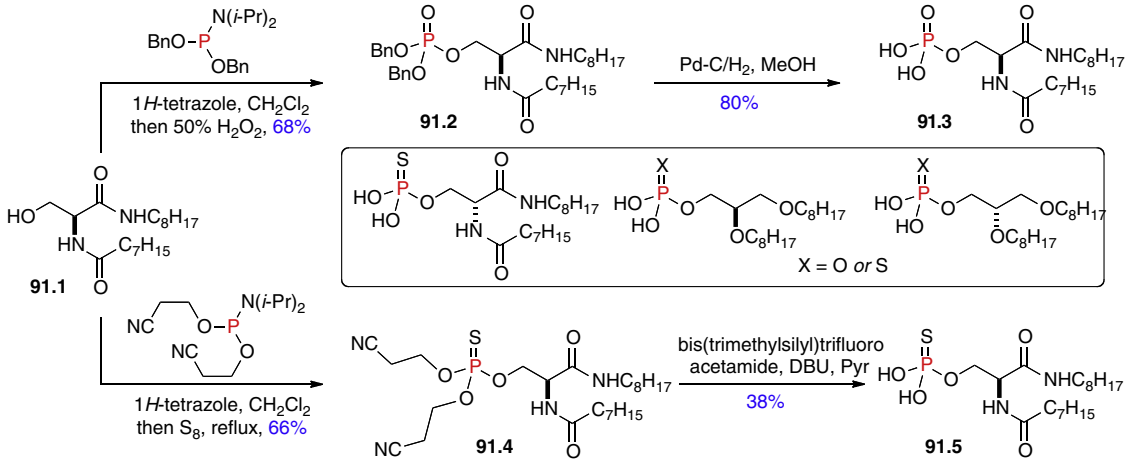
Scheme 88



Scheme 89



Scheme 90

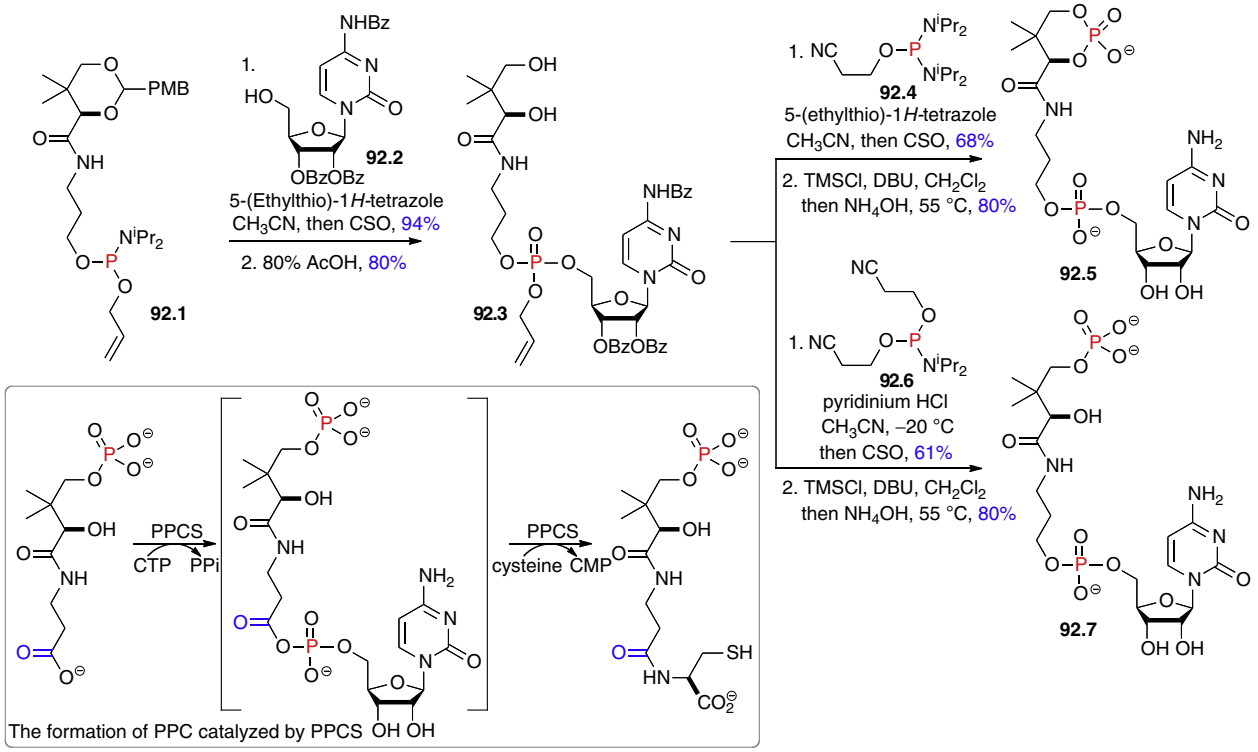


Scheme 91

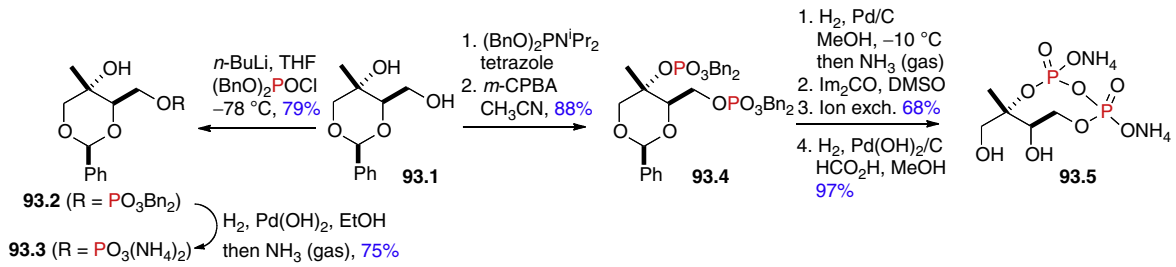
exchange of the phosphoramidite species to *bis*(2-cyanoethyl)-*N*,*N*-diisopropyl phosphoramidite allowed for the formation of thiophosphates **91.4** in moderate yield. Benzyl deprotection of **91.2** with H_2 and Pd/C in MeOH and treatment of thiophosphate **91.4** with bis(trimethylsilyl)trifluoroacetamide and DBU in pyridine furnished the corresponding phosphate **91.3** and thiophosphate **91.5**, respectively. Using this protocol, products **91.3** and **91.5**, their enantiomers, and several other analogs were synthesized and screened for biological activity.

In 2009, Dotson and coworkers published the first design and synthesis of mimics of the phosphopantothenoyl cytidylate (carbonyl group removed from the phosphopantothenoyl cytidylate), which proved to be potent inhibitors of phosphopantothenolycysteine synthetase.[247] Panthenol-derived phosphoramidite **92.1** was coupled to 5′-hydroxy group of a tribenzoyl-protected cytidine (**92.2**), and the resulting intermediate was oxidized with the (1*S*)-(+)-(10-camphorsulfonyl)-oxaziridine (CSO) to yield the corresponding phosphodiester (Scheme 92). Removal of the *p*-methoxybenzylidene with AcOH allowed access to diol **92.3**, which was differentially diversified via two phosphorylation pathways. Treatment of **92.3** with phosphoramidite **92.4**, in the presence of 5-(ethylthio)-1*H*-tetrazole, followed by oxidation with CSO, global deprotection with trimethylsilyl chloride (TMSCl), and hydrolysis with NH_4OH, afforded diphosphate **92.5** in good yield. Conversely, phosphitylation of **92.3** with phosphoramidite **92.6**, in the presence of pyridinium·HCl, followed by oxidation, deprotection, and hydrolysis, generated diphosphate **92.7**, in a synthetically divergent manner.

In 2007, Coates and coworkers reported the regioselective monophosphorylation of **93.1** with *n*-BuLi (hexane-THF, −75 °C) and dibenzyl chlorophosphate (prepared from dibenzylphosphite and *N*-chlorosuccinimide in benzene).[248] Hydrogenolysis of the resulting dibenzyl phosphate **93.2**, followed by treatment with ammonia gas, provided the ammonium salt **93.3** in 75% yield. Bisphosphitylation of **93.1** and subsequent oxidation with *m*-CPBA furnished diphosphate **93.4**. Selective benzyl hydrogenolysis with H_2 and Pd/C, followed by phosphate cyclization and hydrogenolysis of the benzylidene group with H_2 and $Pd(OH)_2$ afforded cyclopyrophosphate diammonium salt **93.5** in excellent overall yield (Scheme 93).



Scheme 92

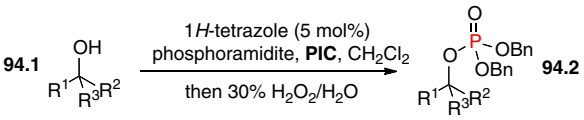


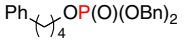
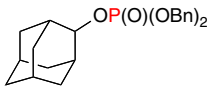
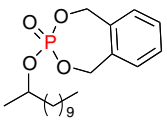
Scheme 93

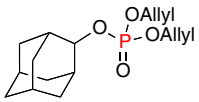
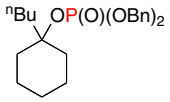
In some cases, additives are utilized for the use of activators in catalytic amount. In 1997, Hayakawa and Kataoka first reported the utilization of molecular sieves 13X as an amine scavenger (to eliminate the amine byproduct of phosphitylation), so that the activator, 5-(*p*-nitrophenyl)-1*H*-tetrazole, could be used in catalytic quantities.[249] Using this method, nearly equimolar amounts of the nucleoside phosphoramidite and the nucleoside could be used to obtain the desired product in excellent yield. In 2009, Sculimbrene and coworkers discovered that isocyanate additives also can act as amine scavengers and, thus, facilitate the catalyst turnover.[250] The best results were obtained with phenyl isocyanate (PIC). As a defining example, the authors demonstrated the facile phosphorylation of primary and secondary alcohols **94.1** with dibenzyl phosphoramidites in the presence of catalytic 1*H*-tetrazole and 1.1 equivalents of PIC (**Scheme 94**). For tertiary alcohols, *N*,*N*-diethylphosphoramidites, which pose less steric hindrance than *N*,*N*-diisopropylphosphoramidites, were used to obtain acceptable yields.

6.12.3.4 *H*-Phosphonates

H-phosphonates are a unique type of phosphorus compounds that are tetravalent (similar to P(V) compounds) but possess a (+3) oxidation state (similar to P(III) compounds), which imparts a distinctive reactivity profile that can be exploited in the formation of phosphates. Although *H*-phosphonates exist in equilibrium with their phosphite tautomers in solution, the equilibrium predominantly favors *H*-phosphonate formation (**Figure 11**).[193,251] Therefore, unlike other P(III) phosphorus species, which are soft nucleophiles, *H*-phosphonates are normally electrophilic at the phosphorus center.



Product	No additive Conversion	With PIC Yield (Conversion)
	31%	84% (>99%)
	18%	96% (85%)
	21%	79% (>97%)

Product	No additive Conversion	With PIC Yield (Conversion)
	NA	80%
	not reported	68%

Scheme 94

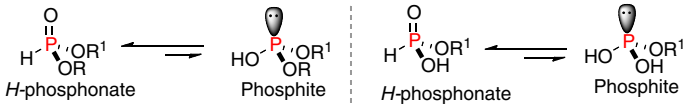
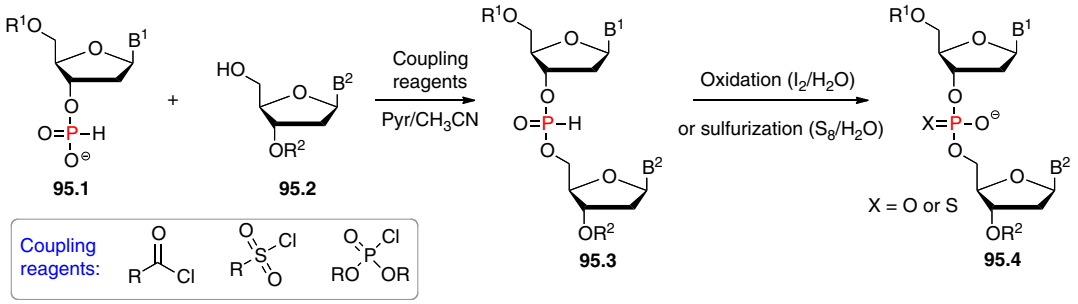


Figure 11 Phosphonate to phosphite equilibrium.

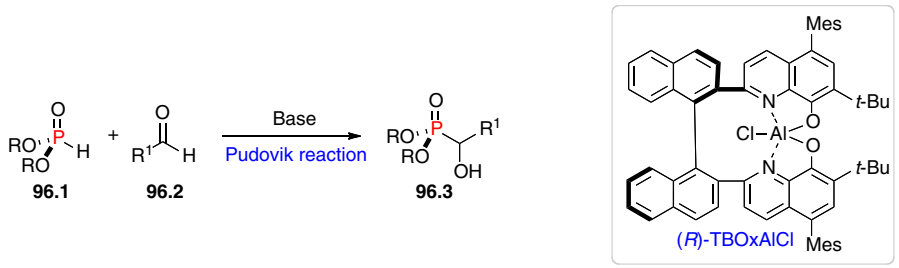
Moreover, as *H*-phosphonates lack an electron pair on phosphorus, they are more resistant to spontaneous oxidation than trivalent P(III) derivatives and are also more stable under acidic conditions.[252] In addition to their chemical and configurational stability, *H*-phosphonates can be oxidized [to P(V)] stereospecifically and can serve as substrates in palladium-catalyzed P–C bond formation.[253] Owing to these attractive attributes, *H*-phosphonate chemistry has been widely explored for use in phosphate synthesis, particularly in the synthesis of oligonucleotide derivatives. As a schematic example (Scheme 95), *H*-phosphonate **95.1** monoester can be coupled with nucleoside **95.2** to form diester **95.3**, which upon sequential oxidation or sulfurization will afford the oligomeric product **95.4**.[193]



Scheme 95

Although *H*-phosphonates are often employed as electrophiles, this role is reversed in the Pudovik reaction[254] where, when treated with base, dialkyl *H*-phosphonates **96.1** can be deprotonated to yield a negatively charged phosphorus nucleophile, which can subsequently add to carbonyl compounds to afford *α*-hydroxy phosphonates **96.3** (Scheme 96). This reaction can be applied to a wide range of electrophiles, including aldehydes, ketones, or imines, to form *α*-amino and *α*-hydroxy phosphonates, accordingly. More recently, catalytic enantioselective Pudovik reactions have been reported and reviewed.[255] In 2008, Yamamoto and Abell used a tethered *bis*(8-quinolinato) aluminum complex (*R*)-TBOxAlCl to catalyze the enantioselective Pudovik reaction of aldehydes **94.4** and aldimines **96.6** with bis(trifluoroethyl) *H*-phosphonate to obtain *α*-hydroxy- and *α*-aminophosphonates **96.5** and **96.7** in excellent yield and enantiomeric excess.[256]

In addition to the synthesis of phosphonates, this 'umpulong' reactivity of *H*-phosphonates can also be exploited to generate phosphate-containing compounds. In cases where carbonyl-containing substrates have anion-stabilizing substituents at the *α*-position, the nucleophilic addition of the *H*-phosphonate anion to a ketone or aldehyde can generate alkoxides that can readily undergo a phosphorus–Brook rearrangement to yield phosphates (see Section 6.12.2.6.4). Thus, this approach serves a

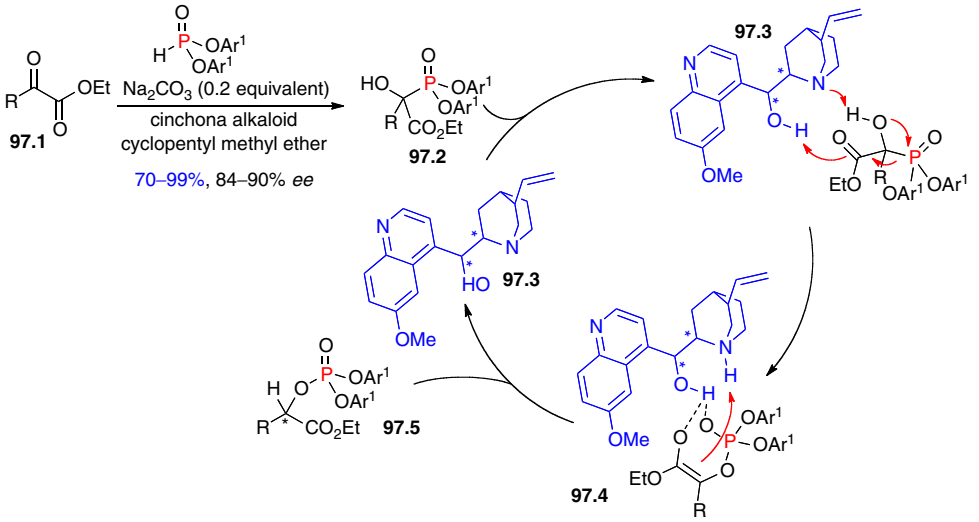


R	Yield (%)	*ee* (%)	R	Yield (%)	*ee* (%)
Ph	95	96	4-MeC_6H_4	94	94
2-Naphthyl	98	95	3-$MeOC_6H_4$	93	95
4-ClC_6H_4	94	95	2-$MeOC_6H_4$	93	93
4-BrC_6H_4	96	95	2-MeC_6H_4	95	95
4-$NO_2C_6H_4$	93	92	*c*-hexyl	95	82
4-$MeOC_6H_4$	93	97	*n*-hexyl	91	82

R	Yield (%)	*ee* (%)	R	Yield (%)	*ee* (%)
Ph	98	96	3-$MeOC_6H_4$	93	98
4-ClC_6H_4	85	90	2-$MeOC_6H_4$	90	90
4-BrC_6H_4	88	92	2-MeC_6H_4	96	92
4-$NO_2C_6H_4$	90	88	2-$Furyl_4$	89	91
4-$MeOC_6H_4$	91	90	2-Thienyl	93	91
4-MeC_6H_4	92	96			

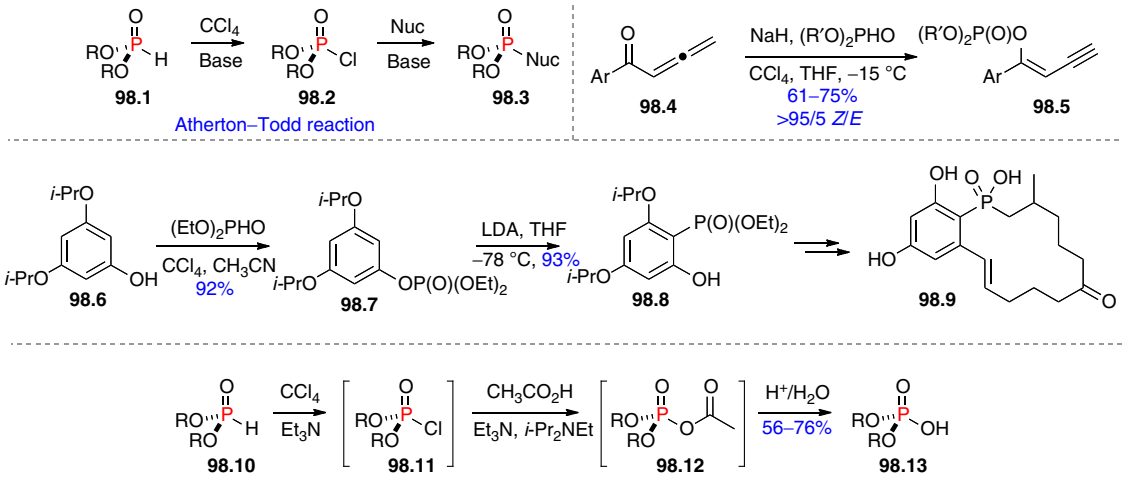
Scheme 96

straightforward strategy of transferring a carbonyl group to phosphate.[257] In 2011, Nakamura and Hayashi utilized α-ketoesters **97.1** to generate chiral, nonracemic phosphate products **97.5** (**Scheme 97**).[258] In the presence of chiral cinchona catalyst **97.3** and Na_2CO_3, α-hydroxy phosphonate **97.2**, formed via the coupling of diaryl *H*-phosphonates and α-ketoesters **97.1**, readily undergoes a [1,2]-phosphorus–Brook rearrangement to yield α-oxygenated ester enolates **97.4**. Subsequent stereoselective protonation of **97.4** regenerates the active cinchona alkaloid catalyst and provides chiral, nonracemic phosphates **97.5**, in good yield and excellent *ee*.



Scheme 97

In the Atherton–Todd reaction, the addition of *H*-phosphonate nucleophiles to CCl_4 allows for the *in situ* generation of a dialkyl phosphoryl chloride intermediate **98.2**, which can be further elaborated via the addition of a second nucleophile (**Scheme 98**).[259] Modifications to halogen sources,[260] as well as the use of phase transfer catalysts,[261] have been published since the first report of the Atherton–Todd reaction in the 1940s. In 2001, Ding et al. reported the synthesis of *Z*-β-alkynyl-enol phosphates **98.5** from β-alkynyl ketone **98.4** and dialkyl phosphite via *O*-enolate trapping by an Atherton–Todd intermediate similar to **98.2**.[262] *En route* to the synthesis of zearalenone phosphonate analog **98.9**, Taylor and coworkers (2005) utilized an Atherton–Todd



Scheme 98

intermediate to generate the trialkyl phosphate **98.7**, which underwent a phospho-Fries rearrangement to furnish phosphonate product **98.8**.[263] In 2003, Engberts and coworkers demonstrated that addition of AcOH to chlorophosphonate intermediate **98.11** produced, upon hydrolysis of mixed anhydride **98.12** with aqueous acid, dialkyl phosphates **98.13**.[264]

In addition to the Atherton–Todd reaction, treatment of *H*-phosphonates with chlorinating agents (such as those shown in Figure 12) can result in the formation of phosphorochloridates that can be used to synthesize a variety of phosphate-containing compounds.[265] In this regard, a number of mild chlorinating reagents have been recently developed and applied to the synthesis of phosphorochloridates from *H*-phosphonates, including *N*-*tert*-butyl-*N*-chlorocyanamide (**12a**,),[266] 1,3-dichloro-5,5-dimethylhydantoin (**12b**),[267] *N*,*N*'-dichloro bis(2,4,6-trichlorophenyl) urea (**12c**),[268] trichloroisocyanuric acid (**12d**),[265] tellurium tetrachloride (**12e**),[269] trifluoromethanesulfonyl chloride (**12f**),[270] and solid-supported *N*,*N*-dichloro poly(styrene-co-divinyl benzene) sulfonamide polymeric beads (**12g**).[271]

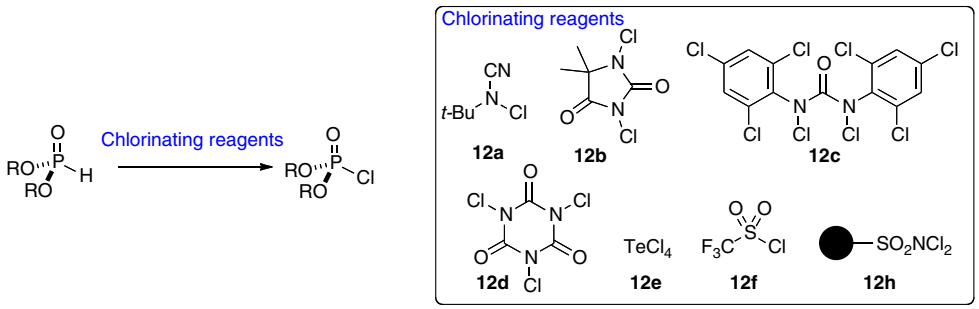


Figure 12 Mild chlorinating reagents.

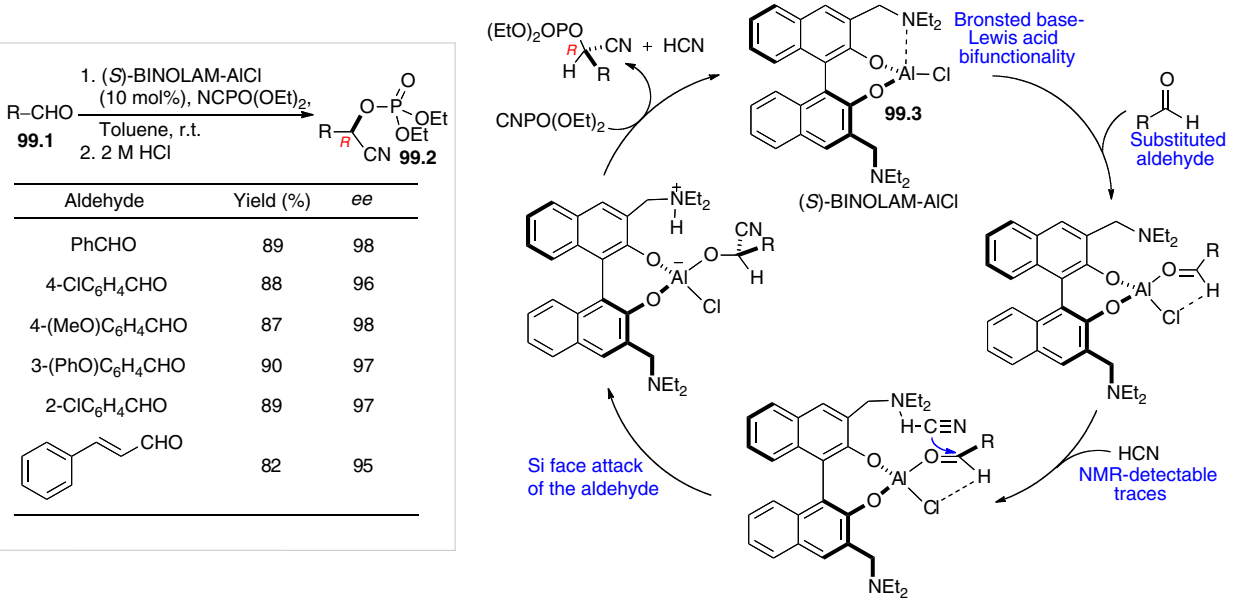
6.12.4 Catalytic and Asymmetric Phosphorylation

Although asymmetric acylation methods have become relatively popular over the past few decades,[272] the development of catalytic and asymmetric phosphorylation protocols has remained relatively unexplored. However, since the turn of the century, several new methods for catalytic and asymmetric phosphorylation have emerged as efficient means of selective phosphorylation of complex substrates, as well as potential means to achieve kinetic resolution of racemic alcohols,[273] *vide infra*. It is noteworthy to mention that several phosphorylation strategies involve the use of a transition metal or Lewis acid catalysts to facilitate phosphate transfer under mild reaction conditions (*vide supra*); such approaches are discussed above, as they relate to the type of phosphorylating reagent.

6.12.4.1 Cyanohydrin O-Phosphates

Cyanohydrin *O*-phosphates are useful intermediates in organic synthesis due to their enhanced stability over their unprotected and silyl-protected counterparts, and a number of synthetic routes have been established to access this moiety from the racemic

cyanophosphorylation of aldehydes and ketones.[274] In recent years, an increased interest in the enantioselective synthesis of these important substrates has led to the development of several catalytic, asymmetric methods to access cyanohydrin *O*-phosphates.[275] The first catalytic enantioselective synthesis of cyanohydrin *O*-phosphates was completed by Sansano and Saá in 2003, whereby a number of chiral Al catalysts were screened and (*S*)-BINOLAM-AlCl (**99.3**) was identified as the most effective to achieve exceptional yields and *ee* in the generation of cyanophosphates **99.2** from aldehydes **99.1** (Scheme 99).[275a] A few years later, that same group published a proposed catalytic cycle to mechanistically account for the stereoselectivity, where selectivity is attributed to both the inherent chirality of the (*S*)-BINOLAM ligand as well as the Lewis acid/Brønsted-base bifunctional nature of the catalytic system (Scheme 99).[275b,c] This catalyst worked well for the cyanophosphorylation of a number of aldehydes, though NO_2-substituted aryl and Lewis-basic heteroaromatic substituted aldehydes showed a dramatic decrease in *ee* (presumably due to the competitive sequestering of HCN).



Aldehyde	Yield (%)	*ee*
PhCHO	89	98
4-ClC$_6$H$_4$CHO	88	96
4-(MeO)C$_6$H$_4$CHO	87	98
3-(PhO)C$_6$H$_4$CHO	90	97
2-ClC$_6$H$_4$CHO	89	97
	82	95

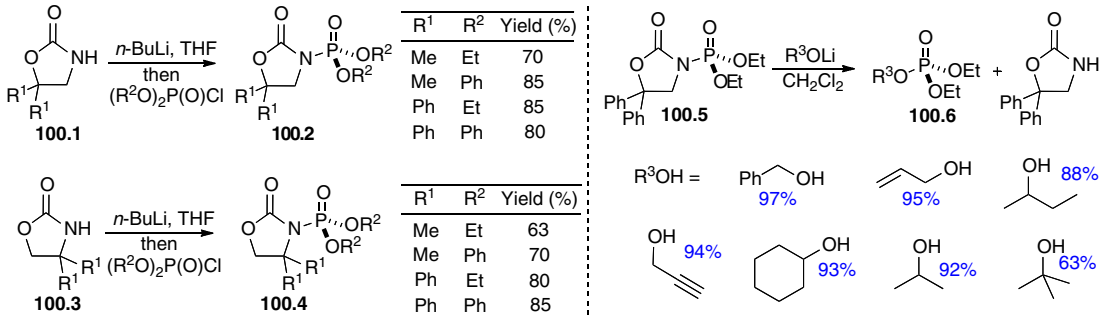
Scheme 99

In addition to the example described above, several racemic syntheses of cyanophosphates, including a solvent-free protocol developed by the same group (Sansano) in 2005,[274,276] and enantioselective syntheses, utilizing yttrium-based catalysis,[277] have been reported.

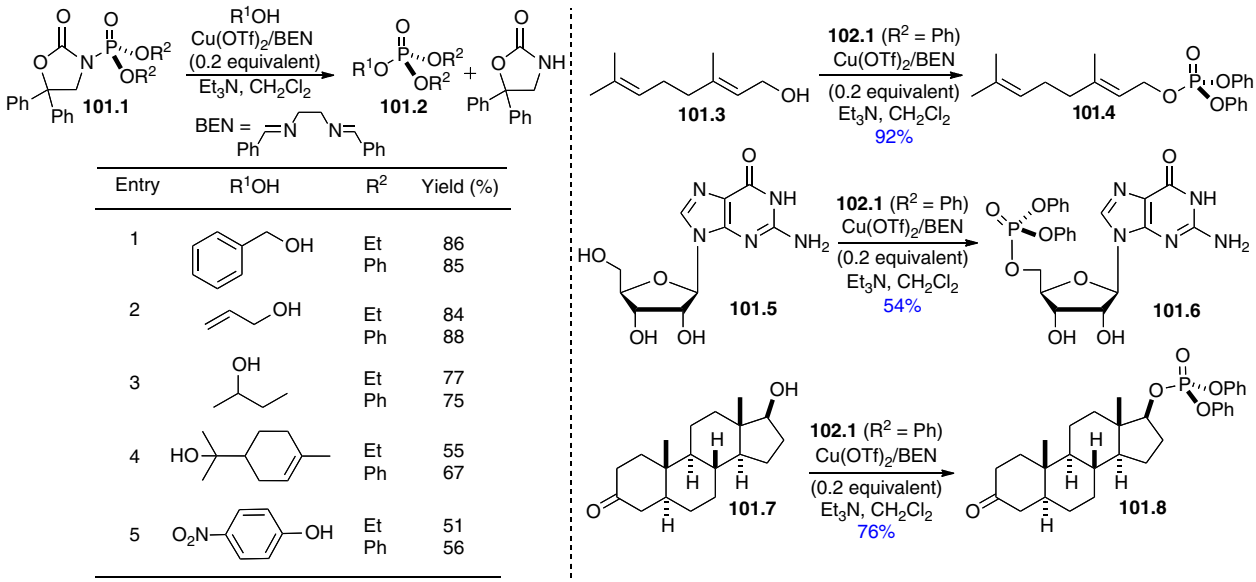
6.12.4.2 N-Phosphoryl Oxazolidinones

N-phosphoryl oxazolidinones have recently emerged as effective phosphorylating reagents in the presence of lithium and magnesium alkoxides, and their inherent stability, presence of a nonnucleophilic counterion, long shelf-life, and ease of handling make them synthetically advantageous alternatives to their halogen-containing analogs. In 2004, Jones and coworker synthesized several *N*-phosphoryl oxazolidinones (**100.2** and **100.4**), via the coupling of oxazolidinones **100.1** and **100.3** with the corresponding phosphorochloridates, and evaluated their ability as phosphorylating reagents of a variety of different alcohols (Scheme 100).[278] Among the generated set, 5,5-diphenyl oxazolidinones (**100.5**) were found to be the most effective phosphorylating reagents across a range of substrates.

As the sensitivity of certain substrates restricts the use of strong bases to generate the alkoxides required to efficiently react with common phosphorylation methods, the development of protocols involving milder reaction conditions for phosphorylation is of fundamental importance, particularly in the world of natural products and complex synthesis. In this regard, in 2005, Jones and coworker reported the use of the Lewis acid catalyst Cu(OTf)$_2$, in conjunction with *N*-phosphoryl oxazolidinone reagents, to phosphorylate both simple and complex alcohols in the absence of a strong base (Scheme 101).[279] Oxazolidinones **101.1** were allowed to react with alcohols (R^1OH), in the presence of Cu(OTf)$_2$ and *N*,*N*′-ethylenebis-(benzaldimine) (BEN) (20 mol%), to yield phosphate triesters **101.2** in excellent yield. In addition, the authors applied this method to the phosphorylation of complex alcohols **101.3**, **101.5**, and **101.7** to generate phosphates **101.4**, **101.6**, and **101.8**, respectively, in good to excellent yields. Most notably, the corresponding yields of these phosphorylations utilizing alkoxide formation with *n*BuLi was never greater than 5%, highlighting the versatility and value of this method to phosphorylate extremely sensitive systems.



Scheme 100



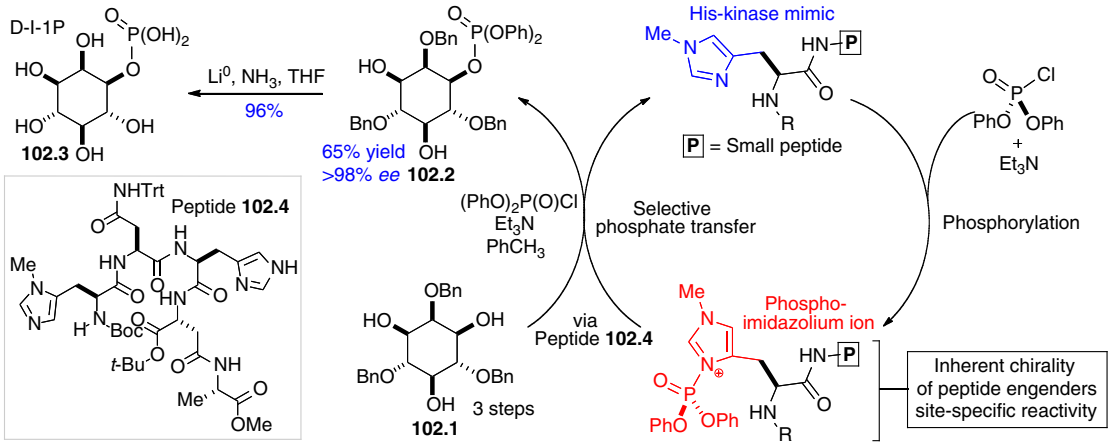
Scheme 101

6.12.4.3 Peptide-Catalyzed Phosphorylation

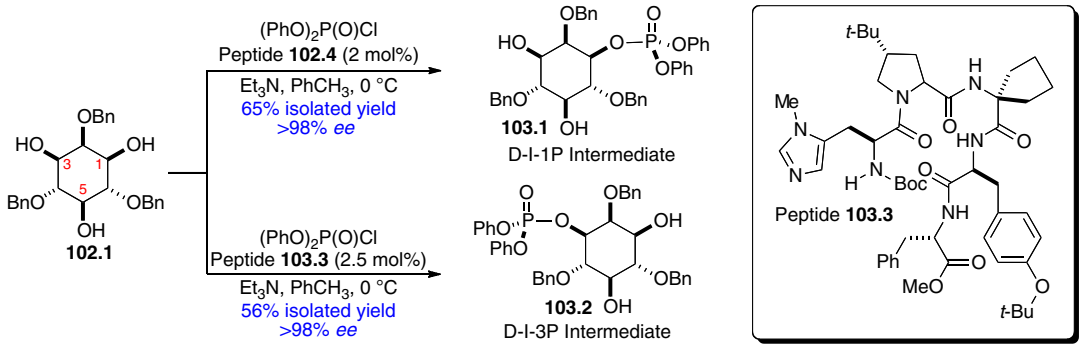
The development of enantio- and regiospecific methods of phosphorylation stands at the forefront of complex molecule synthesis, particularly with respect to natural product and natural product analog syntheses where site-specific phosphorylation is important for bioactivity. However, the generation of reagents that can chemically recognize and react with such specificity, especially when other reactive centers are present in the substrate, represents a significant challenge in organic chemistry. What is more, the transition from stoichiometric equivalents of reagent to small portions of a catalytic species, in order to increase atom economy, even further complicates the process. Thus, in order to match Nature's efficiency, many protocols that seek to address these concerns, turn to biomimetic solutions to this real-world problem.

In 2001, Miller and Sculimbrene reported the regio- and enantioselective phosphorylation of *myo*-inositol derivative triol **102.1** via the use of a small, histidine (His)-kinase-like peptide catalyst (peptide **102.4**).[280] Building upon their experience with low molecular weight peptide catalysts for asymmetric acylation,[281] as well as the expanded general knowledge of histidine (His)-kinase mechanisms,[282] the authors envisioned that the use of a small peptide containing an *N*-methyl imidazole residue could combine with phosphorylating reagent to form a high-energy phosphoimidazolium ion that could then phosphorylate in a site-specific manner due to the inherent chirality and steric bias associated with the attached peptide. Screening of a variety of peptide catalysts identified peptide **102.4** as the most efficient catalyst, with respect to the phosphorylation of benzylated inositol **102.1**, which, in the presence of diphenyl phosphoryl chloride and Et_3N, furnished monophosphorylated **102.2** in good yield and excellent *ee*. Global benzyl and phenyl deprotection with Li metal and Et_3N afforded synthetic D-inositol-1-phosphate (D-I-1P) in 96% yield (Scheme 102).

In 2002, Miller and coworkers further highlighted the utility of the aforementioned peptide-based catalysis in the enantio-divergent phosphorylation of meso-*myo*-inositol-derived triol **102.1** (Scheme 103).[283] Using two different low molecular weight



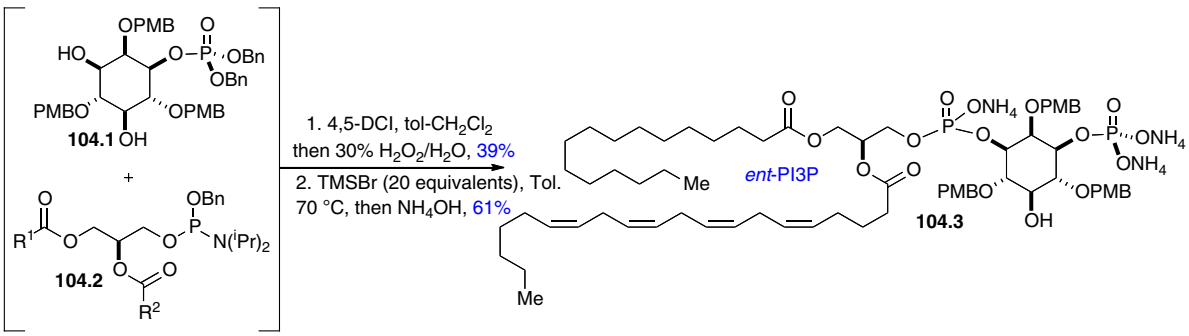
Scheme 102



Scheme 103

peptides (peptide **102.4** and peptide **103.3**), the authors successfully converted benzyl-substituted **102.1** to the corresponding D-I-1P (**103.1**) and D-I-3P (**103.2**) intermediates in good yield and high *ee*, *en route* to the synthesis of the naturally occurring inositol products.

In 2004, Miller and coworkers completed the synthesis of a variety of phosphatidylinosotil-3-phosphates with saturated and unsaturated side chains, utilizing the already described peptide-based catalysts to generate phosphorylated inositol intermediates (Scheme 104).[284] Subsequent coupling of **104.1**, the PMB-protected version of D-I-1P intermediate **103.1** (shown above), with phosphoramidite **104.2**, followed by phosphite oxidation and phosphate hydrolysis with NH_4OH, afforded *ent*-phosphatidylinositol-3-phosphate in modest yield and excellent selectivity.

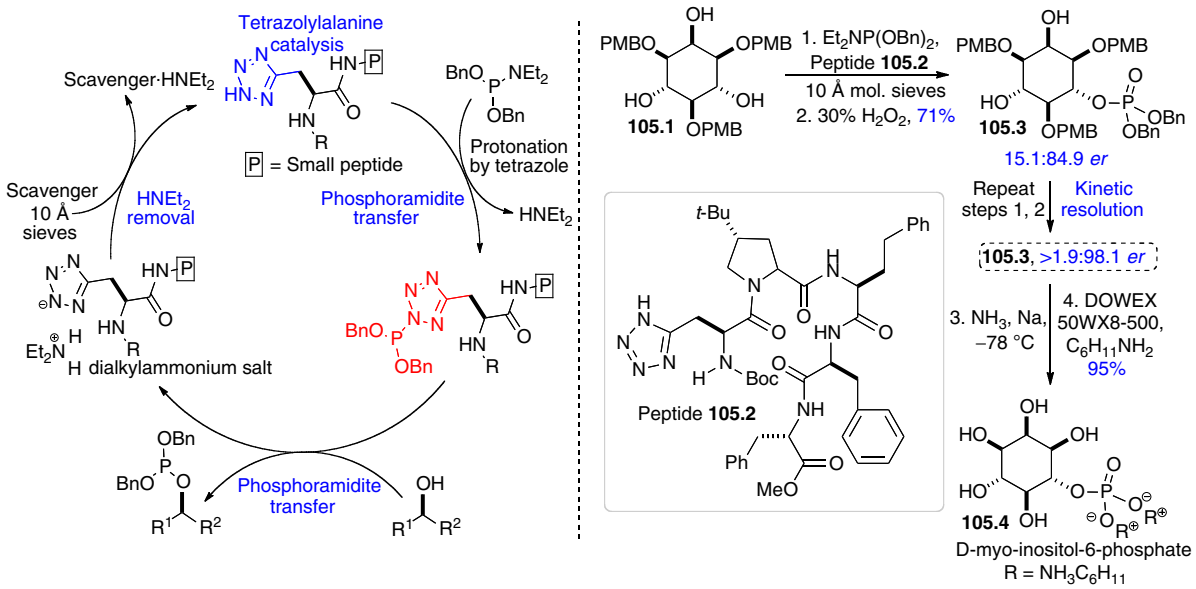


Scheme 104

In 2006, Miller and coworkers utilized this method to complete highly direct total syntheses of PI, phosphatidylinositol-3-phosphate (PI3P), phosphatidylinositol-3, 5-bisphosphate (PI3, 5P2), and a range of deoxygenated versions in diastereomerically

pure forms.[285] In addition, the same group also reported a unified total syntheses of inositol polyphosphates (D-I-3,5,6P3, D-I-3,4,5P3, D-I-3,4,6P3, and D-I-3,4,5,6P4),[286] as well as PI5P–DiC8 and its enantiomer,[287] utilizing their enantioselective and site-selective phosphorylation.

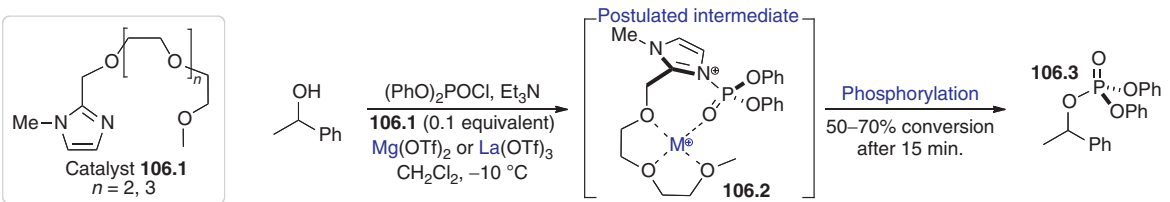
Despite these advances in P(V)-mediated catalytic, asymmetric phosphorylation, several limitations to this method still remained, including the decreased reactivity of P(V)-related phosphorylating reagents with respect to their P(III)-counterparts, as well as the inability of this P(V) method to selectively transfer a phosphate to the 4- or 6-position of *myo*-inositols. To address these issues, in 2010, the Miller group developed another method for catalytic, asymmetric phosphorylation based on phosphoramidite-coupling with tetrazolylalanine-containing peptide catalysis (Scheme 105).[288] Preliminary studies identified tetrazole-functionalized peptide **105.2** as most efficient and selective in the transfer of dibenzyl phosphoramidite, in the presence of 10-Å molecular sieves (amine scavenger), to PMB-protected triol **105.1**. Subsequent oxidation with hydrogen peroxide provided monophosphate **105.3** in good yield and enantioselectivity, though repetition of the phosphorylating cycle (steps 1 and 2) afforded **105.3** in superior enantioselectivity. Global benzyl and PMB-deprotection with dissolving metal conditions, followed by amine salt formation, provided D-*myo*-inositol-6-phosphate **105.4** in good overall yield. The proposed catalytic cycle, which bears several similarities to the previously described peptide-based catalysis, is shown below (Scheme 105).



Scheme 105

6.12.4.4 Bifunctional Imidazole-Derived Catalysis

In 2005, Jones and coworkers prepared the polyether backbone, nucleophilic *N*-methyl imidazole **106.1**, which acts as a bifunctional catalyst in the presence of appropriate metal cations, for cooperative catalysis of phosphorylation of the two model alcohols (1-phenylethanol and cyclohexanol) with diphenyl phosphoryl chloride.[289] The authors postulate that the reaction proceeds via chelated intermediate **106.2**, which results from the activation of the phosphorochloridate with the *N*-methyl imidazole portion of catalyst **106.1**, in the presence of large metal cations, to yield phosphate **106.3** in good conversion after 15 min. The researchers noted that $Mg(OTf)_2$ and $La(OTf)_3$ salts provided the best yields and highlighted the potential of this system for the kinetic resolution of racemic alcohols (Scheme 106).



Scheme 106

6.12.5 Oligonucleotides

6.12.5.1 Oligonucleotide Synthesis

The synthesis of oligonucleotides continues to be a driving force for the development of new and mild methods aimed at controlled and selective introduction of phosphates to a variety of substrates. As almost all the methods in this chapter have been applied to oligonucleotide synthesis and this field has been heavily reviewed,[290] this section will only briefly overview a few common and recently developed phosphorylating strategies to access simple and complex oligonucleotides.

To date, there are four major strategies that have been developed for the synthesis of oligonucleotides (Figure 13). In 1955, Todd and Michelson reported the first synthetic nucleotide employing a phosphotriester approach, which involves the coupling of protected phosphate **13a** with alcohol **13b**.[291] Subsequent deprotection provides dinucleotide product **13e**.

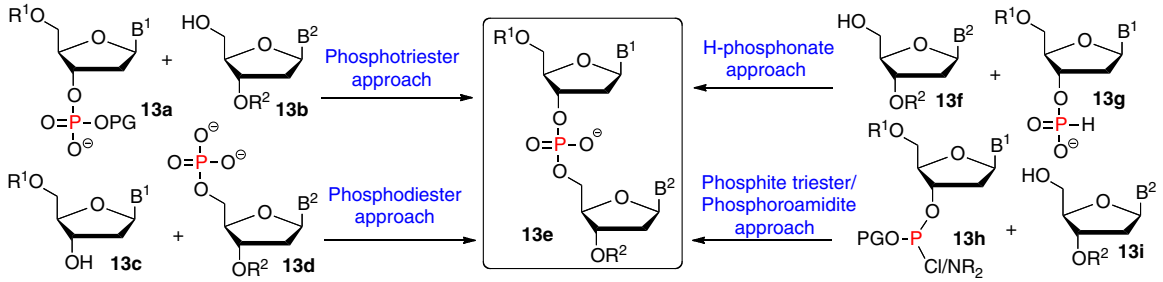


Figure 13 Common approaches to oligonucleotide synthesis.

The direct coupling of alcohols with free phosphate salts was reported by Khorana and coworkers in 1958, in which nucleoside phosphate **13d** was activated with *N*,*N*′-DCC or 4-toluenesulfonyl chloride (TsCl) and coupled nucleoside **13c** to afford dinucleoside product **13e**.[292] It is noteworthy to mention that phosphate coupling with free phosphates, which lack a protecting group is straightforward and step efficient but can suffer from potential side reactions that simple monoprotection can avoid.[290] Several protecting groups are widely used in solid and solution phase oligonucleotide synthesis, including 2-cyanoethyl,[293] 2,2,2-trichloroethyl,[294] and substituted phenyl[295] groups.

In addition to the previously described methods, oligonucleotide synthesis has also been achieved via the coupling of nucleoside **13f** with *H*-phosphonate monoester **13g**.[296] The resulting internucleosidic *H*-phosphonate diester linkages can be oxidized to phosphodiester linkages with a solution of iodine in the presence of water.

Finally, a significant number of strategies used to generate oligonucleotides involve P(III)-mediated phosphorylation, utilizing phosphites/phosphoramidates **13h**.[194] As this approach, initially, relied upon very reactive bifunctional phosphorodichloridite species, deleterious dimerization over desired cross-coupling limited the application of this method in its infancy. This drawback was later addressed by Beaucage and Caruthers, with the development of a less aggressive, more selective and more stable phosphoramidite building block (**13h**).[212] Subsequent advances to this method, including modifications to building blocks, improvements to instrumentation, as well as the development of new synthetic protocols, have made phosphoramidite chemistry a standard practice in the art of oligonucleotide synthesis, particularly with regards to solid-phase synthesis of these biologically important substrates.[297]

6.12.5.2 Phosphorothiolate Oligonucleotides

Synthetic oligonucleotides have been fundamental in the realm of genetic study, including applications to probe gene function, improve genetic diagnosis, and develop gene-targeting therapeutic agents. Owing to the essential role phosphate linkages play in the function of nucleosides within DNA and RNA transcription and translation,[298] modification of synthetic oligonucleotides, particularly within the phosphate linkage via the introduction of sulfur within a phosphate-bridging position (3′-*S*-phosphorothiolate **14a** and 5′-*S*-phosphorothiolate **14b**) or nonbridging position [(R_P)-phosphorothioate **14c** and (S_P)-phosphorothioate **14d**], has been the main aim of recently developed protocols to access synthetic oligonucleotides (Figure 14). A variety of reviews on the synthesis, property, and application of these oligonucleotide analogs have appeared.[299]

In general, oligonucleotide phosphorothiolate synthesis is not fundamentally different from conventional phosphate-based oligonucleotide synthesis. The development of suitable sulfur-containing monomers is the most challenging aspect of this work. As summarized in two seminal reviews by Gaynor and Cosstick[299e] (DNA dinuleotide phosphorothiolates) and Li, Frederiksen, and Piccirilli[299b] (RNA dinuleotide phosphorothiolates), the reported methods for the synthesis of suitable 5′-*S*-monomers include a phosphodiester approach utilizing the condensation of phosphorothioate **107.4** and 5′-iodo-nucleotside **107.5a**[300] or 5′-tosyl-nucleoside **107.5b**[301] (Scheme 107), a phosphoramidite approach that involves the coupling of a phosphoramidite **107.7**

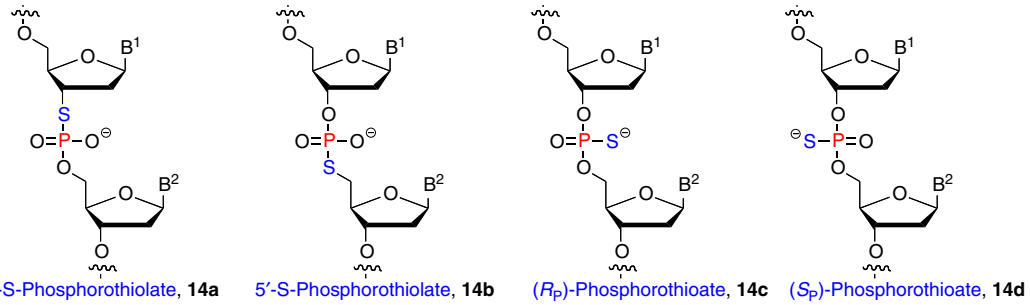
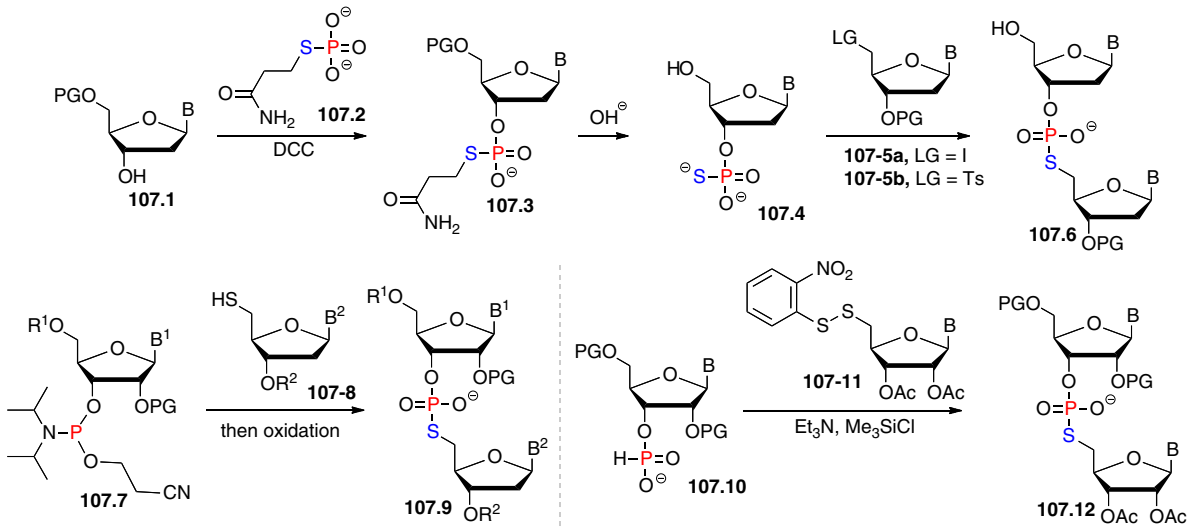


Figure 14 Chiral phosphorothioates.



Scheme 107

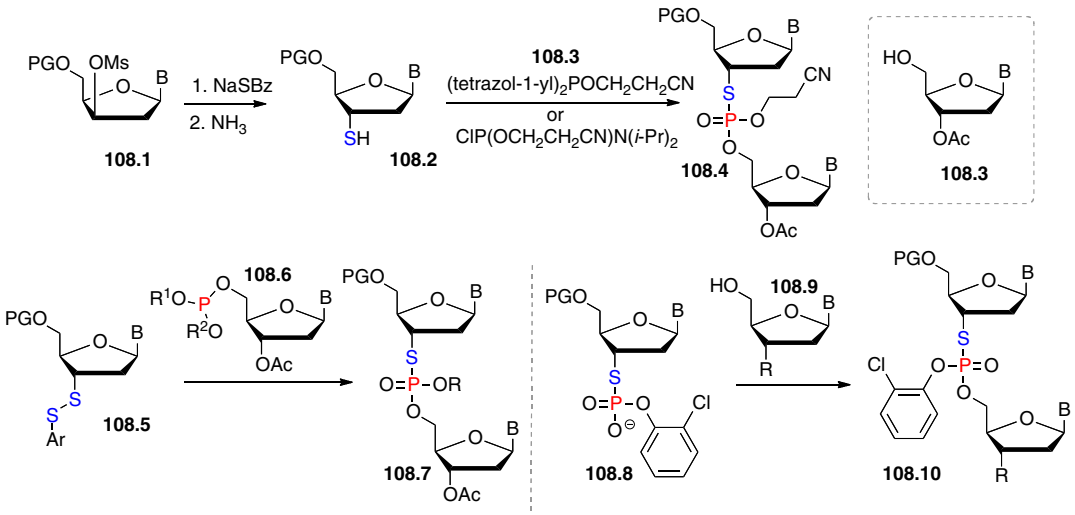
and a 5′-mercapto-nucleoside **107.8**,[302] and the Michaelis–Arbuzov reaction of *H*-phosphonate **107.10** and 5′-*S*-aryl disulfide **107.11**.[303]

Several strategies have been published on the design of suitable 3′-*S*-monomers, as well as their corresponding reactivity patterns, for the synthesis of 3′-*S*-phosphorothiolates. In 1988, Cosstick and Vyle reported the S_N2 reaction of sodium thiobenzoate with mesylate **108.1**, which, upon debenzoylation with ammonia, generated 3′-*S*-monomer **108.2** (Scheme 108).[304] Coupling of **108.2** with nucleoside **108.3** via (tetrazol-1-yl)$_2$POCH$_2$CH$_2$CN[304] or 2-cyanoethyl-*N*,*N*′-diisopropyl chlorophosphoramidite[305] could then furnish 3′-*S*-phosphorothiolate product **108.4**. Conversely, 3′-*S*-monomer **108.2** could also be transformed into 3′-*S*-aryl disulfide **108.5**, which could then be utilized in the Michaelis–Arbuzov reaction with phosphite **108.6**[306] to produce dinucleotide **108.7**. Oligonucleotide synthesis could also be achieved via the phosphorylation of **108.2** to **108.8**, which can be coupled with nucleoside **108.9**, to afford thiophospholate **108.10**.[306a]

In addition, sulfur can be readily introduced into a nonbridging phosphate linkage in the oxidation step (i.e., sulfurization) of phosphite/phosphoramidite-mediated protocols for the synthesis of oligonucleotide phosphorothioates. Some representative sulfurization reagents include 3*H*-1,2-benzodithiol-3-one 1,1-dioxide (Beaucage's reagent, **15a**),[307] tetraethylthiuram disulfide (**15b**),[308] and 3-((*N*,*N*-dimethyl-aminomethylidene)amino)-3*H*-1,2,4-dithiazole-5-thione[309] (**15c**) (Figure 15).

However, when sulfur substituents exists in nonbridging positions, additional chirality on phosphorus is present, and the number of diastereomers increases exponentially if all phosphate–heteroatom bonds are fully modified. Although throughout the history of medicinal chemistry diastereomeric mixtures of oligonucleotide phosphorothioates are useful and common, the construction of stereochemically pure oligonucleotide phosphorothioates is of vital importance in their application to biological study.[310] Chromatographic separation of a diastereomeric mixture of oligonucleotide phosphorothioates is theoretically possible; however, only short oligomers can be separated via high-performance liquid chromatography (HPLC) due to unavoidable similarities in the retention times of the diastereomers of interest. Therefore, *P*-stereoselective synthesis of these oligonucleotides to access stereochemically pure phosphorothioates is highly desirable.

In 1998, Stec and coworkers developed a strategy that utilizes the chromatographic separation of a diastereomeric mixture of 2-thio-1,3,2-oxathiaphospholane monomer **109.4** *en route* to the synthesis of several stereodefined oligonucleotide phosphorothioates (Scheme 109).[311,299d,f] Oxathiophosphoramidite **109.2**, derived from 2,2-disubstituted-2-mercaptoalcohols, was



Scheme 108

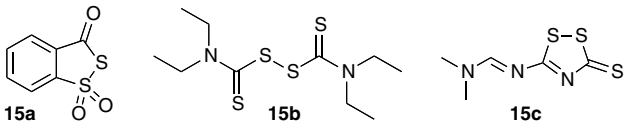
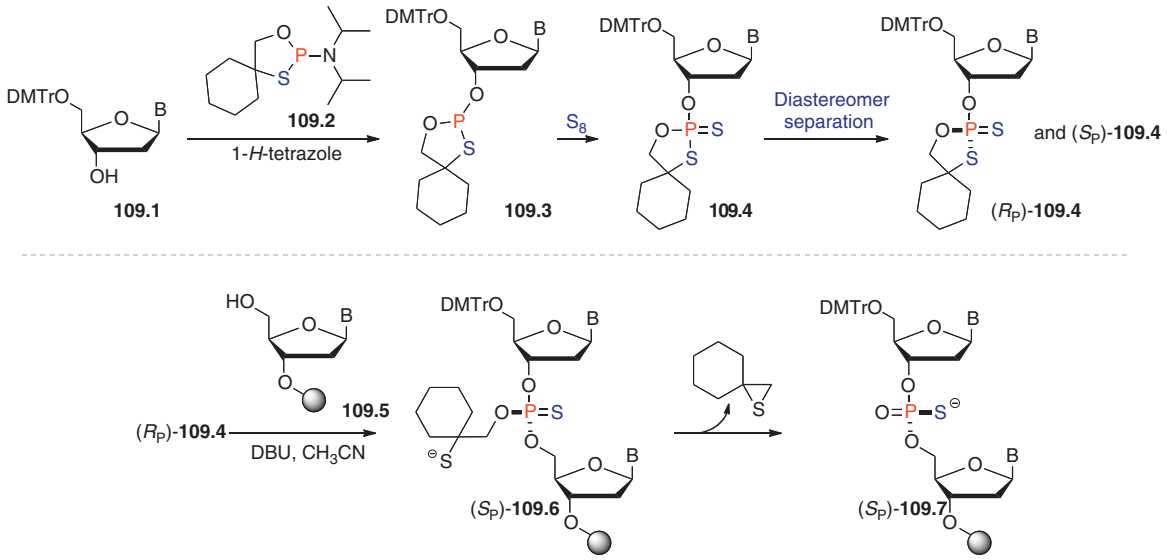


Figure 15 Representative sulfurization reagents.

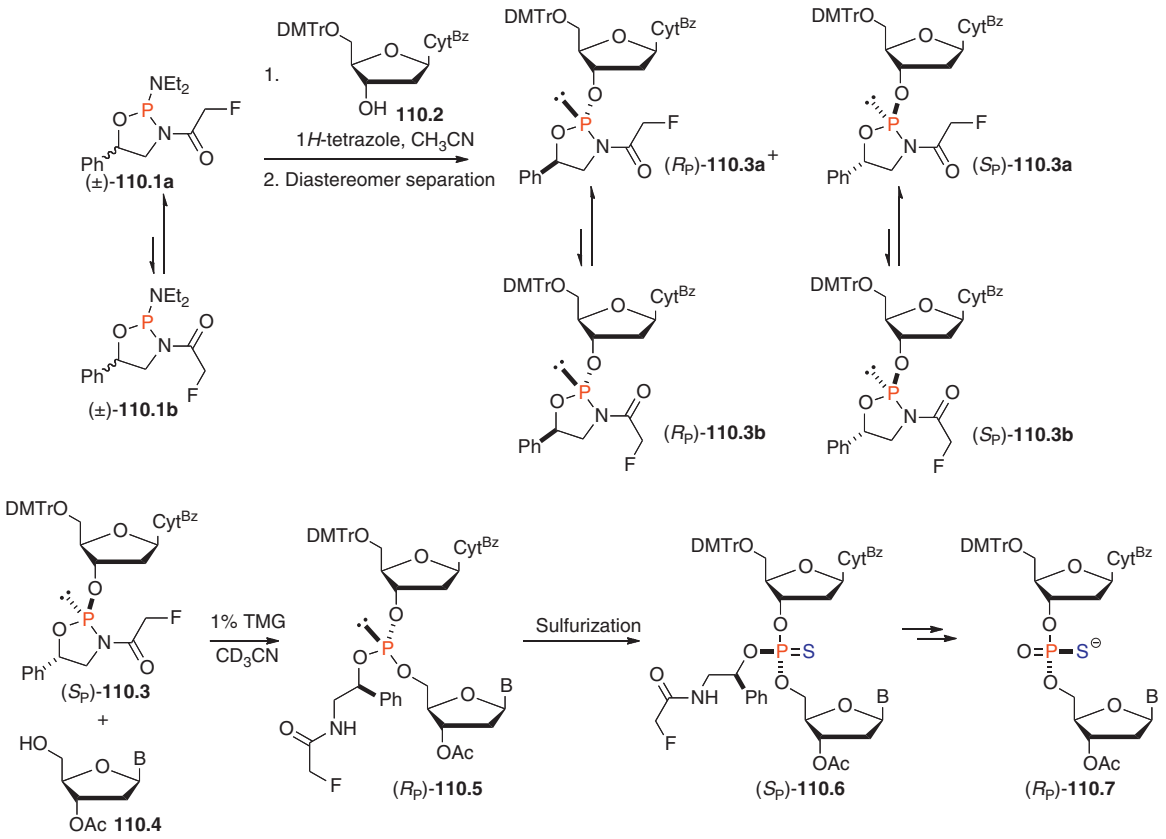


Scheme 109

coupled with trityl-protected nucleoside **109.1** to yield 1,3,2-oxathiaphospholane **109.3**, which on sulfurization, readily afforded a diastereomeric mixture of monomer **109.4**, as a mixture of epimers at phosphorus. After separation with silica gel chromatography, diastereomerically pure (R_P)-**109.4** and (S_P)-**109.4** were then utilized in solid-phase oligonucleotide phosphorothioate synthesis to generate oligonucleotide phosphorothioates, with lengths up to 28 bases, for physicochemical studies and biological evaluation. Coupling of monomer (R_P)-**109.4** with support-bound nucleoside **109.5,** in the presence of DBU, resulted in the cleavage of the endocyclic P–S bond, followed by spontaneous elimination of episulfide, to provide thiophosphate (R_P)-**109.7**. Using this strategy several stereodefined oligonucleotide phosphorothioates with length up to 28 bases were synthesized for physicochemical studies and biological evaluation. The authors note that the stereoselectivity of ring-opening condensation was

higher than 98%, as confirmed by reverse-phase HPLC analysis in the synthesis of all 16 combinations of dinucleoside phosphorothioates.

In 2000, Beaucage and coworkers developed a chiral phosphoramidite approach, in chromatographic separation of diastereomeric mixtures of cyclic *N*-acylphosphoramidites **110.3** allowing for the *P*-stereospecific synthesis of a number of oligonucleotides (Scheme 110).[312] Racemic *N*-acylated cyclic phosphoramidite **110.1** was condensed with protected nucleoside **110.2** to afford monomer **110.3a** as a mixture of diastereomers, as well as amide rotamers (**110.3a** and **110.3b**). Subsequent separation via silica gel chromatography yielded diastereomerically pure (R_P)-**110.3** and (S_P)-**110.3,** as their respective nonisolatable rotamers. Coupling of (S_P)-**110.3** with nucleoside **110.4**, in the presence of *N,N,N′,N′*-tetramethylguanidine, provided phosphite triester (R_P)-**110.5** in near quantitative yield with total *P*-stereospecificity. Sulfurization of (R_P)-**110.5**, with the Beaucage reagent, and successive deprotection, furnished *P*-stereodefined dinucleoside phosphorothioates (S_P)-**110.6** and (R_P)-**110.7**. The authors then highlighted the utility of this method in the solid-phase synthesis of a variety of *P*-diastereomeric dinucleotides and trinucleotides. Unfortunately, this approach is limited by relatively low yield of these cyclic *N*-acylphosphoramidite monomers, which is due to their modest stability toward silica gel chromatography. Therefore, extra caution is needed in chromatography to minimize the contact time of these compounds with silica gel without compromising the chromatographic resolution of these *P*-stereopure phosphoramidites.



Scheme 110

Beaucage and Stec's strategies have proven to deliver oligonucleotides with high stereospecificity; however, chromatographic separation of at least one acquired intermediate is necessary in both approaches, which is both inefficient and time consuming. In addition, the protocols suffer from a number of low-yielding steps, namely the chromatographic separation (in Beaucage's strategy) due to the instability of P(III) monomer **110.3** (Scheme 110) and the coupling of monomer **109.4** and nucleoside **109.5** (Scheme 109, Stec's strategy), originating from the more stable but less reactive P(V) monomer.

To address these issues, efforts have been directed to the diastereoselective synthesis of nucleotide monomers. Between 1996 and 2001, Just et al. developed a series of diastereomerically pure six-membered cyclic phosphoramidites, including imidazo-oxaphosphorines **16a**,[313] indole–imidazo–phosphorines **16b**,[314] indolo-oxaphosphorines **16c** and **16d**,[315] and sugar-derived oxazaphosphorinanes **16e**, via the use of chiral amino alcohols (Figure 16).[223,316] In addition, a variety of diastereomeric pure five-membered cyclic phosphoramidites have been syntheized by Agrawal et al. from the corresponding 1,2-amino alcohols, including ephedrine-derived phosphoramidite **16f**[317] and prolinol-derived phosphoramidite **16g**.[318] Recently, Wada et al. also reported the use of amino alcohol-derived diastereomeric pure monomers (Agrawal's monomers and other monomers such as **16h**

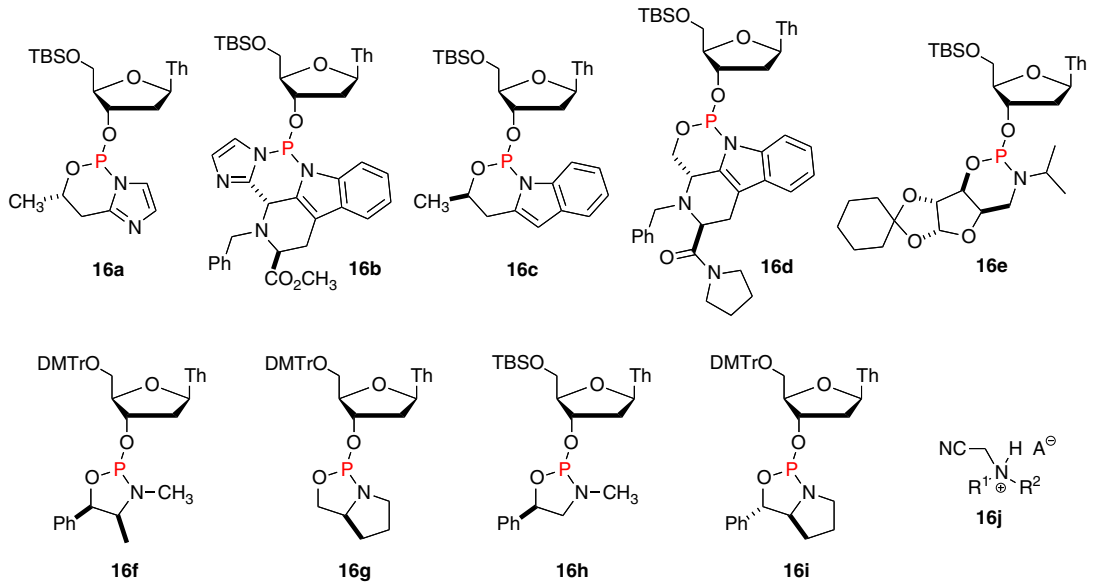
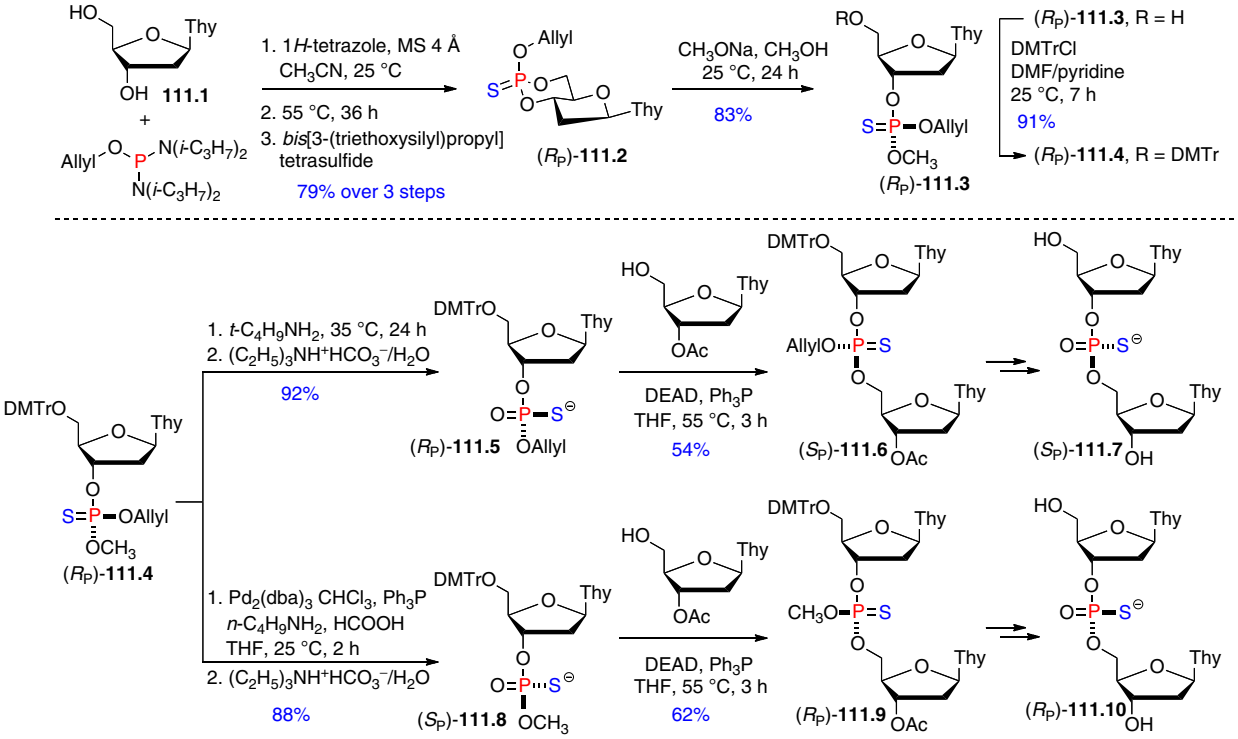


Figure 16 Phosphoramidites generated diastereoselectively.

and **16i**) in the diastereocontrolled solid-phase synthesis of *P*-chiral phosphorothioates with the aid of proton-donating activators such as **16j** during phosphoramidite–nucleoside condensation.[319]

In 2006, Hayakawa and coworkers reported a strategy that enabled the enantiodivergent preparation of stereochemically pure (R_P)- and (S_P)-phosphorothioates from a common nucleoside starting material **111.1** (Scheme 111).[124] The authors ascribed stereoselectivity to conformational bias, where preference of the thermodynamically more stable phosphite triesters with an equatorial *P*-lone pair allows for stereospecific sulfurization to generate the major product [allyl (R_P)-thymidine 3′,5′-cyclic phosphorothioate (R_P)-**111.2**]. Methanolysis of (R_P)-**111.2** resulted in stereoselective and regioselective phosphorothioate ring opening to provide the allyl methyl (R_P)-thymidine 3′-phosphorothioate [(R_P)- **111.3**] the major diastereomer. Selective demethylation of (R_P)-**111.4** then afforded (R_P)-phosphorothioate (R_P)-**111.5**, whereas deallylation of same intermediate [(R_P)-**111.4**]



Scheme 111

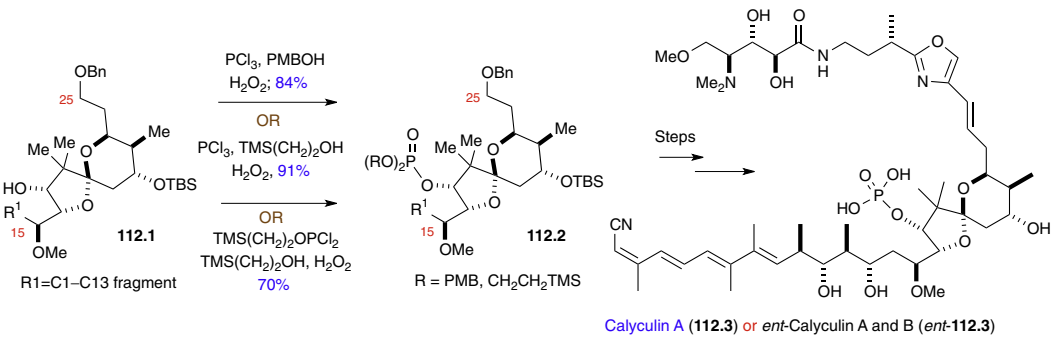
resulted in (S_P)-phosphorothioate (S_P)-**111.8**. Subsequent Mitsunobu coupling with the appropriate nucleoside and allyl-deprotection afforded thiophosphates (S_P)-**111.7** and (R_P)-**111.10**, respectively.

6.12.6 Phosphate Installation in Natural Product Synthesis

Owing to the prevalence of phosphates in biological systems, as well as their prominence in pharmaceutically relevant natural products and FDA-approved drugs and prodrugs, the development of synthetic methods which selectively install phosphates in complex systems maintain the integrity of the phosphate throughout subsequent chemical transformations, and discriminately remove phosphate protecting groups – often in the presence of several other protecting groups within the molecule, spearheads advancements in phosphate-based chemistry, as well as natural product synthesis.

6.12.6.1 Calyculin A

Calyculin A and its analogs have been found to be potent inhibitors of protein phosphatase-1 (PP1) and protein phosphatase-2A (PP2A), which are the key enzymes involved in signaling pathways associated with human disease (Scheme 112).[8a] Most importantly, studies involving structure–activity relationships (SAR) of calyculins indicate that the phosphate, the C13-hydroxyl, and the hydrophobic polyketide tail are essential for their inhibitory action.[8a] To date, six total and formal syntheses have been reported, by Evans, Masamune, Shioiri, Smith, Armstrong, and Barrett, and synthetic efforts toward this interesting natural product were reviewed in 2010.[320]



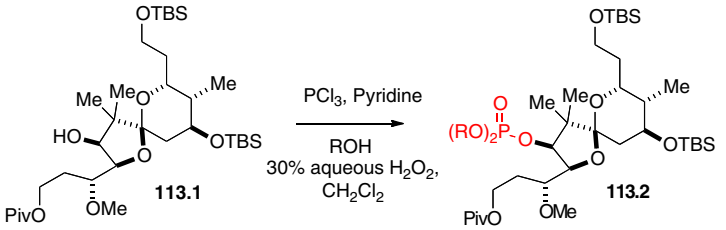
Calyculin A (**112.3**) or *ent*-Calyculin A and B (*ent*-**112.3**)

Scheme 112

Among all the fascinating structural features, the presence of a phosphate group at C17 is of high importance due to promising biological activity as well as structural challenges. In addition, because of the steric environment at C17 and shielding within the spiroketal core, it could be assumed that a reactive electrophile would be required to introduce the phosphate group at C17 (Scheme 112).

In 1992, Evans and coworkers accomplished the first total synthesis of *ent*-calyculin A (*ent*-**112.3**).[321] In their synthesis, phosphorylation at C17 was accomplished via coupling of C1–C25 fragment **112.1** with PCl_3, followed by treatment with *p*MeO-benzyl alcohol (PMBOH) and *in situ* oxidation with H_2O_2, to yield phosphate triester **112.2**. The resulting phosphate-containing C1–C25 fragment was then subjected to four more reactions to complete the total synthesis of *ent*-calyculin A. In addition, model studies performed by the Evan's group to install a phosphate group at C17 illustrated that both $(BnO)_2P(O)Cl$ and $POCl_3$ were not electrophilic enough to react with the sterically hindered C17 alcohol, whereas more electrophilic PCl_3 was successful in phosphorylation (Scheme 113).[322] Further studies revealed that all the four evaluated protecting groups were stable under HF•pyridine conditions, whereas only the *p*-$MeOC_6H_4CH_2$ diester protection was fully cleaved with CH_3CN, 48% HF (aqueous) and H_2O. Most notably, the 2-(trimethylsilyl) ethyl-protecting group proved to be the most robust upon exposure to all conditions.

In addition to studies described above, the Masamune group also reported model studies on the stability of phosphate-protecting groups – namely, allyl and trimethylsilyl protected phosphates – within the context of a fragment similar to **113.1**, and found that the deprotection of diallyl phosphate triesters, upon treatment with $Pd(PPh_3)_4$, did not provide the corresponding monoester, even under a variety of conditions (time and temperature).[323] More importantly, they also found that the 2-trimethyl ethyl-protected triester was able to tolerate a number of reaction conditions, including amide bases (KHMDS) and typical Stille coupling conditions, and can be completely removed via treatment with CH_3CN/47% HF/H_2O = 8.5/0.5/1). Therefore, Masamune and coworkers were able to carry out 12 consecutive steps, including hydrogenation, oxidation, Julia–Lythgoe olifination, and Stille coupling, while maintaining the integrity of a TMS-protected phosphate.[324] With this information in hand, several groups applied the same protocol developed by Evan and Masamune groups in their proceeding syntheses of calyculin A.[325]



Stability of phosphate protecting groups.

R	HF·Pyr	HF, CH_3CN	KHMDS
$NCCH_2CH_2$	Yes	Yes	No
$Me_3SiCH_2CH_2$	Yes	Yes	Yes
$C_6H_5CH_2$	Yes	Yes	
p-$MeOC_6H_4CH_2$	Yes	No	

Scheme 113

6.12.6.2 Fostriecin, Phoslactomycins, Leustroducsins

Fostriecin, a phosphate monoester isolated in 1983 from *Steptomyces pulveraceus*, has shown impressive *in vivo* antitumor activity, as well as *in vitro* cytotoxicity against a broad range of cancer cell lines, including leukemia, lung cancer, breast cancer, and ovarian cancer (Figure 17).[7] Most notably, this significant biological activity has been tied to its unchampioned ability to selectively inhibit PP2A and protein phosphatase-4, which results in these various cytotoxic properties.[326] In combination with these biological activities, the unique structure of fostreicin – which consists of an α,β-unsaturated lactone, C9-phosphate, C8 stereo center, and (Z,Z,E)-triene – have attracted a substantial amount of attention from the synthetic community, and a number of synthetic and biological studies of fostreicin and its analogs have been reported, including eight total syntheses and three formal syntheses.[327] Furthermore, SAR studies performed by Boger and coworkers revealed that the α,β-unsaturated lactone, completely deprotected phosphate at C9, and the C11 hydroxyl group are essential for fostreicin's potent biological activity.[328]

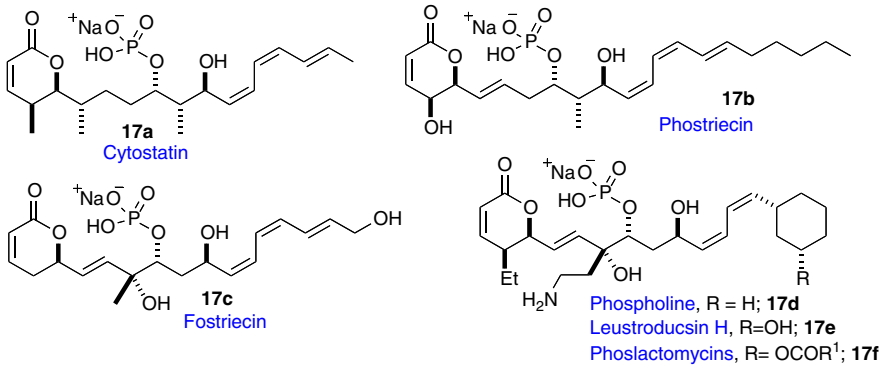
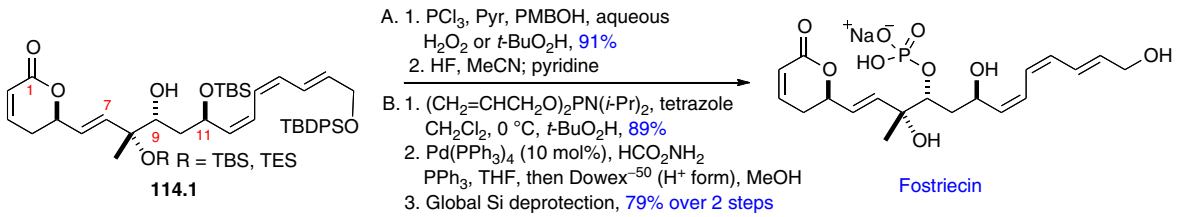


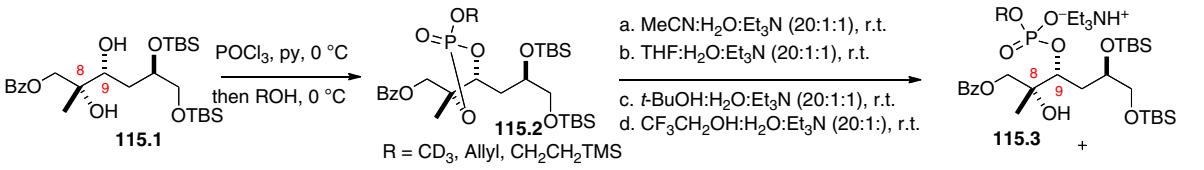
Figure 17 Fostriecin family of phosphate-containing natural products.

In general, the reported total, as well as formal, syntheses of fostreicin have all involved the late-stage installation of the C17 phosphate group, and both phosphoramidite- and phosphite-mediated methods have been employed for phosphorylation, to yield both allyl- and PMB-protected phosphates, respectively (Scheme 114).[327] In 2001, Boger and coworkers observed extensive degradation and olefin isomerization of the phosphorylated version of **114.1** during phosphate PMB-deprotection with prolonged exposure to unbuffered HF, and further attempts at PMB removal with HF-pyr did not afford cleanly deprotected product. Thus, in their synthesis, Boger and coworkers employed a two-stage deprotection, where treatment with HF (15 min) resulted in PMB-deprotection and subsequent addition of pyridine allowed for silyl removal of C8-, C9-, and C18-protected alcohols.[327a] Conversely, when allyl-protected phosphates were utilized, Pd-catalyzed reductive deallylation and HF-pyridine were employed to unveil deprotected fostreicin in good overall yield.[327e]

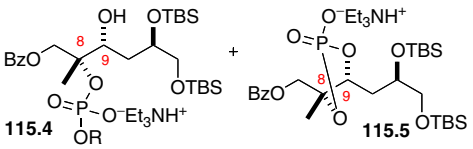


Scheme 114

In 2003, Imanishi and coworkers highlighted a selective cleavage of cyclic phosphate *en route* to fostriecin. Though monophosphorylation of the C9 hydroxyl was unsuccessful within the course of their synthesis, Imanishi and coworkers demonstrated that dipodal coupling of $POCl_3$ with the C8 tertiary hydroxyl and the C9 hydroxyl in diol substrate **115.1** could provide an alternative pathway to fostreicin via the formation of cyclic phosphate **115.2** (Scheme 115).[327f] Model studies with diol substrate **115.1** revealed that hydrolytic cleavage of cyclic phosphoester **115.2** in 2,2,2-trifluoroethanol (method d) provided promising results with respect to both chemical yield and regioselectivity to afford phosphate **115.3**. The authors postulated that, upon hydrolysis, the endocyclic P–O bond of **115.2** is cleaved more easily than the exocyclic P–O bond due to a stereoelectronic effect resulting from a five-membered ring conformation in the trigonal bipyramidal transition state.[329] Therefore, cleavage of more sterically hindered P–O bond occurred preferentially to provide the required monoester **115.3** over the exocyclic P–O bond opened product **115.4**. Notably, the authors also mentioned that phosphorylation via cyclic phosphate intermediate **115.2** was far more effective (23%) in comparison to direct phosphorylation (7%).[327f]



R	Method	(115.3:115.4:115.5)	R	Method	(115.3:115.4:115.5)
CD_3	a	54:15:31	CD_3	d	70:17:13
	b	57:14:29	allyl	d	77:14:9
	c	66:15:13	CH_2CH_2TMS	d	72:14:14



Scheme 115

6.12.6.3 Phoslactomycins, Leustroducsins

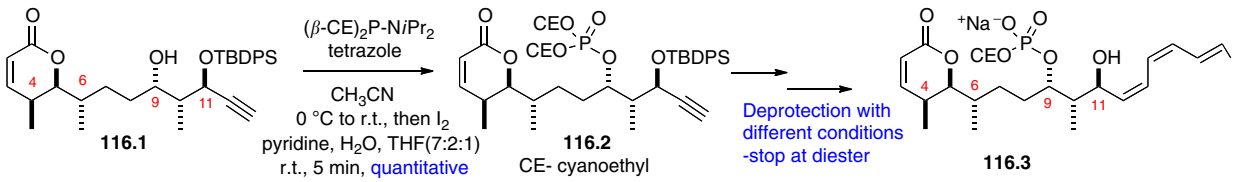
Phoslactomysins (A–F), phospholine, and leustroducsins (A–C) (Figure 17) are phosphate-containing natural products isolated from *Streptomyces nigrescens*, *Streptomyces hygroscoicus*, and *Streptomyces platensis*, respectively, which are known to possess potent antitumor, antibacterial, and antifungal activities, as well as inhibitory activity for human PP2A that have been directly linked to the interaction of the phosphate group within enzyme-binding sites.[330] The key structural features of these families bear striking resemblances to fostriecin but differ slightly at C4 (ethyl group), C8 (2-aminoethyl side-chain, instead of simple methyl group), and C15 (cyclohexyl substituted (*Z,Z*)-diene, instead of a labile (*Z,Z,E*)-triene subunit). In addition, the phospholactomycins and leustroducsins share nearly identical core structures, differing only at the substitution at C18. Several synthetic studies toward the construction of these families of molecules, as well as their analogs, have been reported, including two total syntheses for both phoslactomycin B and leustroducsin B and one total synthesis for phoslactomycin A.[331] In all these syntheses, the C9 phosphate was introduced via one of the two previously described pathways: 1. allyl-protected phosphoramidite chemistry or 2. hydrolytic cleavage of a cyclic phosphate, which are discussed in detail in the portion of this section devoted to the synthesis of fostriecin (Schemes 114 and 115).

6.12.6.4 Cytostatin

Cytostatin (Figure 17), another potent and selective PP2A and PP4 inhibitor, belongs to the fostriecin family of natural products and possesses similar characteristic structural units, including a phosphate monoester, (*Z,Z,E*)-triene and α,β-unsaturated lactone.[332] In addition to the biological activity common to this family, cytostatin has been shown to inhibit the adhesion of B16 melanoma cells to laminin and collagen, display antimetastatic and cytotoxic activity, and induce apoptosis of B16 melanoma cells at submicromolar concentrations. To date, several (3) total and analog syntheses and synthetic studies were reported.[333]

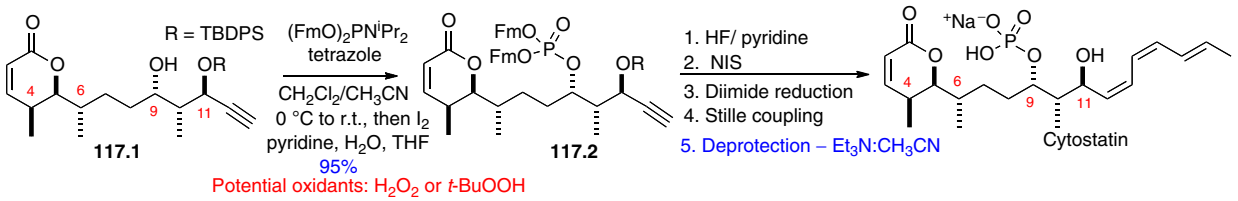
In 2002, Waldmann reported the first total synthesis of cytostatin, involving the late stage introduction of phosphate group before the incorporation of C12–C18 triene (via Stille coupling).[333a,b] Phosphate installation to **116.1** via phosphoramidite coupling, in the presence of 1*H*-tetrazole, followed by oxidation with hydrogen peroxide, provided phosphorylated product **116.2** (Scheme 116). Owing to obvious incompatibilities with planned successive steps, acid- and Pd^0-labile phosphate protecting groups, as well as groups sensitive to hydrogenation conditions (benzyl group), were avoided, and synthetic studies instead utilized base-labile phosphate-protecting groups, such as 2-cyanoethyl group and 9-fluorenylmethyl group.[334] However, efforts to fully deprotect the cynaoethyl group with amine bases in the presence of various solvents were fruitless; thus, this route was limited to the formation of phosphate diester **116.3**, instead of the desired monoester (Scheme 116).

In contrast, the successful installation of the 9-fluorenylmethyl-protected phosphate diester, via the coupling of **117.1** with phosphoramidite $(FmO)_2PN\mathit{i}Pr_2$, followed by oxidation with I_2 in THF:pyridine:H_2O 7:2:1, allowed access to **117.2,** which was



Scheme 116

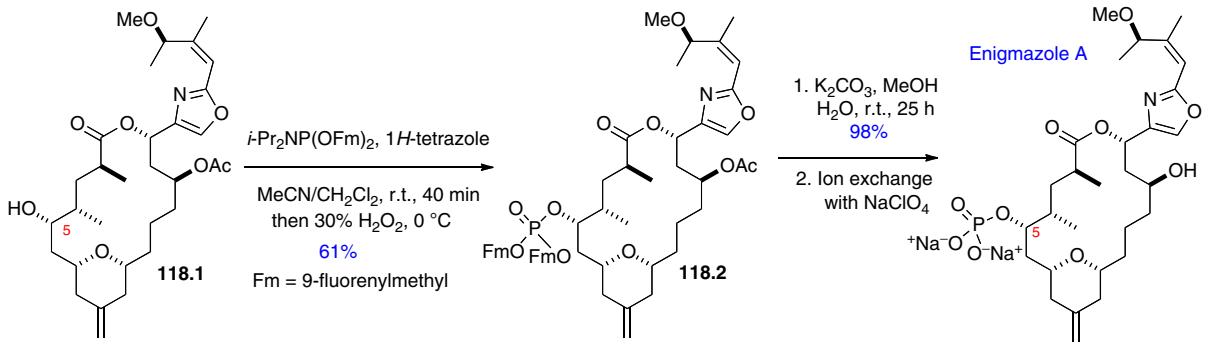
smoothly deprotected with excess Et_3N in CH_3CN, to afford the desired phosphate monoester in cytostatin (Scheme 117).[333a,b] Later syntheses of cytostain – reported by Boger (2006)[333c] and Cossy (2007)[333e] – also applied this phosphorylation–deprotection protocol.



Scheme 117

6.12.6.5 Enigmazole A

Enigmazole A, an 18-membered macrolide which contains a dianionic phosphate monoester, exomethylene-substituted tetrahydropyran ring and densely functionalized 2,4-disubstituted oxazole fragments, was one of the first phosphomacrolides isolated from a marine source (sponge, *Cinachyrella enigmatica*) and has been shown to exhibit significant *in vitro* cytotoxicity toward IC-2 mast cells.[9] In 2010, Molinski reported the first total synthesis of enigmazole A in 22 steps.[335] Phosphorylation at the C5 hydroxyl group of **118.1** was successfully completed, utilizing the same protocol developed by Walderman in cytostatin, via coupling with protected phosphoramidite $i\text{-}Pr_2NP(OFm)_2$ and subsequent oxidation with H_2O_2 to afford phosphate triester **118.2** in 61% yield. Successive phosphate and acetate deprotection was achieved with K_2CO_3 in $MeOH/H_2O$ to generate enigmazole A as the disodium salt in excellent yield (Scheme 118).



Scheme 118

6.12.6.6 Cyclophostin and Cyclipostin P

Cyclophostin and cyclipostin P (Figure 18) are naturally occurring bicyclic organophosphates, which share the same structural core unit and differ only in phosphate triester subunits.[336] Cyclophostin (**18a**) is a potent acetyl cholinesterase (AChE) inhibitor isolated from a fermentation solution of *Streptomyces lavendulae* (strain NK901093), whereas the closely related cyclipostin P (**18b**) is a potent inhibitor of hormone-sensitive lipase.[336] In combination with this impressive biological activity, the interesting structural features of these seven-membered bicyclic enol-phosphate triesters, which possess a 7,5-fused butyrolactone ring and chirality at C3, as well as at phosphorus, have identified them as interesting synthetic and biological targets.

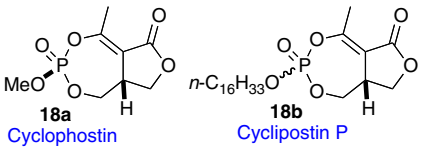


Figure 18 Cyclophostin and cyclipostin P.

In 2011, Spilling and coworkers reported the first total syntheses of cyclophostin, its unnatural diastereomer and cyclipostin P, utilizing two different phosphorylation approaches.[337] The authors envisioned that cyclophostin could be accessed either through the phosphorylation of primary alcohol of **119.1** and subsequent installation and condensation with a distal acetyl group (in **119.3**) or through the selective phosphorylation of butyrolactone to selectively provide *E*-enol phosphate **119.4**, followed by PMB-deprotection and condensation with the distal primary alcohol (Scheme 119).

In light of this, primary alcohol **119.1** was phosphorylated with dimethyl bromophosphate, prepared *in situ* by reaction with $(MeO)_3P$ and Br_2 to afford phosphate triester **119.2** in 75% yield. This phosphorylated butyrolactone was converted to acetyl lactone **119.3** via a two-step acylation–deprotection protocol involving alkylation with LiHMDS and acetyl chloride and demethylation with NaI, followed by protonation with Amberlite® (sulfonic acid) resin. However, cyclization of **119.3** via intramolecular condensation furnished the desired product in extremely low yield. Thus, utilizing the second proposed route, cyclization of enol phosphate **119.6**, prepared in several steps from **119.1** and dimethyl phosphorochloridate, provided the cyclic enol-phosphates (natural and unnatural cyclophostin **119.7**) as 1:1 mixture of diastereomers, which were separable via silica gel chromatography.

Finally, the family of cyclipostins and unnatural cyclipostins (**119.8**) were completed via demethylation of **119.6** and **119.7** with Bu_4NI and subsequent alkylation with the corresponding alkyl bromides to provide the desired phosphate triesters in good overall yield.

6.12.6.7 Moenomycin A

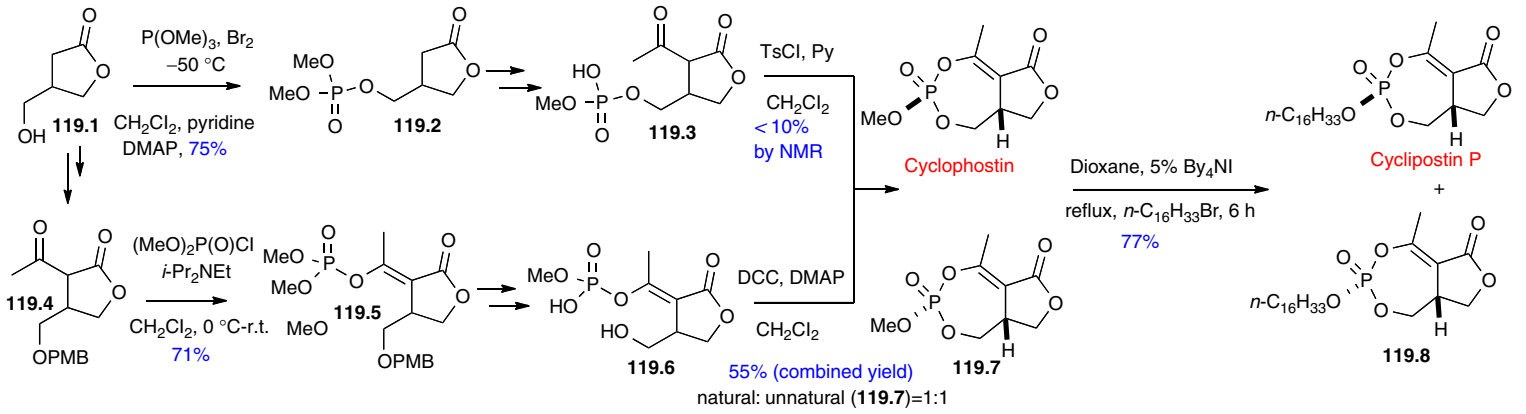
Moenomycin A, a potent antibiotic, inhibits bactereia cell wall synthesis, consists of a highly functionalized pentasaccaride attached to a polyprenyl chain via a unique phosphoglycerate linkage.[338,339] Since the isolation of moenomicin A in 1985, several synthetic studies have been reported,[340] and in 2006, Kahne and coworkers reported the first and only total synthesis of moenomycin A.[341] In this synthesis, the authors utilized *H*-phosphonate chemistry to introduce the phosphate linkage, in which pentasaccharide **120.2** and moenocinyl glycerate (**120.1**) were coupled with cyclic *H*-phosphoryl choloride (2-chloro-1,3,2-benzodioxaphosphorin-4-one), followed by regioselective oxidation with *N*-methylmorpholine (NMM) in the presence of CCl_4, to yield moenomycin A in good yield (Scheme 120).

6.12.6.8 FR901483

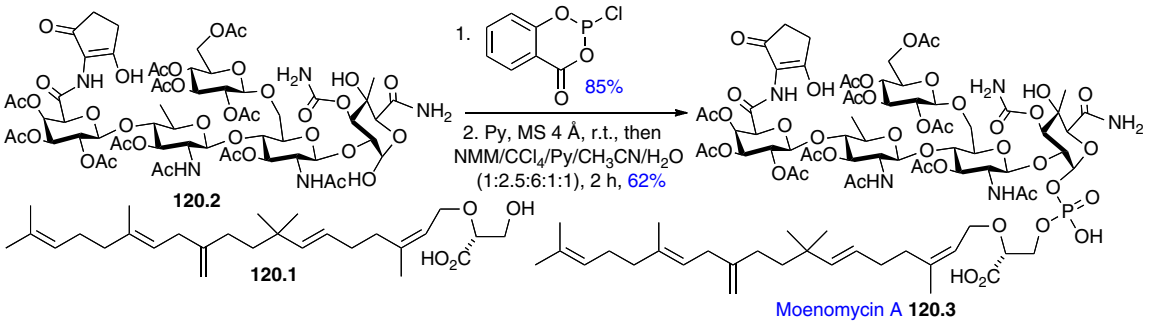
FR901483 is a potent immunosuppressant, which was isolated from the fermentation broth of fungal strain *Cladobotryum sp.* NO. 11231 by the Fujisawa group in 1996.[342] In addition to this biological significance, the novel azatricyclic structure of FR901483 was a synthetically attractive feature, which fueled efforts toward the completion of several elegant total synthesis,[343] as well as synthetic studies. In the reported syntheses, the methods utilized to install phosphate group at C9 hydroxy were dependent on the stereochemistry of the C9 alcohol in starting azatricyclic substrate **121.1** and **121.2** (Scheme 121). In the case where the C9-hydroxyl is axial (**121.1**), direct phosphorylation with dibenzyl-*N*,*N*′-diisopropyl phosphoramidite, in the presence of 1*H*-tetrazole, followed by oxidation with a peroxy acid[344] was utilized to afford **121.3** in 70–95% yield. However, when the C9-hydroxyl is equatorial (**121.2**), Mitsunobu inversion with dibenzyl phosphoric acid (already discussed in the Mitsunobu section) was utilized to generate phosphorylated product **121.3** with suitable C9-stereochemistry. Notably, successful phosphorylation was achieved selectively at C9 in both the approaches, in the presence of the sterically crowded C7 hydroxy group. Finally, amine deprotection/phosphate debenzylation allowed access to the natural product FR901483 (**121.4**) as the hydrochloride salt.

6.12.7 Phosphate-Protecting Groups

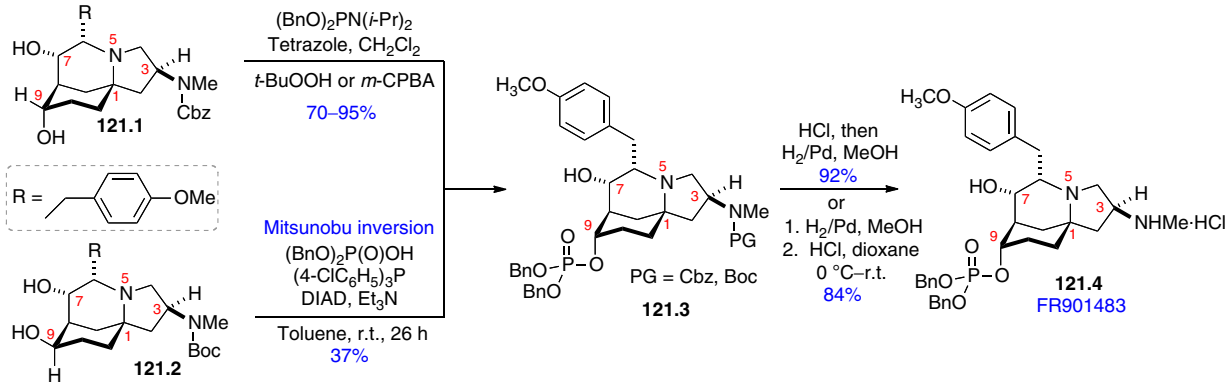
The selection of suitable phosphate-protecting groups is essential in the synthesis of complex molecules, particularly in the realms of oligonucleotide and natural product construction, as almost every phosphorylaton strategy in this chapter highlights. In this regard, a large variety of phosphate-protecting groups have been developed over the last several decades, and several reviews have detailed their installation and removal.[23,241c] Additionally, in 2007, Greene and Wuts extensively described the existing methods for phosphate protection in Protective Groups in Organic Synthesis.[25] In light of these elegant reviews, it is worthwhile to feature a few recent studies that incorporate alternative approaches to phosphate protection via the incorporation of novel protecting groups and removal strategies.


P(OMe)3, Br2
–50 °C
CH2Cl2, pyridine
DMAP, 75%
119.1
119.2
119.3
TsCl, Py
CH2Cl2
< 10%
by NMR
Cyclophostin
Dioxane, 5% By4NI
reflux, n-C16H33Br, 6 h
77%
Cyclipostin P
+
119.8
(MeO)2P(O)Cl
i-Pr2NEt
CH2Cl2, 0 °C-r.t.
71%
119.4
119.5
119.6
DCC, DMAP
CH2Cl2
55% (combined yield)
natural: unnatural (119.7)=1:1
119.7

Scheme 119

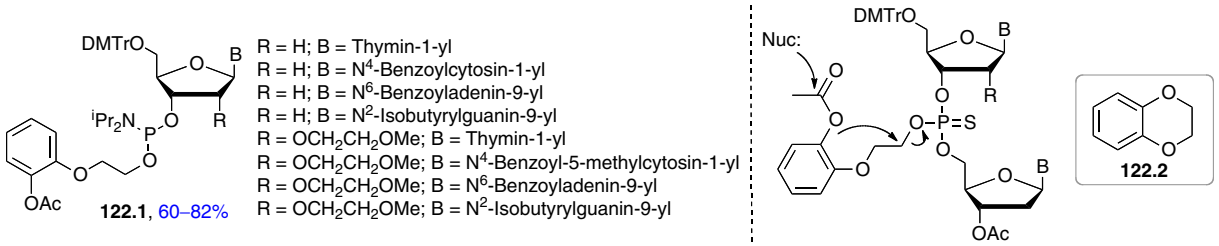


Scheme 120



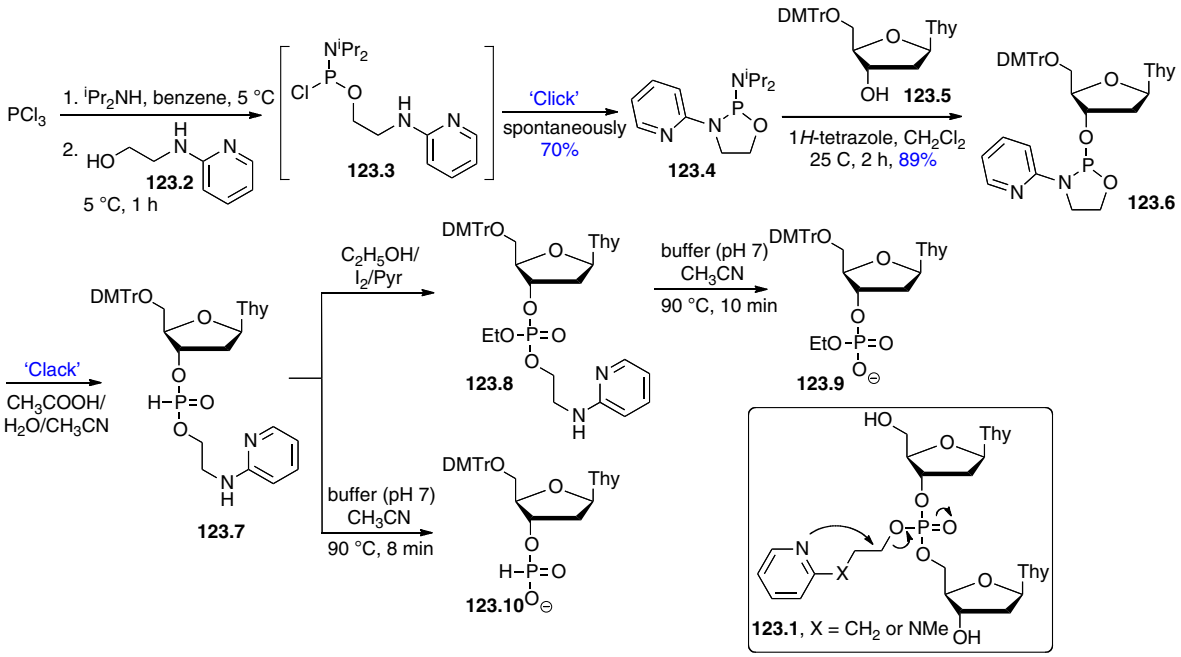
Scheme 121

In 2006, Ravikumar and coworkers developed the (2-acetoxyphenoxy)ethyl (APOE) group as an inexpensive alternative to the conventional 2-cyanoethyl group for phosphate protection.[345] The authors demonstrated the preparation of a variety of phosphoramidite-building blocks (**122.1**) and their use on an automated Pharmacia OligoPilot II DNA/RNA synthesizer (Scheme 122). Deprotection was achieved under standard ammonia deprotection conditions and a probable mechanism involving ether formation, revealing the free phosphate anion and **122.2**, was proposed.



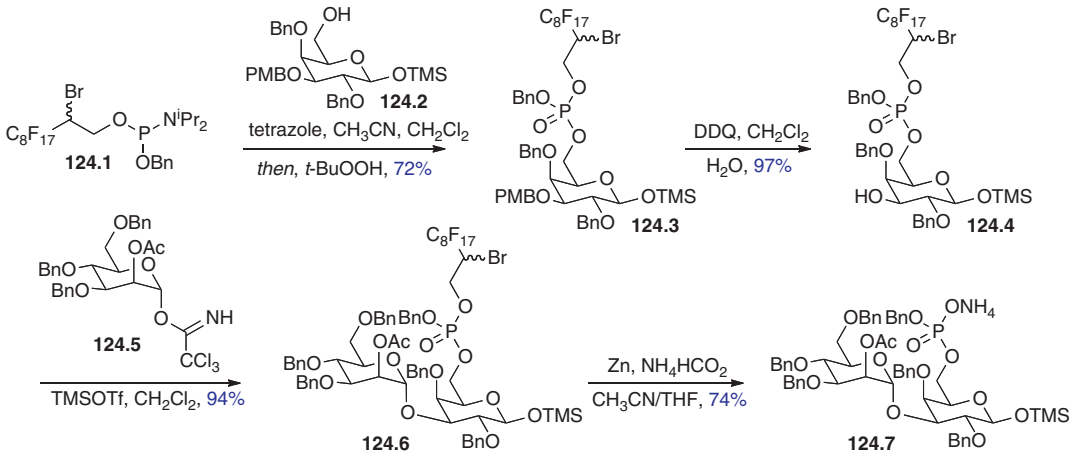
Scheme 122

In 2009, Chmielewski reported the so-called 'click-clack' strategy to address the thermolability of the *N*-(2-pyridyl)aminoethanol-protecting group.[346] Although the previous reports of building blocks **123.1** showed that the 2-pyridinepropanol and 2-[*N*-methyl-*N*-(2-pyridyl)]aminoethanol groups have advantages, such as very mild deprotection with or without ammonia,[347] the thermolability of these groups limited their practical application in nucleotide synthesis (Scheme 123). In this regard, Chmielewski prepared the cyclic 2-isopropyl-3-pyridyl-[1,3,2]oxazaphospholidine (**123.4**) from *N*-(2-pyridyl)aminoethanol (**123.2**) and PCl_3, through the spontaneous cyclization ('click') of acyclic chlorophosphoramidite **123.3**. Coupling **123.4** with **123.5** resulted in phosphoramidite **123.6** as a mixture of diastereomers, and most notably, both **123.4** and **123.6** are stable for months at room temperature. The ring opening of oxazaphospholidine moiety recovered the thermolabile protecting group ('clack'), and the resulting *H*-phosphonate **123.7** could undergo deprotection via one of the two pathways to yield phosphate **123.9** and **123.10**. Overall, this 'click-clack' approach provides a simple and efficient way to manupilate thermolabile properties of protecting groups for the purpose of being used in the synthesis of phosphates.



Scheme 123

In 2011, Pohl and Liu reported the first fluorous phosphate-protecting group and applied it to the synthesis of carbohydrates.[348] The fluorous group can be used as a removable tag, which facilitates purification (via fluorous solid phase extraction (FSPE)) and can be easily removed under mild conditions (zinc and ammonium formate). To demonstrate the application of this strategy, the authors coupled fluorous phosphoramidite **124.1** and galactose derivative **124.2** (Scheme 124). The resulting intermediate was oxidized to form the tagged compound **124.3**. A second coupling of **124.4** with **124.5** to afford **124.6** in 94% yield, and subsequent removal of the tag furnished the desired disaccharide **124.7**.



Scheme 124

Photolabile phosphate-protecting groups have also shown great utility in the area of biomonitoring.[349] In this regard, the development of probe molecules, which are biologically inert and also rapidly release biologically active compounds upon exposure to light, that is, photolysis, is at the forefront of biomonitoring. Photolysis typically proceeds under neutral and reagent-free conditions, providing great utility in monitoring physiological response. Since the seminal review on the photochemistry of phosphoesters by Givens and coworkers,[349] a variety of photolabile phosphate-protecting groups have been reported,[25] including 1-pyrenylmethyl phosphate **19a**,[350] 2-methoxy-5-nitrophenyl phosphate **19b**,[351] and *p*-hydroxyphenacyl phosphate **19c** (Figure 19).[352]

In 2006, Dore and coworkers expanded upon their previously published 8-bromo-7-hydroxycoumarin groups (Bhc-X and Bhc-diol-X) and developed an 8-bromo-7-hydroxyquinoline (BHQ)-protecting group with improved solubility and reduced

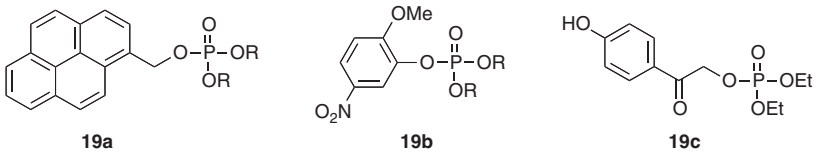
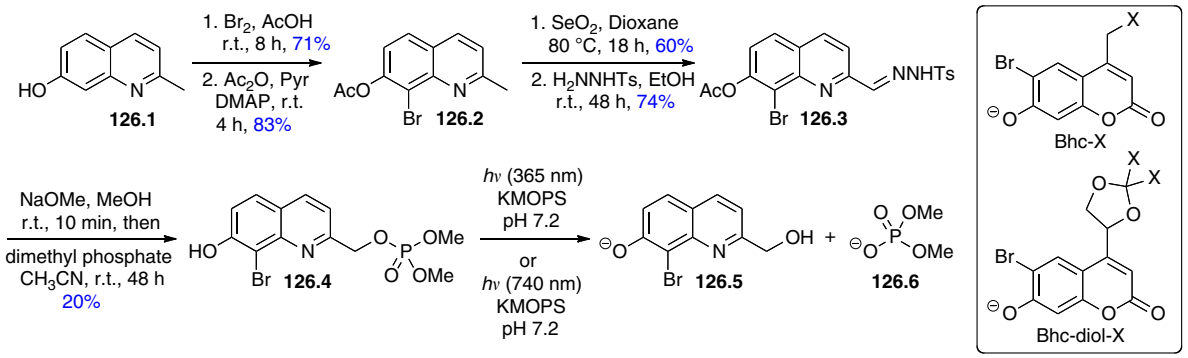


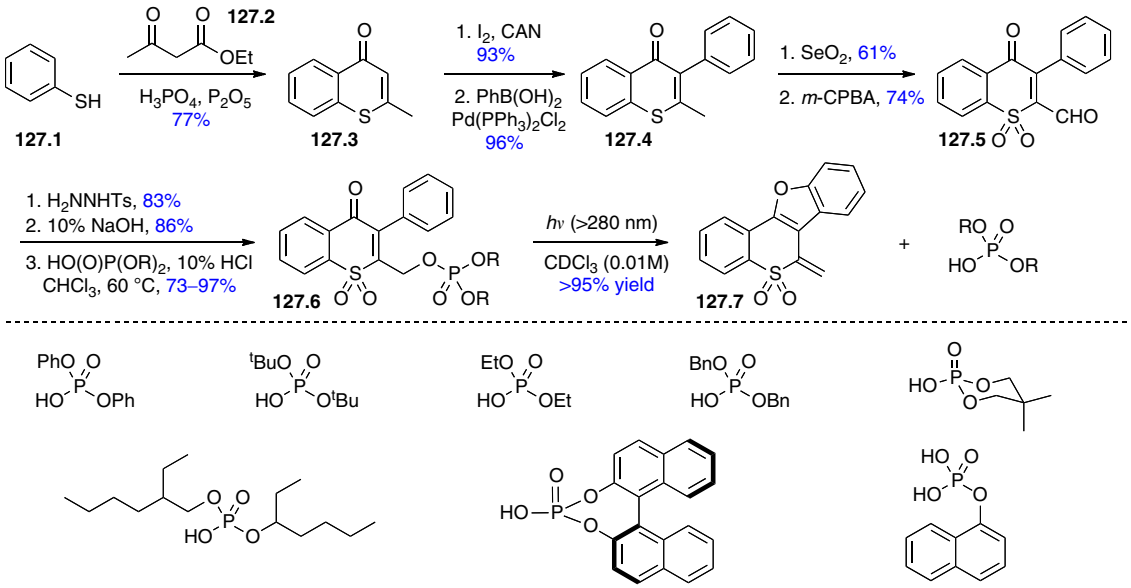
Figure 19 Photolabile phosphate-protecting groups.

fluorescence (Scheme 125).[353] Bromination of **126.1**, followed by acetylation, afforded monobromo **126.2** in good yield. Oxidation on the benzylic methyl group and subsequent tosylhydrazone formation afforded **126.3** in good overall yield. Successive diazo-formation and condensation with dimethyl phosphate, furnished BHQ-protected phosphate **126.4**, which can release phosphates, as well as carboxylates and diols, efficiently and rapidly using one-photon excitation (365 nm) and two-photon excitation (740 nm).



Scheme 125

Recently, in 2012, Kakiuchi and coworkers reported a diazomethyl-containing thiochromone *S,S*-dioxide group for phosphate protection (in **127.6**, Scheme 126).[354] Condensation of thiophenol (**127.1**) and ethyl acetoacetate (**127.2**) yielded methylthiochromone (**127.3**), which was iodonized and coupled with phenylboronic acid to afford the product **127.4**. A two-step oxidation sequence was applied to oxidize the allylic methyl group (SeO_2) and the sulfur (*m*-CPBA). The resulting aldehyde **127.5** was treated with tosylhydrazide, followed by base, to afford a diazo intermediate, which was coupled to phosphate to form the protected phosphate **127.6**. Final deprotection was accomplished smoothly under photoirradiation using a 500 W ultrahigh-pressure mercury lamp (>280 nm) to generate vinyl-sulfone **127.7** in quantitative yield.



Scheme 126

With the advent of photolabile protecting groups and other mild deprotection strategies, which allow for phosphate orthogonality, the value of phosphate chemistry in total synthesis and the synthesis of biologically active small molecules increases at a rapid pace. As challenges in synthesis emerge, undoubtedly, phosphates will continue to play a pivotal role.

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6.13 Use of Carbonyl Derivatives for Heterocyclic Synthesis

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This chapter is a revision of the previous edition chapter by Gerhard Bringmann, Christian L. J. Ewers, Rainer Walter, Vol. 6, pp 733–762, © 1991, Elsevier Ltd.

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Glossary

Bioisostere A chemical group that has similar biological properties to another group due to similarities in chemical or physical structure.

Chemical space The range of molecular structures that represents all synthetically possible compounds within a specific set of boundaries.

Dipole moment The overall net polarity of a molecule due to positive and negative atomic charges. The dipole moment is calculated as the charge times the distance between the charges.

Hydrophobicity The degree of nonpolar character in a molecule. This can be described by the value ClogP, which is the calculated distribution coefficient of a compound between a mixture of octanol and water.

Regioselectivity The degree to which a bond forms or breaks in a particular direction, giving rise to isomeric mixtures.

Topological polar surface area (tPSA) A measure of the overall surface area of a molecule that consists of polar atoms such as oxygen and nitrogen.

6.13.1 Introduction

Heterocycles are essential structures in organic chemistry. Their unique properties make them important components in virtually every field of organic chemistry including pharmaceuticals, materials science, and organic synthesis. As an important structural class, there have been many reviews of heterocycles over the years.[1–4] As an important and diverse group of structures, there are of course many strategies for synthesizing the wide array of heterocycles; however, this chapter will focus on the use of carbonyls and carbonyl derivatives for their synthesis. This chapter will not endeavor to provide a comprehensive catalog of synthetic transformations involving carbonyls and heterocycles. Rather, this chapter will provide a summary of the most important current approaches in use.

Given the widespread functions of heterocycles in organic chemistry, it would be impractical to examine every application of these structures. Therefore, a particular emphasis will be placed on examining the carbonyl-mediated heterocyclic synthesis of biologically active molecules. Even within this subgroup of molecules, it is impractical to provide a useful level of detail for every common heterocyclic structure. In addition, for reasons of chapter length, a subset of heterocycles had to be chosen. Therefore, this chapter will give an overview of five of the most common and important monocyclic heterocycles in the generation of biologically active compounds. Examples of some of the more important heterocyclic United States food and drug administration (FDA)-approved drugs are given in **Figure 1**.

The heterocycles that will be discussed were chosen not only because of their roles in medicinal and synthetic chemistry, but because they provide a reasonably diverse description of the types of carbonyl-heterocycle transformations that are common. For example, while furans and pyrroles are important ring structures, many of their synthetic approaches have commonalities. For instance, the Paal–Knorr synthesis can provide access to thiophenes, furans, and pyrroles through modified cyclizations of 1,4-diketones.[5] Therefore, instead of discussing all three of these heterocycles, this chapter will discuss only thiophenes. It is hoped that this will serve as an anchor point for many approaches to furans and pyrroles instead of including cursory descriptions of all three of those heterocycles.

The usefulness of carbonyl compounds in the synthesis of heterocycles lies fundamentally in several general properties. The first is the high oxidation state of the carbon atoms and the second is the dipole moment that results from the higher electronegativity of the oxygen atom. The increased oxidation state allows cyclization reactions to occur which transform acyclic precursors into aromatic heterocycles, often without additional oxidative transformations. The electronegativity of the oxygen atom of the

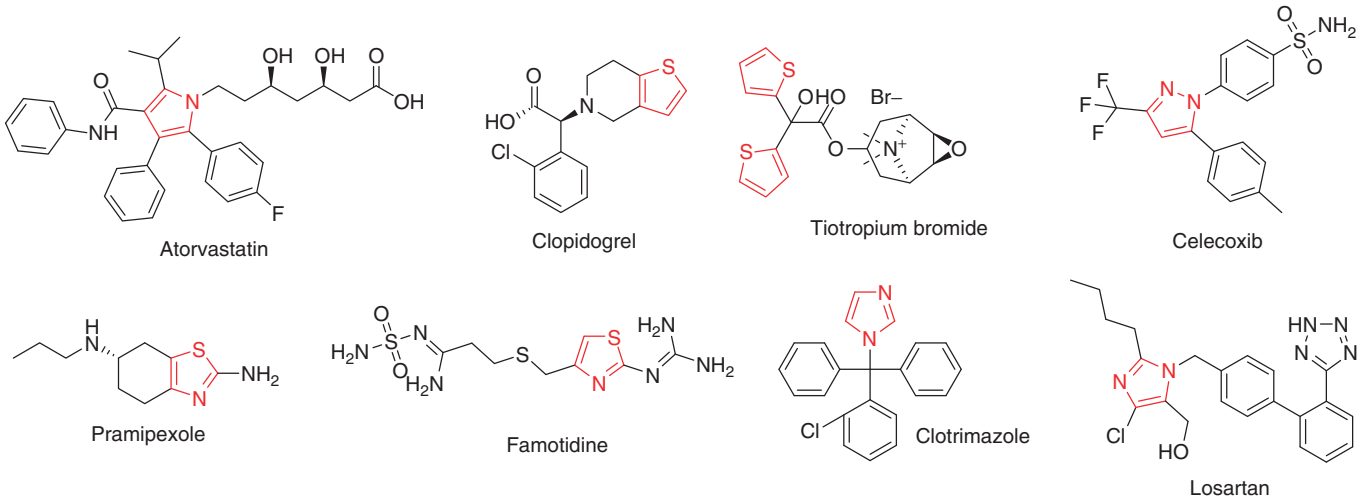


Figure 1 Examples of heterocycle-containing FDA-approved drugs.

carbonyl provides a dipole moment to carbonyls which makes them good electrophiles. This allows a wide variety of nucleophiles to add, which on subsequent cyclization gives rise to many different heteroatom combinations and a rich diversity of heterocycles (Table 1).

Table 1 Dipole moment and bond energy of several carbonyls

Structure	*Dipole moment (debye)*	*Bond energy (kcal mol^{-1})*
	2.3	170
	2.7	175
	2.9	180

While a great many heterocycles have been synthesized (and many more are possible) for many purposes, this chapter will focus on those that are commonly used in the synthesis of biologically active molecules. To a large degree, many heterocycles can be considered isosteres of their carbocyclic counterparts.[6,7] For instance, the pyridine and thiophene rings are generally considered isosteres of benzene (Figure 2).[7] Isosteric replacement of the hydrophobic and weakly polarized phenyl group with heterocycles opens up a more diverse chemical space and enables physical and biological properties to be more finely tuned based on hydrophobicity and polarity (Figure 3).

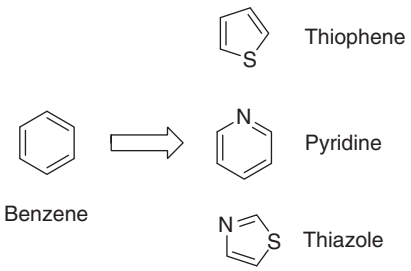


Figure 2 Bioisosteres of benzene.

The previous volume of this series provided an excellent review of many important aspects of heterocyclic synthesis as they relate to the use of heteroatom or charged derivatives of carbonyls in a variety of transformations producing heterocycles.[8] Many of the details of the reactions in this chapter are still valuable and important some 20+ years later, especially the information concerning reaction mechanisms of the Pictet–Spengler and hetero Diels–Alder reactions. In this chapter, however, it was decided that rather than focusing on specific transformations or starting material functional groups, the emphasis would be on demonstrating the overall usefulness of carbonyl compounds in producing common heterocyclic rings that are widely relevant.

6.13.2 Synthesis of Heterocyclic Compounds

6.13.2.1 Synthesis of Thiazoles

The thiazole is one of the most common heterocyclic systems, and in medicinal chemistry it has been used as a bioisostere of various functional groups including pyridine and carbonyl.[9] An especially productive use of thiazoles has been in antibiotics.[10–14] In fact, there are at least 12 thiazole-containing cephalosporin-type β-lactam antibiotics approved for use by the FDA. Many other important bioactive molecules contain the thiazole group (Figure 4).

The most important synthesis of thiazoles is still the classical Hantzsch thiazole synthesis (Scheme 1).[15,16] In this reaction, α-halocarbonyl compounds are condensed with thioamides. In this reaction, the thioamide sulfur of **2** attacks the halogen carbon giving an intermediate imidothioate (**3**). Attack of the nitrogen on the carbonyl produces the dihydro thiazole ring (**4**), which on elimination of water generates the final 2,4-disubtituted thiazole (**5**). The Hantzsch reaction allows for extensive variation of aromatic substitution patterns.

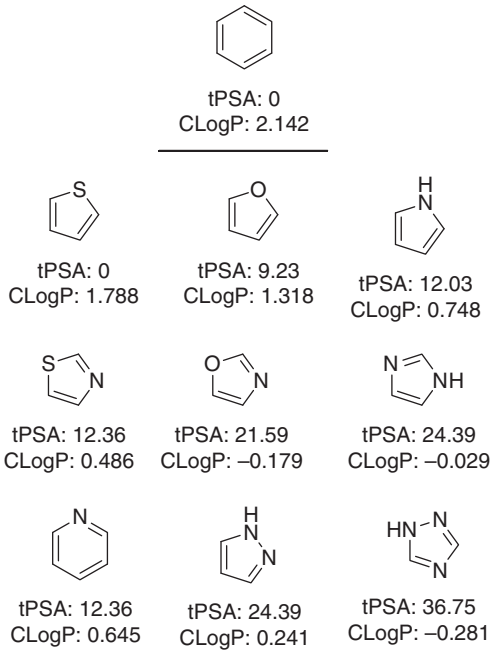


Figure 3 Physiochemical data for some important heterocycles.

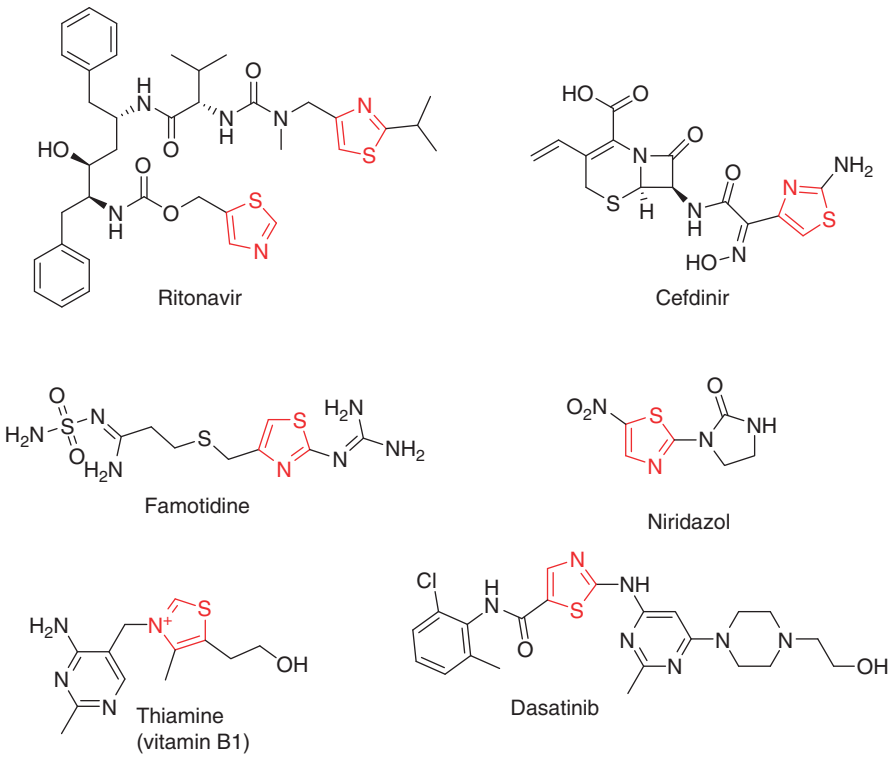
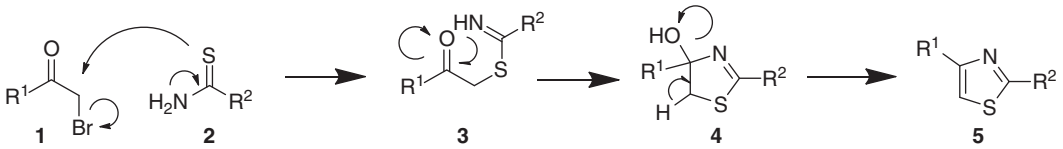


Figure 4 Examples of important biologically active thiazole-containing compounds.

The same general Hantzsch mechanism can be applied to various other thioamide-type reagents to produce other useful thiazole derivatives (Figure 5). For instance, when thioureas (**7**) are used instead of thioamides, the 2-aminothiazole **10** can be obtained generally in good yields.[17] Another important variation uses dithiocarbamic acids (**8**) to condense with α-halocarbonyls to afford 2-sulfanylthiazoles (**11**).[18] Finally, fully trisubstituted thiazoles (**12**) can be produced utilizing secondary halides (**6**, R_2,



Scheme 1 Mechanism of the Hantzsch thiazole synthesis.

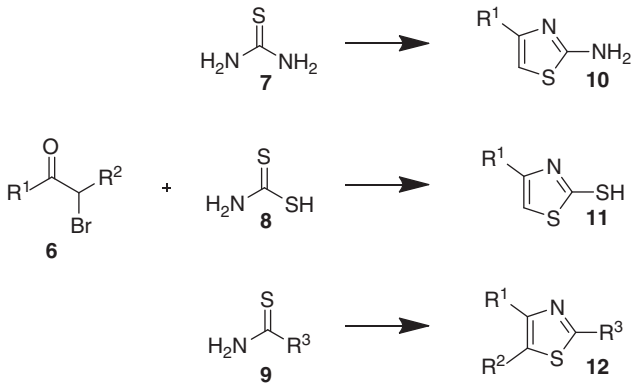
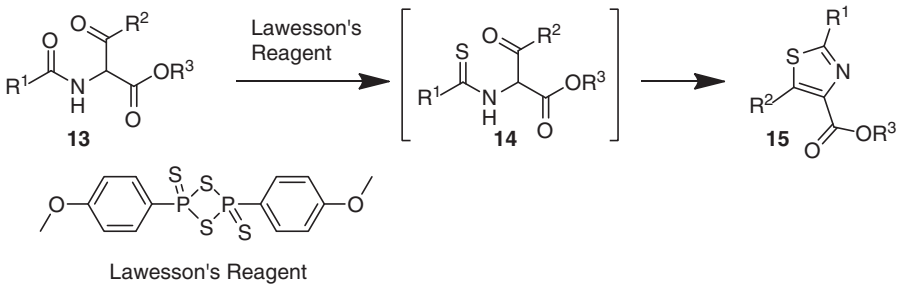


Figure 5 Variations of the Hantzsch thiazole synthesis.

$R_2 \neq H$) and thioamides (**9**) as precursors.[19] This can provide a useful method for regioselectively generating fully substituted thiazoles, although yields are generally not as good because of the additional steric hindrance of the halide position.

Another key synthetic route to highly substituted thiazoles that potentially avoids the use of halocarbonyls employs Lawesson's reagent (Scheme 2).[20] In this scheme, *α*-acylamino ketones (**13**) are treated with Lawesson's reagent, causing *in-situ* formation of the thioamide (**14**) and subsequent intramolecule cyclization to afford the thiazole (**15**). This transformation can also be performed using fluorous and solid-phase synthetic approaches, further expanding its usefulness and efficiency.[20]



Scheme 2 Hantzsch thiazole synthesis using Lawesson's reagent.

The benzothiazole ring is one of the most frequently utilized ring systems in organic and medicinal chemistry (Figure 6). One of the reasons for this is that since the carbon–sulfur bond in aromatic rings can be considered based on bond length to approximate a CH═CH moiety, the benzothiazole itself behaves much like a quinoline isostere.[7,9] As such, numerous approaches have been used in its synthesis.

The most versatile and useful synthetic procedure for preparing benzothiazoles (and benzoxazoles and benzimidazoles using analogous reactions) involves treating 2-aminobenzenethiol (**15**) with carboxylic acids **16** (Scheme 3). Initially, the reaction generates the anilide **17**. Attack of the thiol on the carbonyl carbon generates the 2-hydroxy dihydrobenzothiazole **18**. Finally, loss of water produces the final benzothiazole **19**. The reaction is widely applicable to large variations in the acid and aromatic ring components.

In addition to carboxylic acids, a number of other acid equivalents have been used that have oxidation states appropriate for formation of the thiazole ring in benzothiazole, both carbonyl-containing and noncarbonyl-containing (Figure 7). Among the most common are nitriles, esters, and orthoesters.

A common variation on the dehydrating cyclization of carboxylic acids by aminobenzenethiols utilizes aldehydes as the carbon synthon (Scheme 4). In this procedure, 2-aminobenzenethiols (**15**) are first reacted with aldehydes to afford an intermediate imine (**20**). Cyclization by attack of the thiol on the imine produces the dihydro benzothiazole. Because the initial aldehyde is at a

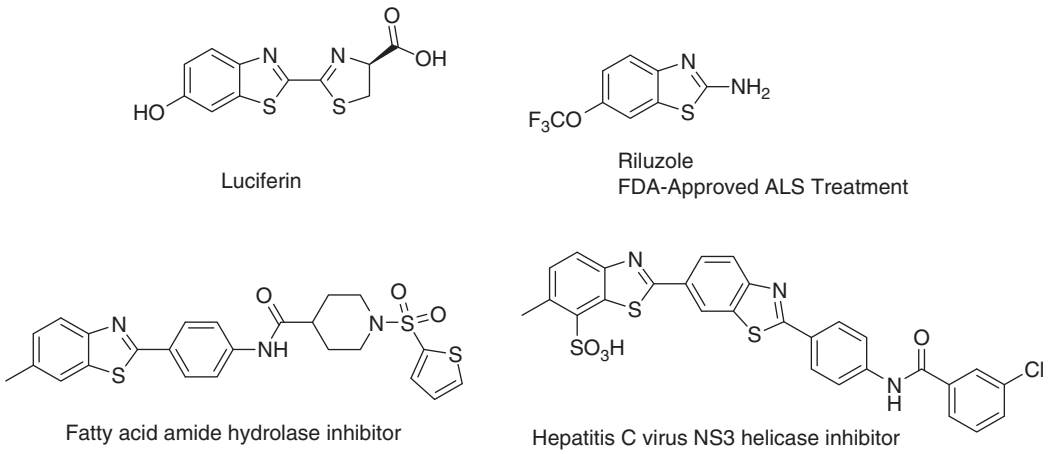
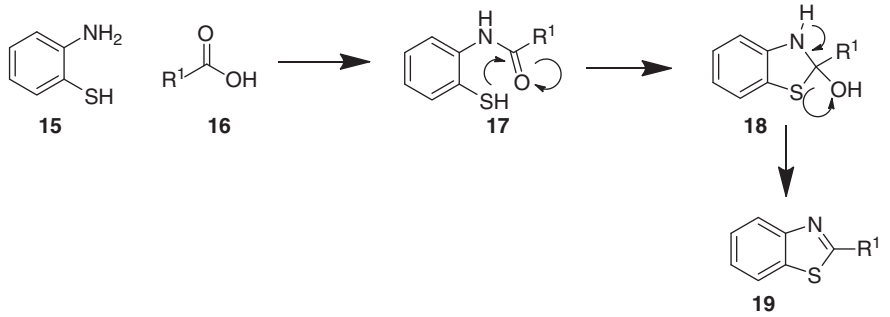


Figure 6 Biologically important benzothiazoles.



Scheme 3 Mechanism for the synthesis of benzothiazoles from 2-aminobenzenethiol.

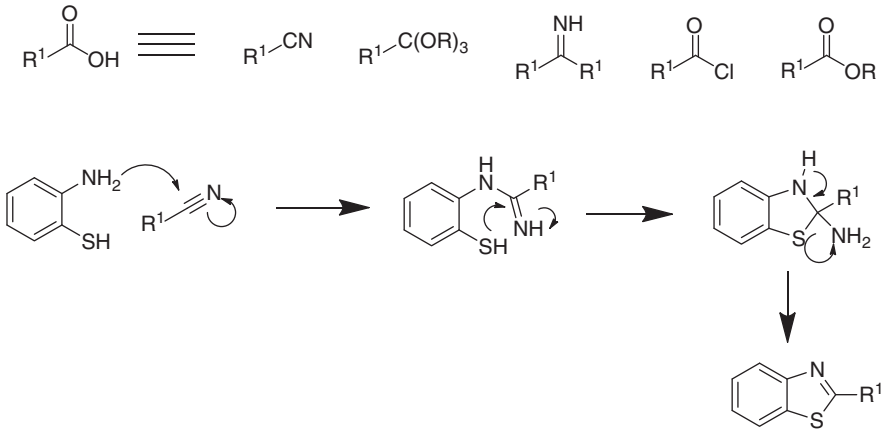
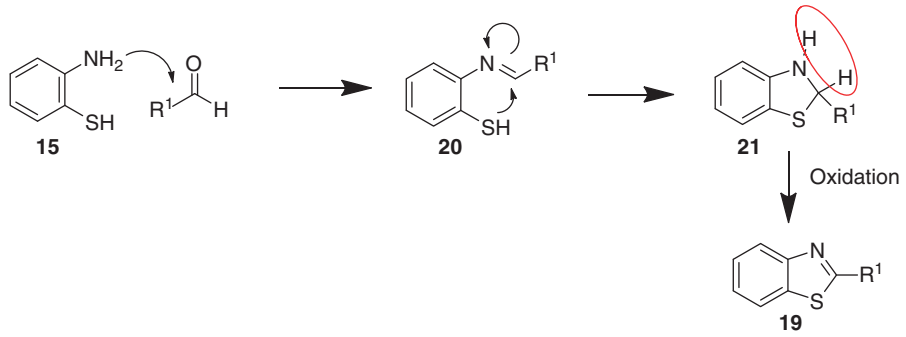


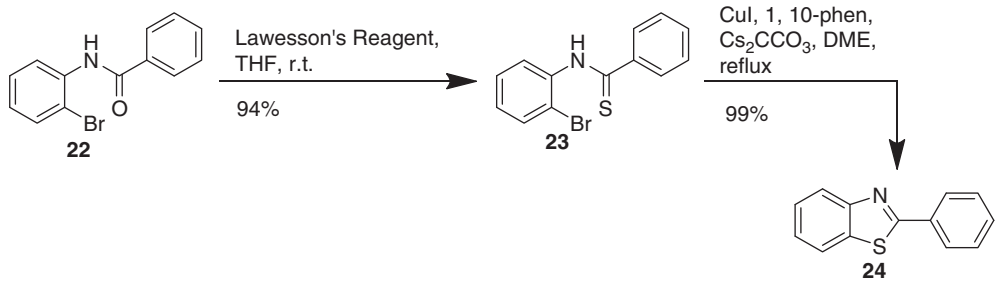
Figure 7 Examples of various acid derivatives that have been used to produce benzothiazoles.

lower oxidation state than the ultimate benzothiazole, this route normally requires addition of an oxidant to convert the transient dihydro benzothiazole **21** into the desired fully aromatic benzothiazole **19**.[21,22] However, examples exist which do not require addition of oxidizing reagents. A plethora of oxidizing agents have been employed in this scheme, among the most useful including 2,3-dichloro-5,6-dicyano-*p*-benzoquinone,[23] MnO_2,[24] and oxone.[25] An important advantage of this protocol over the cyclization of carboxylic acids (above) is the absence of acid catalysts, which can be useful for acid-sensitive starting groups.

Besides the cyclization of 2-aminobenzenethiols with acids or aldehydes (above), another synthetically useful route to benzothiazoles is the intramolecular cyclization of ortho-halothioanilides (Scheme 5). Reaction of anilides (**22**) with Lawesson's reagent is one of the most common methods by which the necessary thioanilide can be prepared. Copper-catalyzed addition of the



Scheme 4 Mechanism of oxidative cyclization of aldehydes to produce benzothiazoles.



Scheme 5 Intramolecular cyclization of thioanilides.

thioanilide to the bromide generates the final benzothiazole. This transformation allows one to begin with the much more available aniline and carry out a straightforward amide coupling to eventually prepare benzothiazoles. In effect, this scheme is complementary to the above cyclization of 2-aminobenzenethiols so that the more readily available 2-aminohalobenzenes can be used as benzothiazole precursors.[26]

The above descriptions of methods to produce benzothiazoles are in many respects similar to those used to construct analogous benzimidazoles and benzofurans. The most practical methods utilize the 1,2-disubstituted aromatic rings (1,2-diaminobenze and 2-aminophenol, respectively) to cyclize to the fused benzo-1,3-azole ring systems. Because of this, generally similar synthetic approaches between the benzothiazole, benzimidazole, and benozfuran rings, specific discussions of these two additional heterocyclic rings will not be provided.

6.13.2.2 Synthesis of Imidazoles

Imidazoles are important heterocycles in chemistry. They are essential components of myriad important molecules including natural products, bioactive molecules, ionic liquids, and imidazoliums. With both an acidic NH and a basic nitrogen, they are amphoteric. They are found in many important FDA-approved drugs (Figure 8). The pK_a of the imidazole NH is 14.5, whereas the pK_a of the conjugate acid is 7.0. These factors contribute to their widespread presence in a variety of chemical applications.

One of the reasons for the prevalence of imidazoles in current medicinal chemistry is the wide range of fused heterocycles that can be formed which contain the imidazole structure (Figure 9). These myriad ring systems provide numerous opportunities to fine-tune the electrostatic, steric, and topographical features of molecules. In addition, successful development of new drugs normally requires compounds possessing strong intellectual novelty so that the developing company can potentially recoup the drug's development costs and ensure revenues to support continued research. The wide variety of imidazole-containing bioactive heterocycles increases the available chemical space to medicinal chemists and provides additional avenues toward development.[27]

The classical method for synthesizing imidazoles is the Debus procedure, which involves the condensation of 1,2-dicarbonyls (Scheme 6).[28,29] The original Debus protocol called for treating a 1,2-diketone **25** with ammonia to initially for 1,2-diimine **27**. Reaction of this with an imine would then produce the acyclic imidazole precursor **29** with three potential sites of modification. Intramolecular attack of the resulting amine on the terminal imine generates the dihydroimidazole (**30**), which on loss of ammonia affords the final imidazole **32**. This method has the advantage of being a fairly general route to trisubstituted imidazole. In particular, the fact that the 2-position is derived from simple aldehydes allows introduction of myriad substituents at this site. The major downside to this synthesis is the poor regiocontrol between the 4- and 5-positions that are derived from the 1,2-diketone.

A variation on the classical Debus synthesis provides an efficient method for rapidly preparing *N*-substituted imidazole.[30] In this route, one of the 1,2-imines is formed by reaction with a primary amine instead of ammonia. Ensuing condensation with an

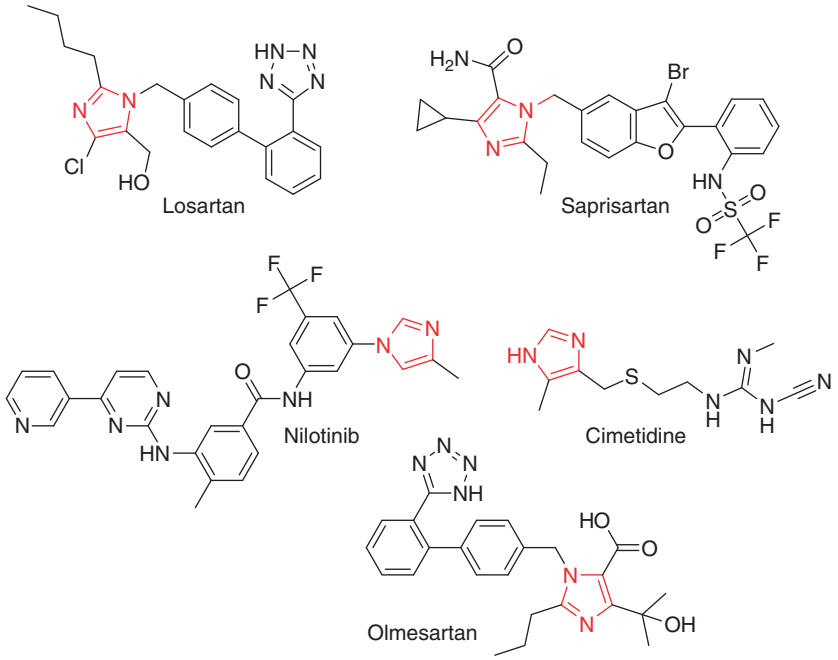


Figure 8 Examples of imidazole-containing FDA-approved drugs.

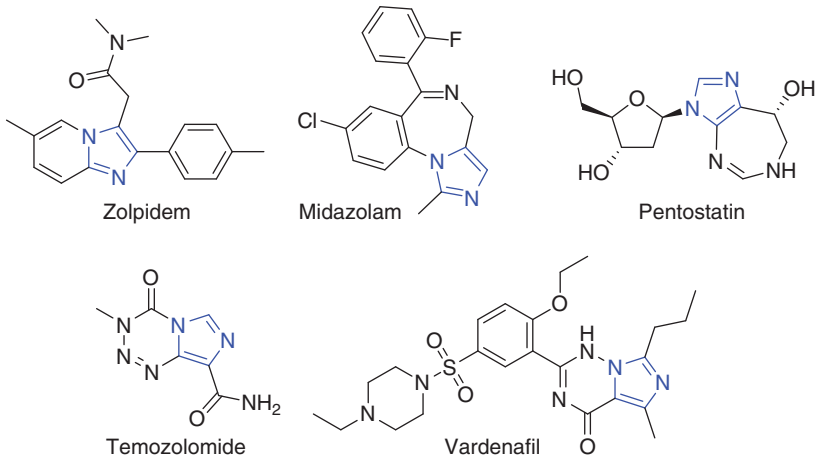
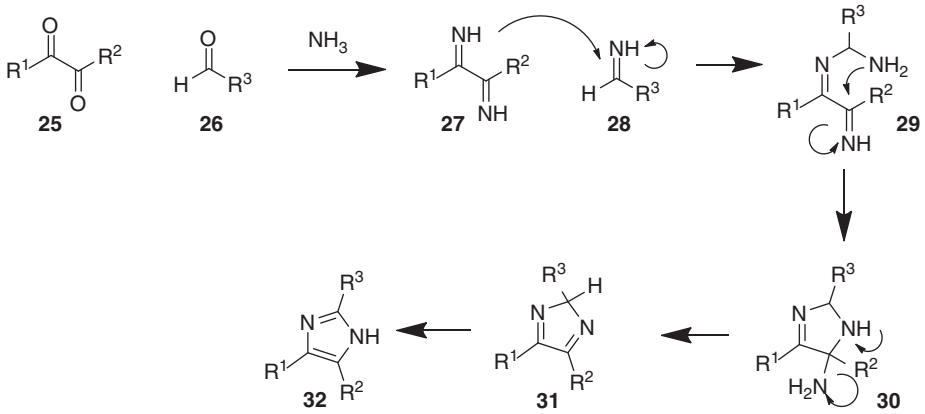


Figure 9 Examples of imidazole-containing heterocycles.

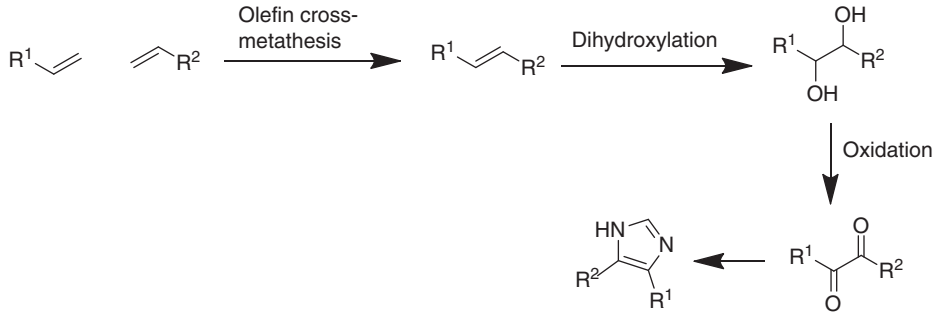


Scheme 6 Mechanism of the Debus synthesis.

aldehyde produces the fully substituted imidazole. While this offers an efficient method for constructing tetrasubstituted imidazoles, regioselectivity is often a problem due to mixtures of imines formed in the initial step.[31]

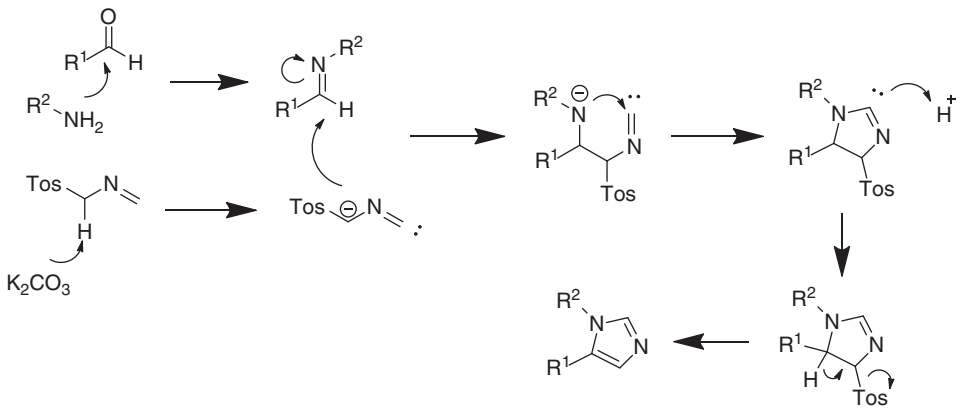
Another useful modification of the Debus synthesis is where an α-hydroxyketone or α-haloketone is used instead of 1,2-dicarbonyl.[32] Reaction of these molecules with amidines or guanidines offer an effective method to produce 2-substituted imidazoles. With the Bredereck modification, α-hydroxyketones are reacted with formamide to rapidly generate 4- and 4,5-substituted imidazoles.

The requisite 1,2-diketones for the Debus-related cyclization can be synthesized in a variety of ways, many of which include oxidation of the alpha position of monoketones.[33–35] Another strategy, which allows installation of specific 4- and 5-position imidazole groups, produces the diketone from the corresponding 1,2-diol and subsequent oxidation. This approach allows one to utilize well-established Grubbs cross-metathesis protocols to synthesize the alkene.[28] Dihydroxylation of the olefin generates the 1,2-diol and ultimately, the 4,5-disubstituted imidazole (Scheme 7).[36–38]



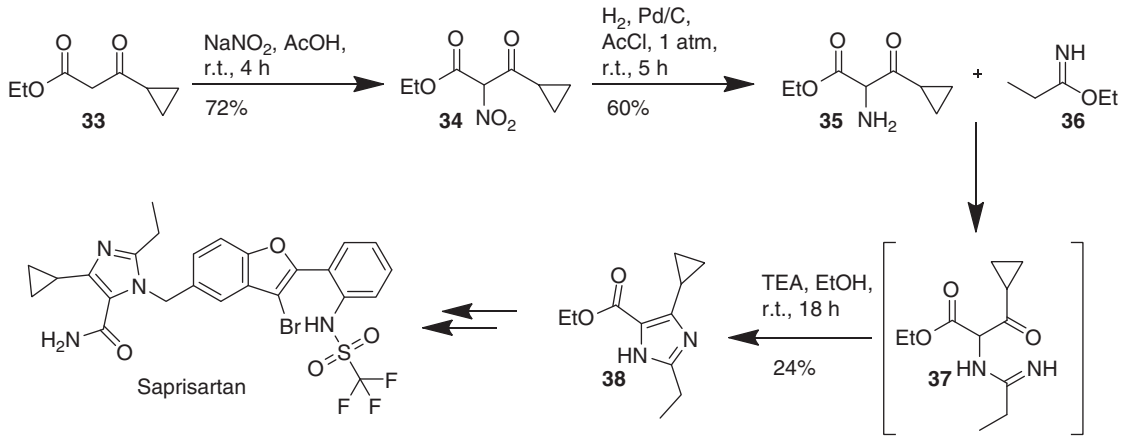
Scheme 7 Cross-metathesis approach to imidazoles.

Another procedure for synthesizing imidazole that has seen considerable use is the Van Leusen imidazole synthesis (Scheme 8).[39] This is one of the most effective strategies for synthesizing 1,5-disubstituted imidazole. This synthesis allows a one-pot transformation of aldehyde, amine, and tosylmethyl isocyanide (TosMIC) reagent, with TosMIC proving the CHNCH component.[40,41] The mechanism involves base-promoted cycloaddition of TosMIC to an *in situ* generated aldimine, followed by cycloaddition and subsequent *p*-toluenesulfinic acid elimination. One of the biggest advantages of the Van Leusen synthesis is its ability to control the regioselectivity.



Scheme 8 Mechanism of the Van Leusen synthesis.

An interesting intramolecular reaction has been published to produce the imidazole moiety of the FDA-approved drug Saprisartan, an angiotensin II type 1 (AT1) receptor antagonist used in treating hypertension and heart failure (Scheme 9).[42] Ketoester **33** is treated with sodium nitrite to produce the α-nitro compound **34**. Reduction using Pd/C at 1 atm affords the amine, which is reacted with imidate **36** to form the imidamide **37**. On treatment with base, this is cyclized to give the trisubstituted imidazole **38**. In this synthesis, a highly functionalized amidine is transiently formed, which then undergoes cyclization to provide the 2,4,5-trisubstituted imidazole.



Scheme 9 Synthesis of imidazole intermediate of Saprisartan.

6.13.2.3 Synthesis of Pyrazoles

Pyrazoles and their related multiring analogs are common elements of a wide variety of bioactive compounds (Figure 10). These ring structures are rare in nature. A consequence of this is that they have previously been thought to be poor moieties to include in potential new drugs. However, in recent years there has been robust utilization of these groups in new bioactive molecules. In fact, some of those important recently FDA-approved drugs have pyrazole or related rings. A central impetus for the diversification of pyrazole syntheses and usage has been the desire to create novel heterocyclic frameworks, similar to the imidazole.

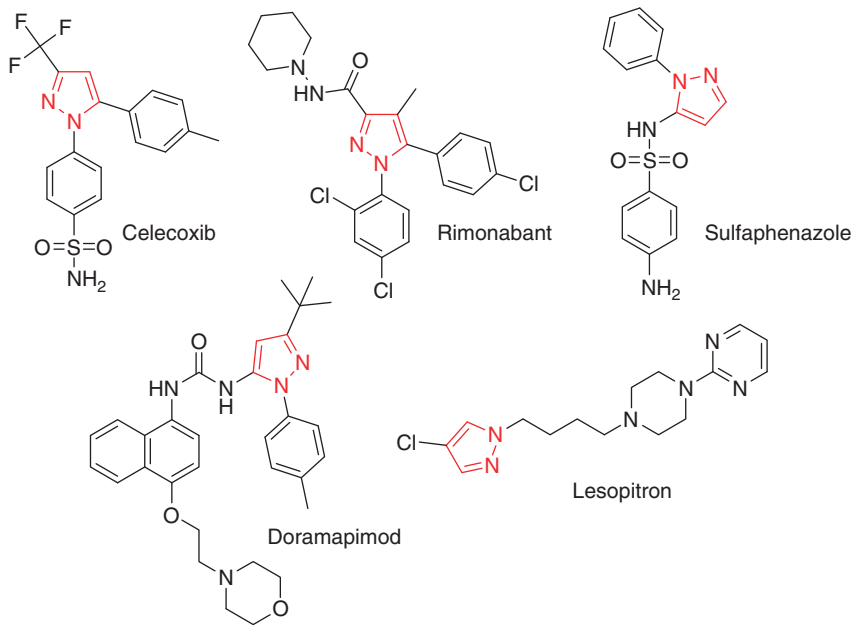


Figure 10 Examples of pyrazoles-containing FDA-approved drugs.

In particular, one of the most important current applications of pyrazoles is in the preparation of kinase inhibitors. Kinase inhibitors typically contain specific domains that allow strong binding at the hinge region of the kinase ATP-binding site.[43] The 1*H*-pyrazole provides an excellent means by which to provide the requisite hydrogen bond acceptor–donor motifs, whether as a monocyclic ring or as a fused indazole ring. As is the case with imidazoles, the pyrazole ring offers many opportunities to create new multiring systems that incorporate this heterocycle (Figure 11).

The most classical and probably versatile synthesis of pyrazoles is the condensation of 1,3-dicarbonyls with hydrazine (Figure 12). This transformation can use a variety of dicarbonyls including ketoesters,[44] ketoaldehydes,[45] diketones,[46] and others.[47] The usefulness of this synthesis derives not only from its use of basic building blocks like substituted hydrazines and

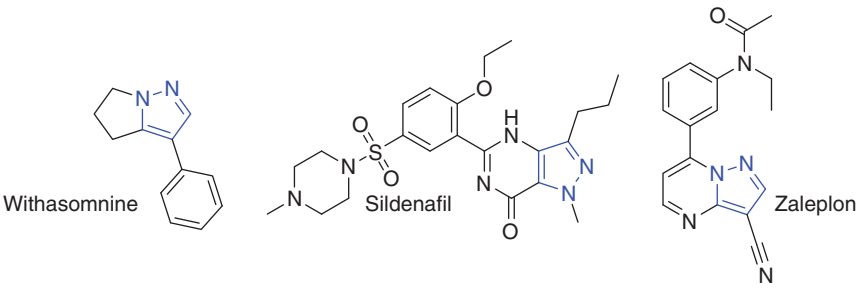


Figure 11 Examples of pyrazole-based heterocycles.

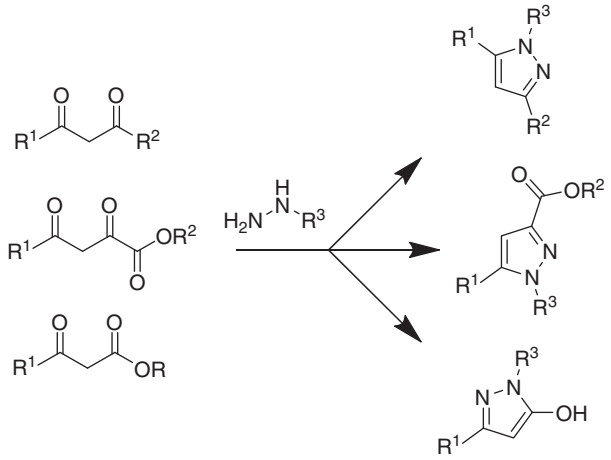
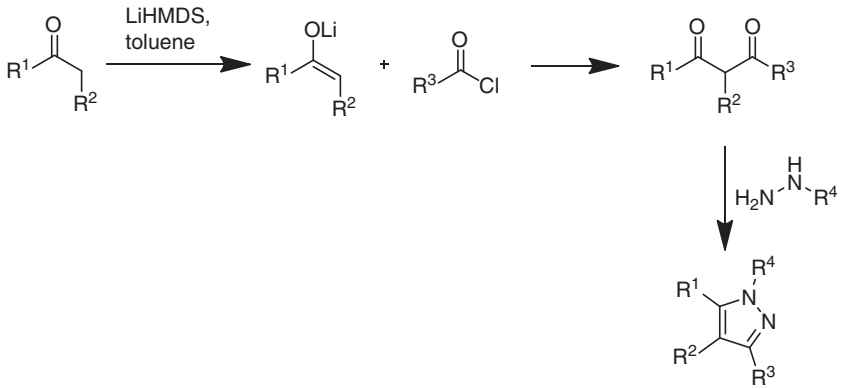


Figure 12 Synthesis of pyrazoles from hydrazines and dicarbonyls.

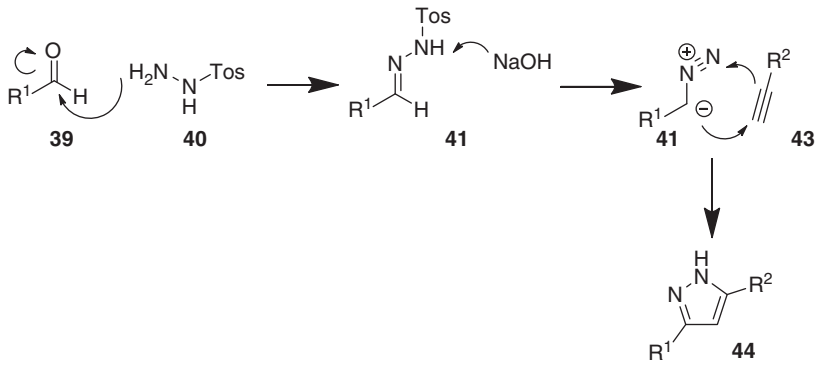
1,3-dicarbonyls, but the wide range of functionalized products that can be produced (Figure 12). These two starting materials can often be obtained commercially with myriad substituents readily available.

In many cases, the necessary 1,3-dicarbonyl is the limiting factor in the rapid preparation of diverse pyrazoles. Recent publications have described a variety of methods for synthesizing 1,3-dicarbonyls that enable efficient preparation of functionalized heterocycles for bioactivity studies. In one example, reaction of *in situ* generated 1,3-dicarbonyls with hydrazines was capable of rapid and efficient pyrazole library synthesis (Scheme 10).[48] This method has the advantage of not requiring isolation and purification of individual dicarbonyl compounds.



Scheme 10 Generation of 1,3-dicarbonyls for pyrazole synthesis.

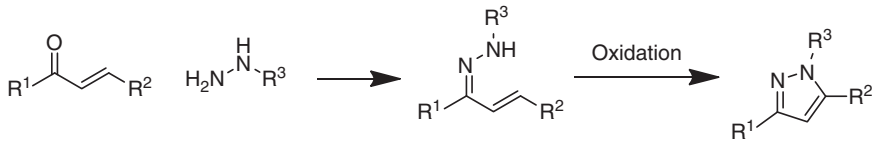
Another especially versatile method for synthesizing 1*H*-pyrazoles uses a 1,3-dipolar cycloaddition reaction of tosylhydrazones (generated by reaction of aldehydes with tosylhydrazine) with alkynes (Scheme 11).[49] Condensation of aldehyde **39** with tosylhydrazine **40** produces imine intermediate **41**. Cycloaddition of this carbonyl derivative **41** with alkyne **43** gives the desired



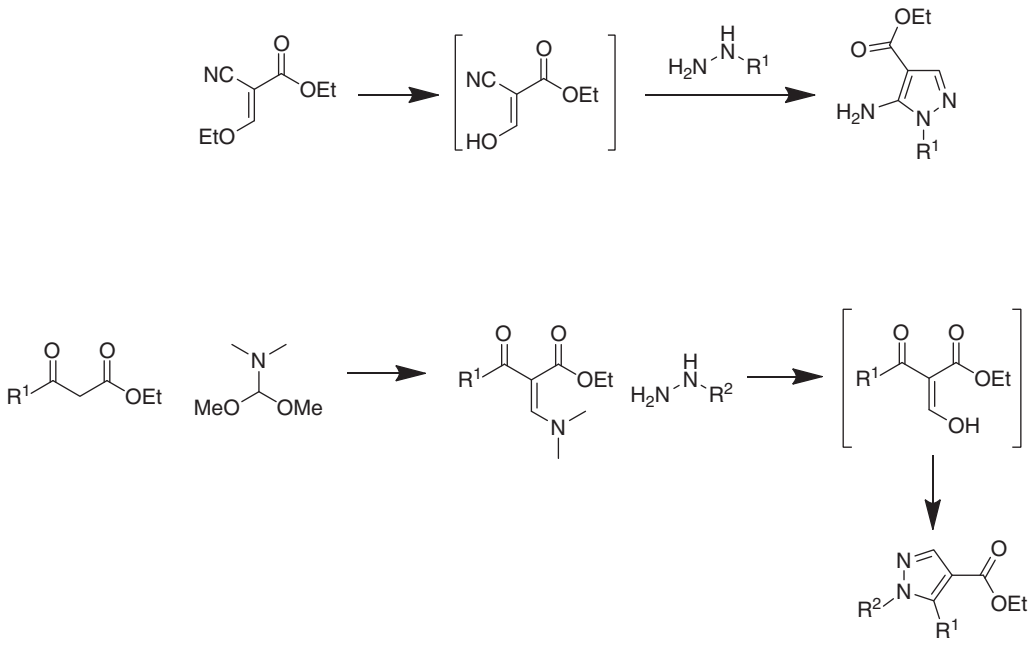
Scheme 11 Generation of tosylimines for cycloaddition reactions.

pyrazole **44**. This method exploits common starting aldehydes and alkynes, which can be used to rapidly synthesize highly functionalized ring systems. Unfortunately, these two general synthetic routes typically afford regioisomeric mixtures of products.

Several methods exist which prepare the pyrazole ring through stepwise additions of substituted hydrazines to unsaturated ketones, followed by cyclization using oxidative (Scheme 12),[50,51] Vilsmeier–Haack (Scheme 13),[52] or Dieckmann (Scheme 14) conditions.[53] These options allow one to synthesize ring systems with useful functional group for subsequent transformations in a more regiocontrolled manner.

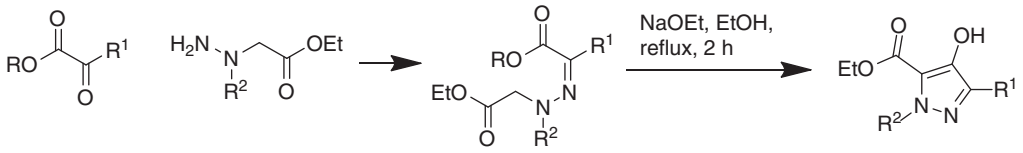


Scheme 12 Use of α,β-unsaturated ketones and hydrazines to prepare pyrazoles.



Scheme 13 Vilsmeier–Haack protocols for generating 1,3-dicarbonyls.

For medicinal chemistry applications, it is often desirable to carry out solid-phase synthesis of heterocyclic rings to enable rapid exploration of structure–activity relationships. As shown in the preceding portion of Section 6.13.2.3, many common techniques for synthesizing pyrazoles allow for the preparation of densely functionalized ring systems. There have consequently been numerous reports of solid-phase protocols for preparing pyrazoles from carbonyl derivatives.[54–56] Many of these rely on typical schemes that are found in the solution-phase versions.

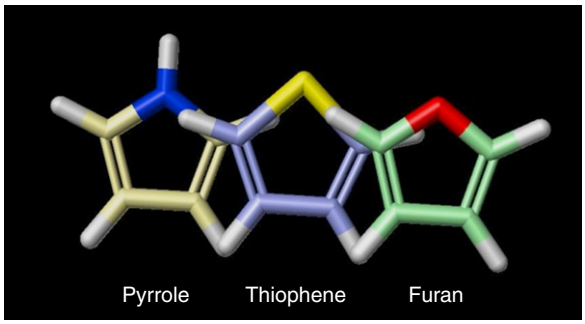


Scheme 14 Dieckmann cyclization to access pyrazoles.

6.13.2.4 Synthesis of Thiophenes

The thiophene ring holds an important place in organic and medicinal chemistry. Of the many bioisosteres commonly used to optimize bioactive molecules, the thiophene is generally considered the most similar to the phenyl ring in terms of size, hydrophobicity, and electronic properties. These characteristics make it one of the most successful replacements when one is attempting to modulate a compound's properties. The biosimilarity of thiophene to benzene can be rationalized by both its electronics and bond geometry (Table 2). Because the electronegativity of sulfur is essentially identical to carbon (2.58 vs. 2.55), the dipole moment in thiophene is quite small (0.52 D). In addition, because of the large size of the sulfur atom, the bond length between the sulfur and the α-carbons is substantially longer (171.4 pm) than that in furan or pyrrole (136.2 pm and 137.0 pm, respectively). Table 2 also shows the energy-minimized structures of pyrroles, thiophene, and furan rings. The larger size of the thiophene relative to the furan is clearly evident.

Table 2 Comparison of benzene, thiophene, and furan physical data



Molecule	*Heteroatom–C2 bond length (pm)*	*C2–heteroatom–C5 bond angle (°)*	*Dipole moment (D)*
Pyrrole	137.0	109.8	1.58
Thiophene	171.4	92.1	0.52
Furan	136.2	106.5	0.71

Given the significance of thiophenes, it is not surprising that there have been great many syntheses reported. Perhaps the most traditional method is the Paal thiophene synthesis. This reaction has been known for over 100 years and is still the basis for fruitful application and improvement. This transformation is analogous to the Paal furan synthesis and the Paal–Knorr pyrrole synthesis. In each case, 1,4-diketones are cyclized to afford the mono-heteroatom heterocycle (Figure 13).

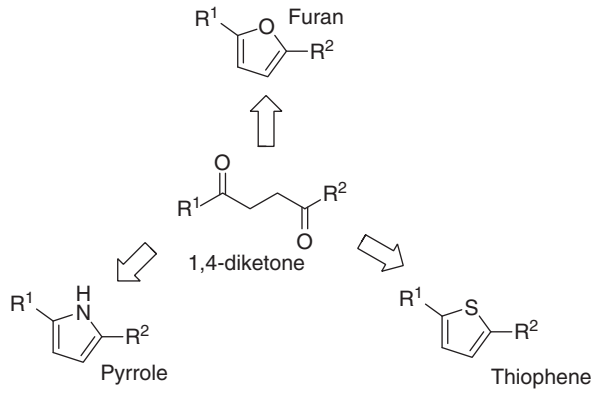
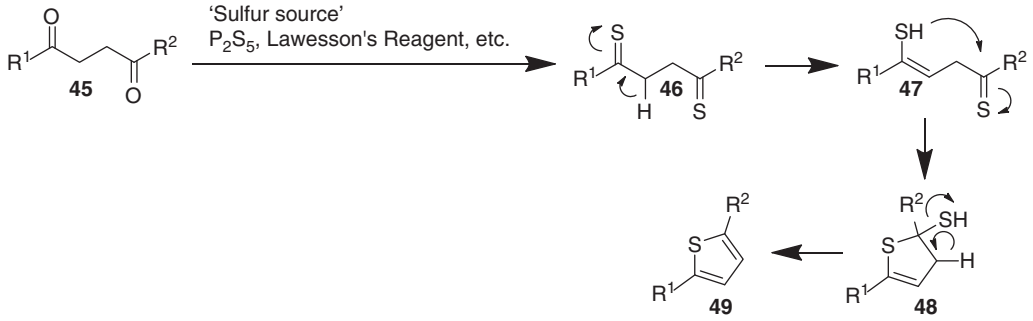


Figure 13 Generality of furan, thiophene, and pyrrole syntheses using 1,4-dicarbonyls.

In the case of thiophenes, the initial step of the Paal thiophene synthesis requires conversion of the ketone groups to the thioketone derivatives (**4**) as shown in Scheme 15. Tautomerization of thioketone **46** to **47** and subsequent intramolecular cyclization generates the dihydrothiophene **48**. Extrusion of H_2S from **48** gives the final thiophene derivative (**49**). Both the transformation of the ketone to the thioketone and the dehydration steps have been subject to modifications over the years. While P_4S_{10} was the original source of sulfur by Paal and is a common thionating agent,[57] a number of variations have been described.[58,59] The most practically useful modification has been the substitution of Lawesson's reagent for phosphorous pentasulfide or hydrogen sulfide. The more toxic and generally lower yielding P_4S_{10} and H_2S have largely been replaced by Lawesson's reagent in current applications of the Paal thiophene synthesis.



Scheme 15 Mechanism of Paal thiophene synthesis.

Another important method for synthesizing 2-carboxythiophenes is the Fiesselmann synthesis and related variations (Figure 14). There are several useful variations of this transformation but generally, they involve reaction of thioglycolates with α,β-unsaturated carbonyls. Frequently, the β-position is functionalized with a halogen or the α,β-unsaturation is an alkyne. The Fiesselmann synthesis is important because of its use of relatively simple starting materials that can be utilized in a wide variety of methods to produce highly functionalized thiophenes.

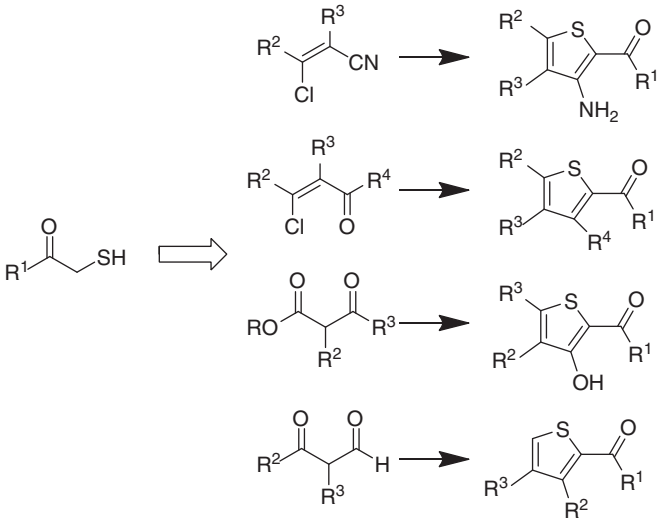
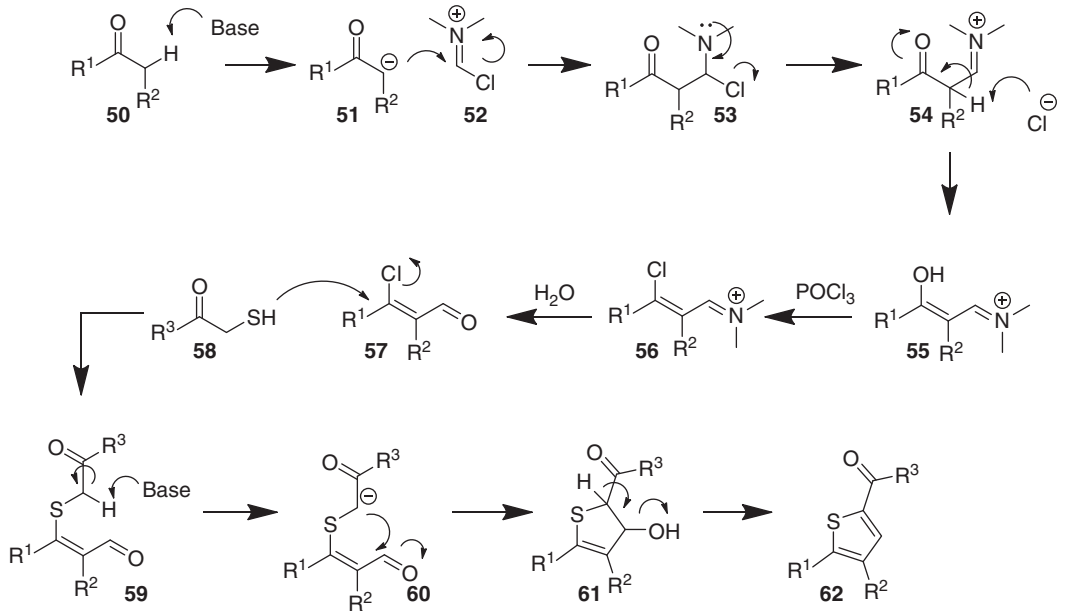
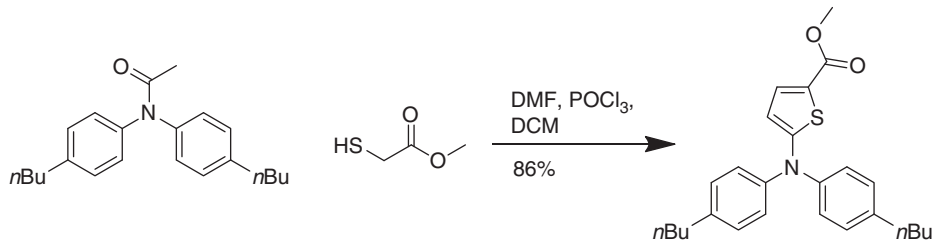


Figure 14 Variations of the Fiesselmann synthesis.

One particular embodiment of the Fiesselmann synthesis generates the requisite β-chloro-α,β-unsaturated carbonyl through a Vilsmeier–Haack reaction of ketones (Scheme 16).[60] This protocol exploits the ubiquitous nature of ketones to produce functionalized thiophenes. One advantage of this sequence is that it generates the final thiophene regioselectively. These two factors have made this one of the most common variations of the Fiesselmann synthesis. In this reaction, deprotonation of the carbonyl **50** followed by addition to the Vilsmeier reagent gives intermediate **53**. Enolization of ketone **54** generates enol **55**, which undergoes chloride replacement using $POCl_3$ to afford **56**. Attack of thioglycolate **58** to displace the chloride from **57** gives alkylated thioglycolate **59**. Deprotonation and intramolecular cyclization gives alcohol **61**, which on dehydration produces desired thiophene **62**. The Vilsmeier–Haack variation can also be used with amides (Scheme 17).[61]



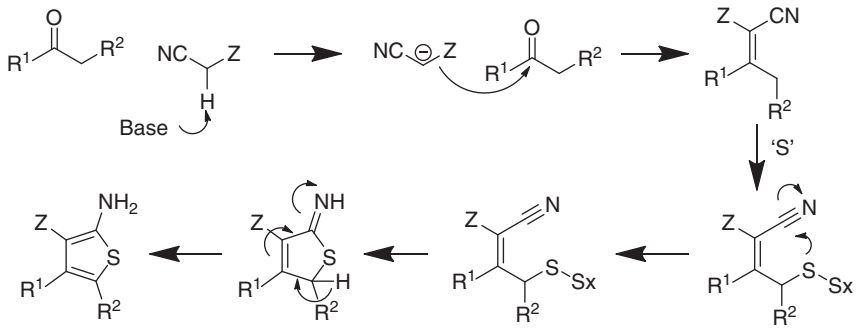
Scheme 16 Mechanism of Vilsmeier–Haack variation of the Feisselmann synthesis.



Scheme 17 Formation of a thiophene from an amide using the Feisselmann synthesis.

Among the myriad variations of the Feisselmann synthesis that has found extensive use in the literature, one which starts with 1,3-dicarbonyls is of particular importance. When the starting material is a diketone, the reaction can generate mixtures of regioisomers owing to the two possible thioketals that can be formed during the reaction. However, when other dicarbonyls are used that can impart chemoselectivity on the initial thiol addition step, the reaction can be used to produce well-defined product isomers.[62]

While there have been many methods for producing thiophenes, the other classical and still commonly employed method is the Gewald synthesis. This route produces 2-aminothiophenes from the reaction between activated nitriles and carbonyls (Scheme 18). While this produces synthetically useful 2-aminothiophenes, a downside to the Gewald synthesis is that regioselectivity can be variable when unsymmetrical ketones are used. This reaction can use a wide variety of starting material types.



Scheme 18 Mechanism of the Gewald synthesis.

6.13.2.5 Synthesis of Oxazoles

Oxazoles constitute a useful heterocyclic ring system in preparing new biologically active molecules, although surprisingly they have seen limited use in FDA-approved drugs (Figure 15). While they have similarities in terms of hydrogen bond acceptor/donor properties as thiazoles, their carbon–oxygen bond length is shorter than the carbon–sulfur bond in thiazole. This makes the overall ring system smaller and directs substituents into different orientations. These factors enable oxazoles to offer modified structural and electronic properties when considering alternative ring systems to phenyl isosteres such as thiazoles and thiophenes.

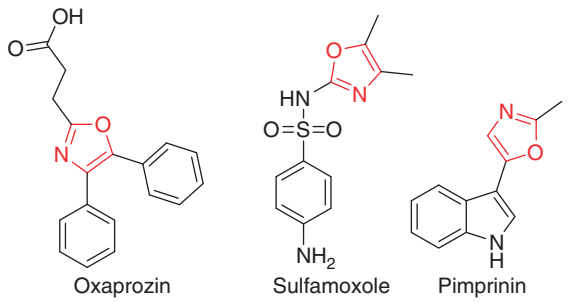
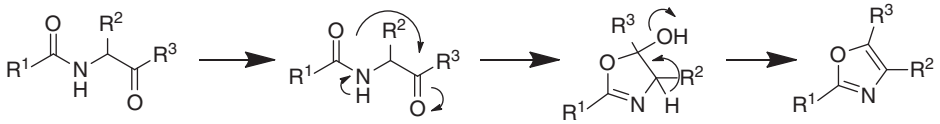


Figure 15 Examples of important oxazoles.

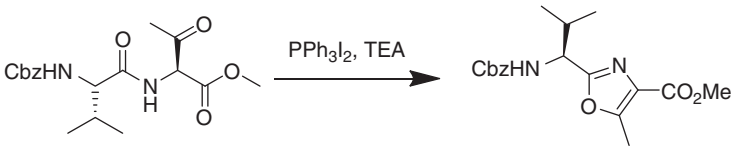
The classical route to oxazoles is the Robinson–Gabriel synthesis (Scheme 19). While this transformation is over 100 years old, it is still commonly used today and is continually being improved.[63] Fundamentally, the reaction is the dehydration cyclization of 2-acylamino ketones to afford either 2,5-disubstituted oxazoles or 2,4,5-trisubstituted oxazoles.



Scheme 19 Mechanism of Gabriel oxazole synthesis.

Traditionally, the reaction has used aggressive conditions with sulfuric or polyphosphoric acid to cause cyclization. A number of improvements have been made to the classic Robinson–Gabriel procedure to use milder conditions (Scheme 20).[64] By using less harsh conditions for the dehydration, functional group tolerance has been improved and the reaction has seen continued use.

Another long-standing method for synthesizing oxazoles is the Fischer oxazole synthesis. This reaction has not seen the robust development and use as the Robinson–Gabriel synthesis; however, its substantial utility derives from the fact that essentially two aldehydes can rapidly be transformed into 2,5-disubstituted oxazoles (Scheme 21).

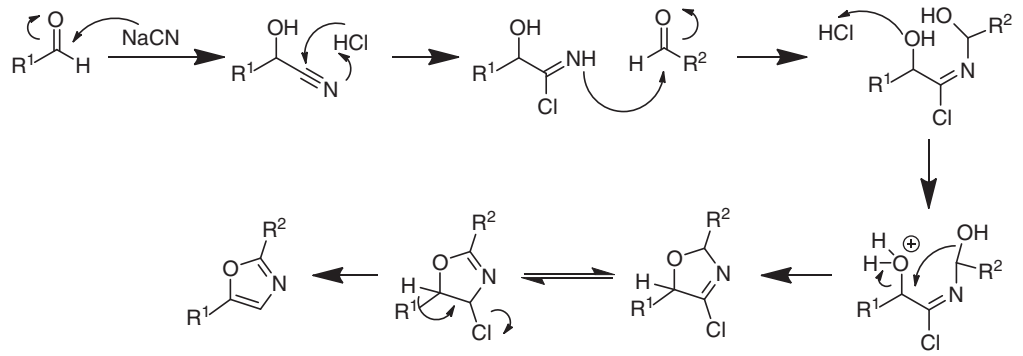


Scheme 20 Use of PPh_3I_2 to affect cyclization and oxazole formation.

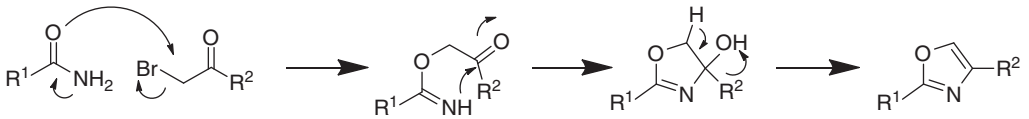
A procedure analogous to that for preparing thiazoles is also an important strategy in synthesizing oxazoles. The Blümlein–Lewy synthesis produces oxazoles from the condensation of amides with α-halo or α-hydroxy ketones (Scheme 22).[65] Like many of the techniques for synthesizing oxazoles, this procedure has the advantage of using common and functionally diverse starting materials. When urea is used as the amide, this reaction offers a good method for producing 2-aminooxazoles. In the analogous case for thiazole, the thioamide (or thiourea) is used.

6.13.3 Conclusion

The application of carbonyl functional group to the synthesis of heterocyclic rings has been a robust area of development in the field of organic chemistry. Many of the fundamental transformations still used today were initially worked out in the early days of modern organic chemistry. While all areas of organic chemistry have benefitted from and contributed to the development of these



Scheme 21 Mechanism of Fischer oxazole synthesis, starting from aldehyde and NaCN addition.



Scheme 22 Mechanism and examples of Blümlein–Lewy synthesis.

reactions, none has been more influenced than medicinal chemistry. Heterocycles have maintained a central role in the advancement of the therapeutic development of new medicines. The diversity of heterocycle electronic, steric, and topographical properties has resulted in their heavy use as isosteres for biologically relevant small molecules. Many facets of drug discovery rely on the fine-tuning required by compounds to balance the many physical, chemical, and pharmacological demands of successful drugs. Because all of these properties are related to chemical structure, it is therefore imperative that practical methods be in place to enable the synthesis of designed compounds. This chapter has described many of the most useful methods for synthesizing various heterocycles using carbonyl derivatives. While there are numerous heterocycles, the discussion herein was limited to some of the fundamental building block ring systems and many of the transformations described can be more broadly applied.

For related chapters in this Comprehensive, you can refer to – Chapters 9.01, 5.03, 6.14, 9.10, and 8.22.

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6.14 Functional Group Transformations via Carbonyl Derivatives

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This chapter is a revision of the previous edition chapter by Keiji Maruoka and Hisashi Yamamoto, Vol. 6, pp 763–793, © 1991, Elsevier Ltd.

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Glossary

ε-Caprolactam ε-Caprolactam is an organic compound of structure $(CH_2)_5C(O)NH$ mainly produced through the Beckmann rearrangement of cyclohexanone oxime. ε-Caprolactam is the precursor of nylon-6, a widely used synthetic organic polymer.

Catalyst A catalyst is a substance, usually used in small amounts relative to the reactants, that accelerates a chemical reaction by reducing the activation energy, but which is left unchanged by the reaction.

Hydrazone Hydrazones are organic compounds derived from condensation of aldehydes or ketones with hydrazine (NH_2NH_2). General formula of an oxime is $R_2C{=}NNH_2$.

Oxime Oximes are organic compounds derived from condensation of aldehydes or ketones with hydroxylamine (NH_2OH). General formula of an oxime is $R_2C{=}NOH$. Those derived from aldehydes are called aldoximes and those from ketones are called ketoximes.

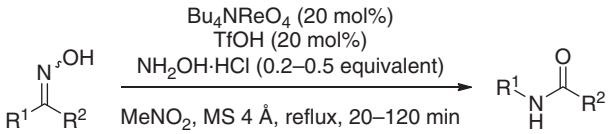
Rearrangement Rearrangement reaction is a class of organic reactions in which a reactant and product are isomers of each other. Chemical bonds within the reactant are broken and re-formed to produce the product.

6.14.1 Beckmann Rearrangement

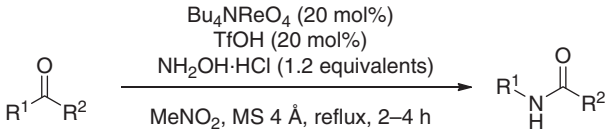
The Beckmann rearrangement is a typical acid-catalyzed reaction that is used to convert aldoximes or ketoximes into primary or secondary amides.[1–3] Most commonly, the Beckmann rearrangement is carried out in strongly acidic and dehydrating media such as phosphorus pentachloride, concentrated sulfuric acid, or 'Beckmann's mixture,' which contains acetic acid, acetic anhydride, and hydrogen chloride. Since these reagents are not suitable for use with acid-sensitive substrates, several attempts have been made to achieve the Beckmann rearrangement under milder conditions. To date, several reagents and catalysts for the liquid-phase Beckmann rearrangement have been evaluated as substitutes for the traditional reagents. This section summarizes recent significant advances in this field. Vapor-phase methods, with a particular focus on the industrial production of ε-caprolactam, a precursor of nylon-6, have also been developed using heterogeneous solid catalysts at high temperatures.[4] This section does not cover the vapor-phase Beckmann rearrangement.

6.14.1.1 Transition Metal Catalysts

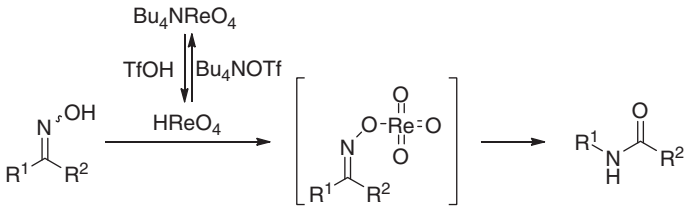
The Beckmann rearrangement of cyclic and acyclic ketoximes catalyzed by a combination of tetrabutylammonium perrhenate (Bu_4NReO_4) and trifluoromethanesulfonic acid in nitromethane under azeotropic conditions gives the corresponding lactams or secondary amides in high yield (Scheme 1).[5] Perrhenic acid, $ReO_3(OH)$, is generated *in situ* from Bu_4NReO_4 and trifluoromethanesulfonic acid (TfOH), and the rearrangement is considered to proceed via the oxime perrhenate **1**. The same product is obtained from both the (*E*)- and (*Z*)-oximes, which can be easily isomerized in the presence of TfOH under these conditions. Since hydrolysis of the oxime to the ketone proceeds as a side reaction, the chemical yields of the amide products are improved with the use of substoichiometric amounts (0.2–0.5 equivalent) of hydroxylamine hydrochloride $(NH_2OH{\cdot}HCl)$ (Scheme 1).[5] Thus, this catalytic system can be used for the direct preparation of amides from ketones via the *in situ* generation of oximes and subsequent Beckmann rearrangement. Several acyclic ketones can be converted directly to the corresponding secondary amides in moderate yields, whereas the reaction of aldoxime **2** and α-*tert*-alkyl ketoxime **3** gives the corresponding nitriles **4** and **5**, rather than amides, in good yields by Beckmann fragmentation (Scheme 2).[5]



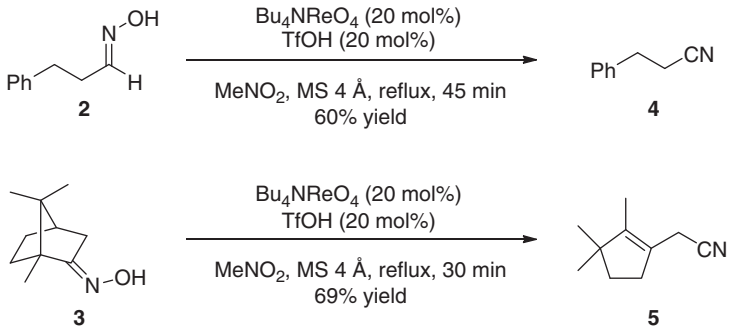
R^1	R^2	Yield
Ph	Ph	98%
Ph	Me	94%
$Ph(CH_2)_2$	Me	88%
$-(CH_2)_5-$		84%



R^1	R^2	Yield
Ph	Ph	66%
Ph	Me	77%
$Ph(CH_2)_2$	Me	52%

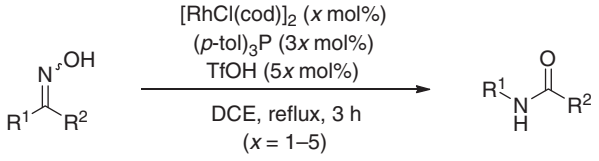


Scheme 1 Re(VII)-catalyzed Beckmann rearrangement of ketoximes and the direct preparation of secondary amides from ketones via the *in situ* generation of ketoximes.[5]



Scheme 2 Reaction of aldoxime **2** and *α-tert*-alkyl ketoxime **3** catalyzed by Re(VII).[5]

The Beckmann rearrangement of ketoximes catalyzed by $[RhCl(cod)]_2$ in the presence of TfOH gives the corresponding amides in good yields (equation 1, Table 1).[6] A TfOH/Rh ratio of more than 5 is critical. Otherwise, the yield of amide decreases, and a considerable amount of ketone is formed. When benzophenone-derived oximes are used, the catalytic amount of Rh can be reduced to 1 mol%. Since a facile isomerization of oximes in the presence of TfOH is known, the stereochemistry of the ketoximes is not important. The migration of an aryl group predominates over that of an alkyl group, even a *tert*-butyl group.



(1)

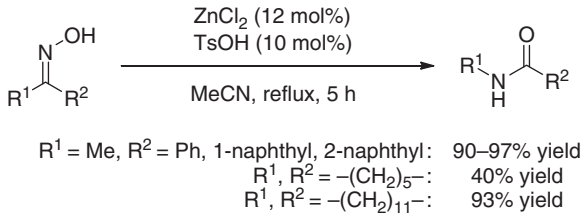
Zinc chloride ($ZnCl_2$) has been found to catalyze the Beckmann rearrangement of aromatic ketoximes in the presence of a catalytic amount of *p*-toluenesulfonic acid (TsOH) in refluxing acetonitrile (Scheme 3).[7] Notably, no rearrangement occurs when Zn(II) or TsOH is used as a sole catalyst. Laurolactam can also be obtained in high yield from cyclododecanone oxime. In contrast, when cyclohexanone oxime is used as a substrate, the *ε*-caprolactam is obtained in low yield.

Mercury chloride ($HgCl_2$) efficiently catalyzes the Beckmann rearrangement of various ketoximes into their corresponding amides/lactams in refluxing acetonitrile (Scheme 4, Table 2).[8] A higher loading (30 mol%) of $HgCl_2$ is required for cyclic ketoximes such as cyclopentanone oxime and cyclohexanone oxime. The rearrangement does not proceed effectively when other

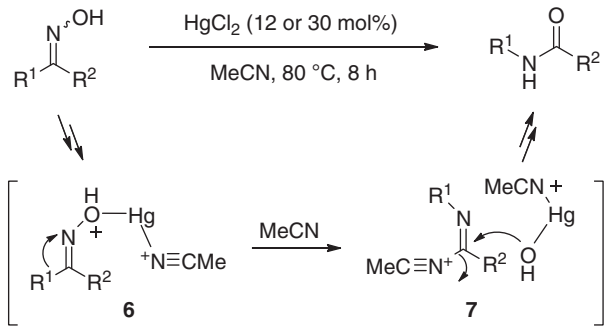
Table 1 Rh-catalyzed Beckmann rearrangement of ketoximes (equation 1)

R^1	R^2	X (mol%)	Yield (%)	References
4-Me–C_6H_4	4-Me–C_6H_4	1	99	6
4-MeO–C_6H_4	Et	2.5	88 (6)[a]	6
4-F–C_6H_4	Et	5	56 (5)[a]	6
Ph	Bu^n	5	70 (2)[a]	6
Ph	Bu^t	5	68 (13)[a]	6
Pr^i	Pr^i	5	71	6
Bu^t	Me	5	30	6

[a]Yields of the minor regiomers are shown in parentheses.



Scheme 3 $ZnCl_2$/TsOH co-catalyzed Beckmann rearrangement of ketoximes.[7]



Scheme 4 Hg(II)-catalyzed Beckmann rearrangement of ketoximes in acetonitrile.[8]

Table 2 Hg-catalyzed Beckmann rearrangement of ketoximes (**Scheme 4**)

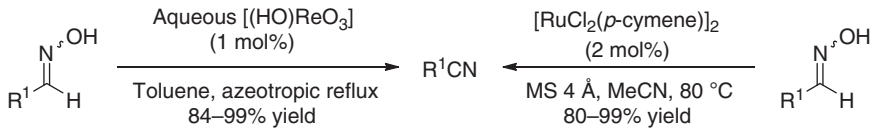
R^1	R^2	$HgCl_2$ (mol%)	Yield (%)	References
4-Me–C_6H_4	4-Me–C_6H_4	12	97	8
4-MeO–C_6H_4	Ph	12	50 (35)[a]	8
Ph	4-F–C_6H_4	12	46 (36)[a]	8
4-MeO–C_6H_4	Me	12	90	8
2-I–C_6H_4	Me	12	74	8
–$(CH_2)_5$–		30	92	8
–$(CH_2)_6$–		30	48	8

[a]Yields of minor regiomers are shown in parentheses.

solvents (i.e., tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), acetone, dimethylacetamide, dimethyl sulfoxide (DMSO), dichloroethane (DCE), toluene, etc.) are used in place of acetonitrile. Acetonitrile may help to promote the reaction by forming an acetonitrile complex with mercury ion, as described in the literature.[9] The rearrangement is considered to proceed via the oxime–Hg(II)–acetonitrile complex (**6**). After the migration of an alkyl *or* aryl group, the nitrilium intermediate is generated, which is solvated with acetonitrile to give complex (**7**). The acetonitrile group of complex (**7**) is displaced with the hydroxyl ligand of the oxo-mercury to provide the amide after tautomerization.

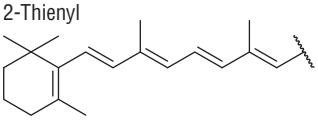
The dehydration of aldoximes catalyzed by aqueous perrhenic acid $[ReO_3(OH)]$[10,11] or $[RuCl_2(p\text{-cymene})]_2$[12] gives nitriles in good-to-excellent yields (equation 2, **Table 3**). Typically, less than 1 mol% of perrhenic acid is used under azeotropic reflux

conditions with the removal of water in toluene or mesitylene.[10,11] However, the reaction rate and selectivity are significantly increased for the Ru-catalyst when the reaction is carried out in the presence of molecular sieves 4 Å in acetonitrile under reflux conditions.[12] Both of these methods are highly efficient for various structurally diverse aldoximes, including aromatic, heteroaromatic, unsaturated, and aliphatic oximes. Additionally, aldoximes can be used as a mixture of (*E*)- and (*Z*)-isomers. Notably, almost no isomerization of olefinic double bonds is detected in these reactions.



(2)

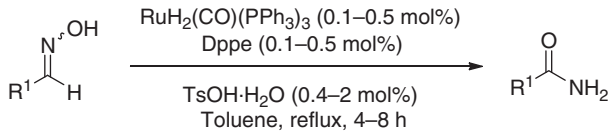
Table 3 Re(VII)- or Ru(II)-catalyzed dehydration of aldoximes to nitriles (equation 2)

R^1	*Catalyst*	*Time (min)*	*Yield (%)*	*References*
$^{c}C_6H_{11}$	Re	60	91	10,11
$^{n}C_{10}H_{21}$	Re	60	99	10,11
2-MeO–C_6H_4	Re	60	94	10,11
3-Pyridyl	Re	180	84	10,11
$^{c}C_6H_{11}$	Ru	10	90	12
4-HO–C_6H_4	Ru	30	99	12
PhCH(OMe)	Ru	60	80	12
2-Thienyl	Ru	10	95	12
	Re	60	91[a]	10,11
	Ru	10	94[a]	12

[a]The isolated product is >98% *all-trans*.

Although the Beckmann rearrangement of ketoximes provides efficient atom-economic access to secondary amides, similar isomerization of aldoximes to primary amides is more difficult due to the poor migratory aptitude of hydrogen. To circumvent this difficulty, several transition metal-based catalytic systems, such as those of Ru,[13–15] Rh,[16–19] In,[20] Ir,[21] Ni,[22] Pd,[23] Cu,[24–26] Zn,[20] and bimetallic species containing Co–Zn[27] and Au–Ag,[28] have recently been developed.

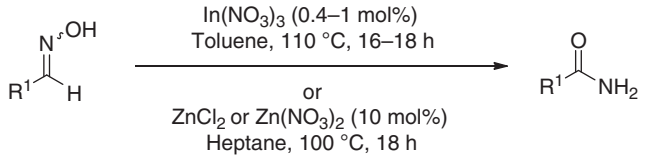
A wide range of aldoximes can be efficiently converted into their corresponding primary amides using the ruthenium-based catalytic system $RuH_2(CO)(PPh_3)_3$/dppe/TsOH in refluxing toluene (**Scheme 5**).[13] The (*E*)- and (*Z*)-oximes give similar results. The addition of TsOH has a beneficial effect on the chemical yield and product selectivity (i.e., primary amide vs. nitrile). Ketoximes are inert under these reaction conditions, and no rearrangement products are obtained. The reaction pathway involves dehydration of the oxime to a nitrile (or coordinated nitrile), followed by hydration to give the primary amide.



R^1	Yield
Ph	94%
4-MeO-C_6H_4	93%
4-O_2N-C_6H_4	82%
PhCH=CH	90%
$^{n}C_7H_{15}$	87%
$^{n}C_3H_7$	91%

Scheme 5 Ru-catalyzed conversion of aldoximes to primary amides.[13]

Cheap and simple indium(III) or zinc(II) salts can also be successfully used as catalysts for the rearrangement of aldoximes into primary amides (equation 3, **Table 4**).[20] Aldoximes can be used as a mixture of the (*E*)- and (*Z*)-isomers. With either catalyst, most aldoximes are converted cleanly into the primary amides in high yields. However, $In(NO_3)_3$ is inefficient for the rearrangement of electron-rich substrates such as 4-methoxybenzaldoxime and 2-furylaldoxime. In contrast, zinc(II) catalysis is effective for both substrates. Additionally, the reaction is sensitive to steric effects, since the reaction of 2-methylbenzaldoxime gives the corresponding amide in low yield.

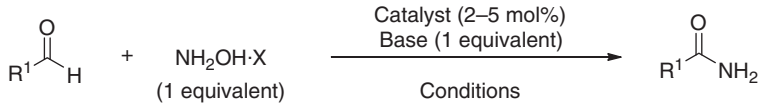


(3)

Table 4 In(III)- or Zn(II)-catalyzed Beckmann rearrangement of aldoximes into primary amides (equation 3)

R^1	*Cat. (mol%)*	*Yield (%)*	*References*
$^nC_3H_7$	$In(NO_3)_3$ (0.4)	87	20
$^nC_3H_7$	$Zn(NO_3)_2$ (10)	93	20
Ph	$In(NO_3)_3$ (1)	79	20
Ph	$ZnCl_2$ (10)	88	20
PhCH=CH	$In(NO_3)_3$ (0.4)	90	20
PhCH=CH	$Zn(NO_3)_2$ (10)	93	20
4-MeO–C_6H_4	$In(NO_3)_3$ (1)	30	20
4-MeO–C_6H_4	$ZnCl_2$ (10)	89	20
2-Furyl	$In(NO_3)_3$ (1)	0	20
2-Furyl	$ZnCl_2$ (10)	93	20
2-Me–C_6H_4	$In(NO_3)_3$ (1)	14	20
2-Me–C_6H_4	$ZnCl_2$ (10)	31	20

A direct one-pot protocol, starting from nearly equimolecular amounts of aldehydes and hydroxylammonium derivatives, has recently been developed using late-transition metal-based catalytic systems such as those of Ru,[14,15] Rh,[18,19] Pd,[23] and Cu[25,26] (equation 4, Table 5). In most cases, hydroxylamine hydrochloride is used for the preparation of oxime *in situ* from the corresponding aldehyde in the presence of a stoichiometric amount of an inorganic base.



(4)

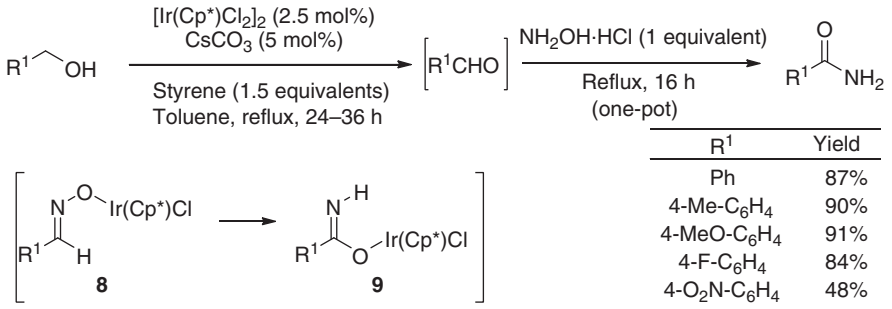
Table 5 Summary of late-transition metal-catalytic systems for the one-pot conversion of aldehydes to primary amides

Catalyst	*$NH_2OH \cdot X$*	*Base*	*Conditions*	*References*
$[terpyRu(PPh_3)Cl_2]$	$NH_2OH \cdot HCl$	$NaHCO_3$	Toluene, 110 °C	14
$Ru(DMSO)_4Cl_2$	$NH_2OH \cdot HCl$	$NaHCO_3$	MeCN, 110 °C	15
$Rh(OH)_x/AlO_3$	$NH_2OH \cdot 1/2H_2SO_4$	None	H_2O, 120–160 °C	18,19
$Pd(OAc)_2$	$NH_2OH \cdot HCl$	Cs_2CO_3	DMSO/H_2O, 100 °C	23
$CuSO_4 \cdot 5H_2O$	$NH_2OH \cdot HCl$	NaOAc	Neat, 110 °C	25
$Cu(OAc)_2$	NH_2OH	None	H_2O, 110 °C	26

The iridium complex, $[Ir(Cp^*)Cl_2]_2$, catalyzes the rearrangement of aldoximes to primary amides.[21] Iridium complexes can also catalyze the transfer hydrogenation of alcohols and carbonyl compounds.[29] Thus, this rearrangement can be combined with transfer hydrogenation between an alcohol and a suitable hydrogen acceptor to allow the direct conversion of alcohols into primary amides in a sequential process with minimal purification (Scheme 6).[21] In the presence of styrene as a hydrogen acceptor, a range of benzylic alcohols can be transformed into the corresponding benzaldehydes, which can be converted *in situ* to the corresponding aldoximes and then further transformed into primary amide. This process is unsuccessful for aliphatic alcohols, since no oxidation of the alcohol is observed. Since *O*-alkylated aldoximes and ketoximes are inert in this reaction, the oxime must contain both hydrogen and a hydroxyl group for the rearrangement. Oxime reacts with iridium to give oxime–Ir(II) complex **8**, which allows the iridium to remove the oxygen and the hydride, which are then replaced in the isomeric form **9**, before the release of amide product (Scheme 6).[21]

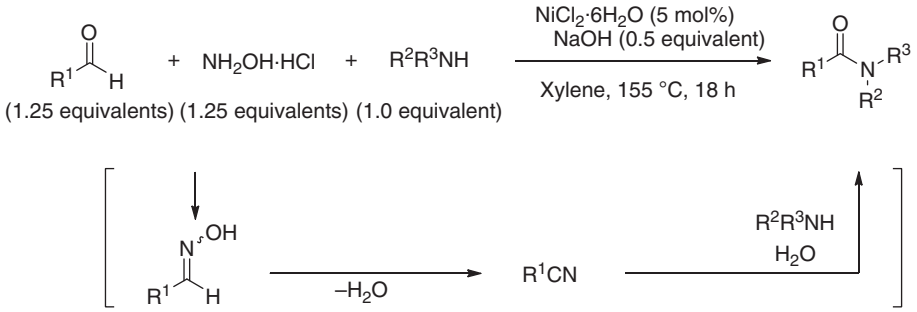
The simple nickel salt $NiCl_2 \cdot 6H_2O$ catalyzes the coupling of aldoximes and amines to give secondary or tertiary amides (Scheme 7).[22] The aldoximes can be generated *in situ* from the corresponding aldehydes and hydroxylamine hydrochloride in the presence of a base. The reaction pathway involves dehydration of the aldoxime to nitriles, followed by interception by amines to

give the corresponding amides. With the use of this process, a range of aldehydes and amines can be coupled to form their corresponding amides in high yields (Table 6).[22]



R^1	Yield
Ph	87%
4-Me-C_6H_4	90%
4-MeO-C_6H_4	91%
4-F-C_6H_4	84%
4-O_2N-C_6H_4	48%

Scheme 6 Iridium-catalyzed one-pot conversion of alcohols to primary amides through oxidation/oximation/Beckmann rearrangement reaction sequences.[21]



Scheme 7 Ni-catalyzed one-pot conversion of aldehydes to secondary or tertiary amides.[22]

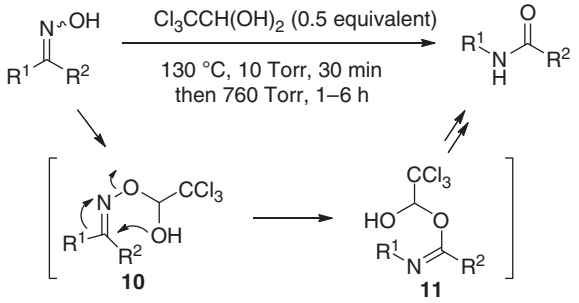
Table 6 $NiCl_2$-catalyzed one-pot coupling of aldehydes with amines into amides via Beckmann rearrangement (Scheme 7)

R^1	R^2	R^3	*Yield (%)*	*References*
$Ph(CH_2)_2$	Bn	H	81	22
Ph	Bn	H	91	22
Me	$(Ph)_2CH(CH_2)_2$	H	81	22
$^nC_6H_{13}$	$CH_2{=}CHCH_2$	H	92	22
$Ph(CH_2)_2$	$-(CH_2)_2O(CH_2)_2-$		80	22

6.14.1.2 Condensing Reagents

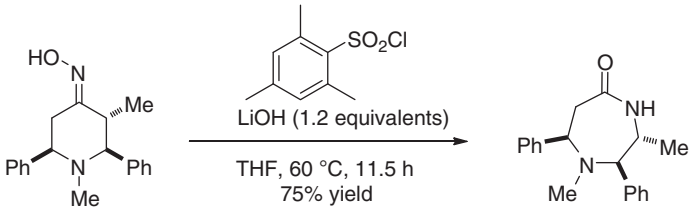
Chloral (trichloroacetaldehyde), a simple reagent, can promote the Beckmann rearrangement. A variety of secondary amides can be obtained in high yields from their corresponding ketoximes via heating with 0.5 M equivalent of chloral hydrate under solvent-free conditions (Scheme 8).[30] However, an initial high-vacuum step (10 Torr) is essential for this process, otherwise the partial hydrolysis of ketoximes will occur. Additionally, the proposed active reagent species, chloral, is formed when the hydrate precursor is heated *in vacuo*. The possible reaction pathway involves the initial formation of the hemiacetal intermediate **10**, which can be converted into imidoyl ester intermediate **11** via rearrangement (Scheme 8).[30] Additionally, some aromatic aldoximes can also be converted to the corresponding nitriles in good yields under similar conditions.[30]

Piperidin-4-one oxime **12** efficiently rearranges into diazepan-5-one **13** through the *in situ* generation of oxime mesitylenesulfonate using mesitylenesulfonyl chloride in the presence of lithium hydroxide in THF at 60 °C (equation 5).[31] Notably, other methodologies using Rh complex,[6] $HgCl_2$,[8] or 2,4,6-trichloro[1,3,5]triazine (cyanuric chloride)[32] (*vide infra*) cannot be applied for the rearrangement of **12**. With the use of this method, a variety of heterocyclic, carbocyclic, and acyclic ketoximes can be converted into their corresponding amides or lactams in good yields.[31]



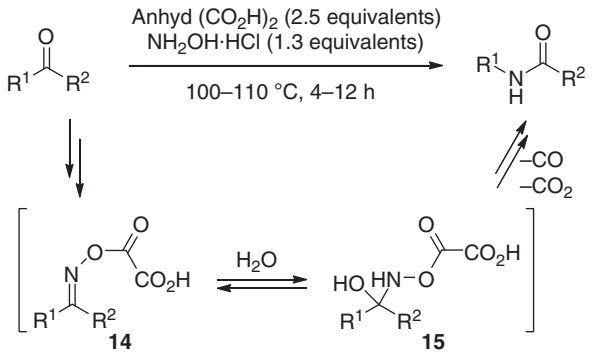
R^1	R^2	Yield
Ph	Ph	84%
Ph	Me	95%
4-MeO-C_6H_4	Me	98%
4-Cl-C_6H_4	Me	85%
Ph	Et	74%
–$(CH_2)_5$–		67%

Scheme 8 Chloral-promoted Beckmann rearrangement of ketoximes.[30]



(5)

Several aromatic ketones and cyclohexanone can be directly converted into their corresponding secondary amides in good yields through the *in situ* generation of ketoximes, by being heated (100–110 °C) with hydroxylamine hydrochloride in the presence of anhydrous oxalic acid (Scheme 9).[33] The proposed reaction pathway involves the generation of the oxime monooxalate **14** and reversible hydration to give tetrahedral intermediate **15**, which can rearrange via the decomposition of the oxalate moiety to CO and CO_2.

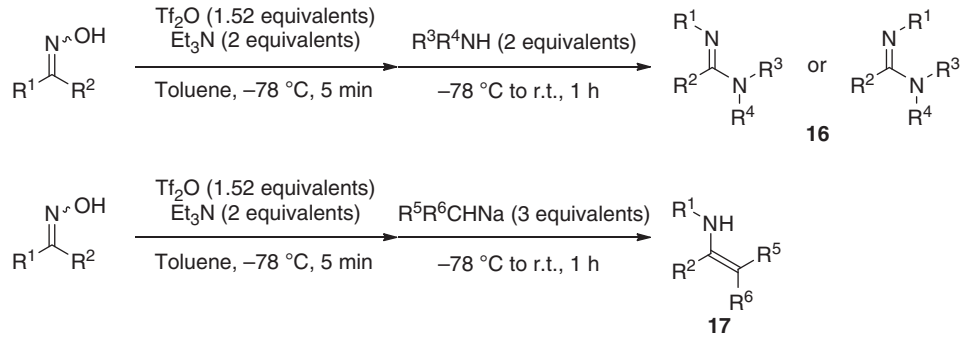


R^1	R^2	Yield
Ph	Ph	96%
Ph	Me	69%
4-MeO-C_6H_4	Me	91%
2-Naphthyl	Me	79%
–$(CH_2)_5$–		67%

Scheme 9 Anhydrous oxalic acid-promoted one-pot conversion of ketones to amides.[33]

The one-pot synthesis of amidines or enamines can be achieved efficiently by trapping nitrilium ion intermediates with amines or carbon nucleophiles (Scheme 10).[34] The nitrilium ion intermediates can be easily generated from their corresponding ketoximes using trifluoromethanesulfonic anhydride in the presence of triethylamine in toluene at –78 °C. After the resulting mixture is stirred for only 5 min, amines or carbon nucleophiles are added and the reaction mixture is slowly warmed to room temperature to give various amidines **16** or enamines **17** in high chemical yields (Tables 7 and 8).[34] Although the geometry of **16** has not been determined, **16** and **17** are obtained as a single product. A proposed reaction mechanism is shown in Scheme 11.[34] The oxime is activated by trifluorosulfonic anhydride to give oxime trifluoromethanesulfonate intermediate **18**. After the migration of an alkyl *or* aryl group, the nitrilium intermediate **19** is generated, which is trapped with an amine or carbon nucleophile to give the corresponding amidine **16** or imine **20**. Enamine **17** is generated via tautomerization.

Similarly, the one-pot synthesis of *N*-substituted thioamides **21** can be achieved by trapping nitrilium ion intermediates, which are generated *in situ* via the treatment of ketoximes with *para*-toluenesulfonyl chloride in the presence of triethylamine, with thiourea (Scheme 12).[35,36] Ketoximes derived from arylalkylketone, diarylketone, dialkylketone, and cycloalkanones give their corresponding thioamides in good yields. This method offers an odorless alternative to conventional methods for the synthesis of thioamides. This method can also be applied for the synthesis of *N*-imidoylbenzotriazoles **22** from ketoximes in good yields by trapping of a nitrilium ion intermediate with benzotriazole (Scheme 13).[37]

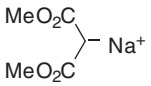
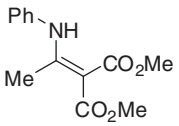
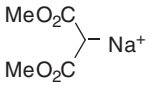
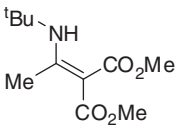
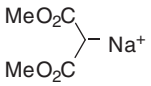
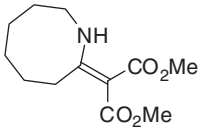
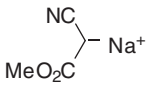
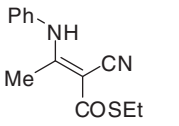
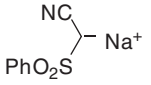
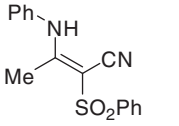
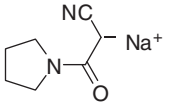
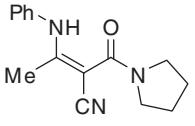


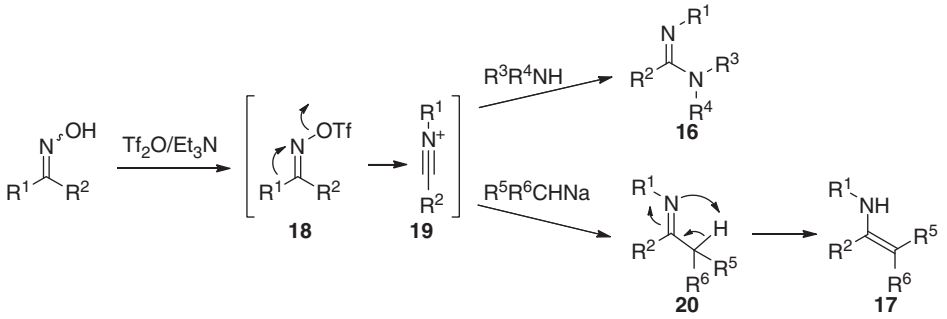
Scheme 10 One-pot synthesis of amidines **16** and enamines **17** from ketoximes via Beckmann rearrangement using trifluoromethanesulfonic anhydride.[34]

Table 7 One-pot synthesis of amidines **16** by trapping with amines (**Scheme 10**)

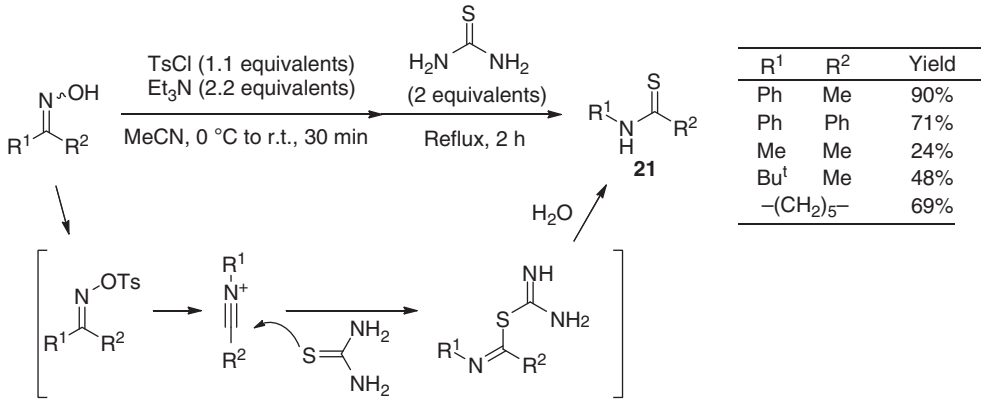
R^1	R^2	R^3	R^4	Yield (%)	References
Ph	Ph	Ph	Me	95	34
Ph	Me	Bn	Me	86	34
Ph	Me	Ph	H	60	34
Me	Me	Ph	Me	93	34
$-(CH_2)_5-$		Ph	Me	83	34
Ph	Ph	$-(CH_2)_2O(CH_2)_2-$		87	34

Table 8 One-pot synthesis of enamines **17** by trapping with carbon nucleophiles (**Scheme 10**)

Nucleophile	Product **17**	Yield (%)	References
		96	34
		84	34
		74	34
		78	34
		69	34
		89	34

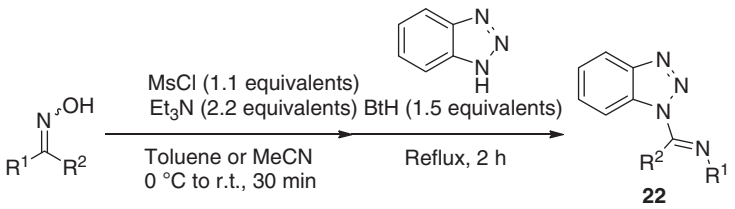


Scheme 11 Proposed mechanism for the synthesis of amidines and enamines from ketoximes via subsequent Beckmann rearrangement and trapping reaction sequences.



R^1	R^2	Yield
Ph	Me	90%
Ph	Ph	71%
Me	Me	24%
Bu^t	Me	48%
$-(CH_2)_5-$		69%

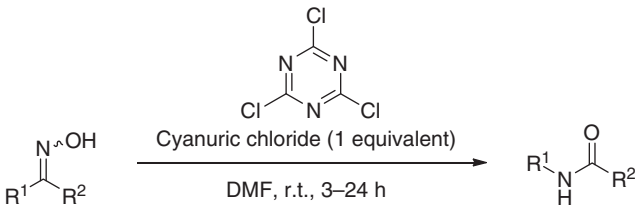
Scheme 12 Synthesis of thioamides **21** from ketoximes by trapping of nitrilium ion intermediate with thiourea.[35]



R^1	R^2	Yield
Ph	Me	95%
Ph	Ph	82%
Me	Me	40%
Bu^t	Me	73%
$-(CH_2)_5-$		53%

Scheme 13 Synthesis of *N*-imidoylbenzotriazoles **22** from ketoximes by trapping of nitrilium ion intermediate with benzotriazole.[37]

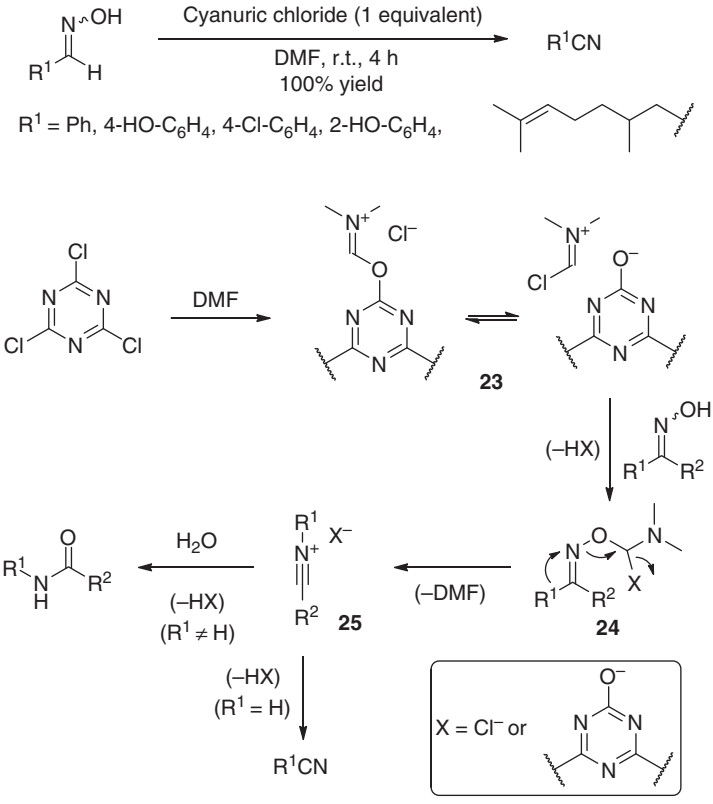
Cyanuric chloride, an inexpensive commercially available reagent, in DMF can promote the Beckmann rearrangement of a range of ketoximes at room temperature to give the corresponding secondary amides in high yields (equation 6, Table 9).[32] In a typical experimental procedure, cyanuric chloride and DMF are mixed together to form a white complex, which is in turn treated with oximes, which leads to the Beckmann rearrangement under mild conditions. Importantly, the use of DMF as a solvent is essential for this method, otherwise no reaction will be observed. Since (*E*)- and (*Z*)-oximes are interconvertible under these reaction conditions, the stereochemistry of the oximes has almost no effect on the reaction. Similar to other methods, the migration of an aryl group predominates over that of an alkyl group. However, in contrast to Rh-catalyzed Beckmann rearrangements (Table 1),[6] the *tert*-butyl group of aryl-*tert*-butyl ketone-derived oximes migrates predominantly over an aryl group. The reaction of the cyclohexanone oxime gives pure *ε*-caprolactam quantitatively. Furthermore, the reaction of aldoximes under similar conditions gives the corresponding nitriles quantitatively (equation 7).[32] The proposed reaction mechanism is shown in Scheme 14.[32] Initially, the Vilsmeier–Haack-type complex[38] **23** is generated *in situ* from the reaction of cyanuric chloride with DMF. The oxime then reacts with **23** to give **24**. Subsequent rearrangement to adduct **25** gives the nitrile, in the case of aldoximes, or the secondary amide on hydrolytic workup.



(6)

Table 9 Cyanuric chloride/DMF-promoted Beckmann rearrangement (equation 6)

R^1	R^2	Time (h)	Conversion (%)	References
Ph	Me	6	100	32
Ph	Pr^i	12	85	32
Bu^t	Ph	24	91	32
2-Naphthyl	Me	12	100	32
	$-(CH_2)_5-$	3	100	32



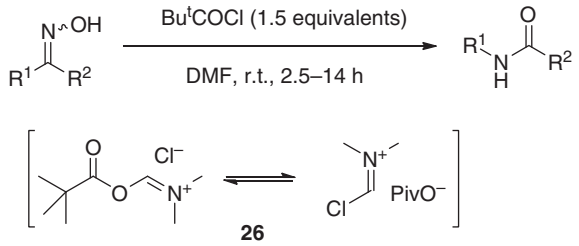
(7)

Scheme 14 Proposed mechanism for the cyanuric chloride/DMF-promoted Beckmann rearrangement.[32]

Pivaloyl chloride, a simple reagent, in DMF is also very effective for the Beckmann rearrangement of ketoximes at room temperature into their corresponding amides or lactams (Scheme 15).[39] As with cyanuric chloride, Vilsmeier–Haack-type complex **26**, formed from pivaloyl chlorine and DMF, is expected to be a reactive intermediate. Using this method, δ- and ε-lactams are obtained quantitatively from their corresponding oximes under mild conditions.

6.14.1.3 Organocatalysts

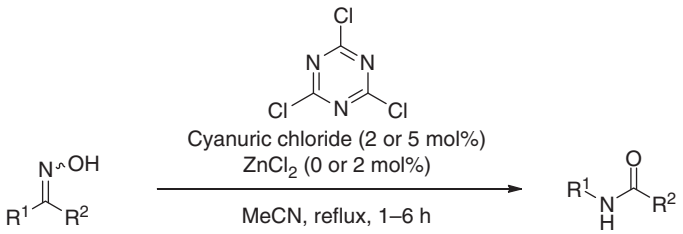
Cyanuric chloride can also be used catalytically for the Beckmann rearrangement of ketoximes under reflux conditions (equation 8, Table 10).[40] Polar and nucleophilic solvents, such as acetonitrile and nitromethane, are most suitable for this system.[40–42]



R^1	R^2	Conversion
Ph	Me	85%
2-HO-C_6H_4	Me	72%
2-O_2N-C_6H_4	Me	78%
Bu^t	Me	90%
Bu^t	Ph	81%
–$(CH_2)_4$–		97%
–$(CH_2)_5$–		100%

Scheme 15 Pivaloyl chloride/DMF-promoted Beckmann rearrangement of ketoximes.[39]

Furthermore, the reaction rate is accelerated with the use of mild Lewis acids, such as $ZnCl_2$, $FeCl_3$, $CoCl_2$, and $BiCl_3$. Brønsted acids, such as TsOH and HCl, are less effective than these Lewis acids. Less-expensive $ZnCl_2$ seems to be the best choice as a cocatalyst. Notably, $ZnCl_2$ is inert for this rearrangement in the absence of cyanuric chloride. Large cycloalkanone oximes are transformed to the corresponding lactams in excellent yields. However, in contrast to the stoichiometric use of cyanuric chloride with DMF,[32] the catalytic reaction of six- to eight-membered cycloalkanone oximes gives the desired lactams in low yields (Table 10).[40] The proposed catalytic cycle is depicted in Scheme 16.[40] Initially, *O*-aryl ketoxime **27** is generated, which then gives *O*-aryl imidate intermediate **28** via migration. The addition of ketoxime to **28** gives the Meisenheimer complex[43] **29**, which releases amide product and intermediate **27**. HCl, which is generated *in situ* from ketoximes and cyanuric chloride, and $ZnCl_2$ probably promote the rearrangement of *O*-aryl ketoxime **27** through protonation or coordination of nitrogen atoms.

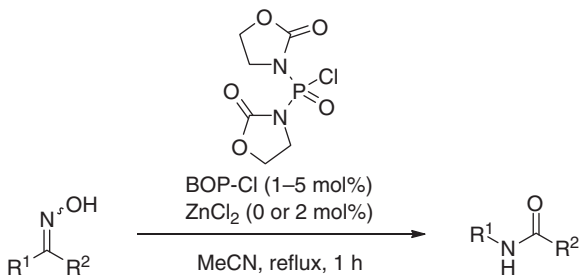


(8)

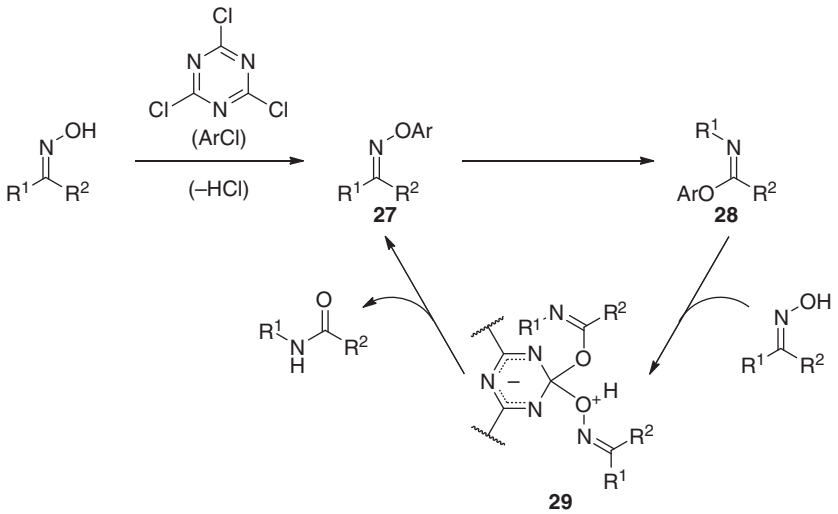
Table 10 Cyanuric chloride-catalyzed Beckmann rearrangement (equation 8)

R^1	R^2	*Cyanuric chloride (mol%)*	*$ZnCl_2$ (mol%)*	*Time (h)*	*Yield (%)*	*References*
Ph	Me	5	0	2	97	40
Ph	Me	2	0	2	31	40
Ph	Me	2	2	2	99	40
2-MeO–C_6H_4	Me	5	0	1	98	40
4-F–C_6H_4	Me	2	2	2	97	40
^{n}C_8H_{17}	Me	2	2	2	96	40
–$(CH_2)_{11}$–		2	2	1	98	40
–$(CH_2)_7$–		2	2	6	27	40
–$(CH_2)_5$–		10	0	2	30	40

As with cyanuric chloride, bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) is a highly active organocatalyst for the Beckmann rearrangement of various ketoximes to the corresponding secondary amides in refluxing acetonitrile (equation 9, Table 11).[44] Similar to cyanuric chloride, the reaction rate is accelerated with the cocatalytic use of $ZnCl_2$. However, the reaction of cyclohexanone oxime is very sluggish and gives ε-caprolactam in very low yield.



(9)

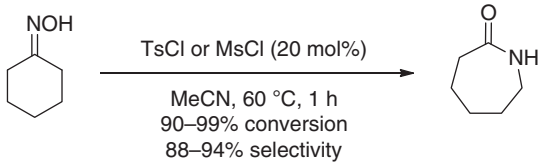


Scheme 16 Proposed mechanism for cyanuric chloride-catalyzed Beckmann rearrangement.

Table 11 BOP-Cl-catalyzed Beckmann rearrangement of ketoximes (equation 9)

R^1	R^2	*BOP-Cl (mol%)*	*$ZnCl_2$ (mol%)*	*Yield (%)*	*References*
Ph	Me	5	0	94	43
Ph	Me	2	0	40	43
Ph	Me	2	2	92	43
Ph	Ph	1	0	99	43
$^nC_8H_{17}$	Me	2	2	95	43
$-(CH_2)_{11}-$		2	2	99	43
$-(CH_2)_5-$		2	2	<5	43

p-Toluenesulfonyl chloride (TsCl) and methanesulfonyl chloride (MsCl) have each been widely used as stoichiometric reagents for the Beckmann rearrangement of ketoximes into the corresponding amides.[2,3,45] These sulfonyl chlorides have also been shown to catalyze the Beckmann rearrangement of a wide range of ketoximes into their corresponding amides in refluxing acetonitrile in the presence or absence of $ZnCl_2$.[46] Additionally, in contrast to cyanuric chloride and BOP-Cl, the reaction of cyclohexanone oxime using 20 mol% of TsCl or MsCl gives *ε*-caprolactam in high yields (equation 10).[46]

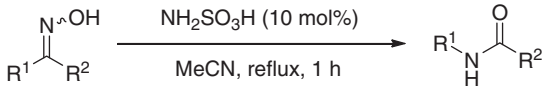


(10)

Sulfamic acid, NH_2SO_3H, shows good catalytic activities for the Beckmann rearrangement of a variety of ketoximes, especially for aryl ketoximes in refluxing acetonitrile (Scheme 17).[47] Due to the zwitterionic property of sulfamic acid, the use of a basic neutralization agent can be avoided during the work-up process. Additionally, sulfamic acid can be easily separated and re-used by dispersing the reaction mixture in diethyl ether.

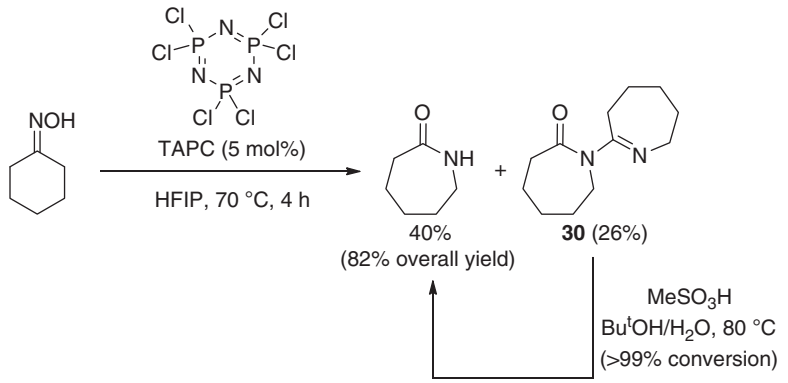
Triphosphazene (1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-chloride (TAPC)), an analog of cyanuric chloride, has been found to be an efficient catalyst for the Beckmann rearrangement of various ketoximes in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP).[48,49] In particular, the efficient rearrangement of cyclohexanone oxime to *ε*-caprolactam, which is not completely successful with cyanuric chloride in similar conditions, can be achieved with TAPC (Scheme 18).[48,49] Thus, treatment of cyclohexanone oxime with 5 mol% of TAPC in HFIP at 70 °C gives *ε*-caprolactam (40%) and its condensate **30** (26%). The condensate product **30** is easily hydrolyzed to *ε*-caprolactam quantitatively. Thereby, the one-pot synthesis of *ε*-caprolactam from oxime can be achieved under the same conditions followed by hydrolysis, and *ε*-caprolactam is obtained in 82% isolated yield.

Furthermore, the Beckmann rearrangement of cyclohexanone oxime runs to completion in the presence of only 0.5 mol% of cyanuric chloride in a 3:2 mixed solvent of trifluoroacetic acid and toluene at 70 °C for 4 h to give *ε*-caprolactam in excellent isolated yield after successive SiO_2 column chromatography (Scheme 19).[50] Similarly, laurolactam can also be obtained almost

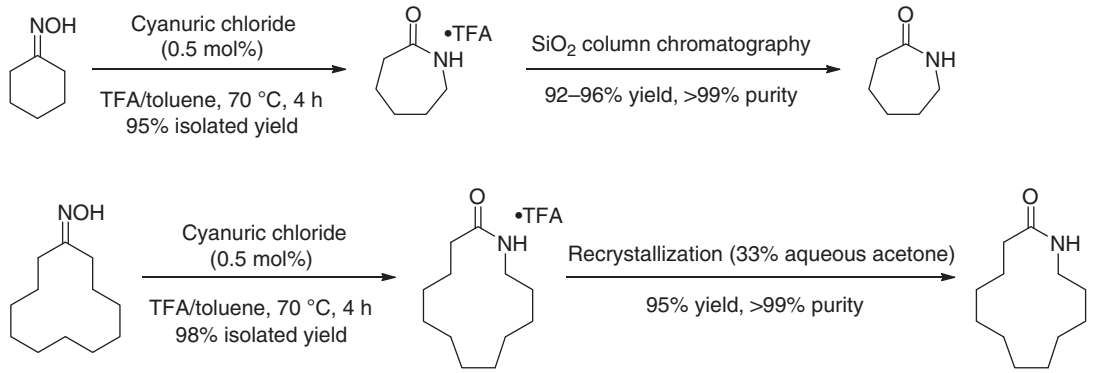


R^1	R^2	Yield
Ph	Ph	96%
Ph	Me	96%
$-(CH_2)_4-$		59%
$-(CH_2)_5-$		40%

Scheme 17 Sulfamic acid-catalyzed Beckmann rearrangement of ketoximes.[47]



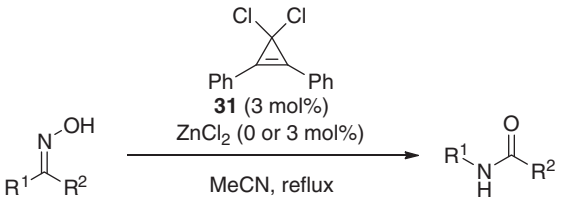
Scheme 18 Synthesis of ε-caprolactam via triphosphazene (TAPC)-catalyzed Beckmann rearrangement of cyclohexanone oxime and hydrolysis of the condensate product **30**.[48,49]



Scheme 19 Synthesis and isolation of ε-caprolactam and laurolactam.[50]

quantitatively after recrystallization from 33% aqueous acetone (Scheme 19).[50] This method provides an environmentally friendly route to nylon-6 and nylon-12.

Recently, 1,1-dichloro-2,3-diphenylcyclopropenone (**31**) was found to be a very efficient organocatalyst (3 mol% loading) for the Beckmann rearrangement of various ketoximes to the corresponding amides in refluxing acetonitrile (equation 11, Table 12).[51] As with cyanuric chloride, the use of $ZnCl_2$ as a cocatalyst further enhances the reaction rate. Both aromatic and aliphatic ketoximes give the corresponding amides in excellent yields. Similar to the cyanuric chloride system, the reaction of cyclohexanone oxime gives ε-caprolactam in low yield.



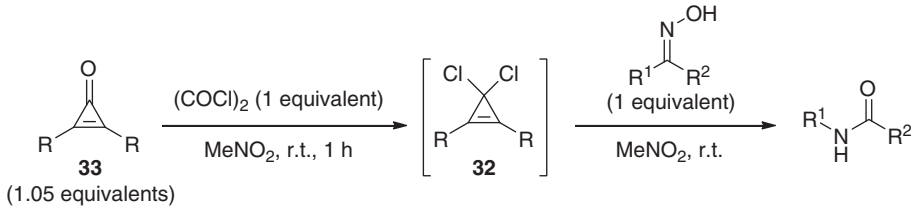
(11)

Substituted dichlorocyclopropenes **32** (R = Ph or Mes) can be easily prepared *in situ* from readily available cyclopropenones **33** by simple treatment with oxalyl chloride in nitromethane at room temperature (equation 12).[52] These reagents rapidly convert ketoximes to the corresponding amides at room temperature, with higher reactivity than other organic-based promoters such as

Table 12 Beckmann rearrangement using cyclopropenium ion (equation 11)

R^1	R^2	$ZnCl_2$ (mol%)	Time (h)	Yield (%)	References
Ph	Me	0	1	90	51
Ph	Me	3	1	98	51
2-Cl–C_6H_4	Me	3	1	96	51
2-MeO–C_6H_4	Ph	3	1	98	51
$^nC_8H_{17}$	Me	3	2	96	51
$-(CH_2)_{11}-$		3	2	96	51
$-(CH_2)_5-$		3	2	18	51

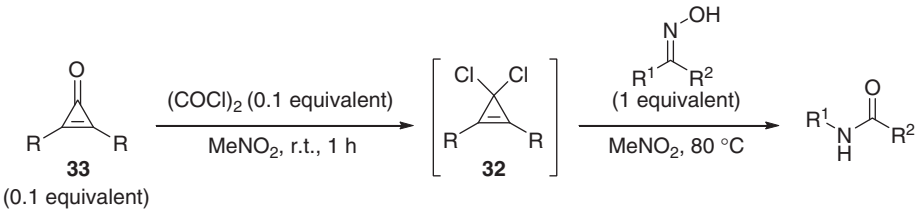
cyanuric chloride/DMF (equation 12, Table 13).[52] Furthermore, *in situ*-generated **32** can be used catalytically (10 mol%) at high temperature in nitromethane (80 °C) (equation 13, Table 13).[52] In particular, the rearrangement of 3β-acetoxypregnenone oxime **34** under catalytic conditions gives the steroidal amide **35** in 94% yield on a 1-gram scale (equation 14). Based on experimental findings, a self-propagating, rather than a catalytic mechanism is proposed (Scheme 20).[52] First, cyclopropenium oxime **36** is generated from the reaction of oxime with dichlorocyclopropene **32**. After migration, the nitrilium ion intermediate **37** or the imidoyl chloride **38** is alkylated by another molecule of oxime directly to give intermediate **39**, which gives the amide product and regenerates nitrilium ion **37** again via the Beckmann rearrangement. Thus, the cyclopropenium ion might act as an initiator rather than a catalyst. These findings imply that other organocatalytic methods (i.e., cyanuric chloride, BOP-Cl, sulfonyl chloride, etc.) might also proceed via self-propagation rather than catalysis.



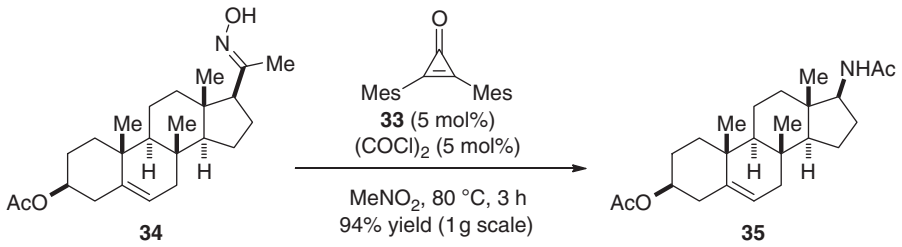
(12)

Table 13 Cyclopropenium-activated Beckmann rearrangement (equations 12 and 13)

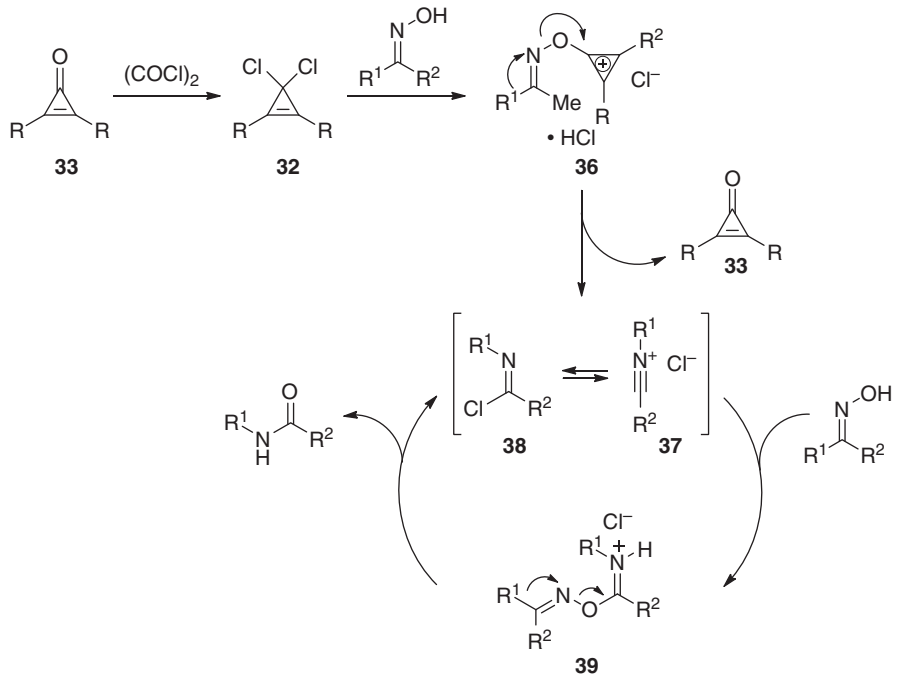
R^1	R^2	R in ***33***	Time (h)	Yield (%) Stoichiometric, Catalytic	References
Ph	Ph	Ph	0.5	98, 97	52
3-MeO–C_6H_4	Me	Mes	0.3	93, 98	52
4-Br–C_6H_4	Me	Mes	0.5	80, 99	52
Ph	Cyclopropyl	Ph	1.5	87, 89	52
$-(CH_2)_{11}-$		Mes	24	99, 93	52
$-(CH_2)_5-$		Mes	0.5	96, no data	52



(13)



(14)

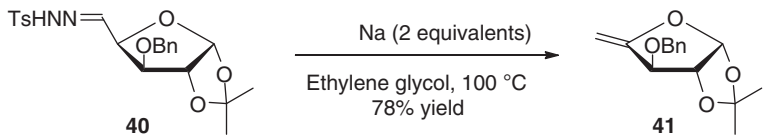


Scheme 20 Proposed self-propagating mechanism for cyclopropenium-activated Beckmann rearrangement.

6.14.2 Bamford–Stevens Reaction

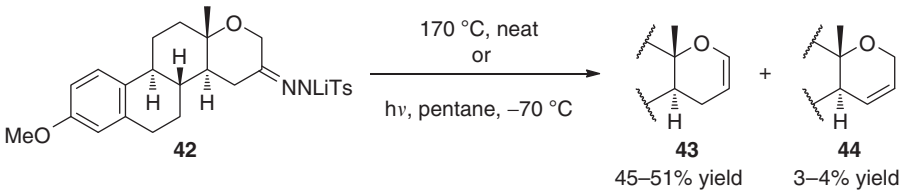
Originally, the Bamford–Stevens reaction was a base-mediated decomposition of arenesulfonylhydrazones of ketones or aldehydes to form alkenes or cyclopropanes via diazo compounds.[53–55] Recently, there has been dramatic growth in the use of diazo compounds, which are intermediates in the Bamford–Stevens reaction, in synthetic organic chemistry.[56–58] This section briefly summarizes recent significant advances in this field.

The reaction of carbohydrate or tartaric acid-derived α-oxy tosylhydrazones with sodium metal in ethylene glycol gives exocyclic vinyl ethers, which are part of the structure of naturally occurring compounds, in good yields.[59] For example, the hydrazone **40** is derived from D-glucose to give **41** in 78% yield (equation 15).[59]



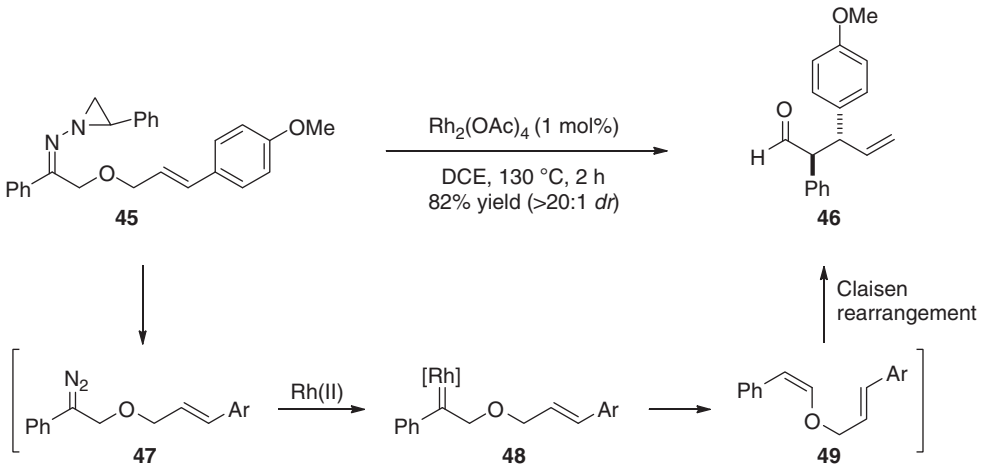
(15)

The interesting stereochemical aspects of a thermal or photic Bamford–Stevens reaction of tosylhydrazones derived from cyclic α-oxy carbonyl compounds has been demonstrated.[60] When the lithium salt of steroidal tosylhydrazone **42** is exposed to thermal (170 °C) or photic ($h\nu$, –70 °C) conditions, enol ether **43** is obtained as a major product (equation 16).[60] Thus, the ring oxygen is a more powerful activator than a ring alkyl by a factor of 14:1 to 21:1.



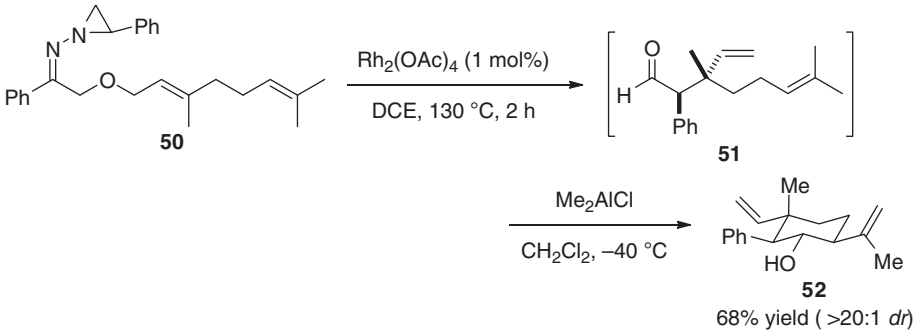
(16)

A tandem Bamford–Stevens/Claisen rearrangement sequence catalyzed by rhodium has been established.[61] The treatment of *N*-aziridinyl imine (Eschenmoser hydrazone) **45** with $Rh_2(OAc)_4$ in DCE at 130 °C gives aldehyde **46** in good yield with excellent diastereoselectivity (Scheme 21).[61] This tandem process proceeds via (1) thermal decomposition of the aziridine **45** to diazo compound **47**, (2) Rh-mediated de-diazotization to a Rh-carbenoid intermediate **48**, (3) stereoselective 1,2-hydride migration to give **49** (>20:1 *Z:E* selectivity), and (4) thermal aliphatic Claisen rearrangement through a chair-like transition state to give final product **46**. Furthermore, this method can be applied to cascade reactions, whereas the third reaction (i.e., intramolecular



Scheme 21 Rh-catalyzed tandem Bamford–Stevens/Claisen rearrangement sequence.[61]

carbonyl-ene reaction, reduction of aldehyde, and Cope-rearrangement) occurs after an initial tandem process.[61] For instance, the Lewis acid-promoted carbonyl-ene reaction of **51**, which is derived *in situ* from geranyl ether **50**, produces cyclohexanol **52** with excellent diastereoselectivity (equation 17).[61]



(17)

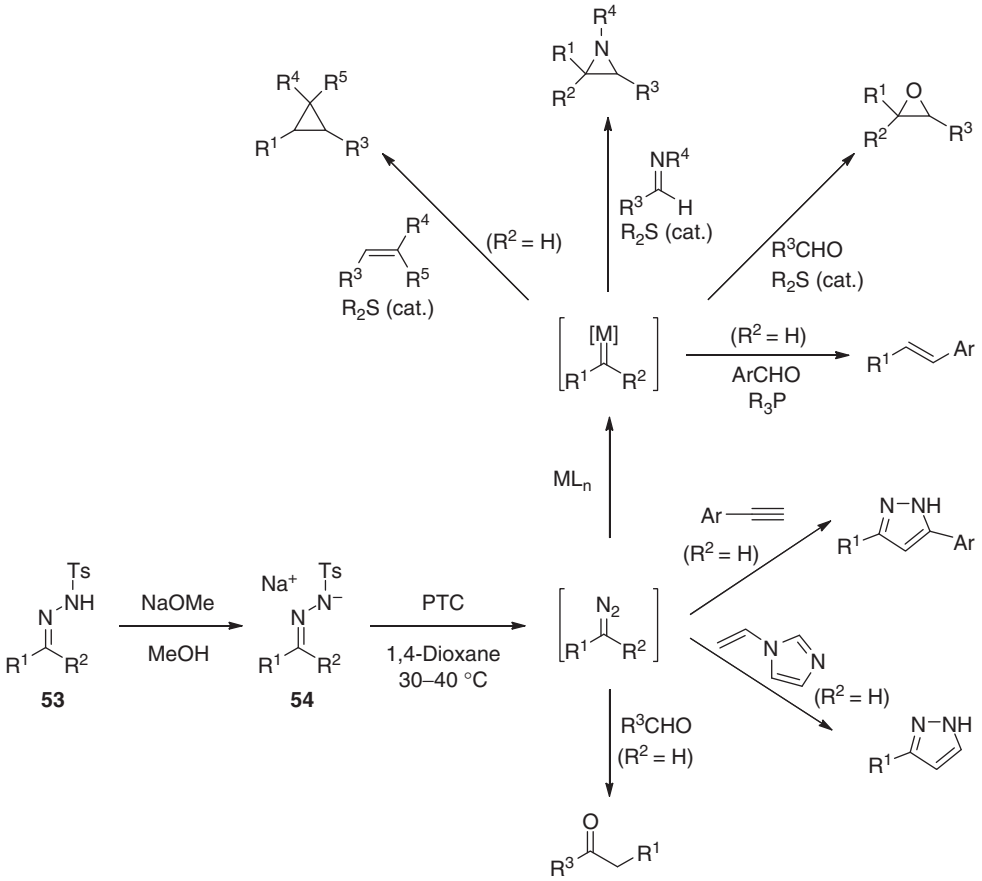
Recently, a reliable method for the *in situ* generation of diazo compounds from a tosylhydrazone based on the Bamford–Stevens reaction was established.[56] Tosylhydrazone salts **54**, which can be easily prepared and isolated from the corresponding hydrazones **53**, can be cleanly converted to diazo compounds in the presence of phase-transfer catalysts (PTC), such as $BnEt_3NCl$ or $(n\text{-}Oct)_3MeNCl$, under mild reaction conditions by gentle warming at 30–40 °C (Scheme 22).[56] The hydrazone salt is almost insoluble under these reaction conditions, and thus a PTC is necessary to aid the transfer of the anion from the solid to the liquid phase where decomposition (diazo formation) occurs. Furthermore, these *in situ*-generated diazo compounds can then be induced to react directly with alkenes or alkynes to synthesize pyrazoles[62] or with aldehydes to generate ketones.[63] Additionally, diazo compounds can react with transition metals that are capable of carbene transfer reactions, such as olefination,[64] sulfur ylide-mediated epoxidation,[65] aziridination,[66] and cyclopropanation reactions.[66] The rich chemistry of diazo compounds has been reviewed extensively.[56–58]

6.14.3 Shapiro Reaction

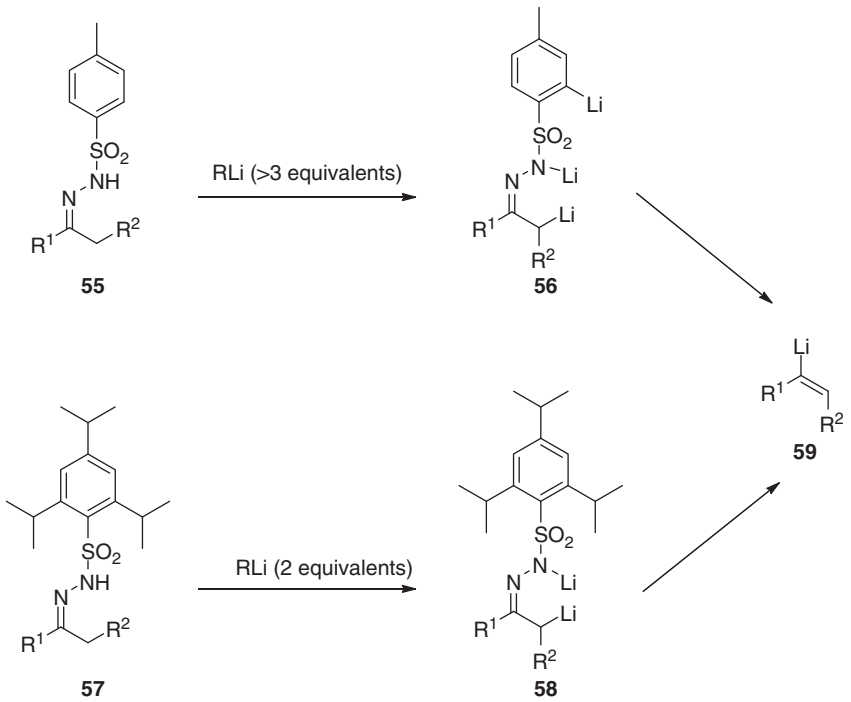
The Shapiro reaction is a convenient, easy, and straightforward method for converting arenesulfonylhydrazone of ketones to various olefinic compounds in high yields via a vinyllithium intermediate.[54,55,67] This section briefly summarizes recent significant advances in this field.

As with the Bamford–Stevens reaction, tosylhydrazone **55** is generally used for the Shapiro reaction.[55] However, due to the acidic *ortho*-hydrogen of the tosyl group, an excess amount of base (more than 3 equivalents) is required to obtain good conversion into alkenyl lithium derivatives **59** (Scheme 23). To reduce the amount of alkyllithium reagents, a modified sulfonylhydrazone leaving group such as 2,4,6-triisopropylbenzenesulfonyl (Trisyl) is introduced.[68] As a result, trisylhydrazones **57** need only 2 equivalents of alkyllithium reagents (Scheme 23). Moreover, the decomposition of trisylhydrazone dianions **58** to the desired vinyl carbanions **59** occurs much faster than that of tosylhydrazone derivatives **56**, due to steric destabilization by the bulky *ortho* substituents.[69]

In general, α-chiral tosylhydrazones are much more sensitive to acid-catalyzed epimerization than the parent ketones.[70] Indeed, hydrazone **61** epimerizes approximately 150 times faster than ketone **60**. The ease of epimerization of hydrazone, relative to that of ketone, can be attributed to the greater basicity of nitrogen versus oxygen.[70] Menthonetosylhydrazone (**61**) can be prepared in

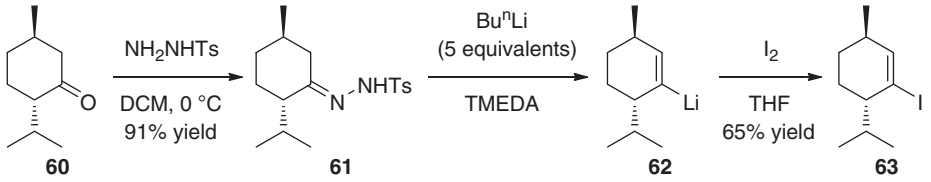


Scheme 22 *In situ* generation of diazo compounds based on the Bamford–Stevens reaction and its application to several transformations.[56]



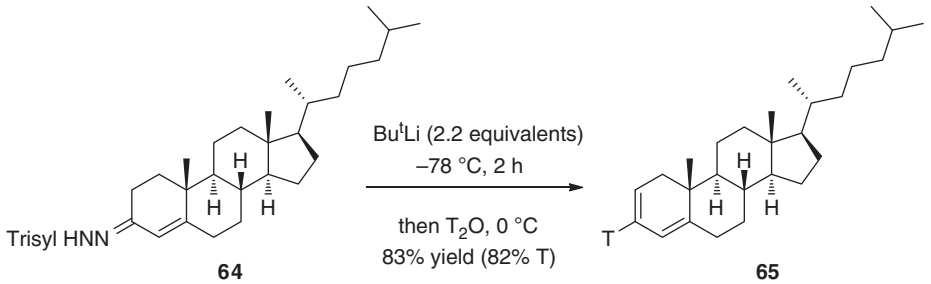
Scheme 23 Leaving group effect on the Shapiro reaction.

diastereomerically pure form from menthone (**60**) in the absence of any acid in cold dichloromethane (equation 18).[70] In sharp contrast, the reaction of **60** with tosylhydrazine in the presence of acid (e.g., HCl) gives a mixture of hydrazone **61** and its epimer, even at 0 °C.[70] Furthermore, the Shapiro reaction of **61** using an excess amount of *n*-butyllithium occurs without epimerization. Thus, diastereomerically pure 1-iodomenthone **63** can be obtained by treatment of vinyl lithium **62** with iodine *in situ* (equation 18).[70]



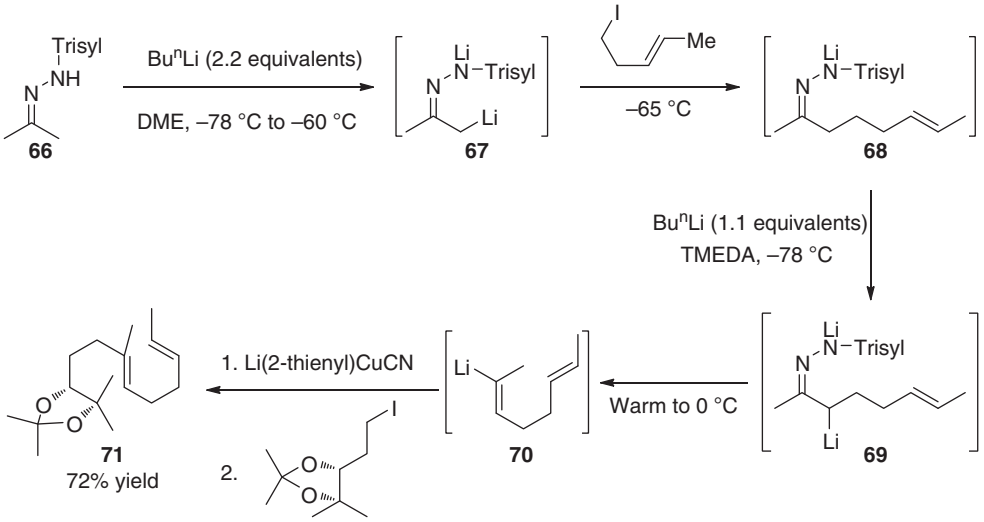
(18)

The Shapiro reaction can be used for the synthesis of a variety of tritiated alkenes in good yields, with high specific radioactivity and radiochemical purity.[71] For instance, the reaction of steroidal trisylhydrazone **64** with *tert*-butyllithium gives tritiated alkene **65** after being quenched with tritiated water (T_2O) (equation 19).[71]



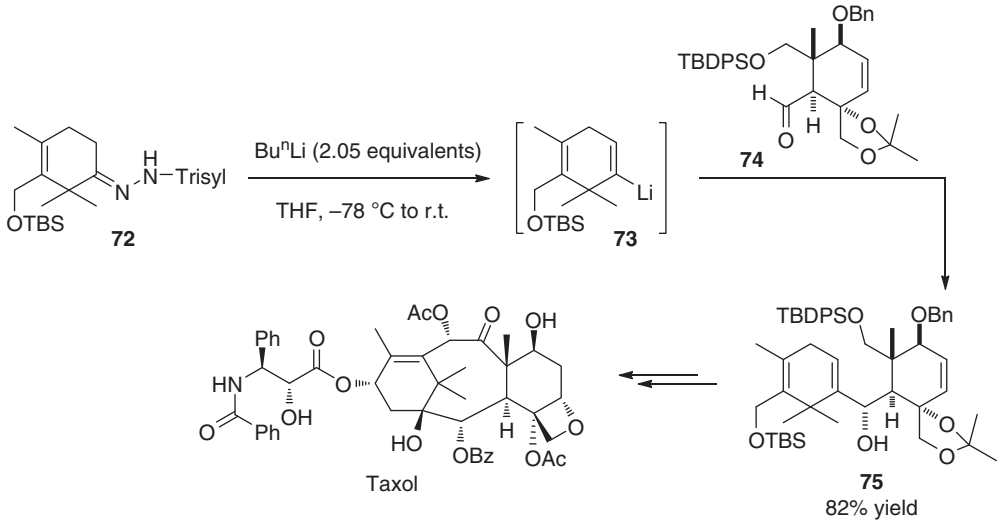
(19)

In unsymmetrical hydrazones, *syn*-deprotonation of the monoanion of arylhydrazones occurs at less-substituted α-position to give the less-substituted (*E*)-vinyllithium due to lower steric interactions (**Scheme 23**).[55] The *syn*-directed deprotonation of arylhydrazones can be used to reverse the normal preference of the less-substituted vinyllithium. For example, using this strategy, acetone trisylhydrazone **66** can be converted to the trisubstituted olefin **71** in 72% yield in a one-pot operation (**Scheme 24**).[72] Sulfonylhydrazone **66** is converted to the corresponding dianion **67** via double deprotonation (first at nitrogen and then at the α-methyl, that is, *syn* to the *N*-trisyl group), followed by alkylation at low temperature to give **68**. Importantly, this unsymmetrical hydrazone monoanion intermediate is regiochemically stable at low temperatures, and the *N*-trisyl group remains *syn* to the alkylated carbon. On addition of one more equivalent of *n*-butyllithium in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), dianion **69** is obtained via an exclusive *syn*-deprotonation at the more highly substituted α-position. Dianion **69** can rearrange to **70** through simple warming of the reaction mixture. Conversion of **70** to a mixed cuprate with lithium 2-thienylcyanocuprate and coupling with a second electrophile produces the trisubstituted olefin **71** in a one-pot operation.



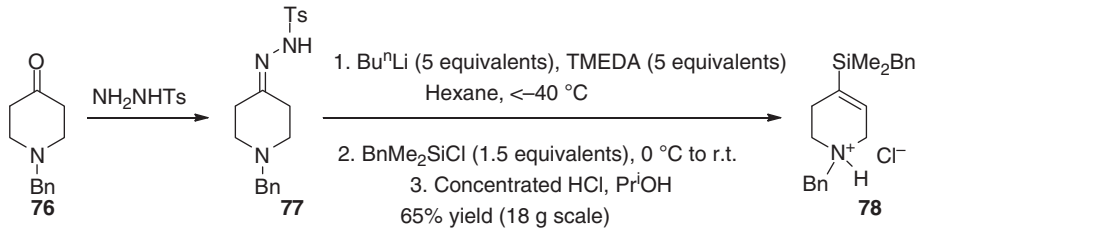
Scheme 24 One-pot reaction sequences that use the Shapiro reaction for the stereoselective synthesis of (*E*)-trisubstituted olefin **71**.[72]

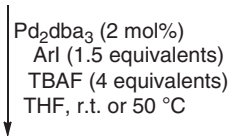
An elegant application of the Shapiro reaction can be found in the total synthesis of Taxol (Scheme 25).[73,74] Indeed, vinyllithium **73** generated *in situ* from trisyl hydrazone **72** can be coupled with aldehyde **74** to furnish alcohol **75** as a single diastereomer in 82% yield.[73]



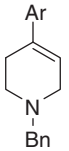
Scheme 25 Total synthesis of Taxol using the Shapiro reaction as a key step.[73]

Another useful application of the Shapiro reaction is in transition metal-catalyzed cross-coupling reactions.[75,76] For example, 1-benzyl-4-piperidone **(76)** can be converted to various 3,4-unsaturated 4-arylpiperidines **79** in high yields via (1) a modified Shapiro reaction of the corresponding tosylhydrazones **77** into benzyldimethylsilyl reagents **78** and (2) the Pd-catalyzed cross-coupling reaction of various aryl iodides with **78** (Scheme 26).[76]





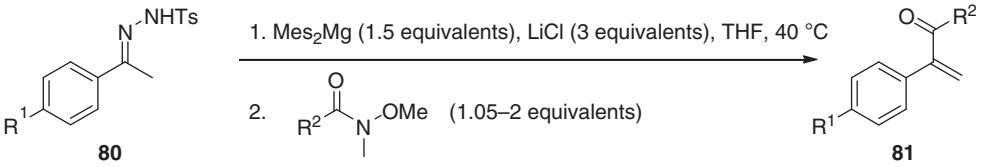
Ar	Yield
Ph	90%
2-Me-C_6H_4	91%
4-MeO-C_6H_4	88%
4-CF_3-C_6H_4	99%
4-CN-C_6H_4	90%
2-Thienyl	64%



Scheme 26 Synthesis of 3,4-unsaturated 4-arylpiperidines **79** from 1-benzyl-4-piperidone (**76**) using Shapiro and Pd-catalyzed cross-coupling reactions.[76]

Very recently, a modified Shapiro reaction that uses bismesitylmagnesium (Mes_2Mg) as an efficient base was reported (equation 20).[77] This new method, which is conducted at conveniently accessible temperatures (i.e., 40 °C) and with a comparably small excess of base reagent (1.5 equivalents), offers an efficient alternative to the alkyllithium-mediated process. Importantly, the use of 2 equivalents of LiCl with respect to the magnesium reagent is key for the desired reactivity of these

magnesium base systems. As with other reported magnesium-base systems,[78] the formation of an ate-type complex is presumed, which accounts for the enhanced reactivity observed. This modified Shapiro reaction can be applied to the synthesis of α-aryl enones **81** from the corresponding arylhydrazones **80** (equation 20, Table 14).[77] Importantly, only 1.05 equivalents of Weinreb amides are required to furnish various enones in consistently good yields.

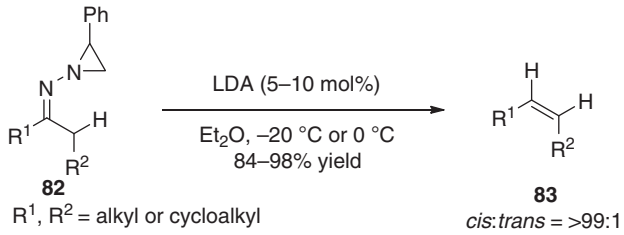


(20)

Table 14 Modified Shapiro reaction with bismesitylmagnesium as a base and the use of Weinreb amides as electrophiles (equation 20)

R^1	R^2	*Yield (%)*	*References*
Ph	Ph	75	77
Ph	Bu^t	64	77
Ph	Me	45	77
Ph	CD_3	72	77
4-Cl–C_6H_4	Ph	70	77
4-$(CH_2)_4$N–C_6H_4	Phs	52	77

In general, the Shapiro reaction requires stoichiometric or even excess amounts of bases (more than 2 equivalents) to generate the vinyllithium intermediate.[55] The only catalytic method for the Shapiro reaction was reported in 1996.[79] The reaction of ketone-derived 2-phenylaziridinyl hydrazones **82** in the presence of a catalytic amount of lithium amides, such as lithium *N*,*N*-diisopropylamide (LDA) gives the corresponding alkenes **83** in high yield with excellent regio- and stereoselectivities (equation 21).[79] According to the proposed mechanism (Scheme 27), a regioselective deprotonation with LDA by abstraction of the α-methylene hydrogen *syn* to the phenylaziridyl moiety in **82** and subsequent decomposition of the resulting monoanion **84** furnishes the vinyllithium **85**, which abstracts the proton of the diisopropyl amine, to produce the *cis*-alkene **83** with the regeneration of LDA for further use in the catalytic cycle.

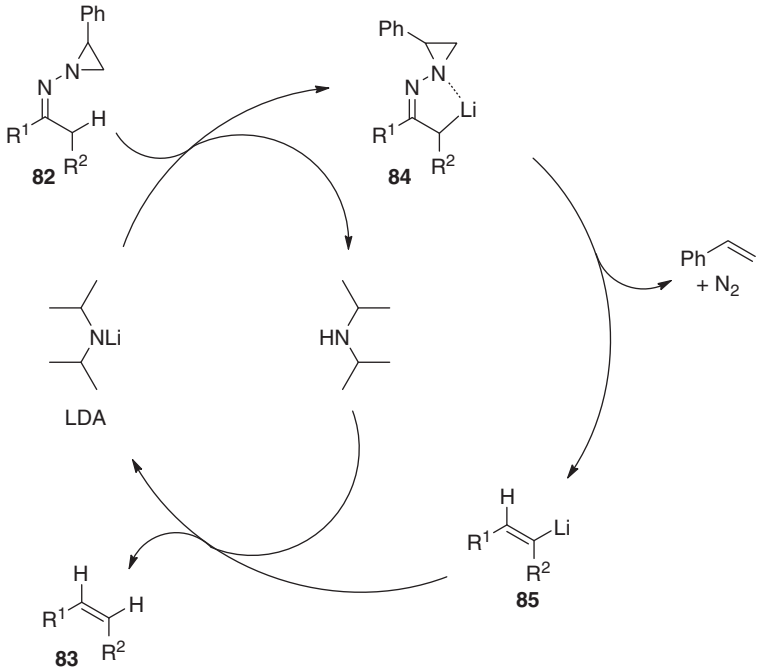


(21)

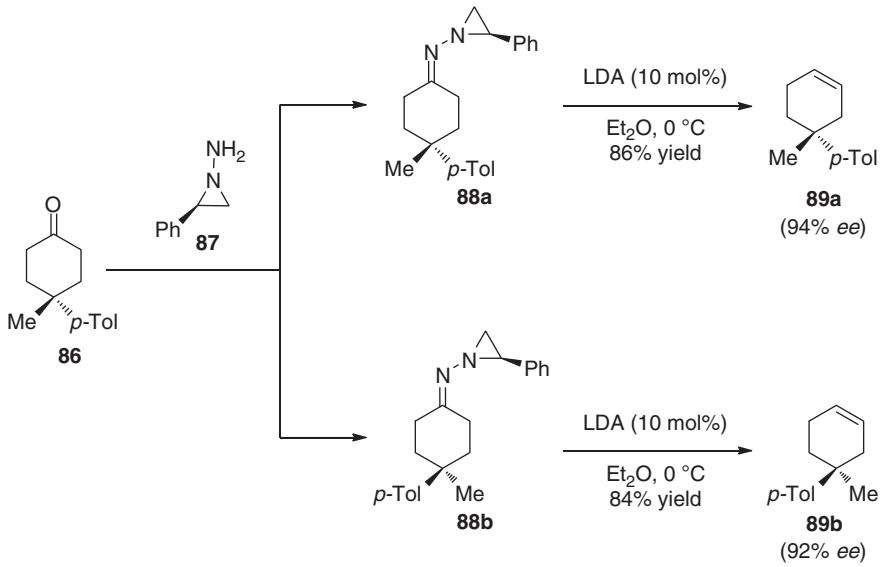
The synthesis of optically active alkenes can be achieved using optically pure aziridine for this catalytic Shapiro reaction. For example, diastereomeric hydrazones **88a** and **88b** can be prepared by the condensation of ketone **86** with optically pure 1-amino-2-phenylaziridine (**87**) (>99% *ee*) (Scheme 28).[79] Individual treatment of **88a** and **88b** with a catalytic amount of LDA at 0 °C gives the corresponding alkenes **89** in high yield and high optical purity (≥92% *ee*).

6.14.4 Neber Rearrangement

The Neber rearrangement of oxime sulfonates (**90**) has been recognized as a promising method for the preparation of a variety of both mixed alkyl–aryl and cyclic α-amino ketones (**97**).[80] The Neber reaction probably occurs either through an internal concerted nucleophilic displacement at nitrogen and the leaving of a sulfonate moiety (**91**→**94**→**95**, anion pathway) or via a vinylnitrene, a reactive intermediate formed by base-promoted loss of the sulfonate moiety (**91**→**92**→**93**→**95**, nitrene pathway) (Scheme 29).[80] The isolable 2*H*-azirine intermediate **95**, the smallest nitrogen-unsaturated heterocycle, represents a class of compounds that are important due to their high reactivity.[81–84] They can be used as key intermediates in synthetic organic chemistry for preparation of a variety of nitrogen-containing compounds.[81–84] Moreover, they are constituents of several naturally occurring antibiotics.[85–88] Recent studies have focused on the development of enantioselective Neber reactions. This section briefly summarizes recent significant advances in this field.

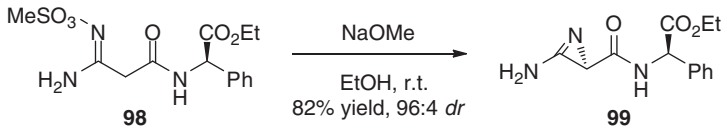


Scheme 27 Proposed mechanism for the catalytic Shapiro reaction.[79]



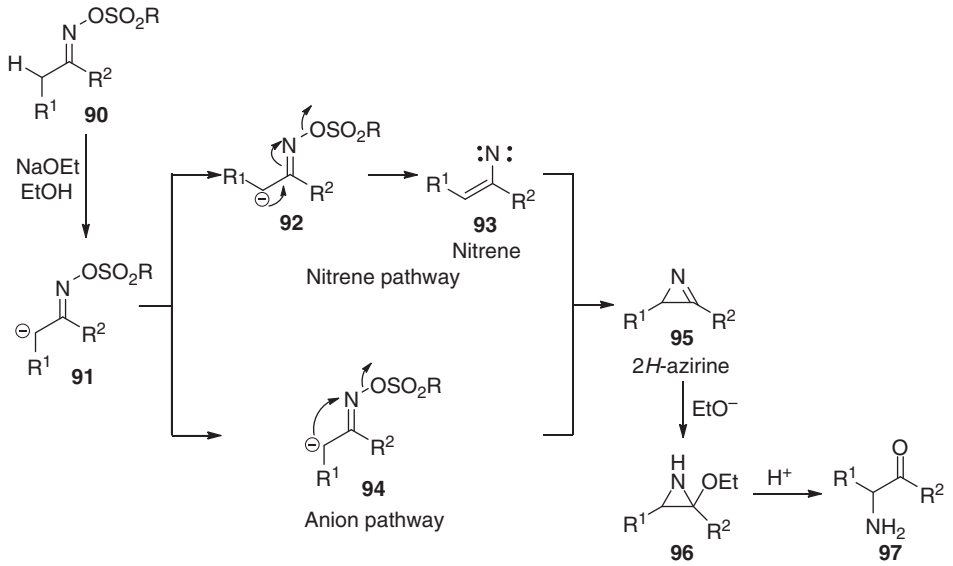
Scheme 28 Synthesis of optically active alkenes **89** utilizing the catalytic Shapiro reaction.[79]

Optically active 2*H*-azirines can be prepared using the Neber reaction of an *O*-mesyl derivative of amidoxime (**98**), where phenylglycine is introduced as a chiral auxiliary.[89] Treatment of this derivative with sodium methoxide gives the 3-amino-2*H*-azirine **99** in good yield and high diastereoselectivity (96:4) (equation 22).[89]

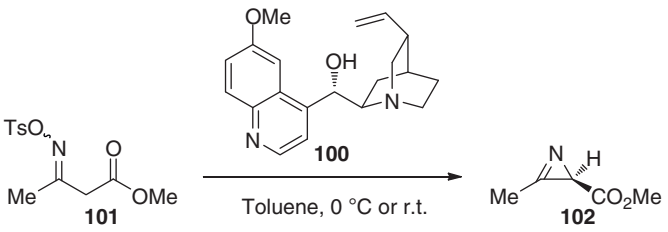


(22)

The first enantioselective Neber reaction was achieved using a chiral tertiary base, such as quinidine **100** (Scheme 30).[90] The enantiomeric excess of azirines **102** is up to 82% *ee*, when a stoichiometric amount of **100** is used. Furthermore, a good result



Scheme 29 Neber reaction of oxime sulfonates to α-amino ketones via a 2*H*-azirine intermediate.[80]

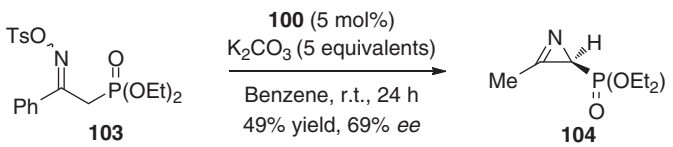


Conditions	Yield (%), *ee* (%)
100 (1 equivalent), 0 °C	43, 82
100 (25 mol%), K_2CO_3 (1.5 equivalents), r.t.	70, 71

Scheme 30 Quinidine (**100**)-promoted enantioselective Neber reaction.[90]

(up to 71% *ee*) is also obtained when a catalytic amount of **100** is used in the presence of an excess amount of solid potassium carbonate. The nature of the solvent is crucial for this transformation. The highest *ee* is observed in a nonpolar solvent such as toluene, whereas in acetonitrile, ethanol, or ether, the *ee* falls between 0 and 45%.

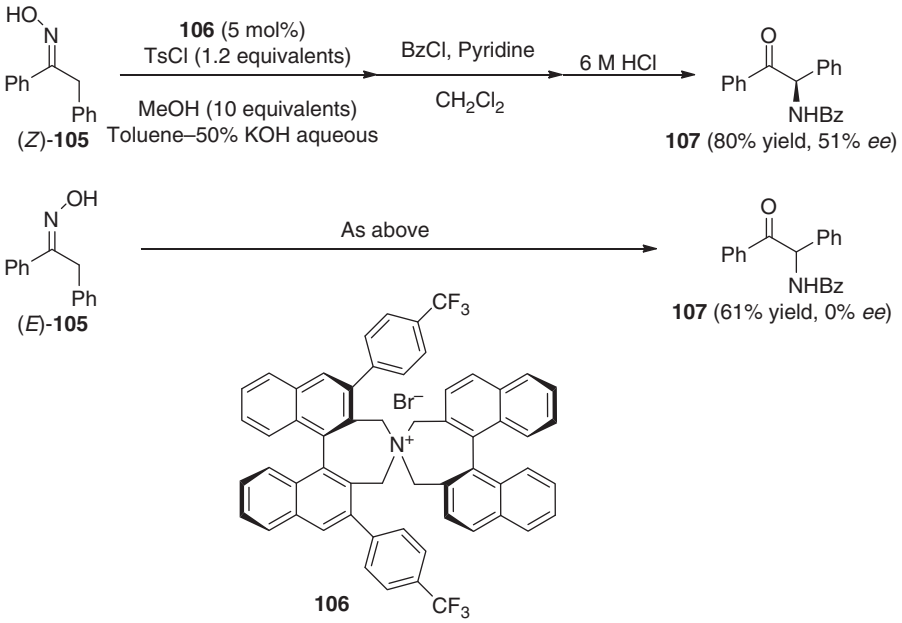
This strategy has been applied to the first synthesis of enantiomerically enriched 2*H*-azirine phosphonates and phosphinates.[91–94] For instance, the quinidine-catalyzed reaction of the mixture of (*E*)- and (*Z*)-isomers of oxime tosylate **103** gives the corresponding azirine **104** in good yield and moderate enantioselectivity (69% *ee*) (equation 23).[94] Notably, the enantioselectivity is not increased with the use of only one isomer, either *E*- or *Z*-**103**. Nevertheless, the 2*H*-azirine-2-carboxylic and the corresponding isosteric phosphonic esters such as **102** and **104**, which can be obtained using this method, are of particular interest, since nonproteinogenic amino acids and their isosteric analogs can be prepared by reduction to the corresponding aziridines followed by ring opening.[82,84]



(23)

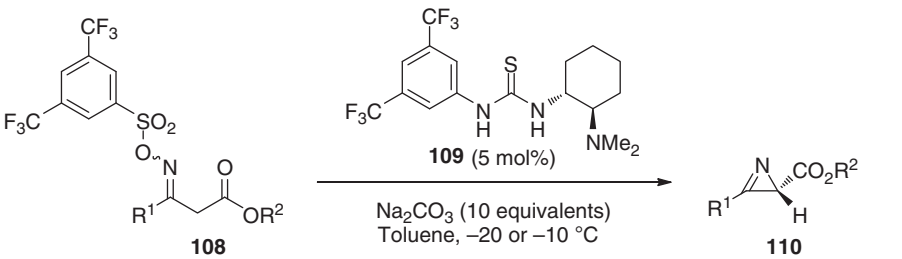
Liquid–liquid phase-transfer catalysis[95] can be used for the enantioselective Neber rearrangement of simple ketoxime tosylates (Scheme 31).[96] Taking the well-known instability of oxime sulfonates into consideration, oxime tosylate can be generated *in situ*

from the parent ketoxime **105** under the reaction conditions. Indeed, treatment of (*Z*)-**105** with *p*-toluenesulfonyl chloride in the presence of structurally rigid, C_2-symmetric quaternary ammonium bromide **106** as a catalyst (5 mol%) and methanol in toluene–50% KOH aqueous solution, and subsequent benzoylation followed by acidic hydrolysis gives the protected α-amino ketone **107** in 80% yield with 51% *ee*. Notably, the reaction with (*E*)-**105** under otherwise similar conditions affords racemic **107** in 61% yield, which suggest a nitrene pathway rather than the *syn*-displacement.[96]



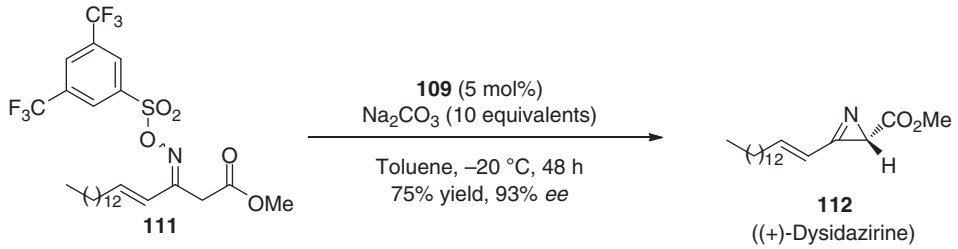
Scheme 31 Enantioselective Neber rearrangement using chiral PTC **106**.[96]

The highly enantioselective catalytic Neber reaction has been achieved using a bifunctional aminothiourea catalyst.[97] The reactions of various β-ketoxime esters **108** (as an isomeric mixture) proceed smoothly in the presence of 5 mol% of **109** and an excess amount of sodium carbonate in toluene to give their corresponding 2*H*-azirine carboxylic esters **110** in excellent chemical yield with up to 93% *ee* (Scheme 32).[97] Notably, the use of a 3,5-bis(trifluoromethyl)benzenesulfonyl group as a leaving group is effective for achieving high enantioselectivity. In addition, the resulting azirines can be successfully used in the stereoselective synthesis of di- and trisubstituted aziridines.[97] Furthermore, the synthetic utility of this asymmetric Neber reaction has been explored in the asymmetric total synthesis of (+)-dysidazarine (**112**),[88] an antipode of the natural product (equation 24).[97] The asymmetric Neber reaction of ketoxime tosylate **111** provides the desired (*S*)-azirine **112** in 75% yield with 93% *ee*.



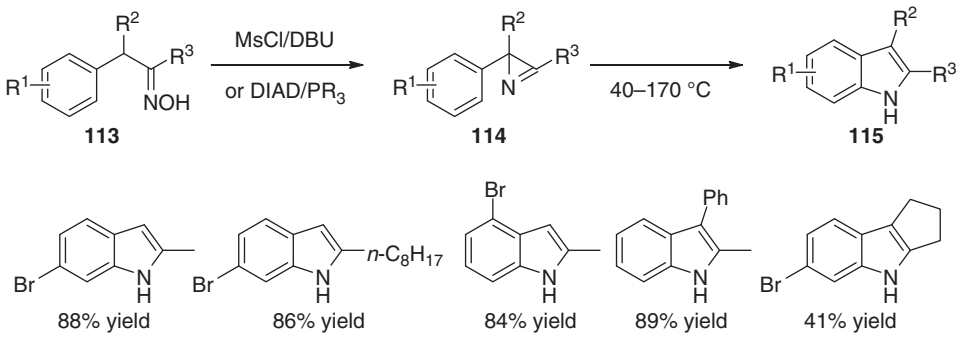
R^1	R^2	Yield (%), *ee* (%)
Me	$CHPh_2$	64, 80
Pr^n	Et	71, 86
Bn	Et	78, 93
(*E*)-PhCH=CH	Et	96, 90
Ph≡C	Et	81, 82

Scheme 32 Chiral thiourea-catalyzed enantioselective Neber reaction.[97]



(24)

The Neber reaction can also be used for the novel synthesis of substituted indoles.[98] A variety of α-aryl azirines **114**, which can be obtained by the Neber reaction of ketoximes **113** derived from α-aryl ketones, can undergo thermolytic rearrangement to give the corresponding indoles **115** in high yields (**Scheme 33**).[98] As expected, activation of the oxime with a leaving group is an invitation to a competing Beckmann rearrangement and/or Beckmann fragmentation. Thus, two complementary procedures have been developed to effect this transformation.[98] For monoaryl acyclic ketones, exposure of the oxime to MsCl and Et_3N at 20 °C followed by the addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) leads smoothly to the azirine. For the diaryl ketone and the cyclic ketone, an alternative procedure, Mitsunobu cyclization of the oxime with diisopropyl azodicarboxylate (DIAD)/Bu_3P or Ph_3P, is more satisfactory.



Scheme 33 Substituted indole synthesis using the Neber reaction.[98]

References

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6.15 Hofmann, Curtius, Schmidt, Lossen, and Related Reactions

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Glossary

1,3-Diaxial strain An unfavorable steric interaction between two substituents that have a 1,3 relationship on a cyclohexane that adopts a chair conformation. This results in a higher energy conformation than the analogous axial-equatorial and diequatorial conformers.

Antiperiplanar Consider a 4-atom molecular fragment A-B-C-D. The fragment is said to have an antiperiplanar conformation when the angle between the ABC and the BCD planes is 180°. Practically, conformations that deviate less than 30° from 180° may also be viewed as antiperiplanar.

Concerted reaction A reaction where all the bond breaking and bond forming events occur simultaneously, and therefore does not proceed via reactive intermediates.

Density Functional Theory (DFT) calculations A quantum mechanical method for molecular modelling, which uses an estimate of the electron density functional to calculate the total energy of a given system.

Domino reactions A concerted series of chemical transformations that occur in a single reaction vessel to afford products of greater complexity. Commonly, an intermediate or product from an initial reaction is consumed *in situ* by acting as a substrate for second transformation.

Kinetic isotope effect (KIE) A method used to investigate the rate determining step of a reaction. The KIE is the ratio of reaction rates in a chemical reaction of two differently isotopically labelled compounds. If the isotopic substitution is in a chemical bond whose cleavage or formation determines the rate determining step, then the reaction rate of the two isotopic species can differ greatly.

Stereospecific A reaction is described as stereospecific if the mechanism of the reaction necessitates that a stereocenter in the starting material is carried through to the product with either complete retention or inversion of stereochemistry. A stereospecific reaction must occur with 100% stereoselectivity, but a reaction with 100% stereoselectivity need not be stereospecific, merely highly stereoselective.

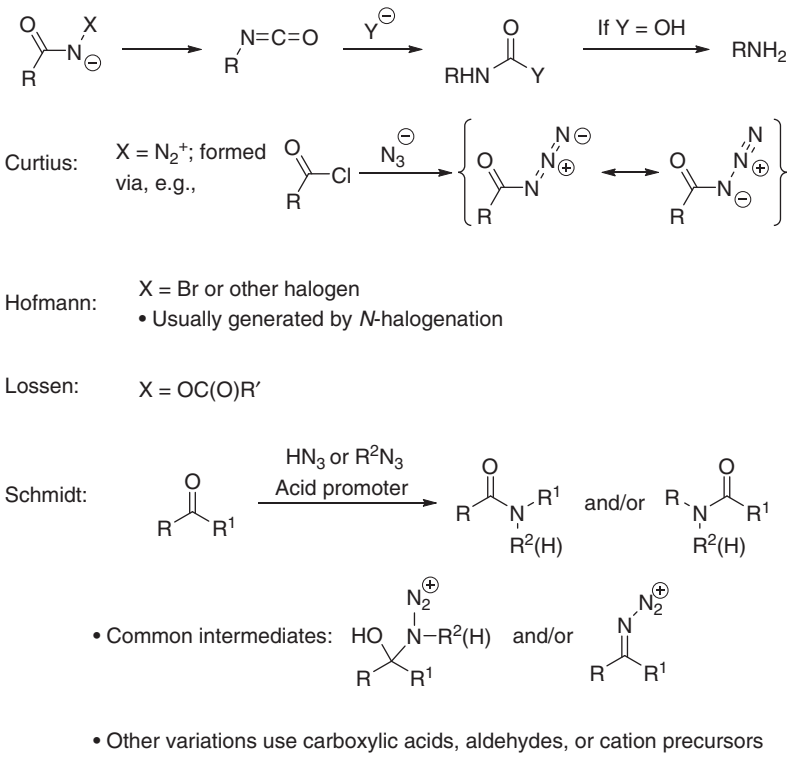
6.15.1 Overview

The title reactions of this chapter collectively convert a carbonyl-containing starting material to a nitrogenous product, either an amine or an amide, via a formal insertion process that simultaneously results in the breakage of a C–C bond. Although nitrogen is

 doi:10.1016/B978-0-08-097742-3.00623-6

introduced most commonly into an organic molecule through substitution (e.g., azide displacement of a leaving group, the Mitsunobu reaction, or the Gabriel amine synthesis) or condensation (imine forming) chemistry, insertion methods offer alternative routes to useful structures and have been continuously used since their discoveries in the late nineteenth and the early twentieth centuries. This chapter provides the reader with an update of the analogous chapter in the first edition of Comprehensive Organic Synthesis (COS), published in 1991.[1] Readers are requested to consult that chapter for much of the basic material underlying this topic and access to older reviews. The present chapter will concentrate on developments since that time.

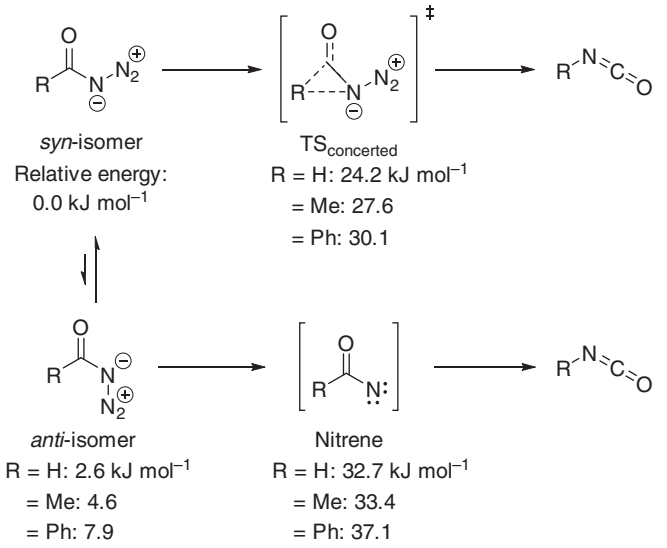
The Curtius, Hofmann, and Lossen rearrangements are mechanistically and strategically related as shown in Scheme 1. Conceptually, each begins with the generation of a reactive N–X amidate or its formal equivalent. For example, the Curtius reaction, which is both the most commonly used and the oldest member of this class, entails the synthesis of an acyl azide by displacement of an acid chloride with NaN_3 or, most commonly, by treatment of a carboxylic acid with diphenylphosphoryl azide (DPPA). Here, X is formally N_2^+, as evident in one of the two most commonly invoked resonance structures for this species. In contrast, the Hofmann and Lossen reactions each go through literal amide anions generated *in situ* by basic treatment of species, where X is a halogen or an acyloxy group, respectively. Once formed, these intermediates undergo rearrangement coupled with loss of the X^- group (N_2 in the case of the Curtius reaction) to afford an isocyanate as the primary product. These reactions are popular in part because isocyanates are versatile synthetic intermediates. Most commonly, the isocyanate is treated with acid or base to yield a carbamic acid that itself undergoes loss of carbon dioxide to afford a primary amine. As this overall sequence results in the conversion of a carboxylic acid equivalent to an amine containing one fewer carbon atoms, it is commonly referred to as a 'degradation reaction' (which was, incidentally, the title of the 1991 COS chapter[1]). This is only the tip of the iceberg insofar as isocyanates may be reacted with numerous nucleophiles to afford carbamates (Y=OR), ureas (Y=NR_2), or related compounds. Cycloaddition reactions of isocyanates are also well known.[2–4] Many of the recent developments in this field involve the simultaneous use of the Curtius or Hofmann reactions with other transformations.



Scheme 1

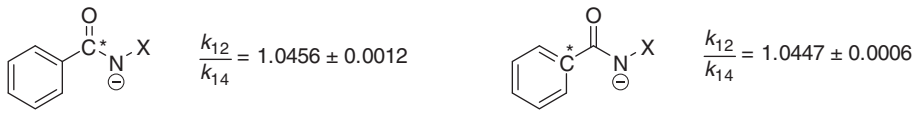
Mechanistically, the rearrangement step of these reactions is usually viewed as a concerted process rather than going through a discrete nitrene intermediate. An important pragmatic consideration is that this step essentially takes place with retention of configuration of a stereogenic migrating group R, as is the case for nearly all rearrangement reactions of this ilk (including many not covered in this chapter, like the Beckmann or Baeyer–Villiger reactions).

It is generally accepted that the Curtius, Hoffman, and Lossen rearrangements occur via a concerted mechanism, based on experimental observations as well as theory. The two-step pathway, which would involve the intermediate formation of a nitrene, was compared with the concerted reaction in the context of the Curtius rearrangement, as shown in Scheme 2.[5] The barrier for interconversion from *syn*- to *anti*-acyl azide in addition to the significantly higher barrier for nitrene formation suggests that this reaction proceeds exclusively through the concerted pathway.[6]



Scheme 2

In the 1970s, the kinetic isotope effects (KIEs) of the Hofmann reaction were measured and determined to strongly support a concerted mechanism (Scheme 3).[7] Because both migrating carbon and carbonyl-carbon KIEs were observed, they are both implicated in the rate-determining step, and as they are of almost identical magnitudes, they likely arise in the same mechanistic step. In contrast, in studies of the Schmidt reaction, only the carbonyl carbon showed a measurable KIE (1.045±0.02), suggesting some different features between it and the Curtius reaction.[7] However, DFT calculations did indicate that the migration step also occurred via a concerted but asynchronous mechanism in which the loss of N_2 slightly preceded the 1,2-shift.[8] Linear free energy relationships observed in the Lossen and Hofmann reactions were comparable, suggesting related mechanisms for the two transformations.[9]



Scheme 3

The Schmidt reaction (Scheme 1) differs from the three reactions discussed up until this point in that it usually entails the reaction of a ketone rather than a carboxylic acid derivative (see Section 6.15.5). Thus, a ketone is treated in the presence of a strong acid promoter to generate an amide or lactam product directly. In the classical Schmidt reaction, the reagent is exclusively hydrazoic acid (HN_3) and the promoter is a strong mineral acid like H_2SO_4.[10] New variations introduced in the 1990s extended the range of this reaction to include alkyl azides as the nitrogen-containing reaction partner and various acids, often including a Lewis acid promoter. The development of an alkyl azide Schmidt reaction also permitted for the first time the possibility of an intramolecular Schmidt reaction.[11] The mechanism, which will be discussed in Section 6.15.5.1, involves the initial formation of an RN_3 adduct with the carbonyl group. When HN_3 is used, dehydration affords a diazoiminium species that undergoes the migration step followed by rehydration, whereas alkyl azides undergo direct rearrangement of the RN_3 adduct to afford amide products.

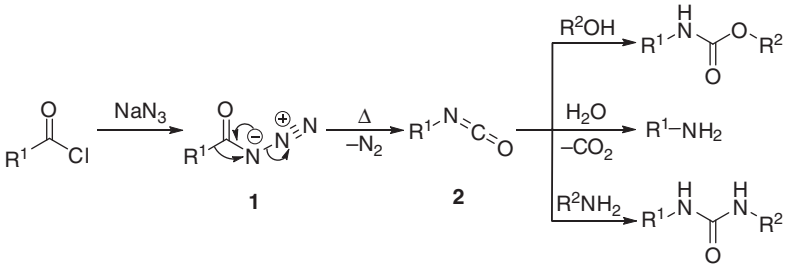
Other variations of the Schmidt reaction use aldehydes or carboxylic acids as starting materials. Aldehyde reactions are less commonly used than those of ketones because aldehydes can afford either amide insertion products (often as mixtures resulting from competing carbon or H migration) or nitriles, which arise from elimination of the diazoiminium intermediate. Carboxylic acids afford amine products through the intermediacy of acyl azide intermediates, but this process is less common due to the greater popularity of the Curtius reaction in provoking the same conversion. Schmidt reactions of carbocations derived from alcohols or alkenes are also known (Section 6.15.5.3.2).

The choice of particular nitrogen insertion reaction depends largely on the availability of the corresponding starting material and the desired synthetic outcome. The order of popularity among the reactions beginning with carboxylic acid derivatives is Curtius > Hofmann > Lossen, which reflects the ease of obtaining the respective intermediates for each process. As discussed above, the family of Schmidt reactions most commonly involve ketone ≫ aldehyde ≈ carboxylic acid starting materials, with ring-expansive conversions of a readily available cycloalkanone to a less-common lactam product being particularly popular. For these cases, the most common alternative reaction is the Beckmann reaction, which is the subject of Chapter 7.25 in the current series. The choice between the two is often subjective, although considerations like selectivity for a given migrating group also play a key role.

6.15.2 The Curtius Rearrangement

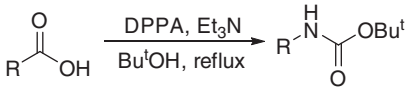
6.15.2.1 General Overview

The Curtius rearrangement involves the conversion of an acyl azide **1** to an isocyanate **2** through a concerted mechanism.[12] The acyl chloride obtained from a carboxylic acid is treated with sodium azide to generate an acyl azide intermediate, which decomposes thermally, leading to the formation of an isocyanate through rearrangement and extrusion of nitrogen gas. The isocyanate may be isolated or trapped with a variety of nucleophiles such as water, alcohols, or amines to yield amines, carbamates, or ureas, respectively (Scheme 4). The reaction sequence involving the conversion of an acid to an isocyanate, followed by its hydrolysis to afford an amine is commonly referred to as the Curtius reaction.[13]



Scheme 4

The modified Curtius rearrangement involves the direct conversion of carboxylic acids to acyl azides using diphenylphosphoryl azide (DPPA, Shioiri reagent) in the presence of base. When this reaction is carried out in refluxing *tert*-butanol, *tert*-butylurethanes are obtained in a single-pot process through *in situ* rearrangement of acyl azides into isocyanates and their trapping with the *tert*-butanol (equation 1).



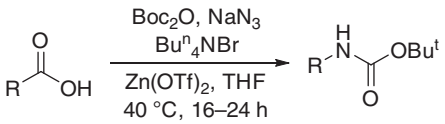
(1)

6.15.2.2 Modifications and Improvements

Acyl azides needed in the conventional Curtius rearrangement are well known to be unstable. Thus, recent method development has focused on the development of one-pot processes that allow the direct conversion of carboxylic acids into ureas or carbamates; *in situ* generation of acyl azides has been of particular interest.[14] Another general issue with the Curtius rearrangement is the requirement for high temperature for rearrangement to occur, so several modifications have been developed to achieve rearrangement at lower temperatures.

6.15.2.2.1 Novel methods for the generation of acyl azide intermediates

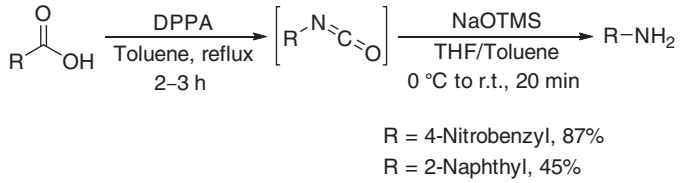
Lebel and coworkers developed a process whereby reaction of carboxylic acids with di-*tert*-butyl dicarbonate and sodium azide in the presence of tetrabutylammonium bromide and zinc(II) triflate at low temperature provided *tert*-butyl carbamates in high yield (equation 2).[14,15] The rate-limiting step for this variation is the addition of the nucleophile onto the isocyanate intermediate; this step could be accelerated by the addition of tetrabutylammonium bromide and zinc(II) triflate via the proposed zinc carbamoyl bromide. In contrast, it is not believed that the zinc catalyst plays a role in the non rate-limiting rearrangement step to form the isocyanate from the acyl azide.



(2)

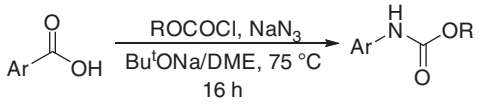
R = 1-Adamantyl, 90%
R = 3-Hexyl, 94%
R = Isobutyl, 77%

The hydrolysis of isocyanates to provide primary amines typically requires high temperatures and long reaction times. By quenching the isocyanate intermediates with sodium trimethylsilanolate (NaOTMS) at low temperature, an efficient one-pot modification allowed the direct isolation of free amines (Scheme 5).[16]

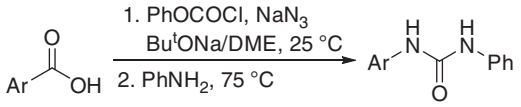


Scheme 5

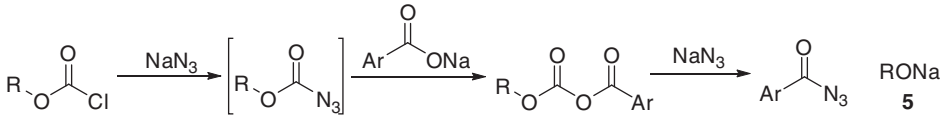
Curtius rearrangement of aromatic carboxylic acids to their corresponding carbamates and ureas was also achieved using di-*tert*-butyl dicarbonate or chloroformates and sodium azide (Scheme 6).[17,18] The chloroformate reacted with sodium azide to generate the corresponding azidoformate **3**, which then reacted with an equivalent of carboxylic acid to produce a mixed anhydride **4**. Reaction with azide anion afforded an acyl azide that underwent rearrangement under thermal conditions to produce an isocyanate, which was trapped by alkoxide by-product **5** to afford the carbamate product. Alternatively, addition of an amine to the isocyanate intermediates generated ureas.



Ar = Ph, R = Allyl, 57%
Ar = Ph, R = Bn, 64%
Ar = 4-MeOC$_6$H$_4$, R = Allyl, 45%
Ar = 4-MeOC$_6$H$_4$ R = Bn, 62%

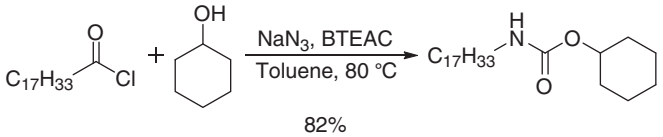


Ar = Ph, 89%
Ar = 4-O$_2$NC$_6$H$_4$, 74%
Ar = 2-IC$_6$H$_4$, 59%



Scheme 6

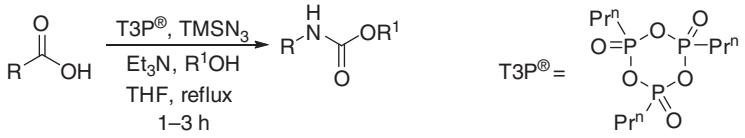
Another modest improvement involves a one-pot modification to synthesize urethanes by employing benzyltriethylammonium chloride (BTEAC) as a phase-transfer catalyst (equation 3). BTEAC facilitates the reaction of sodium azide with acyl chloride in a nonpolar solvent like toluene.[19]



(3)

Propylphosphonic anhydride (T3P®) is a reactive and relatively nontoxic anhydride used as a water scavenger and mild coupling reagent in peptide synthesis. It was used in combination with a soluble azide source, azidotrimethylsilane (TMSN$_3$), and an alcohol to directly provide carbamates from corresponding carboxylic acids in a one-pot fashion (Scheme 7).[20] The reaction is high yielding and provided a diverse set of carbamates.

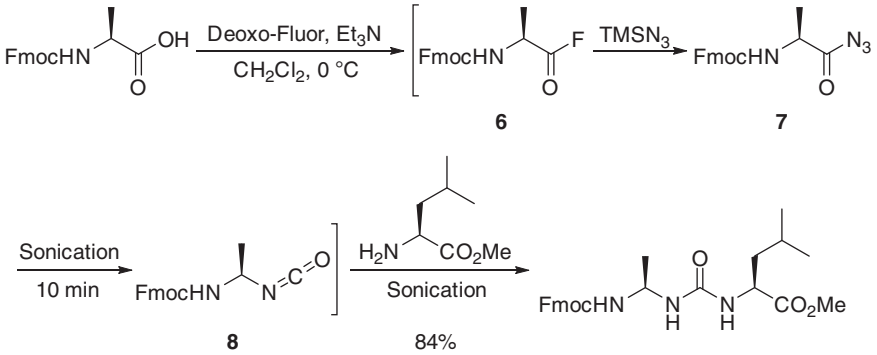
The Curtius rearrangements of Fmoc-amino acyl azides to their corresponding isocyanates both in toluene solution and as neat powders have been efficiently carried out at room temperature, using ultrasonication.[21] Further extension of this method was



R = 4-BrC_6H_4, R^1 = Bu^t; 98%
R = 2-F, 4-NCC_6H_3, R^1 = Bu^t; 96%
R = 4-$CHOC_6H_4$, R^1 = Allyl; 96%
R = 4-BrC_6H_4, R^1 = Bn; 95%

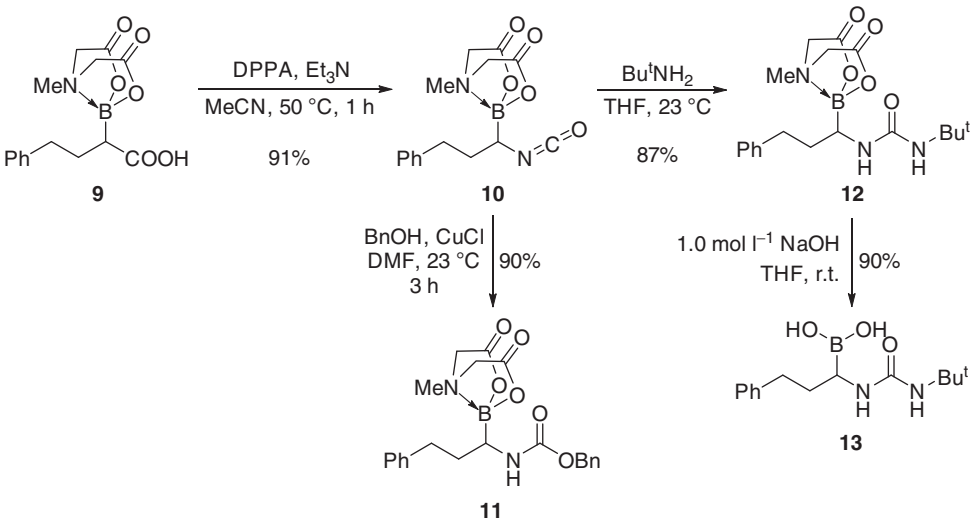
Scheme 7

utilized for the synthesis of ureido peptides and neoglycopeptides in a one-pot procedure employing Deoxo-Fluor® (bis(2-methoxyethyl)aminosulfur trifluoride) and $TMSN_3$ (Scheme 8),[22] avoiding the isolation of acyl azide and isocyanate intermediates. This process involves four independent steps: the formation of an acyl fluoride **6**, conversion into an acyl azide **7**, rearrangement into the corresponding isocyanate **8**, and eventual coupling with the amine to give the observed urea product.



Scheme 8

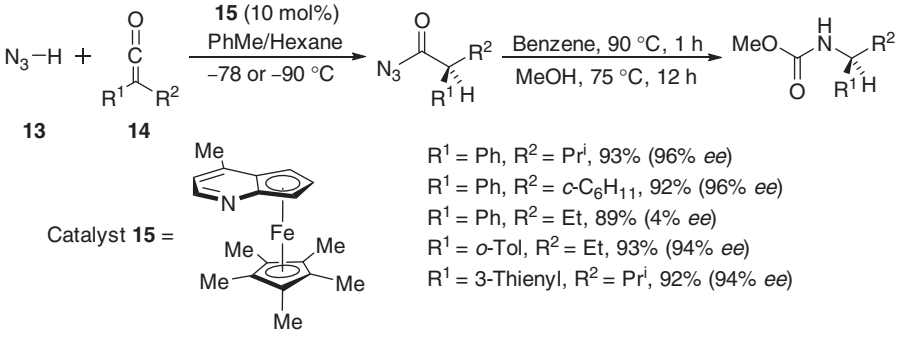
A range of stable α-boryl isocyanates like **10** were synthesized from α-borylcarboxylic acids **9** via one-pot Curtius rearrangement through migration of α-boroalkyl groups from carbon to nitrogen. In addition to carbamates **11** and ureas **12**, this method enabled the synthesis of a wide range of α-aminoboronic acids, e.g., **13** (Scheme 9).[23]



Scheme 9

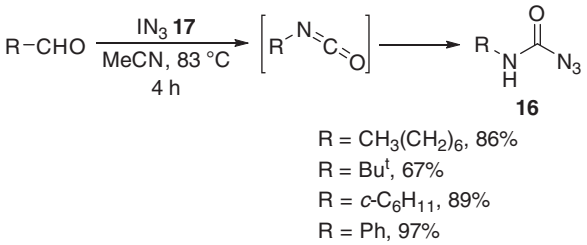
Fu and coworkers have developed an effective method for the catalytic asymmetric addition of hydrazoic acid **13** to ketenes **14** through Brønsted acid catalysis.[24] This was accomplished through fine-tuning of structure and reactivity of a planar-chiral pyridine

catalyst **15** bound to iron. The chiral acyl azides generated underwent Curtius rearrangement with stereochemical retention at the migrating stereogenic center to provide access to enantioenriched amine derivatives (Scheme 10).



Scheme 10

Radical azidonation of aldehydes in the presence of iodine azide at low temperature was reported to provide acyl azides, which underwent Curtius rearrangement on heating to provide carbamoyl azides **16** (Scheme 11).[25] Iodine azide **17** was formed *in situ* by mixing ICl (2 equivalents) and NaN_3 (3 equivalents) in MeCN; under these conditions, the reagent is relatively safe to handle (Caution: solid iodine azide is explosive). Similarly, combined iodobenzene dichloride ($PhICl_2$) and sodium azide were also used for the conversion of aliphatic or aromatic aldehydes into the corresponding carbamoyl azides.[26]

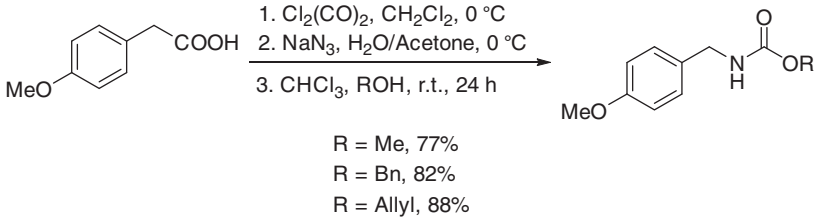


Scheme 11

The Curtius rearrangement of 5-amino-3-methyl-4-isoxazolecarboxylic acid azide was impeded when reacted with amines and hydrazides having a p*K*a of 10.2 or more to provide the expected ureides. Instead, the corresponding amides and hydrazides were obtained in these experiments.[27]

6.15.2.2.2 Novel rearrangement conditions and reactions of isocyanates

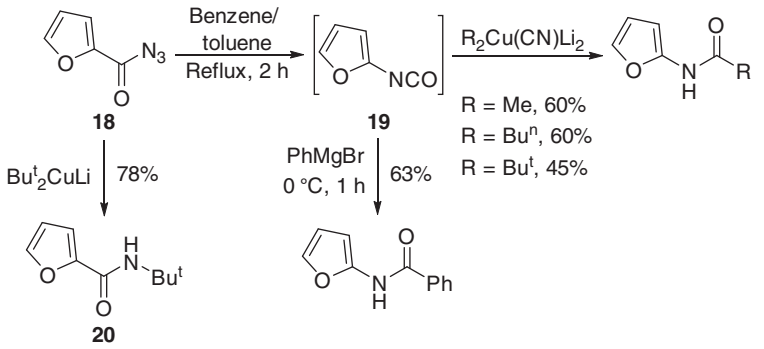
A room temperature Curtius rearrangement was developed for the conversion of benzylic and heteroarylmethyl carboxylic acids to the corresponding carbamates (equation 4).[28] This stepwise procedure involved the use of oxalyl chloride for generation of acyl azide intermediates and their treatment with alcohols in the presence of chloroform as a solvent. The use of 5 equivalents of the alcohol nucleophile was required to achieve a reasonable yield in 24 h.



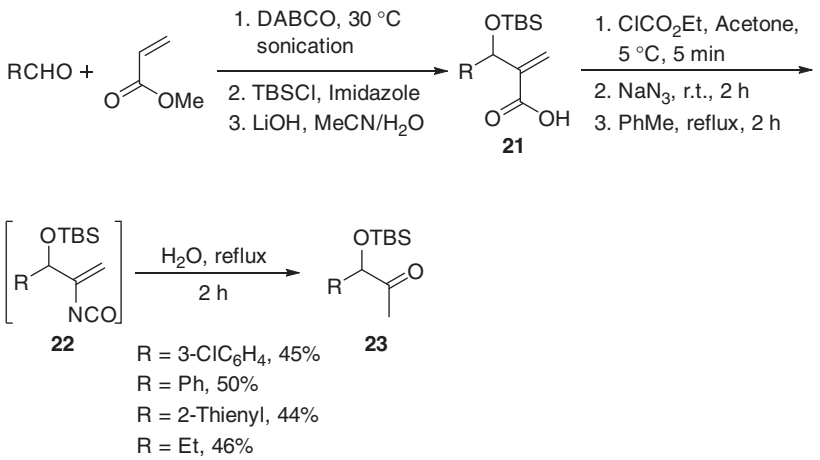
(4)

Padwa and coworkers have reported the trapping of *in situ*-generated isocyanates with organometallic reagents. Thus, furanyl isocyanate **19**, obtained from furan-2-carbonyl azide **18**, afforded a series of 2-amido-substituted furans when treated with Grignard reagents or higher order cyanocuprates (Scheme 12).[29,30] In contrast, the isomeric furanyl amide **20** was obtained on treating furan-2-carbonyl azide **18** with the *tert*-butyl Gilman reagent directly.

Curtius rearrangement of Morita–Baylis–Hillman adducts **21** resulted in the formation of ene-isocyanate intermediates **22**, which on hydrolysis produced acyloins **23** in good overall yields over three steps, rather than amines, which are typically observed on hydrolysis of isocyanates (Scheme 13).[31] Reductive amination of these acyloins gave *anti*-vicinal amino alcohols in good yields and high diastereoselectivity.

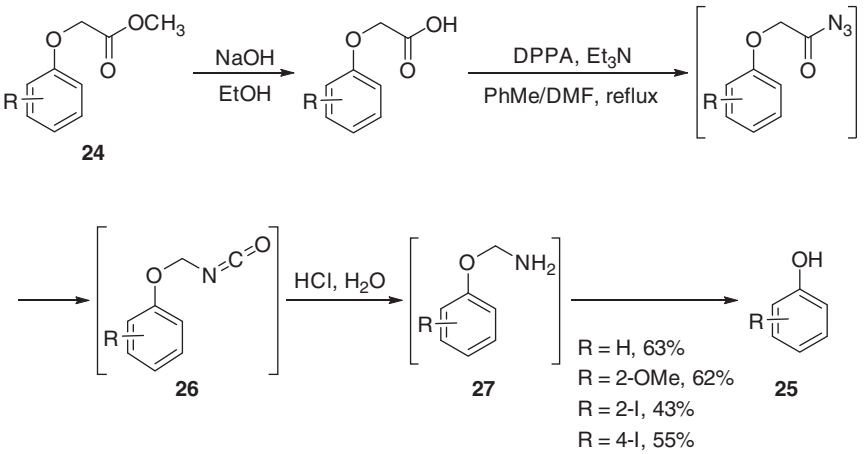


Scheme 12



Scheme 13

The Curtius reaction has found utility in contexts other than the installation of a nitrogen group. For example, deprotection of phenoxy acetates **24** to yield free phenols **25** generally requires harsh reaction conditions. A milder two-step deprotection strategy was developed for the methoxycarbonylmethyl group to yield corresponding phenols in moderate to good yields. This procedure involved ester saponification followed by Curtius rearrangement to provide isocyanates **26**. Hydrolysis and acidic work-up led to an unstable aminal intermediates **27** that suffered hydrolysis to provide the free phenols (Scheme 14).[32]

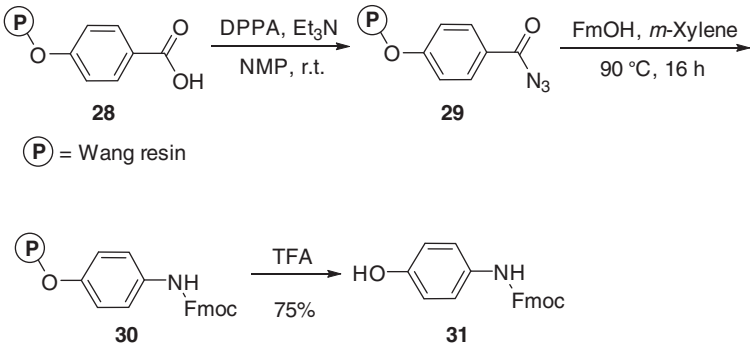


Scheme 14

6.15.2.2.3 Solid-phase synthesis and other technological advances

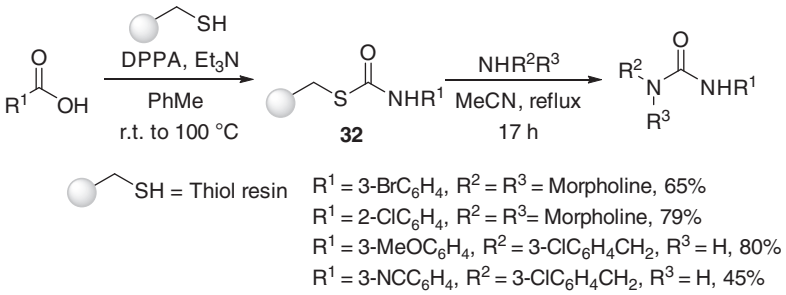
Curtius rearrangements have also been performed in the solid phase for the synthesis of quinazolinediones,[33] ureas and perhydroimidazo[1,5-a]pyrazines,[34] and amines and carbamates (Scheme 15).[35] Thus, carboxylic acids **28** were immobilized on a

polystyrene support and converted into the corresponding acyl azides **29** on treatment with DPPA and base. Subsequent Curtius rearrangement in the presence of 9-fluorenylmethanol (FmOH) afforded Fmoc-protected anilines **30**, which were cleaved from resin with 50% trifluoroacetic acid (TFA) in dichloromethane to provide crude carbamates **31** in good yields and purity.



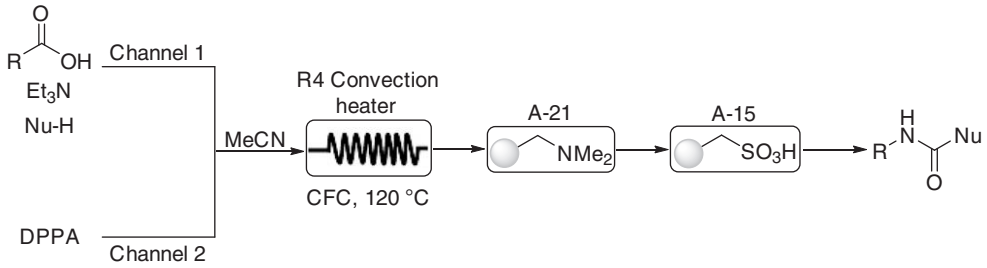
Scheme 15

Thiol resin on a silica support has been used as a 'catch and release' support for the synthesis of ureas (Scheme 16).[36] The thiol resin traps the isocyanate intermediates generated by Curtius rearrangement of carboxylic acids as silica-bound thiocarbamates **32**; these compounds are stable isocyanate equivalents. The urea products are then released from the silica-bound thiocarbamates on treatment with amines.



Scheme 16

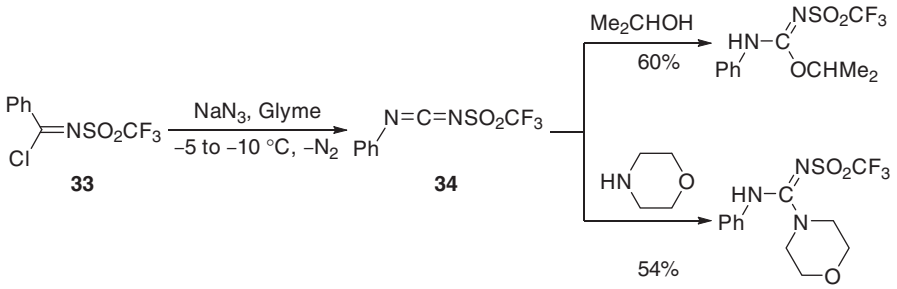
Jensen and coworkers have reported a multistep continuous-flow microchemical synthesis of carbamates from acid chlorides, using the Curtius rearrangement.[37] This technique was used for the parallel synthesis of a family of compounds by making simultaneous use of a network of microreactors and separators. Ley and coworkers have also described a technology in which azide anions were immobilized onto ion-exchange resins and used in flow reactors to facilitate Curtius rearrangement reactions.[38] A modular flow reactor system has also been developed for Curtius rearrangements (Scheme 17).[39] Here, a mixture of carboxylic acid, triethylamine, and a suitable nucleophile as a solution in acetonitrile was loaded into channel 1 and a solution of DPPA in acetonitrile was introduced into channel 2. The reactant streams from both channels were united and directed toward the convection flow coil (CFC) reactor. At room temperature, acyl azides were rapidly generated; the temperature was subsequently increased to promote rearrangement into isocyanates, which were trapped by a variety of nucleophiles in the flow reactor. Purification of the resulting flow stream over a mixed bed of solid-supported scavengers Amberlyst 21 (A-21) and Amberlyst 15 (A-15) to trap acid and base by-products as well as unreacted reagents and starting materials afforded products in good yields and high purity after solvent evaporation. An advantage of flow process chemistry is that it offers the safe handling of hazardous compounds such as azides and isocyanates, which are generated and consumed *in situ*. A microflow reaction of the Curtius rearrangement has also been utilized for the synthesis of oseltamivir.[40]



Scheme 17

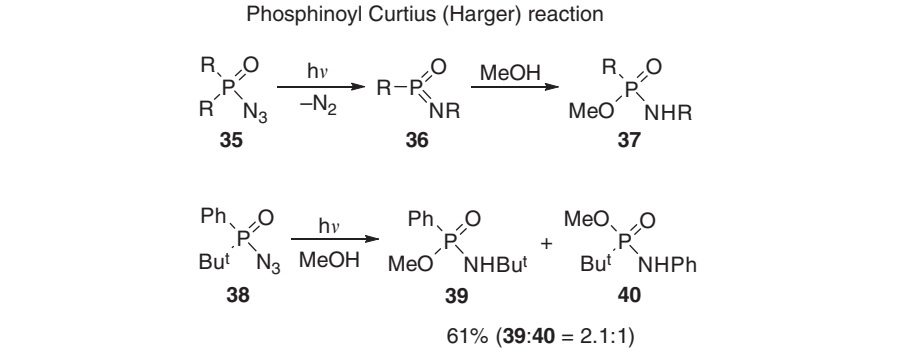
6.15.2.2.4 Miscellaneous variations

The reaction of *N*-(trifluoromethylsulfonyl)carboximidoyl chlorides **33** with NaN_3 resulted in an aza-Curtius rearrangement leading to the formation of carbodiimides **34** in good yields. Ureas, isoureas, and guanidines were synthesized from these initial carbodiimide products by reaction with water, alcohols, and secondary amines, respectively (Scheme 18).[41]



Scheme 18

On photolysis, phosphinic azides (**35**; R=alkyl or aryl) eliminate nitrogen to produce unstable metaphosphonimidate intermediates **36**, which can be trapped with methanol to afford phosphonamidates **37** (Scheme 19). The metaphosphonimidate intermediates **36** are analogous to the isocyanates formed in the Curtius rearrangement of acyl azides. This reaction is also known as the phosphinoyl Curtius (Harger) reaction.[42] The photolysis of an unsymmetrical phosphinic azide **38** resulted in two rearrangement products, both from *tert*-butyl (**39**) and phenyl group (**40**) migrations.



Scheme 19

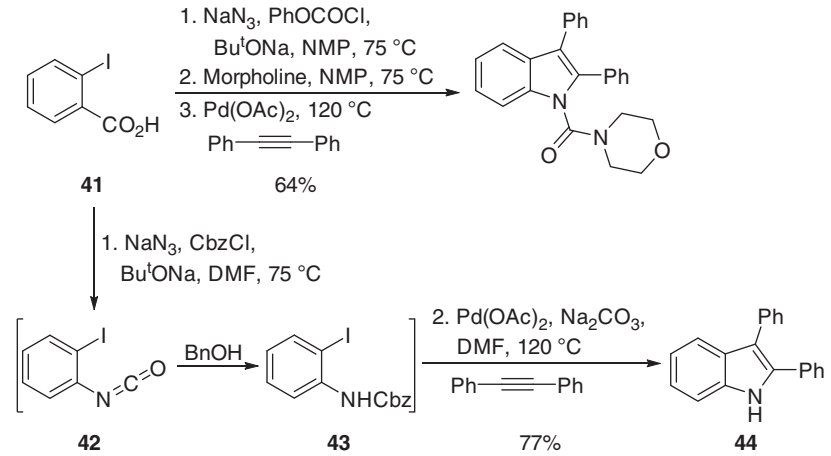
6.15.2.2.5 Multicomponent/domino reactions

Various nitrogen-containing heterocyclic ring systems such as isoquinolin-1-ones,[43] oxazolidinones,[44] pyrrolo[1,2-a]pyrazines, and pyrazino[1,2-a]indoles[45] have been synthesized via the Curtius rearrangement. However, combining other reactions with the Curtius rearrangement offers an attractive strategy for the synthesis of various target molecules, especially heterocycles. For example, a one-pot Curtius rearrangement/palladium-catalyzed indolization process for the synthesis of 2,3-substituted indoles from readily available 2-iodobenzoic acid has been reported (Scheme 20).[46] This multicomponent process has advantages over palladium-catalyzed annulation of 2-iodoanilines with internal alkynes in that it avoids the isolation of potentially unstable 2-iodoanilines in addition to minimizing chemical waste. The aromatic carboxylic acid **41** undergoes Curtius rearrangement under reaction conditions developed by this group (as described in Section 6.15.2.2.1)[17] to generate aryl isocyanate **42**, which is trapped with the *in situ*-generated benzyl alcohol/alkoxide. The resulting carboxybenzyl (Cbz)-protected aniline intermediate **43** undergoes a palladium-catalyzed indolization process to provide substituted indole **44**.

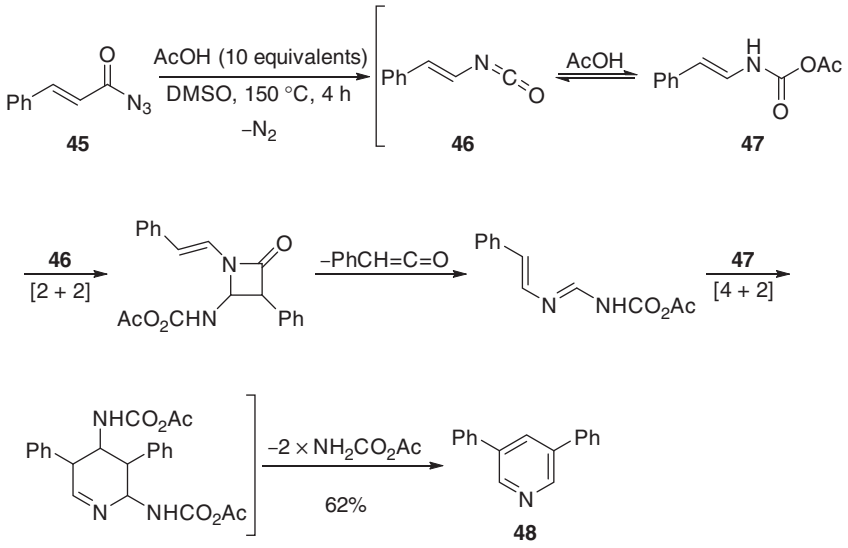
Curtius rearrangement of cinnamoyl azide **45** in refluxing *o*-dichlorobenzene formed isocyanate **46** that subsequently underwent a $Hg(OAc)_2$-catalyzed cyclization to afford isoquinolinone.[47] However, the isocyanate intermediate **46** in the presence of acetic acid at 150 °C resulted in a carbamic anhydride intermediate **47**, which underwent a series of cyclo- and retrocycloaddition steps to afford 3,5-diphenylpyridine **48** along with 2-benzyl-3,5-diphenylpyridine as a minor product (Scheme 21).[48]

A one-pot synthesis of novel photochromic oxazines was developed starting from acrylic acids (Scheme 22). Acrylic acid **49** was converted into acyl azide **50**, which underwent Curtius rearrangement to form an isocyanate intermediate **51**. Triphenylarsine oxide **52** then enabled an ensuing domino reaction sequence by first trapping the isocyanate to form the corresponding arsonium ylide **53**. A subsequent aza-Wittig reaction with 9,10-phenanthrenequinone **54** formed a quinone imine intermediate **55**, which was ultimately cyclized to form an oxazine **56**.[49]

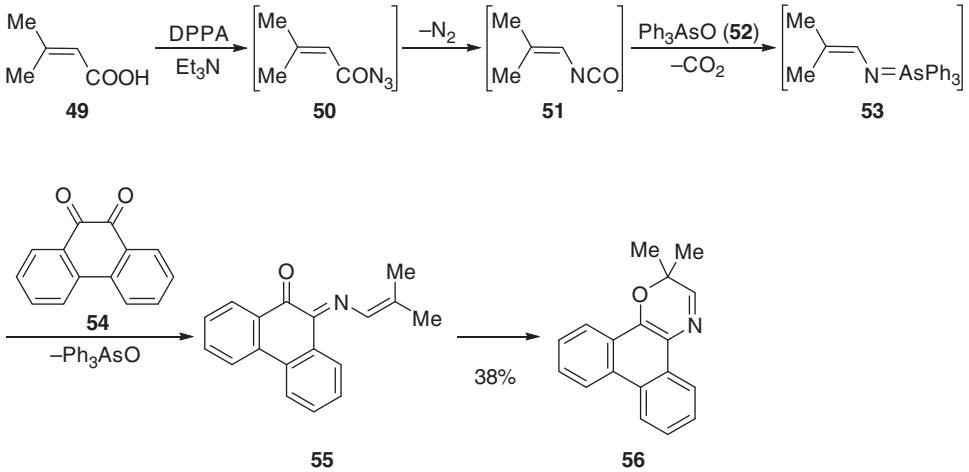
A microwave-assisted domino sequence has been utilized for the direct synthesis of 1,3-oxazine-2,4-diones (Scheme 23).[50] In this protocol, intermediate isocyanates generated from the Curtius rearrangement of acyl azides **58** underwent hetero-Diels–Alder cycloaddition with an acylketene partner generated by a Wolff rearrangement of 2-diazo-1,3-diketone **57** to produce oxazinediones **59**.



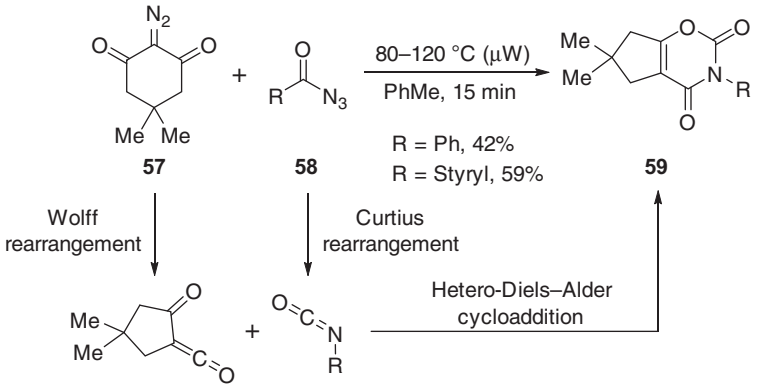
Scheme 20



Scheme 21

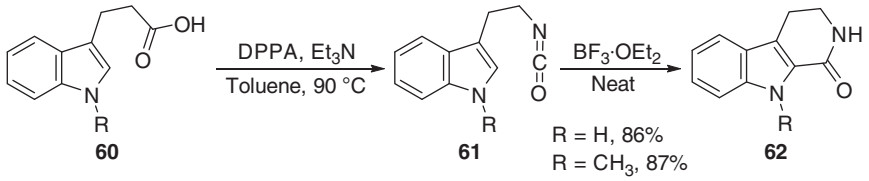


Scheme 22



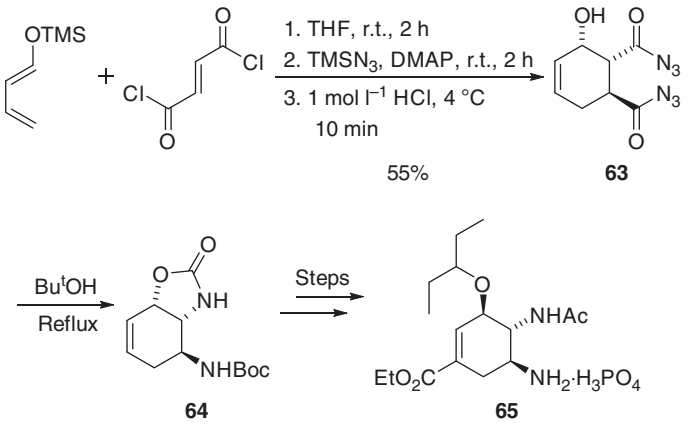
Scheme 23

Isocyanate intermediates **61** generated from the corresponding carboxylic acids **60** through Curtius rearrangement were trapped by an electron-rich tethered aromatic ring in the presence of $BF_3{\cdot}OEt_2$ to yield various lactams including tetrahydro-β-carbolin-1-ones **62** and dihydroisoquinolin-1-one in a one-pot fashion (Scheme 24).[51]



Scheme 24

The Curtius rearrangement has been applied to the total synthesis of several natural products such as streptonigrone,[52] tilivalline,[53] mycalamide B,[54] and isocryptolepine.[55] Other classes that have been made using this chemistry include dendritic poly(amide-urea)s,[56] glycopeptides,[57] and carbamate- and urea-linked glycoconjugates.[58] To cite one notable example in medicinal chemistry, a double Curtius rearrangement was applied to the synthesis of the antiviral drug oseltamivir (Tamiflu) **65** (Scheme 25).[59] In this large-scale sequence, the Diels–Alder adduct was converted into a diacyl azide **63**; heating afforded exclusively the key intermediate cyclic carbamate **64** through intramolecular trapping of the isocyanate intermediate by the adjacent allylic alcohol.



Scheme 25

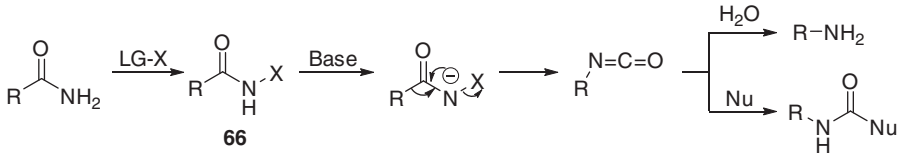
6.15.3 The Hofmann Reaction

6.15.3.1 General Overview

The Hofmann reaction, which has been known for more than 130 years, converts carboxylic primary amides to isocyanates, which are subsequently transformed into primary amines or other derivatives. Many novel reagents have been developed for the

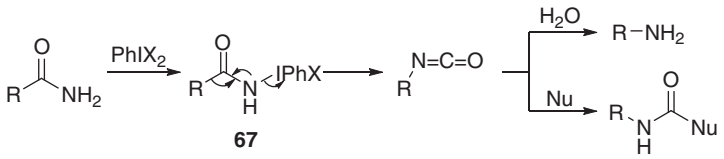
Hofmann reaction since it was last reviewed in this series. Most can be categorized into two groups: halogen reagents and hypervalent iodine species.

Halogen reagents were the first activating species to be employed in the Hofmann reaction, and the mechanism by which these reactions proceed is outlined in Scheme 26. The amide first reacts with the halogen reagent to afford *N*-halogenated amide **66**, containing an electron-deficient nitrogen atom, which is deprotonated with various bases. Rearrangement then occurs by heating to generate isocyanates, whose isolation may be possible under some reaction conditions (e.g., in aprotic solvents). More commonly, the isocyanate undergoes solvolysis in protic solvents to afford free amines or is attacked by various nucleophiles to afford a diverse range of products.



Scheme 26

Hypervalent iodine species have also been employed as activating species in the Hofmann reaction (Scheme 27). Here, the amide reacts with the periodinane to form an *N*-iodine(III) species **67**. Owing to the lability of the nitrogen–iodine bond, no base is necessary to effect rearrangement which occurs spontaneously to provide an isocyanate.



Scheme 27

6.15.3.2 Modifications and Improvements

6.15.3.2.1 Hofmann reactions with halogen reagents

Common oxidizing reagents employed in the halogen-promoted Hofmann reaction include *N*-bromosuccinimide (NBS),[60,61] trichloroisocyanuric acid (TCCA),[62] tribromoisocyanuric acid (TBCA),[63,64] 1,3-dibromo-5,5-dimethylhydantoin (DBDMH),[64] *N,N*-dibromo-*p*-toluenesulfonamide ($TsNBr_2$),[65] bromine, tetraalkylammonium tribromide,[66] alkaline hypothalite, and similar reagents (Figure 1). Primary amines are generally obtained from the initial isocyanate products when DBU or aqueous NaOH is used as the base, whereas carbamates are usually obtained in the presence of alcohols or alkoxides.

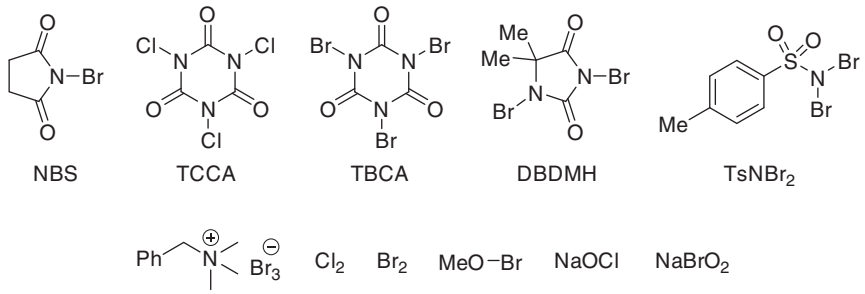
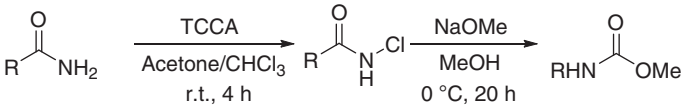


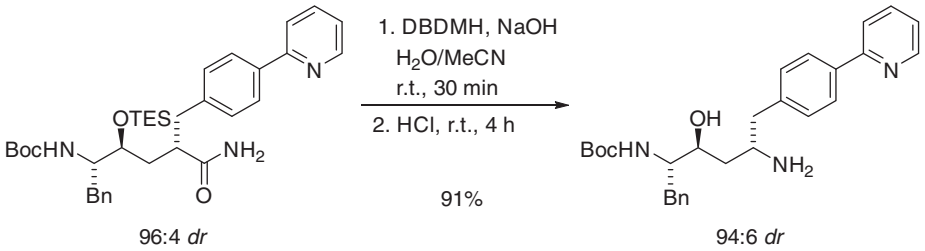
Figure 1 Halogen reagents.

Although *N*-halogenation and rearrangement are usually carried out in a single vessel with halogen-related reagents and base, a two-pot procedure is also available (Scheme 28). The first step is to prepare an isolable *N*-haloamide, typically using reagents such as chlorine, *tert*-butyl hypochlorite, calcium hypochlorite, or TCCA.[67] The rearrangement is then initiated by treating the *N*-chloroamide with sodium methoxide in methanol to afford methyl carbamates in high yield.[68]

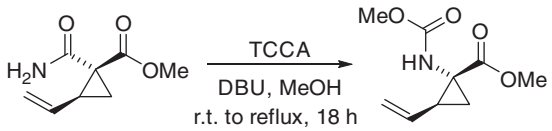
The one-pot Hofmann reaction with halogen reagents is most frequently employed using aliphatic amides. The amide must be primary, whereas the α-carbon center can be variously substituted (cf., equations 5–7).[62,64,69] As with the case with related reactions, the Hofmann rearrangement occurs with retention of stereochemistry (e.g., equations 5 and 6).



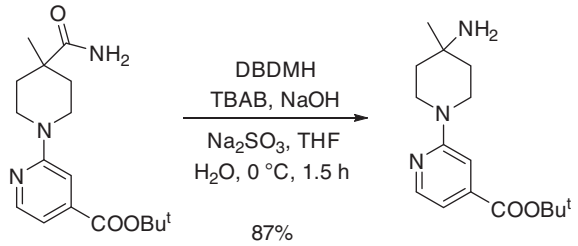
Scheme 28



(5)

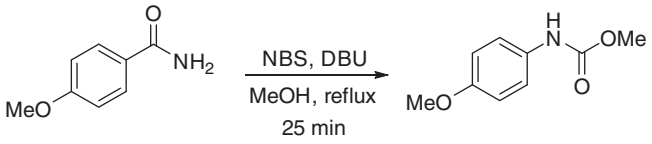


(6)

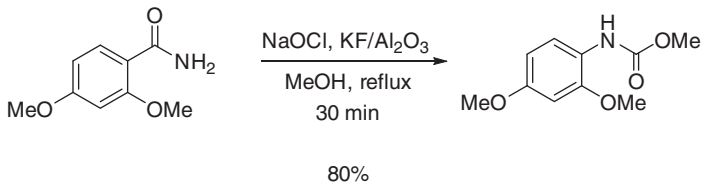


(7)

The Hofmann reaction with halogen reagents can also be extended to aromatic primary amides (equations 8 and 9).[61,70] Electron-rich aromatic amides are generally higher yielding in this reaction than their electron-deficient counterparts.



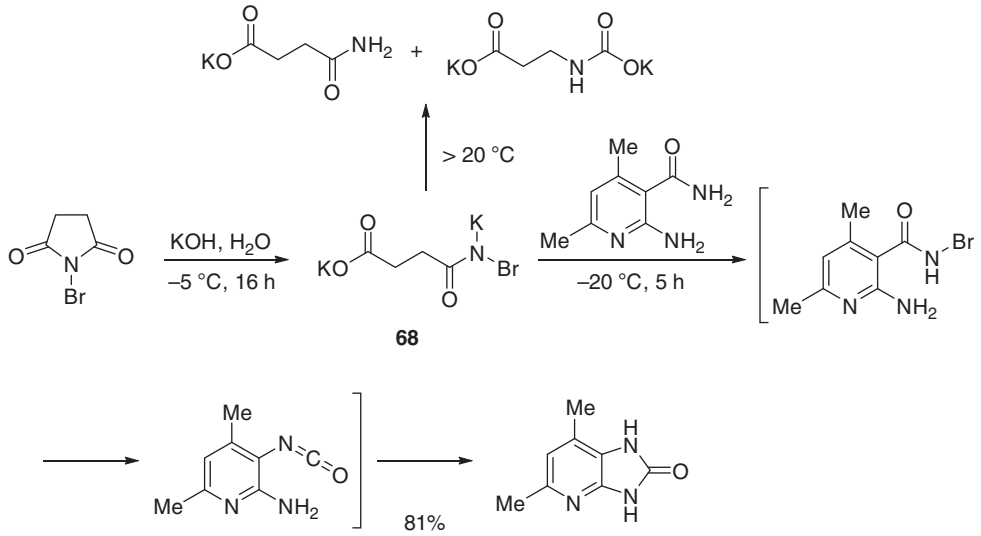
(8)



(9)

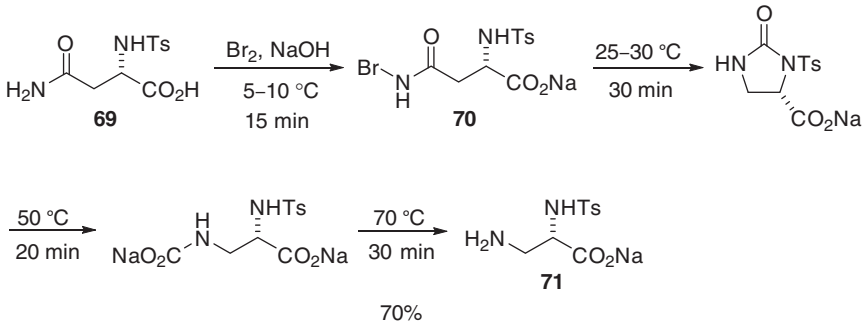
A frequently encountered problem with the Hofmann reaction is that many reactions suffer from variable yields. In an attempt to understand this phenomenon, the Hofmann reaction using NBS shown in Scheme 29 was closely studied. NBS has two modes of reactivity: in the absence of base, NBS acts primarily as a free radical-brominating agent, whereas in the presence of base, an

electropositive *N*-halogenating species is generated. Using low-temperature NMR, it was found that the actual oxidizing reagent in this rearrangement was not NBS but rather the *N*-bromosuccinic acid dipotassium salt **68** (Scheme 29).[71] At low temperatures, its formation could be cleanly achieved, affording consistent yields of the desired Hofmann products. However, when the temperature was allowed to rise more than 20 °C, incomplete reaction resulted from the decomposition of **68**.



Scheme 29

A similar study of the Hofmann rearrangement of protected asparagine **69** found that each step of the reaction was highly temperature-dependent (Scheme 30).[72] Thus, treatment of amide **69** with bromine and sodium hydroxide generated *N*-brominated amide **70**. Subsequent Hofmann rearrangement, imidazolidine hydrolysis, and decarboxylation afforded amine **71**. The key to obtaining a consistently high yield in this reaction was to maintain tight control of the reaction temperature and to ensure that all of amide **69** was consumed before initiating the rearrangement step.



Scheme 30

6.15.3.2.2 Hofmann reactions with hypervalent iodine reagents

Hypervalent iodine species have emerged as suitable oxidizing reagents for the Hofmann reaction; they are typically able to react with amide substrates without added base. The most common reagents in this class are organoiodine(III) compounds such as [bis(trifluoroacetoxy)iodo]benzene **72**,[73–75] (diacetoxyiodo)benzene **73**,[76] [hydroxyl(tosyloxy)iodo]benzene **74**,[77] (tosylimino)phenyl-λ^3-iodane **75**,[78] and iodosylbenzene **76** (Figure 2).[79] Amines are usually obtained from the initial isocyanate products on hydrolysis; however, in the presence of alcohol, carbamates can be prepared. These reagents are mild, powerful, and compatible with many functional groups; hence, they offer useful alternatives to older electrophilic halogenating agents.

Hypervalent iodine species are generally more effective at activating electron-deficient aromatic amides than traditional halogen sources. For example, treatment of *p*-nitrobenzamide with PhINTs in methanol afforded the corresponding carbamate in good yield (equation 10).[78] Under some hypervalent iodine oxidation conditions, aromatic amides have been converted to benzoquinone derivatives via further oxidation (Scheme 31).[80]

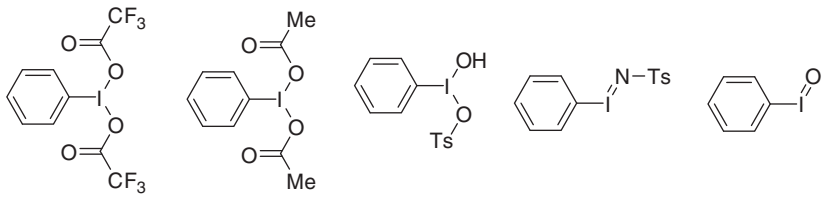
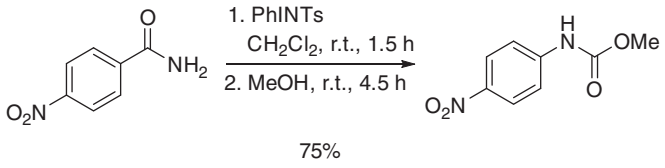
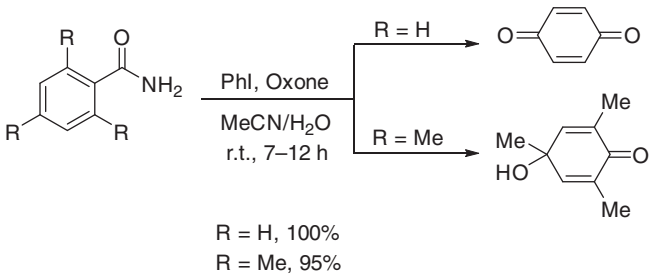


Figure 2 Hypervalent iodine reagents.

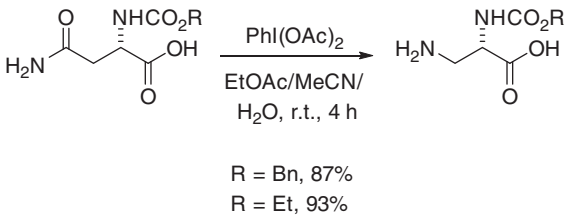


(10)

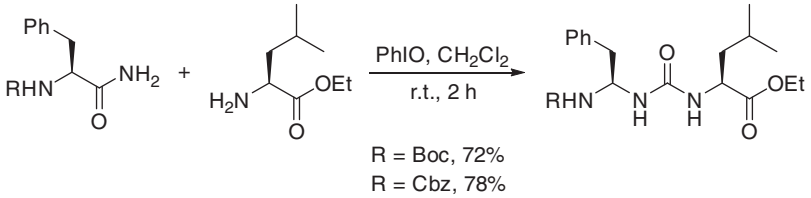


Scheme 31

Hofmann rearrangements can be performed on aliphatic primary amides using hypervalent iodine reagents. Several labile amino acid-protecting groups are stable to these conditions (equation 11).[81] When α-amino amides were employed, geminal diamine derivatives were formed under Hofmann conditions, albeit with limited stability (equation 12).[79] Note that the product formed is also an unsymmetrical urea derivative.



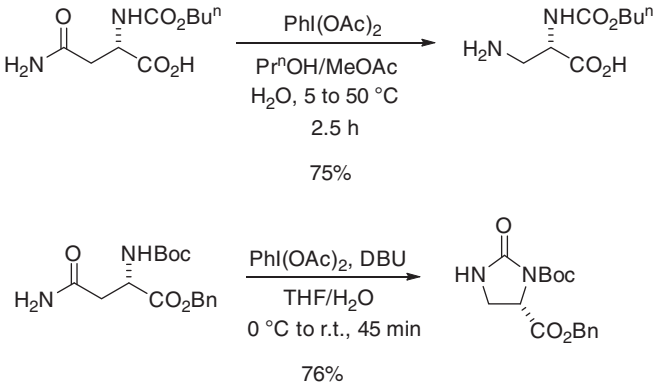
(11)



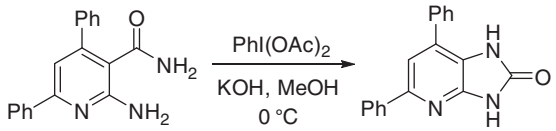
(12)

The outcome of the Hofmann reaction may depend on the reaction conditions employed. For example, the Hofmann reactions of two closely related aspartic acid derivatives with $PhI(OAc)_2$ led to the formation of either a primary amine or a urethane product under slightly different reaction conditions (Scheme 32).[82,83]

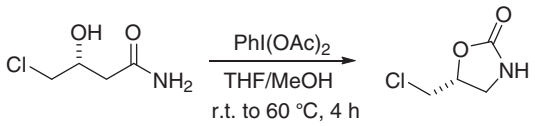
For Hofmann substrates containing an attached nucleophilic group, heterocycles can arise from intramolecular trapping of the isocyanate intermediate. Imidazolidin-2-ones (equation 13),[84] oxazolidin-2-ones (equation 14),[85] and 1,3-oxazinan-2-ones (equation 15) were synthesized using this strategy.[86]



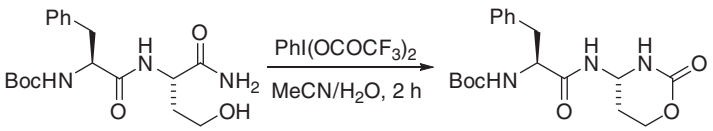
Scheme 32



(13)

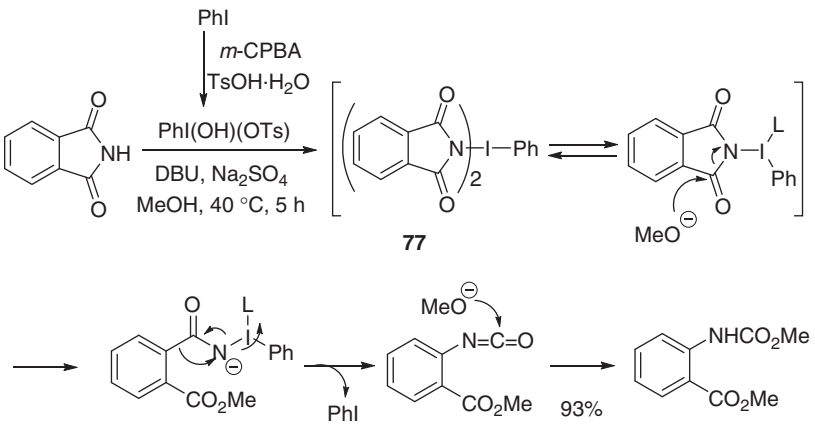


(14)



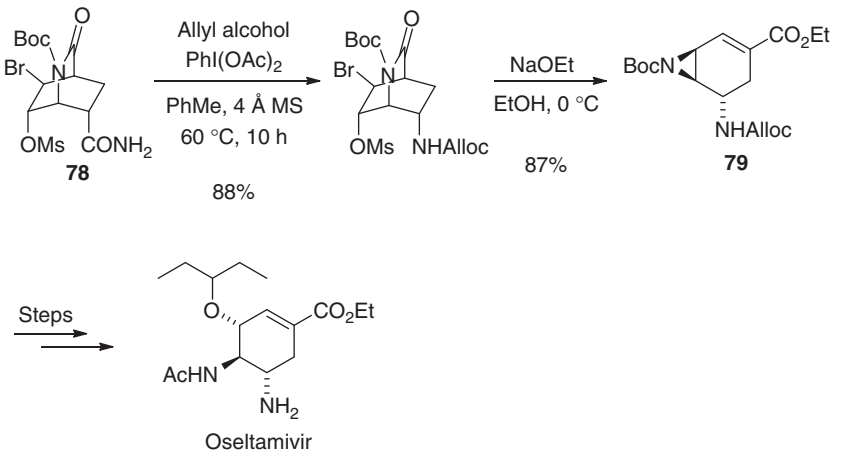
(15)

Phthalimides were also reported as substrates for the Hofmann reaction using *in situ*-generated trivalent iodines (Scheme 33).[87] Phthalimide oxidation first generated the activated species 77, which on methanolysis and rearrangement afforded a variety of anthranilic acid derivatives in high yield.



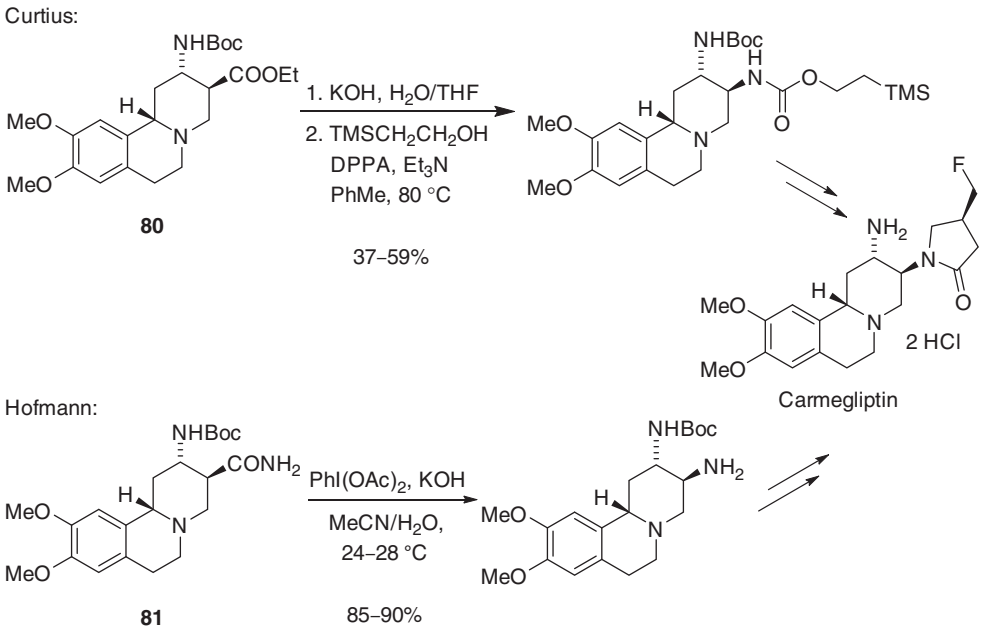
Scheme 33

An application to the preparation of oseltamivir, marketed under the trade name Tamiflu, used a Hofmann reaction of amide **78** to install a protected amine group. Subsequent basic treatment afforded advanced intermediate **79** (Scheme 34; cf., Scheme 25).[88]



Scheme 34

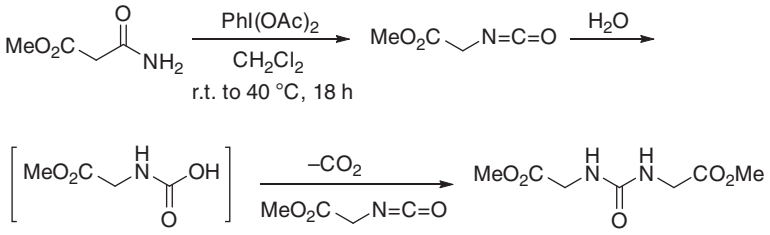
Carmegliptin, a DPP-IV inhibitor developed by Roche, is indicated to treat type 2 diabetes (Scheme 35). A Curtius rearrangement of **80** was utilized in the initial medicinal chemistry route but was quickly abandoned as a scale-up route due to safety concerns about the stability of DPPA at elevated temperatures. Instead, Hofmann reaction of the related amide **81** with phenyliodine diacetate was employed to generate the corresponding amine in high yield on a large scale.[89]



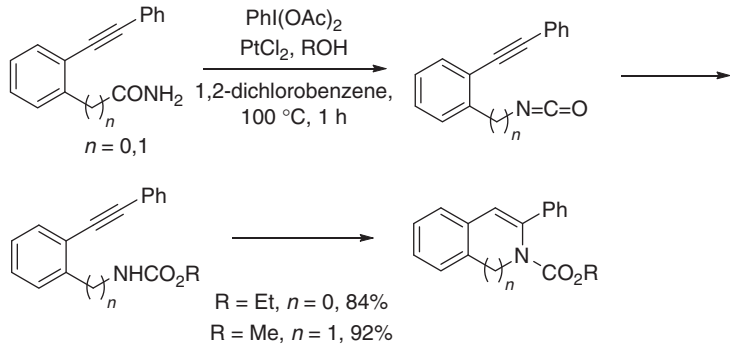
Scheme 35

For aliphatic substrates, urea formation is a common side product due to the strong nucleophilicity of amines resulting from decomposed isocyanates. Ureas can predominate under certain conditions such as the addition of 3 equivalents of water as shown in Scheme 36.[90]

The Hofmann reaction has been combined with a platinum-catalyzed cyclization to afford indoles and isoquinolines (Scheme 37).[91] The success of this strategy depended on whether the reactivity of the metal catalyst would be retained in the presence of the Hofmann reaction oxidants and products. Hypervalent iodine species were able to achieve the rearrangement without deactivating the catalyst.



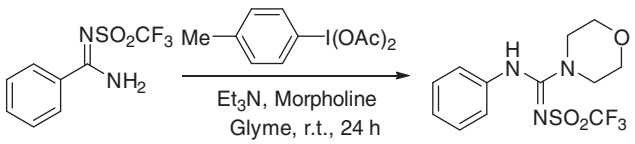
Scheme 36



Scheme 37

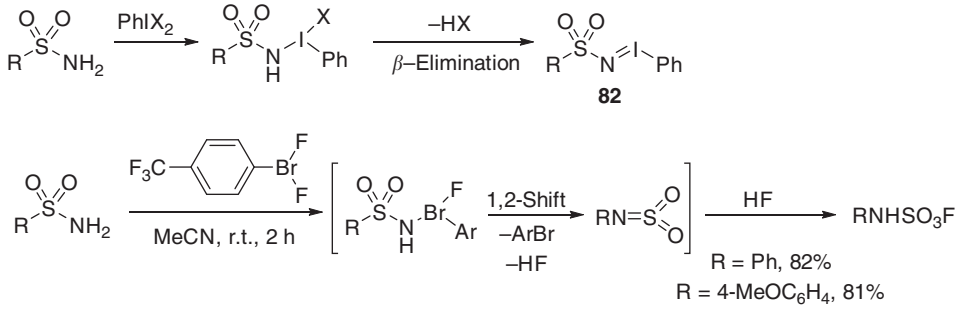
6.15.3.2.3 Miscellaneous Hofmann-related reactions

An aza-Hofmann rearrangement has been reported that allows the formation of substituted guanidines. The reaction of an amidine with a hypervalent iodine reagent affords an initial carbodiimide, which then reacts with an amine to generate the observed guanidine product (equation 16).[92]



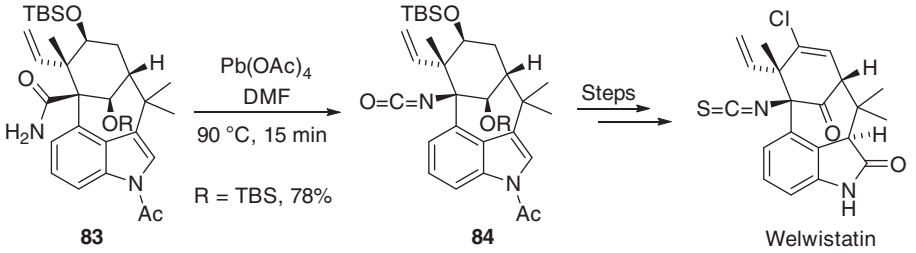
(16)

An analogous version of the Hofmann rearrangement has been reported with sulfonamides.[93] The greater acidity of sulfonamides relative to amides has made this variant more difficult to develop due to competing β-elimination. When traditional hypervalent iodine reagents were used, β-elimination occurred to yield imino-λ^3-iodane **82**. However, by increasing the nucleofugality of the hypervalent iodine-leaving group, the tendency toward 1,2-migration was enhanced. Indeed, an aryl-λ^3-bromane promoted this rearrangement in good yield, with no β-elimination product isolated (**Scheme 38**).



Scheme 38

Lead tetraacetate can also be used to promote Hofmann reactions and was employed in a total synthesis of the structurally complex indole alkaloid welwistatin. Treatment of advanced amide intermediate **83** with lead tetraacetate generated isocyanate **84** (Scheme 39). Conversion to the analogous isothiocyanate and further functional group manipulation provided the natural product.[94]

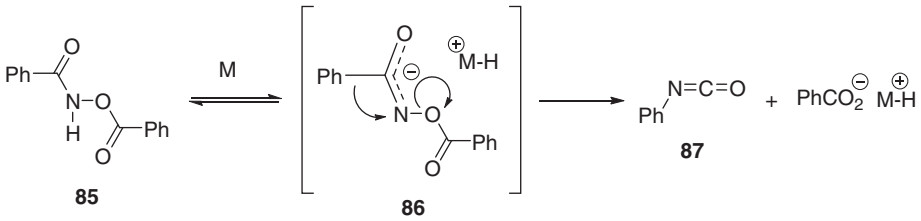


Scheme 39

6.15.4 The Lossen Reaction

6.15.4.1 General Overview

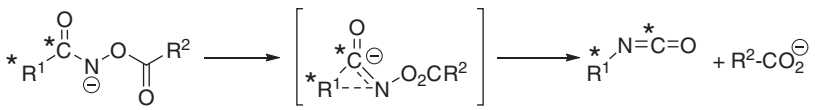
The Lossen reaction is driven by the expulsion of a carboxylate group from a bis-acylated hydroxylamine. Compared with the Curtius rearrangement, the Lossen reaction has the advantage of avoiding azide-containing intermediates. This reaction dates to 1872, when Lossen discovered the formation of phenyl isocyanate during the pyrolysis of the mixed anhydride **85**.[95,96] This classic example of the reaction expels benzoic acid and phenyl isocyanate **87**, a lachrymator, the properties of which facilitated identification (Scheme 40).[97]



Scheme 40

The Lossen reaction has been developed extensively under basic conditions that promote the formation of anionic intermediates such as **86**.[1] However, these themselves constrain the reaction to a limited set of harsh conditions, which is a major drawback to its use in practical synthesis. Another limitation is the unavailability of a wide range of hydroxamic acids, which are less common than the corresponding acids or acid chlorides and may require additional synthetic steps. A third problem traditionally associated with the rearrangement is the undesired dimerization of any starting hydroxamic acids with the highly reactive isocyanate formed.[98]

Like other members of this class, the Lossen reaction has been established as a thermal, ionic, concerted decomposition process. In this case, the substrate is defined as a hydroxamic acid or derivative thereof.[97] The formation of a univalent, six-electron nitrogen center had been proposed in the years after the reaction was discovered,[99,100] but all attempts to capture a nitrene intermediate have failed.[96] A concerted mechanism based on the stereospecific nature[6] of the reaction replaced the nitrene theory in the early twentieth century. More rigorous evidence from kinetic studies using labeled carbons further supported the mechanism outlined in Scheme 41.[7,9,101]

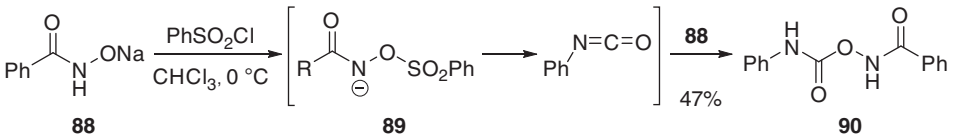


Scheme 41

Mass spectrometry experiments have agreed with an ionic mechanism, at least in the gas phase.[102] Moreover, the alkali metal salt crystal structure of a metal-complexed, deprotonated *N*-acylhydroxamate was solved in 1998, which underwent the Lossen reaction under mild conditions.[103] Also of note is that the reaction rate is directly proportional to the ionization constant of the acidic leaving group, which also agrees with an ionic mechanism.[104]

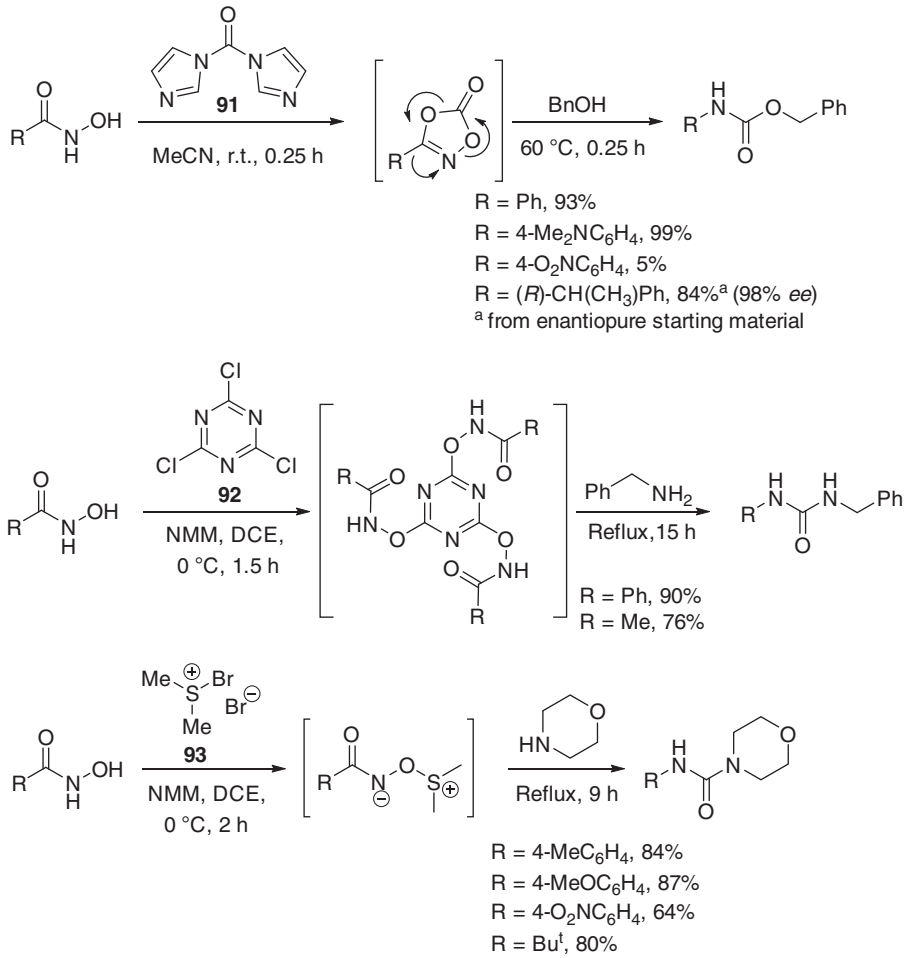
6.15.4.2 Modifications and Improvements

Early activating agents for free hydroxamic acids were plagued by a self-dimerization side reaction (Scheme 42). Unreacted **88** was found to condense with isocyanates formed at low temperatures via the Lossen reaction of **89**, forming the carbamoyloxyamide derivative **90**.[98] This was attributed to incomplete conversion of the hydroxamic acid to its activated species before the 1,2-shift was initiated (cf., discussion of the Hoffman reaction associated with Schemes 29 and 30).



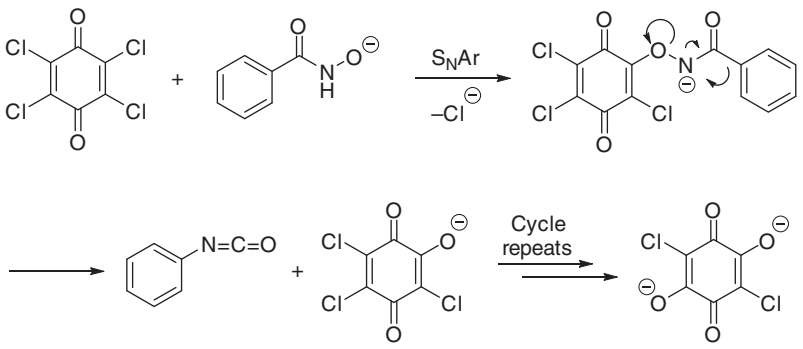
Scheme 42

Several superior promoters for the Lossen reaction have been described (Scheme 43). These reagents allow the more efficient use of free hydroxamic acids without prior acylation, and by providing a facile and complete activation of the hydroxamic acid, they eliminate the propensity for self-dimerization.[105] All three reagents – carbonyldiimidazole[106] (**91**), cyanuric chloride[107] (**92**), and bromodimethylsulfonium bromide[108] (**93**) – can be used in a 'one-pot' sequence for further synthetic convenience.



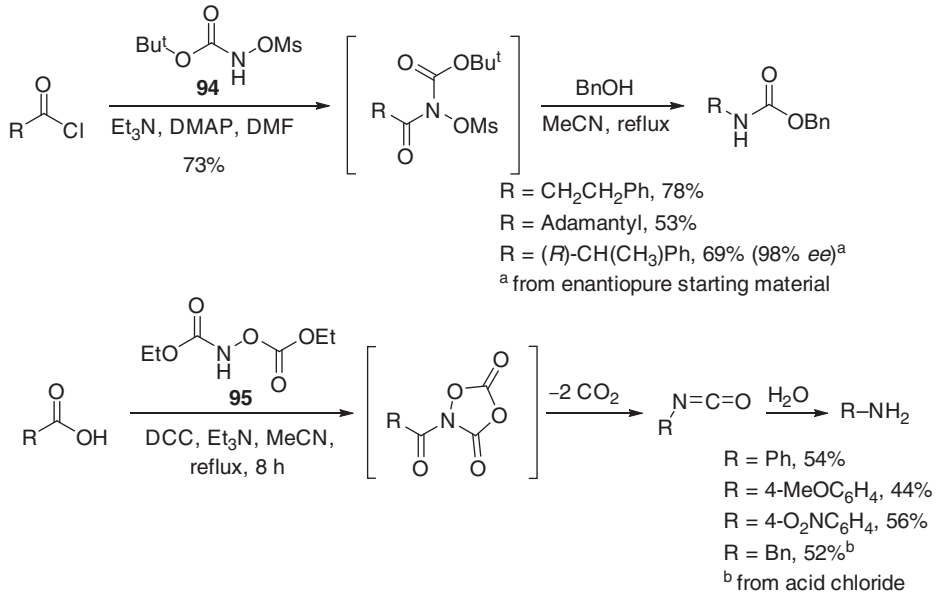
Scheme 43

Lossen chemistry has been employed to detoxify polyhalogenated quinoid species found as environmental pollutants or the toxic by-products of drug metabolism (Scheme 44).[109] Two cycles of Lossen reaction on the halogenated quinoid toxins afforded oxidized congeners, which could be readily dissolved in water for removal.



Scheme 44

To address the availability of hydroxylamine-starting materials, several 'reagent-based' modifications have been developed (Scheme 45). For example, either *N*-(*tert*-butyloxycarbonyl)-*O*-methanesulfonyl-hydroxamic acid[110] (**94**) or *N*,*O*-bis-(ethoxycarbonyl)hydroxylamine[105] (**95**) has been used to generate activated hydroxamic acid species directly from the acid chloride or carboxylic acid, respectively.

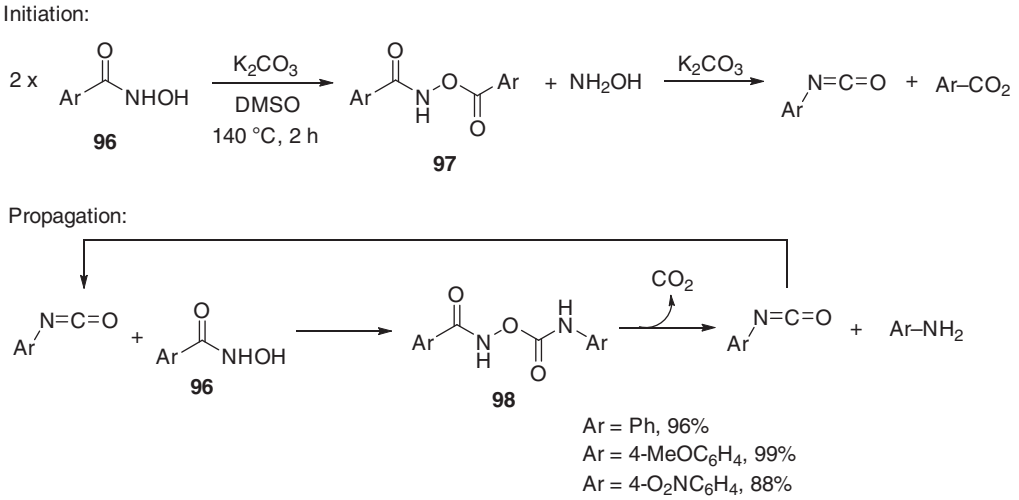


Scheme 45

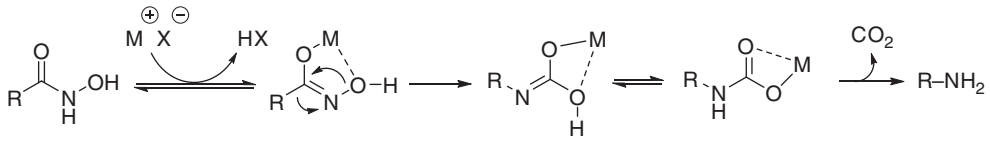
Unacylated aryl hydroxamic acids such as **96** have also been found to efficiently undergo Lossen reaction when heated with basic metal salts as catalysts. A mechanism was proposed whereby an acylated Lossen substrate **97** was formed in base followed by rearrangement. The resulting isocyanate was then trapped by **96** to form dimer **98**, which expelled CO_2 to furnish the aryl amine and regenerate the isocyanate (Scheme 46).[111] This isocyanate could then acylate the starting hydroxamic acid, again forming **98** and thus propagating this reaction.

An alternative mechanism has been proposed on the basis of DFT calculations and spectroscopy.[112] These workers suggested that the direct decomposition of the metal-complexed hydroxamic acid could furnish the amine via the rearrangement of the metallated hydroxamic acid as shown in Scheme 47. They obtained some support for this mechanism by demonstrating the formation of aryl amines via heating the preformed potassium hydroxamate salt in water (albeit in lower yields), precluding the isocyanate cycle in Scheme 46.

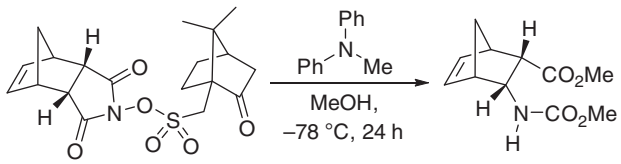
The Lossen reaction of *N*-hydroxyimides has also been reported,[96] including the modestly enantioselective variant shown in equation 17. This sole example of a chiral Lossen reaction has been demonstrated on *N*-acylhydroxyimide **99**.[113]



Scheme 46

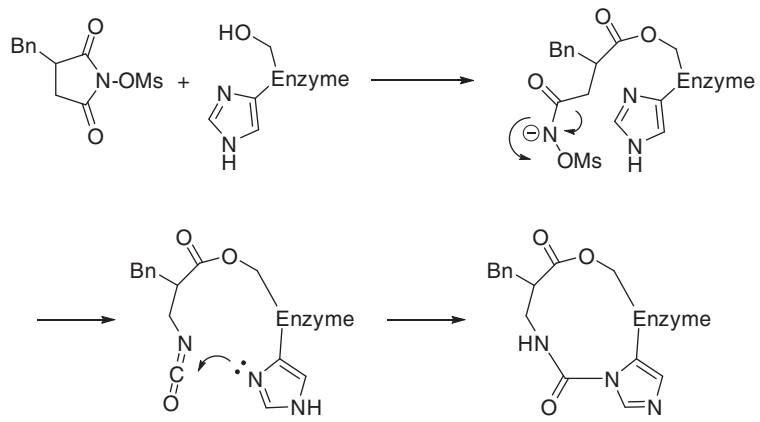


Scheme 47



(17)

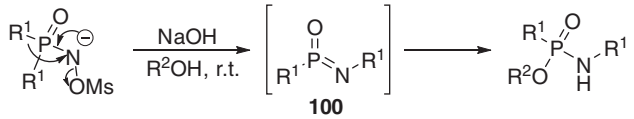
This variant of the Lossen reaction was implicated in the mechanism of action for a series of serine protease inhibitors (Scheme 48). *N*-mesyloxysuccinimide compounds were shown to be activated by *α*-chymotrypsin to inhibit the enzyme covalently.[114] Similarly, a crystal structure of a serine protease clearly indicated *in situ* trapping of an isocyanate formed by a Lossen reaction occurring in the active site.[115]



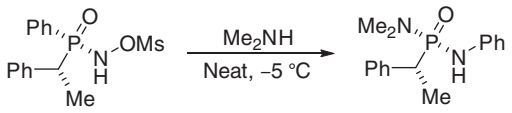
Scheme 48

Finally, the Lossen reaction has been extended to systems beyond carbonyl centers. It was discovered in 1983 that *N*-phosphinoylhydroxylamines undergo analogous reaction under thermal conditions (Scheme 49).[116] Species **100** was proposed in

analogy to the isocyanate **87** but was not isolable. Subsequent studies confirmed that benzyl groups could also migrate,[117] expanding the scope beyond aryl groups, and also showed this transformation to be stereospecific.[118]



R^1 = Ph, R^2 = Me, 96%
R^1 = Bn, R^2 = Me, 25%
R^1 = Bn, R^2 = Pr^i, 70%
R^1 = Bn, R^2 = Bu^t, 80%

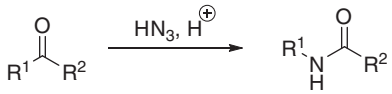


Scheme 49

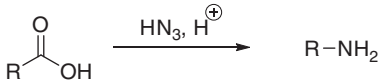
6.15.5 The Schmidt Reaction

6.15.5.1 General Overview

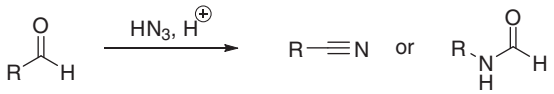
The Schmidt reaction has traditionally described the addition of hydrazoic acid to electrophiles (ketones, aldehydes, carboxylic acids, and carbocations), resulting in the incorporation of nitrogen into the product (equations 18–20). Of these variants, the reactions of ketones are most commonly used in synthetic applications. This chapter shall focus on significant changes and improvements to the Schmidt reaction since the previous edition of this series. The interested reader is directed to a number of reviews for a more extensive survey of the recent literature.[10,11]



(18)

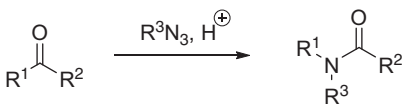


(19)

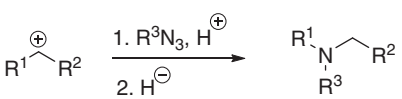


(20)

The Schmidt reaction has also been extended to include the reactions of alkyl azides with ketones (equation 21) and carbocations (equation 22) to afford amides and amines (after reduction), respectively.

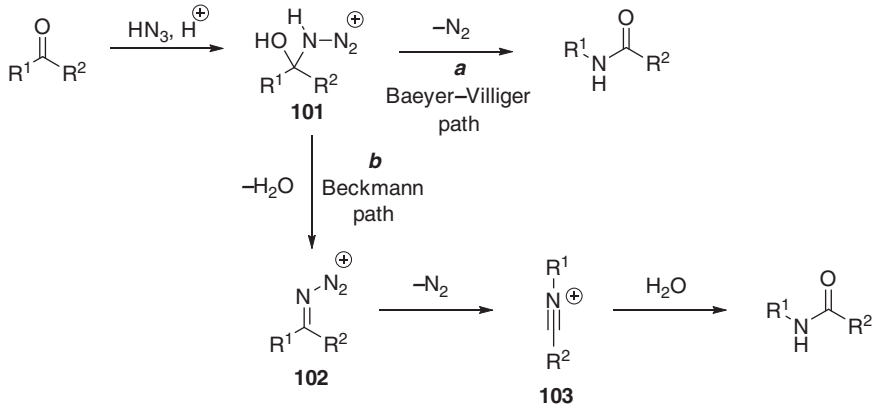


(21)



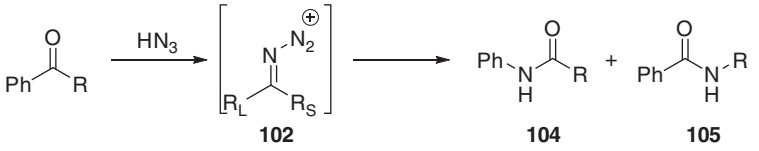
(22)

During the early investigations into the Schmidt reaction of ketones with hydrazoic acid, two competing mechanisms were proposed. Both mechanisms proceed by the initial addition of hydrazoic acid to a ketone to provide protonated azidohydrin **101** under the acidic reaction conditions (Scheme 50). In path ***a***, collapse of the tetrahedral intermediate with concurrent migration of R^1 and subsequent loss of nitrogen leads directly to the amide product, in a manner similar to the Baeyer–Villiger reaction. Alternatively, path ***b*** requires dehydration of **101** to provide diazoiminium **102**, which can undergo rearrangement to nitrilium ion **103** followed by hydration to afford the amide product, in a mechanism analogous to that of the Beckmann rearrangement.



Scheme 50

The Beckmann mechanism is now generally accepted, in part due to the observed formation of tetrazoles when higher concentrations of hydrazoic acid are used (from reaction of iminium ion **103** with a second equivalent of hydrazoic acid). Additionally, the propensity of an alkyl group to migrate increases with increasing steric bulk (Scheme 51). This can be explained by diazoiminium ion **102** adopting the least sterically demanding configuration where the diazo moiety is *trans* to the bulkier R group, followed by antiperiplanar migration.[119] Furthermore, detailed mechanistic investigations have shown that diazoiminium species **102** can serve as reactive intermediates in Schmidt reactions.[120]



R	Ratio **104** : **105**
Me	95 : 5
Et	85 : 15
Pr^i	51 : 49
Bu^t	0 : 100

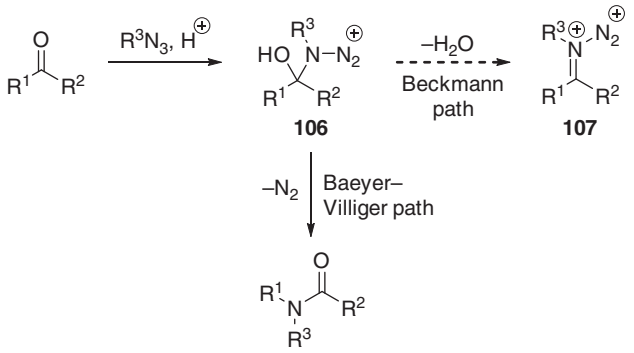
Scheme 51

When alkyl azides are employed, the Beckmann pathway is effectively eliminated due to the prohibitively high energy of the required diazoiminium dication **107** resulting from elimination of water from azidohydrin **106** (Scheme 52). The reaction is, therefore, thought to proceed through the Baeyer–Villiger pathway.

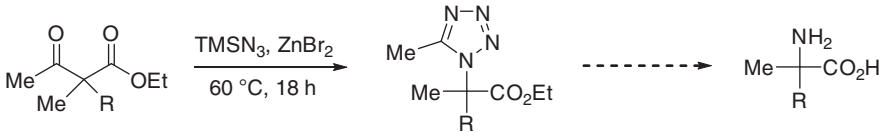
Schmidt reactions with alkyl azides generally require the use of at least 2 equivalents of protic or Lewis acid. This is likely due to the lactam product being more basic than the starting ketone, sequestering an equivalent of acid.

6.15.5.2 Schmidt Reactions with Hydrazoic Acid

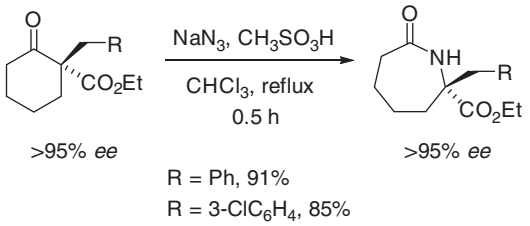
Many of the Schmidt reactions with hydrazoic acid were reported in the early to mid-twentieth century and were reviewed in the earlier edition of this book. However, a few improvements to the scope of this reaction have since been reported. Two of these involve the use of the starting material in constructing nonproteinogenic amino acids. In one, β-ketoesters undergo Schmidt rearrangement with 2 equivalents of trimethylsilyl azide to provide substituted tetrazoles as precursors to α-dialkylated amino acids (Scheme 53).[121] Chiral azepane-2-carboxylic acids can be prepared from enantioenriched cyclic β-keto esters and hydrazoic acid (equation 23).[122] No loss of enantiopurity was observed during the ring expansion step.



Scheme 52

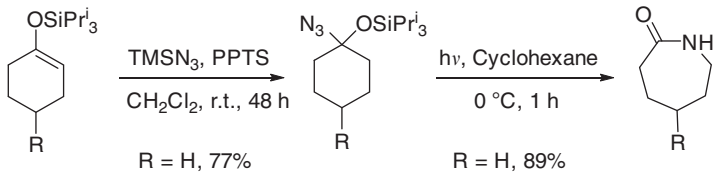


Scheme 53



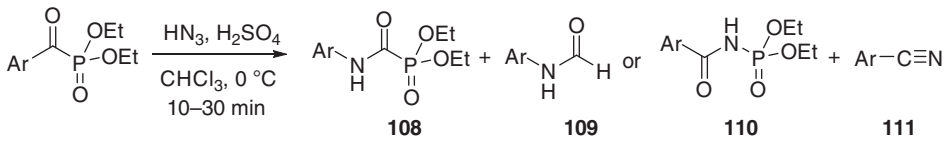
(23)

A disadvantage of the classical Schmidt reaction is that the use of strong protic or Lewis acids limits the substrates to acid-stable compounds. One alternative procedure employs α-azido triisopropylsilyl ethers which, on exposure to UV light, undergo a photoinduced Schmidt reaction to afford lactams (**Scheme 54**).[123] Although this method provides lactams under milder conditions, the lack of regioselectivity in the ring expansion limits its use to symmetrical Schmidt precursors.



Scheme 54

Dialkyl acylphosphonates have been shown to undergo the Schmidt reaction to afford a variety of products (equation 24).[124] The outcome of the reaction is dependent on the electronics of the benzoyl substituent, with electron-withdrawing groups favoring migration of the aryl group (**108** and **109**) and strongly electron-donating groups favoring phosphonate group migration (**110** and **111**).



Ar = 4-ClC$_6$H$_4$, 19% **108** + 65% **109**
Ar = 4-MeOC$_6$H$_4$, 30% **110** + 62% **111**

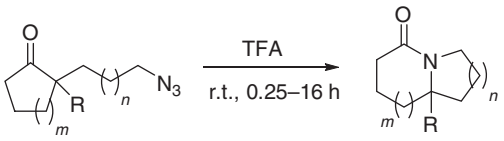
(24)

Research into the use of milder catalysts for the Schmidt reaction has revealed $FeCl_3$,[125] H_2SO_4/SiO_2,[126] and P_2O_5/SiO_2[127] as suitable alternatives. The use of dimethoxyethane[128] and ionic liquids[129] as alternatives to the commonly employed halogenated solvents has also been reported.

6.15.5.3 Schmidt Reaction with Alkyl Azides

6.15.5.3.1 Reactions with carbonyl compounds

The Schmidt reaction with alkyl azides and carbonyl compounds had been briefly investigated in the mid-twentieth century, but these efforts were hampered by a lack of reactivity when protic acids or $AlCl_3$ were employed.[130,131] However, in 1991, it was reported that an intramolecular Schmidt reaction could be brought about by the use of TFA or $TiCl_4$ to afford fused lactams **112** (Scheme 55).[132,133] This method was successfully applied to cyclic ketones of various ring sizes, although the azide tether was limited to a 4- or 5-carbon chain. Moreover, reactions of α,β-unsaturated cyclic ketones with azides provide formal conjugate addition products.[134]



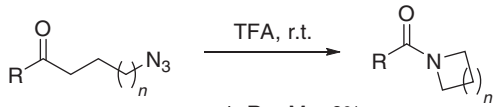
112

m	*n*	R	Yield (%)
0	1	Me	66
1	1	H	83
1	1	CO_2Me	66
2	0	H	0
2	1	H	85
2	2	H	91[a]
2	3	H	0
4	1	H	96

[a] With $TiCl_4$.

Scheme 55

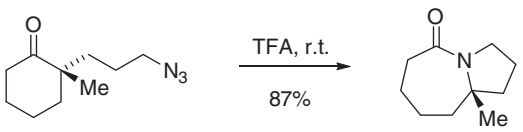
Acyclic ketones also readily underwent intramolecular Schmidt rearrangements to afford amides (equation 25). The optimal azide tether was found to be a 4-carbon chain, with shorter linkages proving unreactive.



n = 1, R = Me, 0%
n = 2, R = Me, 75%
n = 2, R = Ph, 77%

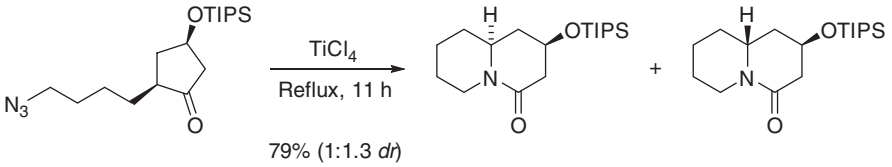
(25)

As with the case with related reactions, the intramolecular Schmidt rearrangement proceeds with retention of configuration at the migrating carbon center (equation 26). In contrast, apparent loss of stereospecificity was noticed where the substrate contained an enolizable stereogenic center (equation 27).[135] Rather than indicating an erosion of stereoselectivity in the Schmidt reaction per se, this result more likely occurred via enolization/epimerization before the ring expansion step.



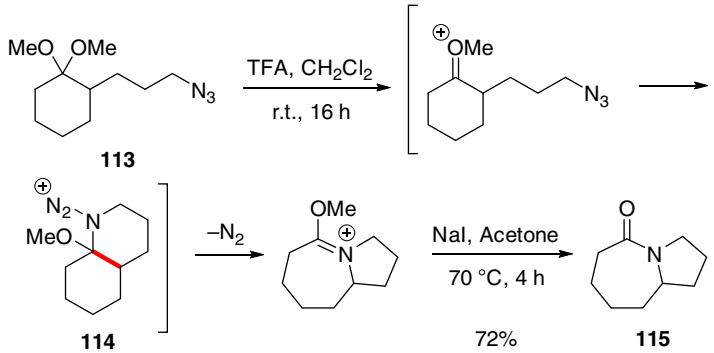
96% *er* 95% *er*

(26)



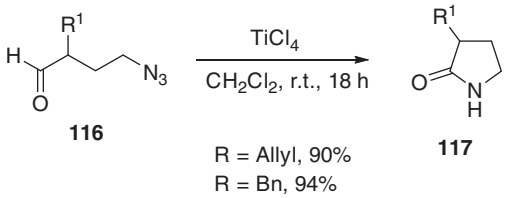
(27)

Schmidt reactions with alkyl azides can also be performed with ketals and enol ethers. For example, on treatment with Lewis or protic acid, dimethyl acetal **113** forms an oxonium ion, which cyclizes to intermediate **114** (Scheme 56).[136] Bond migration with loss of N_2 followed by treatment with sodium iodide reveals bicyclic lactam **115**.

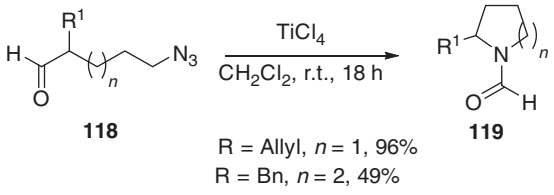


Scheme 56

The intramolecular Schmidt reaction of alkyl azides with aldehydes gives different products, depending on the length of the azide tether. Treatment of azido aldehydes **116** and **118** with TFA or $TiCl_4$ resulted in the formation of either lactams **117** (through hydride migration in the azidohydrin intermediate, equation 28) or formamides **119** (from alkyl migration, equation 29).[137]

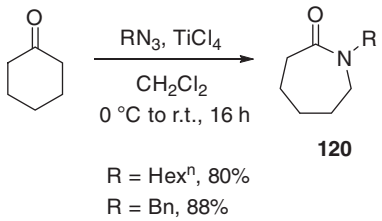


(28)



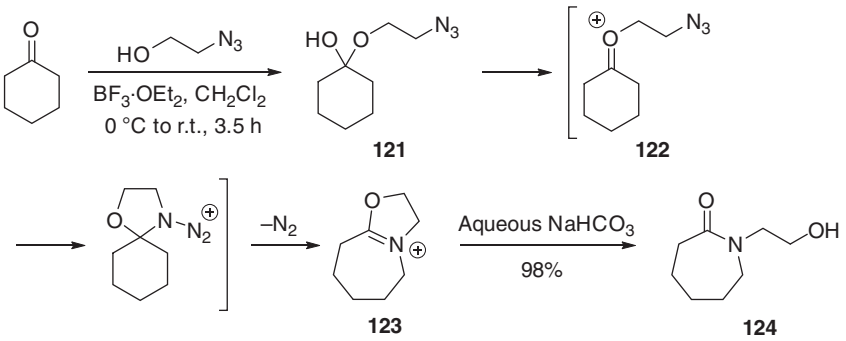
(29)

Intermolecular variations of the Schmidt reaction of ketones with alkyl azides are generally unsuccessful with protic acids,[130,131] but can in some cases be effected with $TiCl_4$.[138] For example, cyclohexanone reacts with *n*-hexyl and benzyl azide to afford lactams **120** using $TiCl_4$ as Lewis acid (equation 30). The reaction is limited to highly reactive (generally 6-membered) cyclic ketones; other ring sizes or acyclic ketones are problematic.[139]



(30)

A more general method involves the use of hydroxyalkyl azides. A variation of this reaction was reported by Boyer in the 1950s, in which aldehydes were converted to oxazolines and dihydrooxazines.[140] Later work expanded the scope of the reaction to include the conversion of ketones to lactams (Scheme 57).[141] Here, reaction of a ketone with an azido alcohol provides oxonium ion **122** via hemiketal **121**, rendering the azide attack intramolecular. Alkyl group migration with concomitant loss of N_2 affords iminium ether **123**, which is converted into lactam **124** on addition of water.

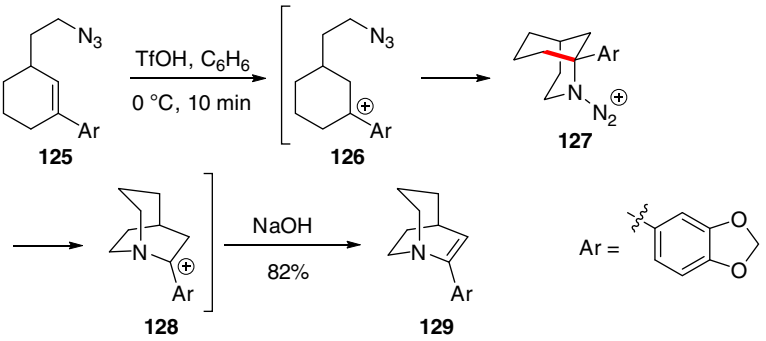


Scheme 57

Intermolecular reactions of alkyl azides with α,β-unsaturated ketones lead to a variety of non-Schmidt products.[142,143] This is thought to arise due to Lewis acid activation of the enone, which favors a 1,3-dipolar cycloaddition over the Schmidt reaction pathway.

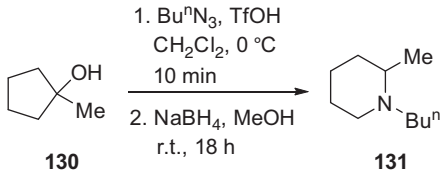
6.15.5.3.2 Reactions with carbocations and carbocation precursors

Alkyl azides also undergo Schmidt reactions with carbocations.[144–146] Thus, treatment of azido alkene **125** with triflic acid provided benzylic cation **126** (Scheme 58). Formation of aminodiazonium ion **127** followed by alkyl group migration with expulsion of N_2 afforded cation **128**, which when quenched with base provided bicyclic amine **129**. The carbocation precursors can also be obtained by treatment of tertiary alcohols with acid. As a general rule, the carbocation must be tertiary, allylic, benzylic, or propargylic for this variation of the Schmidt reaction to proceed.



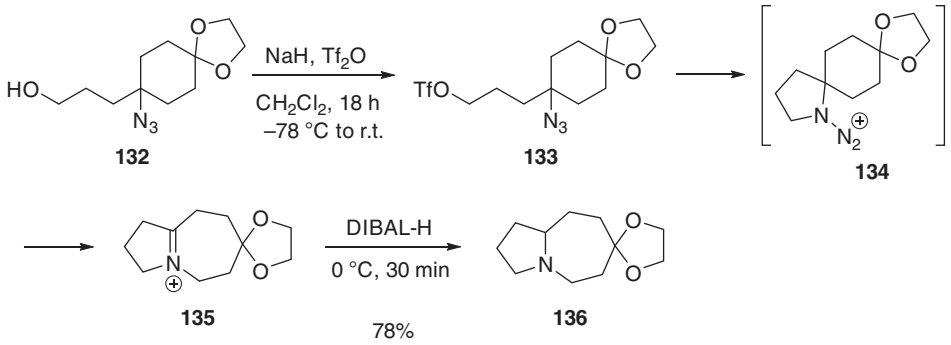
Scheme 58

Intermolecular Schmidt reaction of carbocations with alkyl azides can also be performed by reacting cyclic or acyclic tertiary alcohols with aliphatic azides in the presence of $SnCl_4$ or TfOH and reducing the resulting iminium ion with $NaBH_4$.[147] For example, cyclopentanol **130** was reacted with *n*-butyl azide to afford substituted piperidine **131** (equation 31).



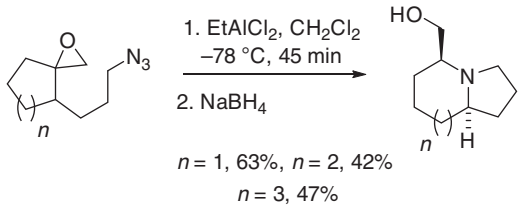
(31)

A complementary method to the Pearson carbocation chemistry has been described, where a primary azido alcohol **132** was activated by formation of the corresponding triflate **133** (Scheme 59).[148] Displacement of the triflate by the azide led to aminodiazonium ion **134**, which underwent alkyl migration to iminium ion **135** and subsequent hydride reduction to bicyclic amine **136**.

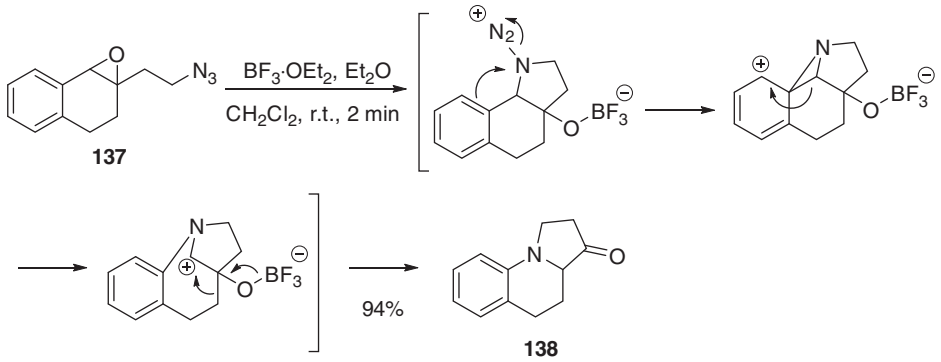


Scheme 59

Epoxides can also be employed as carbocation precursors. Azido epoxides undergo a Lewis acid-promoted Schmidt reaction to afford bicyclic amines after hydride reduction of the initial iminium ion (equation 32).[149] Aryl epoxy azide **137** has also been shown to undergo Schmidt rearrangement to provide ketone **138** (Scheme 60).[150]

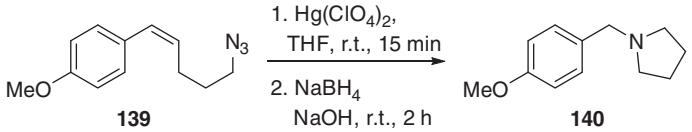


(32)



Scheme 60

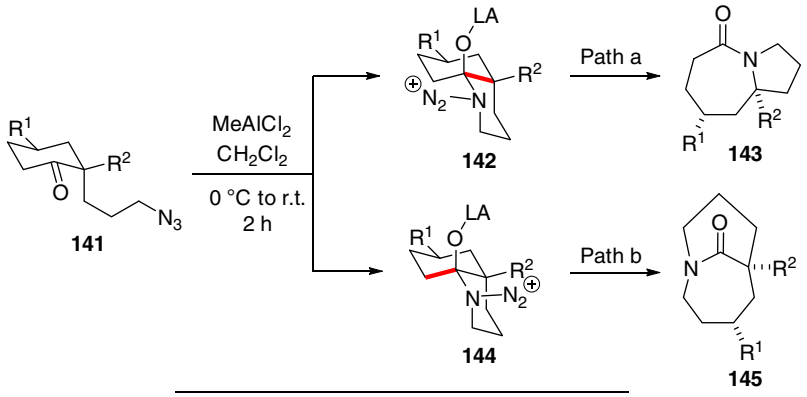
Schmidt reactions of carbocations and alkyl azides can also be promoted by mercuric ion.[151] Thus, unsaturated azide **139** was treated with mercury perchlorate to afford an initial iminium ion, which was reduced to amine **140** (equation 33). The azidomercuration reaction has greater substrate scope than the corresponding acid-promoted Schmidt reaction, with aliphatic secondary carbocations being tolerated. For a discussion of the mechanism of the mercury(II)-promoted Schmidt reaction, see Section 6.15.5.3.3.



(33)

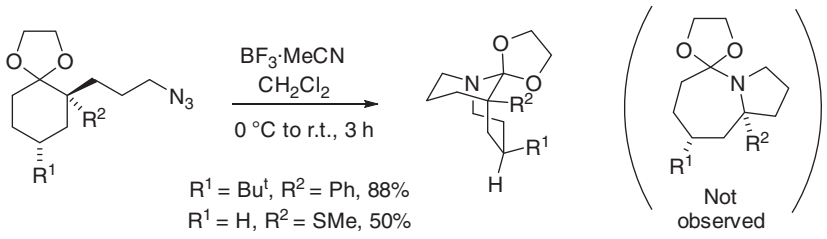
6.15.5.3.3 Regiochemistry and stereochemistry

The intramolecular Schmidt reaction of 2-alkylazido ketones **141** can potentially provide two different lactam products, arising from migration of one of two alkyl groups in the azidohydrin intermediates (Scheme 61). Migration through path ***a*** leads to fused lactam **143**, whereas migration through path ***b*** affords a bridged lactam **145**. For the majority of substrates, path ***a*** predominates and fused lactams are the sole products of the rearrangement (Scheme 61, entry 1). However, it was shown to be possible to obtain bridged lactams via path ***b*** by introducing a through-space cation-stabilizing group at the 2-position on the cyclohexanone ring (Scheme 61, entries 4–7).[152–154] This was ascribed to the greater stability of intermediates **144** relative to **142** when R_2=Ar or SMe. Still higher ratios of bridged products were obtained when the Schmidt reaction was carried out on ketal substrates (Scheme 62).[155]



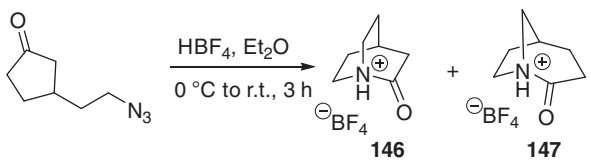
Entry	R^1	R^2	Yield (%) 143	145
1	H	H	85	0
2	H	Ph	96	0
3	Bu^t	H	57	17
4	Bu^t	Ph	20	51
5	Bu^t	4-$MeOC_6H_4$	11	71
6	H	SMe	16	64
7	Bu^t	SMe	10	64

Scheme 61



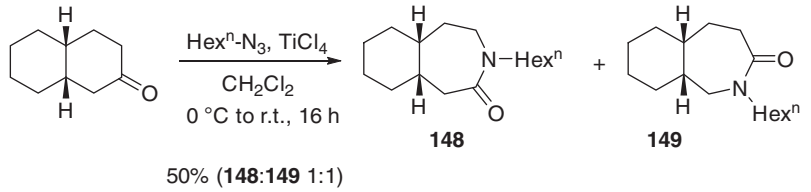
Scheme 62

Another method to prepare bridged lactams is by the intramolecular Schmidt reaction of keto azides where the azide tether is not adjacent to the carbonyl, thus necessitating the formation of bridged products (equation 34).[156]



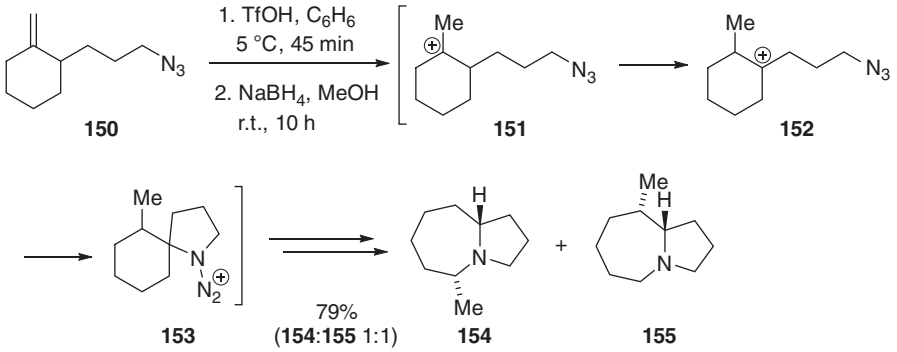
(34)

The regioselectivity of intermolecular Schmidt reactions of unsymmetrical cyclic ketones and alkyl azides is highly substrate dependent but typically suffer from poor regiocontrol in the migration step (e.g., equation 35).[138]



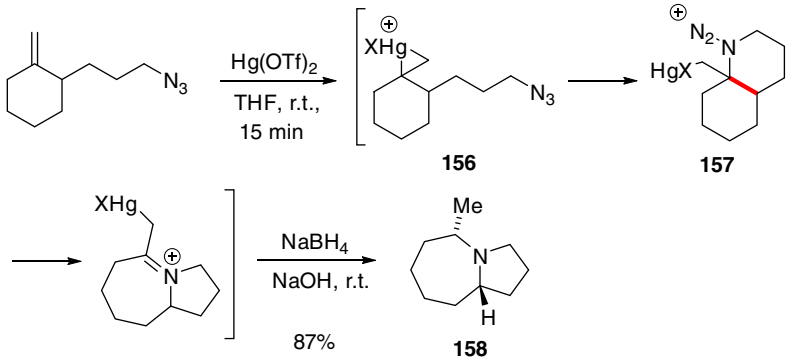
(35)

Likewise, the selectivity of Schmidt rearrangements of carbocations is generally low relative to those of ketones.[145] This is due to the potential migration of a larger number of bonds than reactions of ketones, wherein the OH group cannot migrate. There is also potential for a cation shift, leading to an even greater number of potential products. For example, on treatment with TfOH, alkene **150** was protonated to afford cation **151** (Scheme 63). A 1,2-hydride shift then occurred to provide **152**, which cyclized to spiroaminodiazonium ion **153**. Competing migration of two of the carbon bonds led to the formation of a mixture of amine products **154** and **155** after reduction of the corresponding iminium species.



Scheme 63

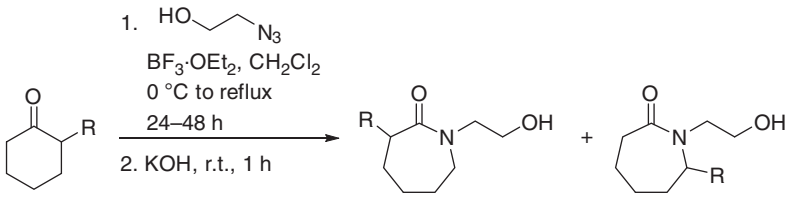
Conversely, mercury(II)-mediated Schmidt reactions of similar substrates display much higher regiocontrol, often resulting in the formation of a single product.[151] The cation rearrangement observed under protic conditions is presumably prevented when mercury is employed by the formation of a mercuronium ion **156** (Scheme 64). The migration precursor is then a fused bicyclic aminodiazonium ion **157** (rather than its spiro analog **153**), which led to the isolation of a single product **158**.



Scheme 64

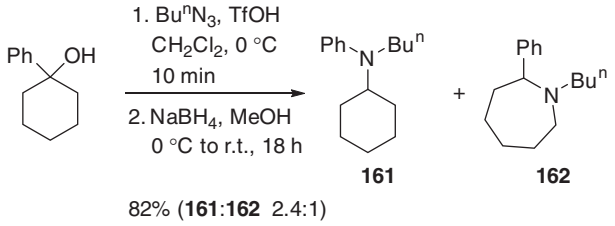
Schmidt reactions of α-substituted cyclic ketones with azido alcohols provide a mixture of lactam products **159** and **160** depending on the nature of the substituent (Scheme 65).[157] Substrates containing a small alkyl group afforded an approximately equal mixture of products (entry 1). Increasing the size of the alkyl group favored the migration of the more substituted carbon atom (entry 2); when R=OMe, the opposite product was favored (entry 3).

Intermolecular Schmidt reactions of alkyl azides with carbocations tend to suffer from poor regiochemistry in the migration step. Even when symmetric cyclic alcohols are employed, a mixture of products from competing exo- and endocyclic group migration is possible (equation 36).



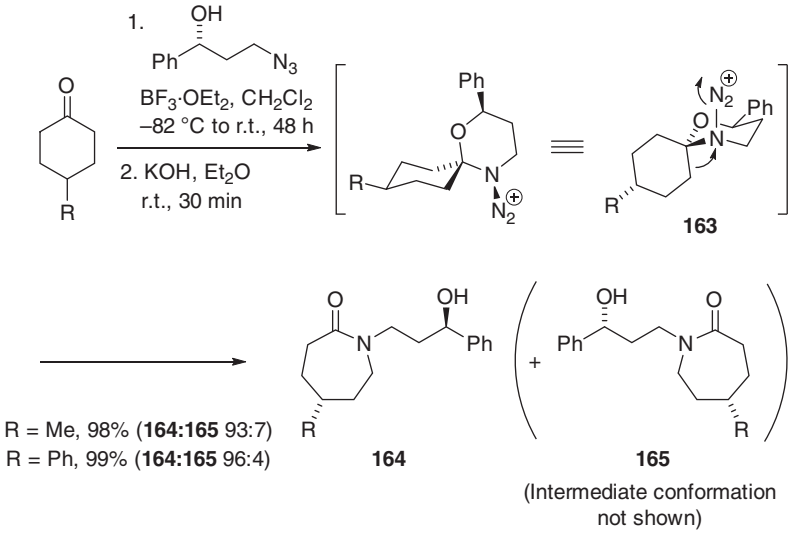
Entry	R	Yield (%)	Ratio **159**:**160**
1	Me	83	45:55
2	Pr^i	80	21:79
3	OMe	52	91:9

Scheme 65



(36)

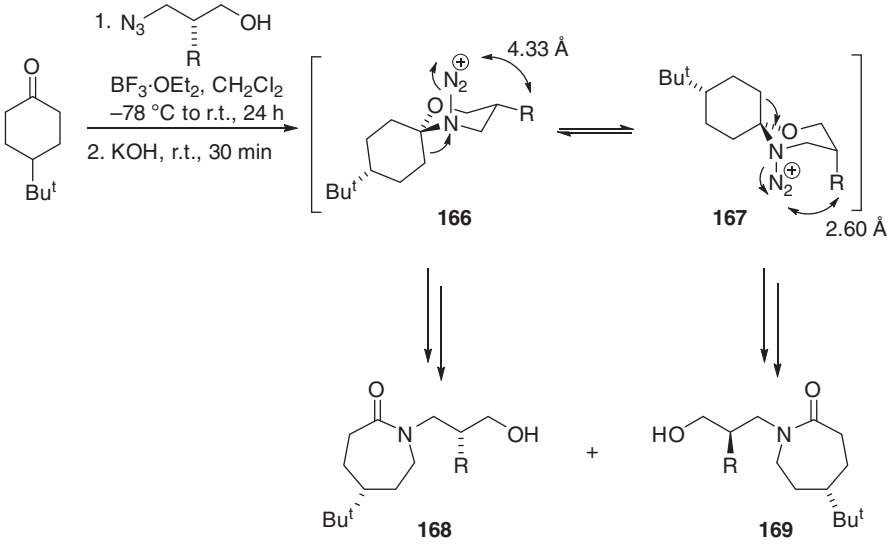
The intermolecular Schmidt reaction between cyclic ketones and azido alcohols can be rendered asymmetric by employing a chiral azide fragment (Scheme 66).[158,159] When cyclohexanones were reacted with (*R*)-3-azido-1-phenylpropanol, lactams **164** were isolated in a >93:7 ratio with stereoisomers **165**. The selectivity was ascribed to (1) pseudoequatorial attack of the tethered azide to the oxonium intermediate, (2) adoption of conformer **163**, and (3) migration of the alkyl group antiperiplanar to the pseudoaxial diazonium-leaving group to afford the major lactam products **164**.



Scheme 66

A similar effect was observed when 2-alkyl-substituted azidopropanols were employed (Scheme 67; entries 1 and 2). However, when a phenyl group was introduced at the 2-position, the predominance of lactam **168** decreased (entry 3).[160,161] This effect was further enhanced by the use of electron-rich arenes so that lactam **169** became favored (entry 4). When R=alkyl, conformation **166** was favored, so that the *tert*-butyl and R substituents are in pseudoequatorial positions. However, when R=aryl, conformation **167** was preferred, arising from a stabilizing cation–π interaction between the aryl and diazonium moieties, leading to lactam **169**. The equilibrium between the two intermediates could further be shifted toward **167** if R was OMe or SMe (entries 5 and 6).[162] This

enhancement in selectivity is more likely due to the smaller steric size of these groups, which minimizes 1,3-diaxial strain while still being able to provide a stabilizing cation–n interaction with the diazonium moiety; when R = OMe, intermediate **167** was calculated to be 3.8 kcal mol^{-1} more stable than **166**. The opposite sense of selectivity was achieved by the use of 1-azido-3-methoxypropan-2-ol as the chiral tether.[162]

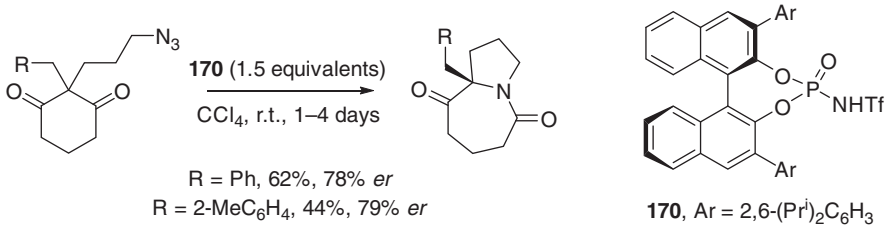


Entry	R	Yield (%)	Ratio **168**:**169**
1	Me	98	74:26
2	Pr^i	85	88:12
3	Ph	98	64:36
4	Ar[a]	99	43:57
5	OMe	98	4:96
6	SMe	90	2:98

[a]Ar = 3,4,5-$(MeO)_3C_6H_2$

Scheme 67

Early attempts to carry out an enantioselective Schmidt reaction of a symmetrical 1,3-diketone using a chiral acid catalyst were met with limited success.[163,164] However, a chiral 1,1′-bi-2-naphthol-derived *N*-triflylphosphoramide catalyst was able to impart up to 79% *er* on the intramolecular Schmidt reaction of substituted 1,3-hexanediones (equation 37).[165]

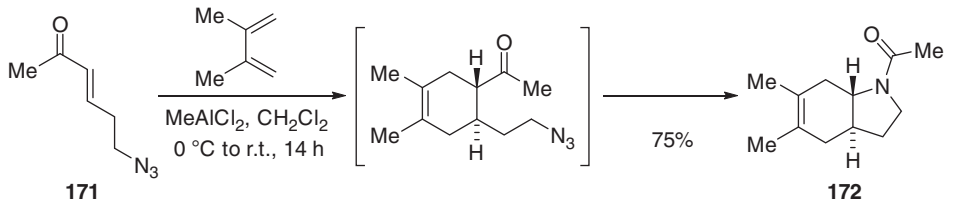


(37)

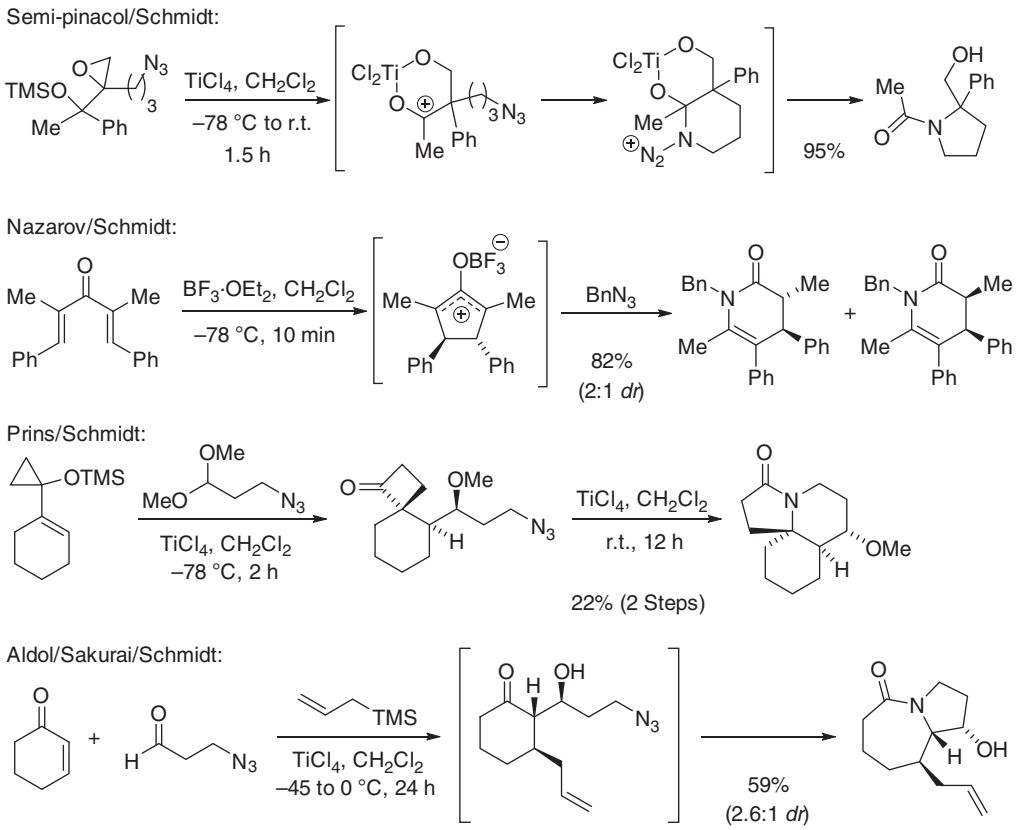
6.15.5.4 Schmidt Rearrangements Combined with Other Reactions

In principle, Schmidt reactions can be carried out in a domino fashion with other Lewis acid-promoted processes. For example, Schmidt rearrangement was combined with the Diels–Alder reaction by treating an α,β-unsaturated ketone **171** with a diene under Lewis acidic conditions (Scheme 68).[166] On cyclization, the Schmidt rearrangement proceeded to afford lactam **172**. A variety of heterocycles were synthesized in this manner by altering the diene and dienophile components.

Similarly, it proved possible to carry out Schmidt chemistry on intermediates generated *in situ* from semipinacol,[167] Nazarov,[168] Prins,[169] aldol, and Sakurai[170] reactions (Scheme 69).



Scheme 68



Scheme 69

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6.16 Functional Group Transformation via Allyl Rearrangement

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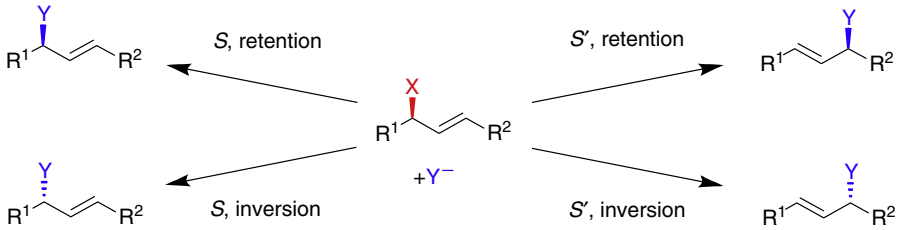
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6.16.1 Introduction

The allylic system provides a rich foundation for reaction development by virtue of widespread availability of suitable substrates, versatile and in many cases well-defined reactivity, and the potential for multifaceted functionalization of initial reaction products. Nucleophilic, electrophilic, pericyclic, organometallic, and radical pathways of reactivity are available, and substitutions can occur directly at the allylic position by α-substitution (S_N, S_E, S_R) or with allylic rearrangement through γ-substitution (S_N', S_E', S_R'). For substrates possessing a stereogenic center at the allylic position, the reactions can proceed with retention or inversion of configuration (**Scheme 1**). These diverse patterns of reactivity characteristic of the allylic system enable a broad array of powerful reactions, but also contribute to challenges in reaction development rooted in selectivity. In addition to the usual requirements for chemoselectivity, useful new methods are expected to provide high level of regiocontrol, and, if chiral products are formed, enantio- and diastereocontrol.

Transformations with allylic substitution have found an especially broad application in chemical synthesis, which involves organizing the material a challenge in itself. A SciFinder search produced over 18 000 references for the concept 'allylic substitutions,' approximately 8600 of which dated in the year 2000 or later. The authors found the organization of material by Altenbach in the first edition of these series to be suitable, and they have followed similar formatting here.

 doi:10.1016/B978-0-08-097742-3.00624-8



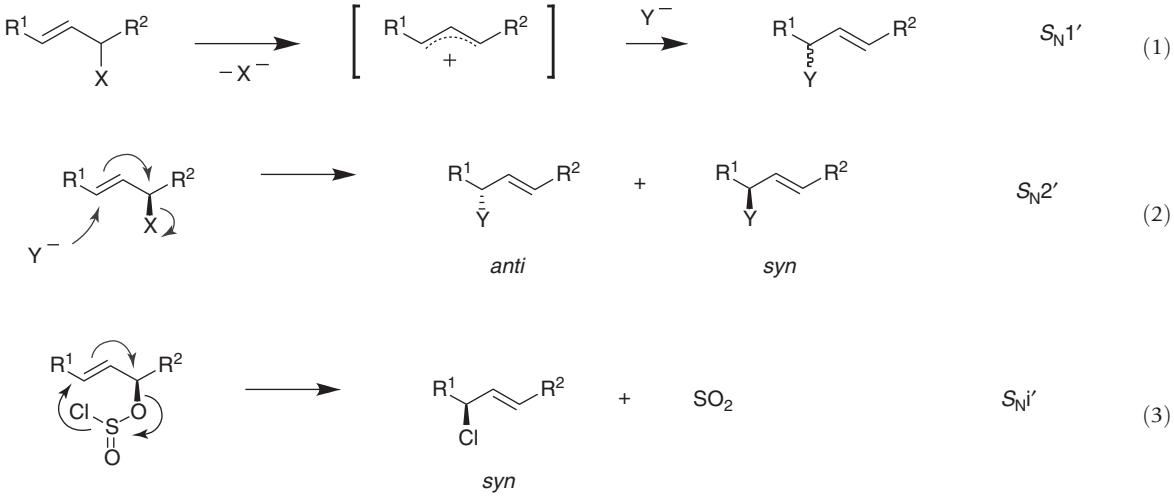
Scheme 1

In the introduction to this chapter, a brief overview is provided of the different commonly accepted mechanisms by which allylic substitutions can take place. In the subsequent sections, various reactions have been grouped based on the identity of the atom at the newly installed bond (**Y**) and that of the leaving group (**X**), irrespective of the mechanism of the reaction. The emphasis has been on applications in complex settings that put to test various aspects of chemo-, regio-, and stereoselectivity. Because of the increasingly important considerations of environmental impact, methods aiming to conform to the principles of green chemistry have also been highlighted. In addition, the emphasis has been placed on the representative methods in modern synthetic chemistry that provide practical and innovative solutions to selectivity problems, which have been supplemented by examples of application in natural products synthesis. Within the limitations of space in this chapter, the authors have attempted to cover a broad range of approaches to allylic substitution from different research groups rather than providing an exhaustive coverage of the topic from a few. This chapter encompasses the literature from the late 1990s until the middle of 2012, concentrating on more recent contributions.

6.16.2 Mechanistic Continuum of Reactions Occuring with Allylic Transposition

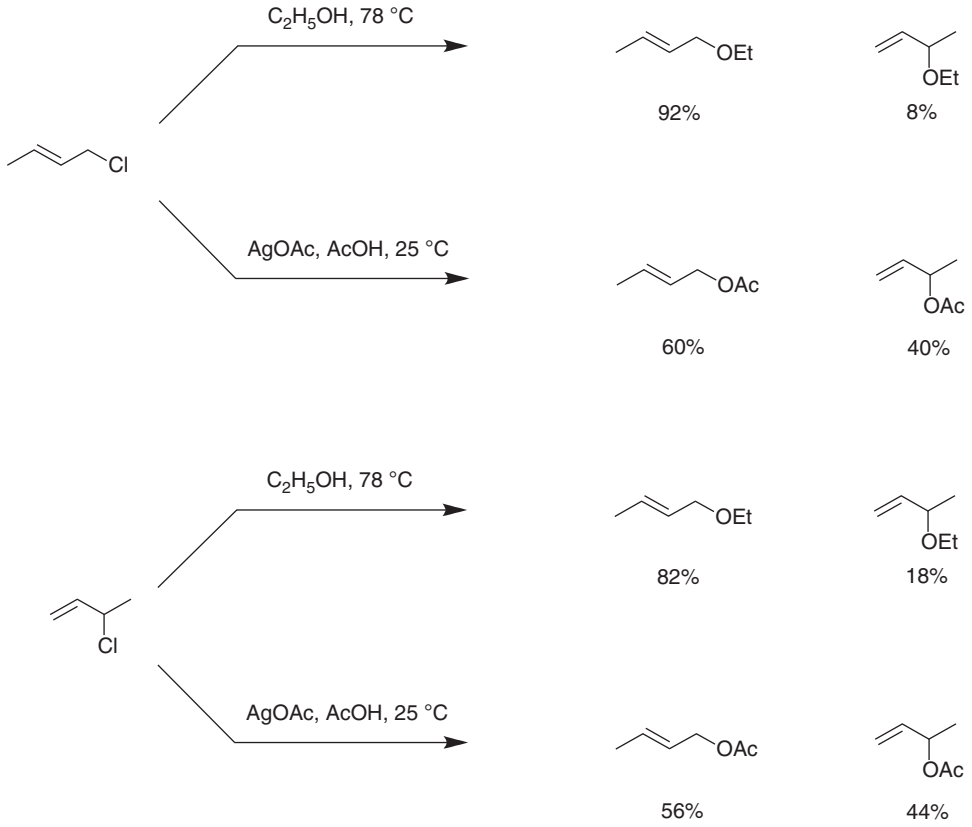
6.16.2.1 Unassisted Nucleophilic Substitutions

Direct unassisted nucleophilic substitution is a classic and broadly utilized process in allylic systems. This topic is covered adequately in textbooks on Organic Chemistry, and a seminal comprehensive review on nucleophilic allylic substitution was published by DeWolfe and Young in 1956.[1] Allylic electrophilies incorporating halide or sulfonate-leaving groups typically show enhanced reactivity and effectively participate in substitutions with a broad range of carbon or heteroatom nucleophiles. The substitution reactions are facilitated due to stabilization of the cationic intermediate or transition states by resonance with the π-bond of the allylic or propargylic substrate. Three commonly accepted mechanisms for nucleophilic allylic substitution are shown in equations 1–3.



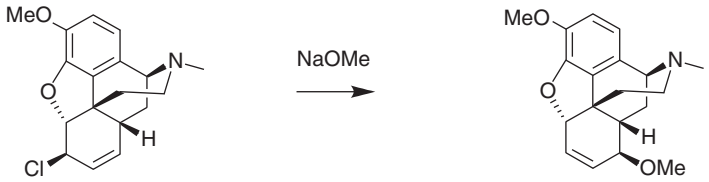
Allylic transposition is observed commonly if the reaction takes place by an S_N1'-type mechanism. These reactions proceed through a carbocationic intermediate stabilized by resonance where the charge is delocalized between the C1 and C3 carbon atoms of the allylic system, both of which can form a bond with an incoming nucleophile. There is evidence that ion pairs are involved in S_N1' reactions, which can influence the product distribution (product spread), especially in solvents of lower polarity. There are many examples of reactions where the product distribution is different for isomeric allylic substrates reacting by an S_N1 pathway and presumably proceeding through an identical carbocationic intermediate, strongly suggesting the intermediacy of isomeric ion

pairs (Scheme 2). The product distribution becomes similar for isomeric substrates under more ionizing reaction conditions. The factors that influence S_N1' reactions include the structure of the allylic system, the nature of the leaving group, and the ionizing power of the solvent.[1]



Scheme 2

The typical S_N2-type mechanism is implicated in the great majority of reactions of primary and secondary allylic substrates in solvents of low polarity and normally give only products with no allylic rearrangement.[2] In fact, the exclusive formation of the normal substitution products is often an indication that the S_N2 mechanism is operative, because the S_N1-type or S_N2' reactions give varying amounts of allylic rearrangement substitution products. The S_N2' mechanism for allylic compounds was first defined by Hughes and Winstein in 1938,[3,4] yet the kinetic evidence for its existence was elusive until 1949, when the substitution reaction between 3-chloro-1-butene or 3-chloro-1-pentene and sodium diethyl malonate giving an appreciable amount of the rearrangement products was found to be second order.[5] Subsequently, it was discovered that a range of nucleophiles can react by the S_N2' pathway, especially amines, alkoxides, and sulfides. Stork suggested that displacement of chloride with methoxide in α-chlorocodide is due to steric hindrance of the normal substitution (Scheme 3).[6] The most important factors affecting the product spread in the S_N2'-type reactions are the structure of the allylic system, especially steric factors,[7] the nature of the reagent, and the solvent composition. The S_N2' substitution can take place with the retention (*syn*)[8] or inversion (*anti*)[9] of configuration, with the *syn* pathway predominating in many cases.[10]



Scheme 3

Bordwell and coworkers proposed that there is no true concerted S_N2' mechanism with simultaneous bond-breaking and bond-forming events involving the movement of the three electron pairs (equation 2).[11] There is evidence both in support[12] and against this proposal.[13]

A classic example of the S_Ni' reaction is the treatment of allylic alcohols with thionyl chloride, which predominantly or exclusively gives the product of allylic rearrangement.[14] Evidence in support of the concerted mechanism illustrated in equation 3 has been reported.[15]

Noncatalytic nucleophilic allylic substitution can also occur by addition–elimination mechanism if there is a strong electron-withdrawing group present at the C2 position of the allylic system. Two recent examples are illustrated in Scheme 4. The first is an example of kinetic resolution in amine-catalyzed Michael addition to a nitroalkene substrate displacing an acetate group.[16] The second example illustrates a dramatic effect of the medium on the mechanism of allylic substitution. Under thiourea hydrogen bond catalysis, allylic carbonates derived from Morita–Baylis–Hillman adducts react as electrophiles with phthalides.[17]

6.16.2.2 Electrophillic Substitutions and Reactions with Allyl and Propargylmetal Reagents

Electrophilic substitutions with allylmetallic reagents is an exceedingly broad set of reactions with widespread utility in organic synthesis. Alternatively, these reactions may be viewed as nucleophlic additions of allylmetal reagents to carbonyl compounds. Several reviews offer generally accepted mechanistic models of these processes. In addition, numerous experimental and theoretical studies on the mechanism of allylation of carbonyl compounds with allylmetal and allylmetaloid compounds have appeared during the past 20 or so years, probing reactions with allyllithium and allylpotassium,[18] allylboron,[19] allylsilane,[20] allylgermanium,[21] allylstannane,[21] and allylruthenium reagents.[22] For the majority of these reactions, two general pathways have been adopted based on the open and the classic chair-like cyclic transition state models.

For reactions proceeding through the open acyclic transition state, it has been demonstrated that the addition of allylsilanes to aldehydes, among other electrophiles, involves an S_E' mechanism with antiperiplanar orientation of the trialkylsilyl and the incoming carbonyl groups (Scheme 5).[23] However, a substantial set of examples involving either stannane or silane reagents is more consistent with a preference for the synclinal pathway. A more recent study provides computational and experimental evidence for an eight-membered cyclic *anti*-S_E' transition state for BF_3-promoted reactions between allylsilanes and aldehydes.[20a]

Six-membered cyclic Zimmerman–Traxler-type model for transition state is common to many electrophilic alkylations of allylmetallic reagents with carbonyl compounds or related electrophiles (Scheme 6). In many situations the chair-like transition structures are favored. The distribution of stereoisomeric products is commonly predicted based on relative energies of various conformers, which are typically dictated by the nature, position, and orientation of substituents around the six-membered cyclic transition structure.

Both of these major mechanistic models allow clear understanding for the high degree of allylic rearrangement observed in these types of electrophilic allylation reactions.

A theoretical study that compared the relative reactivity of a large number of allylmetal reagents with electrophiles as diverse as water and carbonyl compounds revealed that reagents derived from group IA, IIA, and low-valent IIIA and IVA metals, which exist as either π-complexes or σ-complexes, are more reactive toward hydrolysis. Allylmetal reagents of group IIB, trivalent group IIIA, tetravalent group IVA, and pentavalent group VA metals exist as σ-complexes and are more reactive with carbonyl compounds than water.[24] These results have been found to be generally consistent with experimental results from allylmetalation reactions of carbonyl compounds in aqueous media.

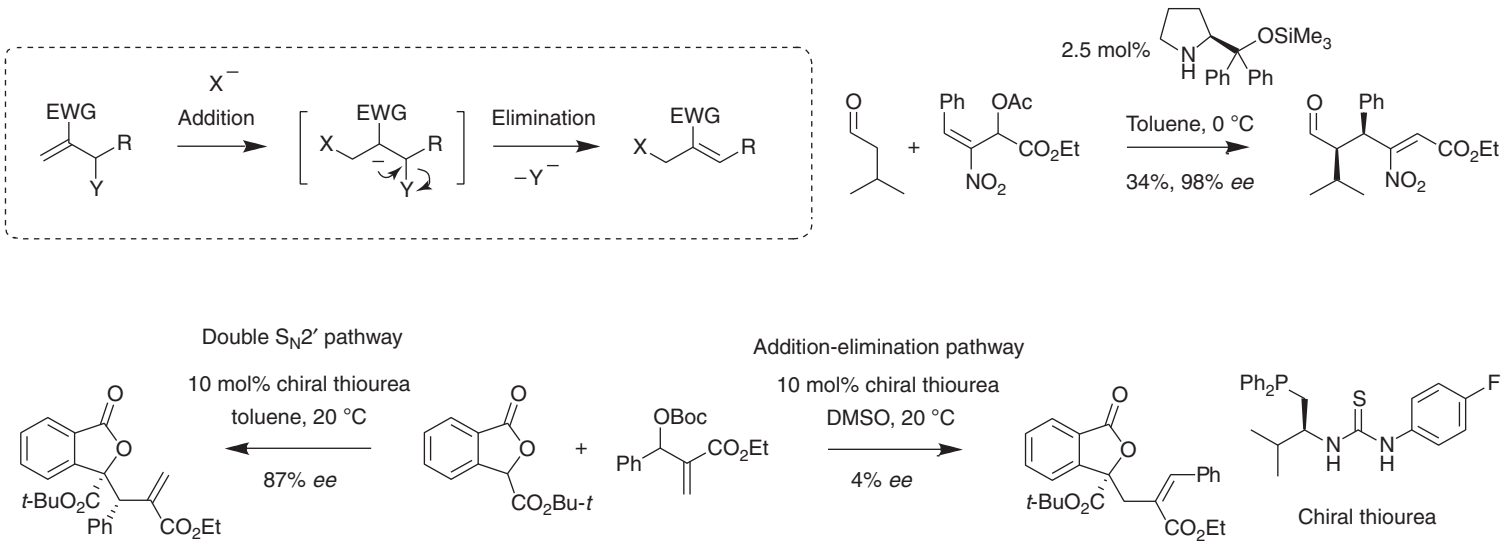
Additional discussion of various aspects of the mechanism of electrophilic substitution with allylmetallic reagents can be found in several reviews published on the synthetic utility of methods that belong to this class of reactions.[25–28]

6.16.2.3 Metal-Catalyzed Allylic Substitutions

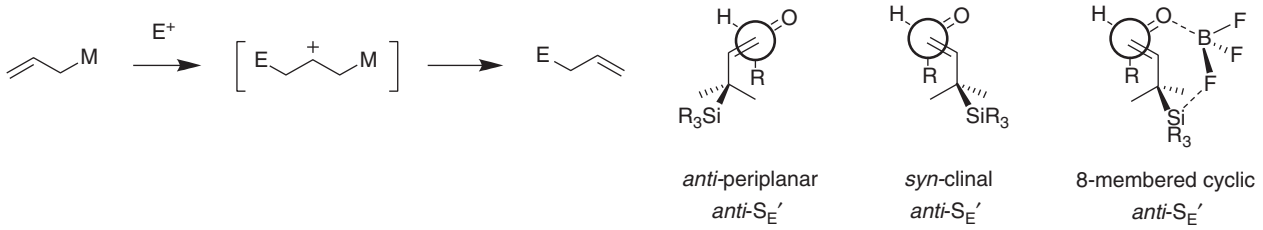
Metal-catalyzed allylic substitution is an extremely important class of reactions because of its utility in asymmetric synthesis and in economical and environmentally benign synthetic applications.[29] In general, metal-catalyzed allylic substitution leads to a displacement of a leaving group with a nucleophile at an allylic position giving products of S_N2 or S_N2' substitution depending on the identity of all the reactants involved. In most cases, the key difference with the uncatalyzed reactions is the intermediacy of the η^3-allyl complex formed initially by the displacement of the allylic-leaving group by the metal catalyst, which is subsequently attacked by a nucleophile to form the product with varying degrees of regioselectivity (Scheme 7).

It is generally accepted that the oxidative addition reaction of palladium(0) onto the allyl substrate occurs on the opposite face of the allylic system with respect to the leaving group. Soft nucleophiles then displace the palladium in the π-allylpalladium intermediate on the opposite face of the *p*-system, whereas hard nucleophiles attack the palladium atom followed by the internal delivery of the nucleophilic group. Two typical examples of using sodium malonates and $NaBD_4$ as nucleophiles are illustrated in Scheme 8.[30]

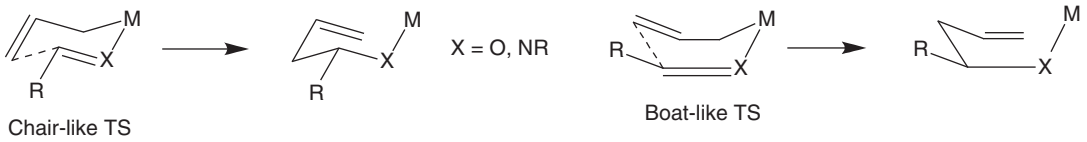
Early work on metal-catalyzed allylic substitutions concentrated heavily on palladium-catalyzed transformations, which in most cases favor products placing the incoming nucleophile at the least substituted position of the allylic system. With symmetrically substituted allylic systems, highly enanatioselective palladium-catalyzed substitutions can be achieved with a broad range of substrates.[31] At least five distinct mechanisms of enantiodiscrimination have been proposed,[31b] which include: (1) enantioselective complexation to the alkene followed by ionization; (2) enantioselective insertion into enantiotopic C–X bond; (3) attack at enantiotopic termini of the prochiral π-allyl complex; (4) selective enantioface exchange between the π-allyl complex (A vs. B, Scheme 7); and (5) differentiation of prochiral nucleophile faces. With asymmetrically substituted allylic substrates, the


EWG
R
Y
X⁻
Addition
X
EWG
R
Y
Elimination
−Y⁻
X
EWG
R
2.5 mol%
OSiMe3
N
H
Ph
Ph
O
+
Ph
OAc
CO2Et
NO2
Toluene, 0 °C
34%, 98% ee
O
Ph
CO2Et
NO2
Double SN2′ pathway
10 mol% chiral thiourea
toluene, 20 °C
87% ee
t-BuO2C
Ph
CO2Et
O
O
CO2Bu-t
+
OBoc
Ph
CO2Et
Addition-elimination pathway
10 mol% chiral thiourea
DMSO, 20 °C
4% ee
t-BuO2C
Ph
CO2Et
Ph2P
S
N
H
N
H
F
Chiral thiourea

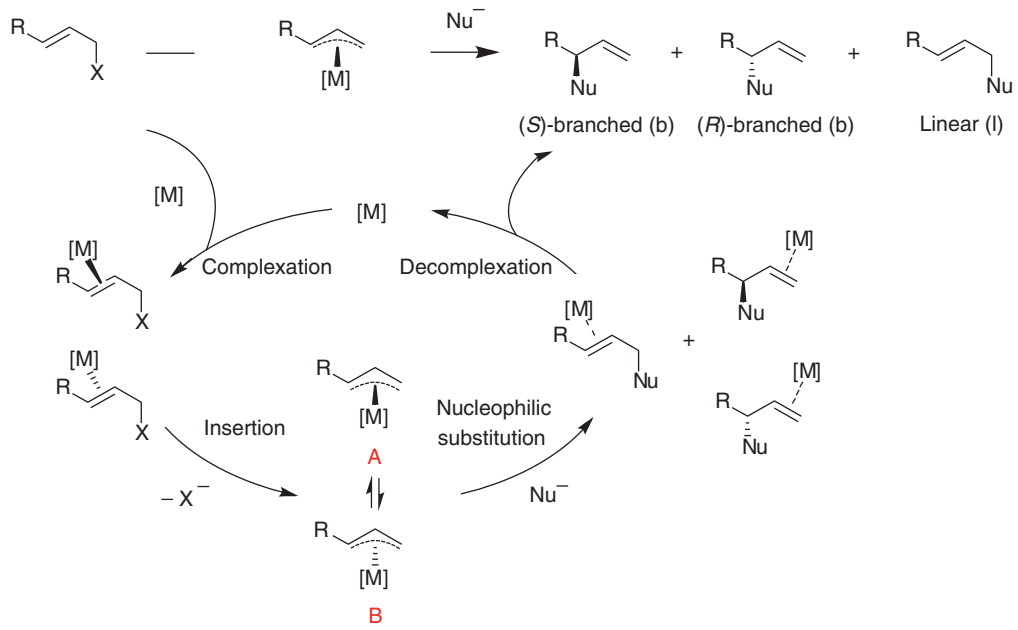
Scheme 4



Scheme 5



Scheme 6

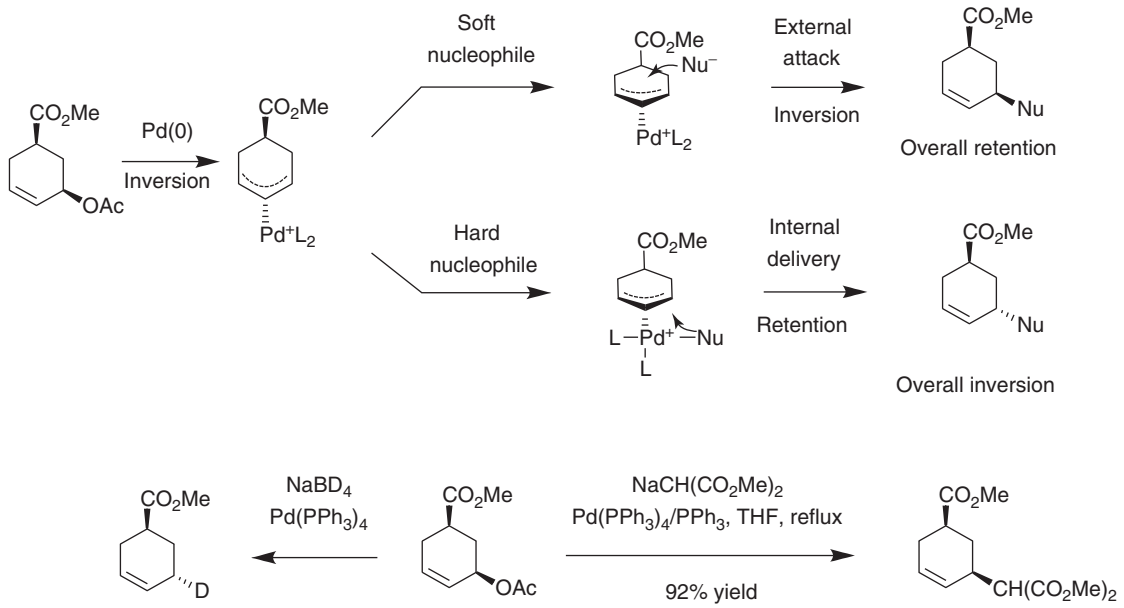


Scheme 7

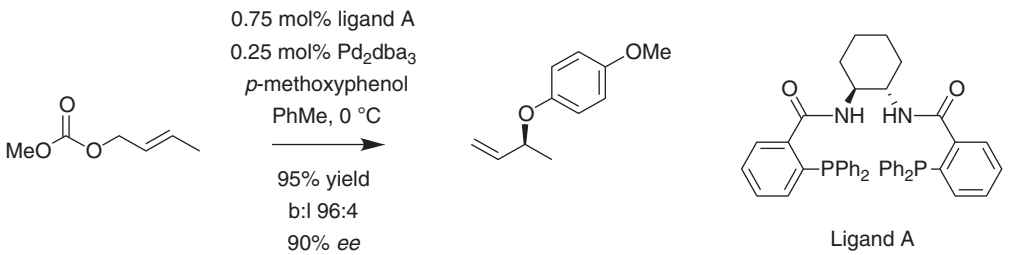
linear products are typically formed in Pd-catalyzed reactions. The reaction in Scheme 9 exemplifies an exception to this generalization. The origin of enantioselectivity in this reaction has been proposed to be the enantioselective complexation to the alkene occurring during the first step of the catalytic cycle shown in Scheme 7, with the rate of π-σ-π equilibration of enantiomeric intermediates being relatively slow.[31b]

Rhodium-catalyzed allylic substitutions using branched allylic carbonates giving branched products with high regioselectivity were first described in the 1980s. The reaction gave modest-to-excellent regioselectivity (Scheme 10).[32] Subsequent studies indicated that the regioselectivity of this type of transformation was dependent on the substrate regiochemistry. With branched allylic carbonates, branched products were formed predominantly, whereas the reaction favored linear products when linear substrates were used (Scheme 10). These results are in sharp contrast to palladium-catalyzed allyl substitution reactions. A σ-allyl organorhodium intermediate was proposed, although no experimental evidence for its intermediacy was presented.[33]

The regioselective allylic transposition of linear substrates to branched products displaying high generality for a broad range of nucleophiles underwent a rapid development beginning in the late 1990s with the advent of iridium catalysis,[34] which proved to be especially useful in effecting highly enantioselective transformations leading to chiral branched products. Most reactions selective for branched products have been carried out with $[Ir(cod)Cl]_2$ precatalyst and electron-accepting phosphite ligands. With



Scheme 8

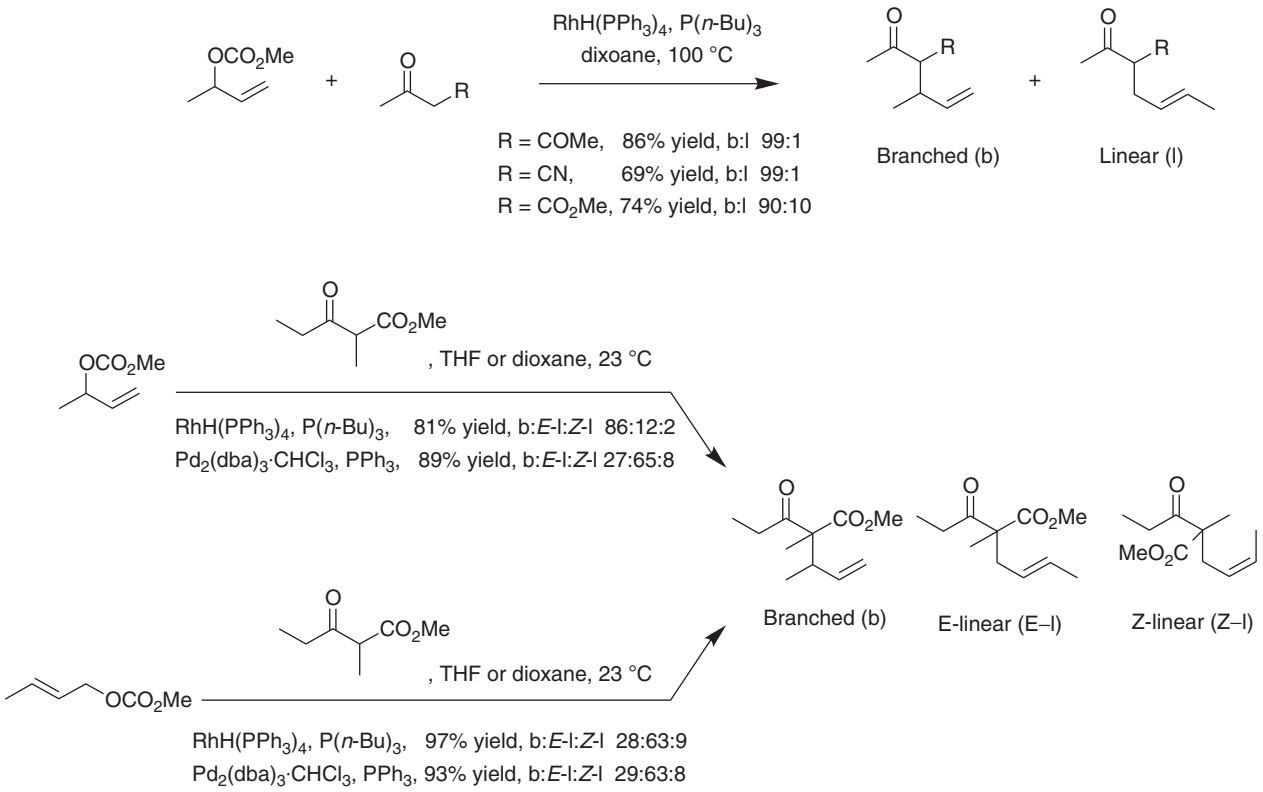


Scheme 9

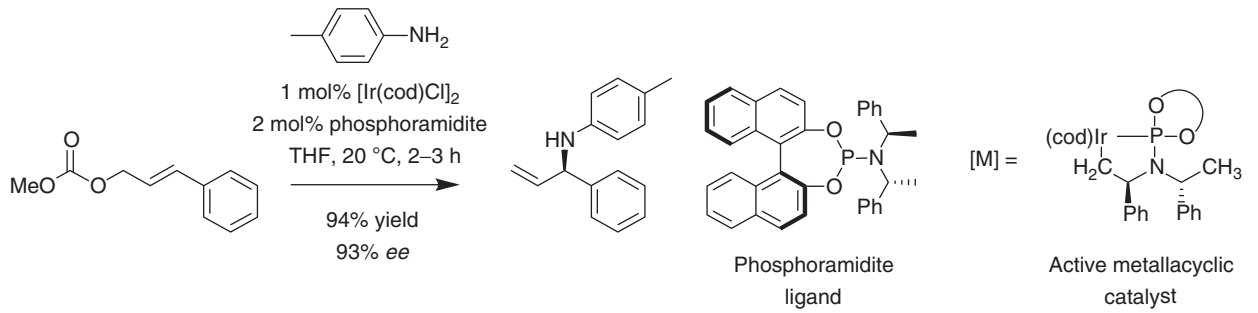
respect to facial selectivity in chiral allylic substrates, the reactions have been shown to take place by a double-inversion pathway leading to products with retention of configuration.[35] Some of the most useful and general catalytic systems for asymmetrical sysnthesis are based on C2-symmetrical phosphoramidite ligands. Detailed mechanistic studies revealed that the reaction follows the general format outlined in Scheme 6; however, the active catalyst is a metallacyclic iridium-phosphoramidite adduct, which has been isolated, prepared independently, and shown to be catalytically active in allylic substitutions (Scheme 11).[36] The active π-allyl iridium complex has also been isolated and structurally characterized.[35b]

Another important class of reactions occurring with a high degree of allylic transposition is copper-mediated or copper-catalyzed allylic substitutions.[37] The current commonly accepted mechanistic model is outlined in Scheme 12.[38] It is generally expected that monoalkylcopper intermediates lead to products of S_N2' substitution, whereas dialkylcopper species provide products of direct substitution, or displacement at the least substituted carbon of the allylic system. There is evidence that electron-deficient ligands increase the rate of reductive elimination thereby reducing the rate of equilibration to the less substituted allylcopper intermediate via the π-allyl complex, and thus favoring the S_N2' substitution.[39] However, donating substituents, such as strongly σ-donating alkyl group in the dialkylcopper reagent, reduce the rate of reductive elimination, favoring equlibration to the most stable allylcopper species.

Consistent with this mechanistic model, the regioselectivity of copper-catalyzed allylic substitution can often be controlled by the rate of addition of the organometallic reagent. Copper bromide-catalyzed substitution of cinnamyl chloride with methylmagnesium bromide in the presence of a phosphoramidite chiral ligand occurs with poor regioselectivity if the addition of methylmagnesium bromide is relatively fast, however, selectivity for the allylic transposition product increases as the rate of addition is reduced, reaching 83% when the addition time is 4 h (Scheme 13).[40] It is postulated that when the concentration of methylmagnesium bromide in the reaction medium is low, the monoalkylcopper reagent is formed and allowed to proceed to the reductive elimination stage forming the chiral S_N2' substitution product before the dialkylcopper reagent is formed. The dialkylcopper reagent diverts the reaction to the alternative pathway involving equilibration via the π-allyl copper species, which begins to predominate at faster addition times.



Scheme 10



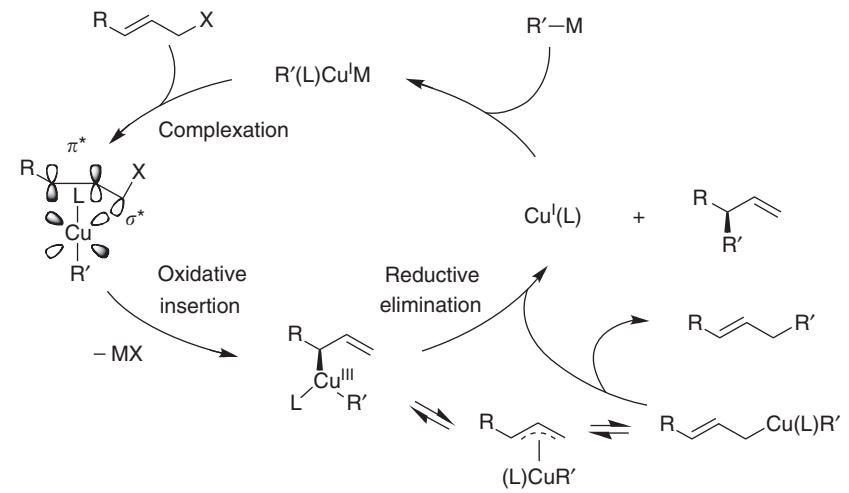
Scheme 11

With respect to the leaving group within the allylic system, organocuprate S_N2' substitutions typically occur with *anti*-selectivity, with the exception of allylic carbamates, which afford products of chelation-assisted *syn*-substitution (Scheme 14).[41,42]

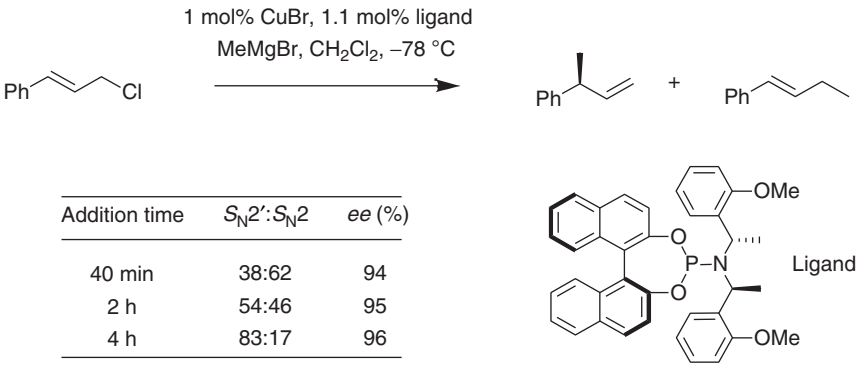
Another group of metal-catalyzed allylic transpositions is the direct transposition of allylic alcohols catalyzed by rhenium(VII), vanadium(V), and molybdenum(VI) oxo compounds (Scheme 15). In the presence of $(Me_3SiO)_2$, catalytic amounts of $VO(acac)_2$ or $MoO_2(acac)_2$ can effect a direct transposition of allylic alcohols at room temperature.[43] Rhenium(VII) catalysts such as $Ph_3SiORe O_3$ have been found to be even more reactive, showing high reactivity at −50 °C or lower temperatures. Kinetic studies and thermodynamic analysis of the $Ph_3SiORe O_3$-catalyzed transposition revealed first order in both the catalyst and alcohol with a large negative entropy of activation (Scheme 15).[44] These studies support a cyclic transition state suggestive of a [3,3]-sigmatropic rearrangement with a polarized, highly ordered chair-like transition structure.[45] The high polarization of intermediate allylic perrhenates leads to partial ionization to allylic cationic species that accounts for the observed epimerization of chiral secondary allylic alcohols, double bond isomerization, as well as the formation of other by-products.[46]

6.16.2.4 Metal-Catalyzed Allylic C–H Functionalizations

Metal-catalyzed allylic C–H oxidation and C–C bond formation is a rapidly growing area of research. These reactions formally represent displacement of a hydrogen atom with a carbon or heteroatom substituent, which can occur with allylic transposition.

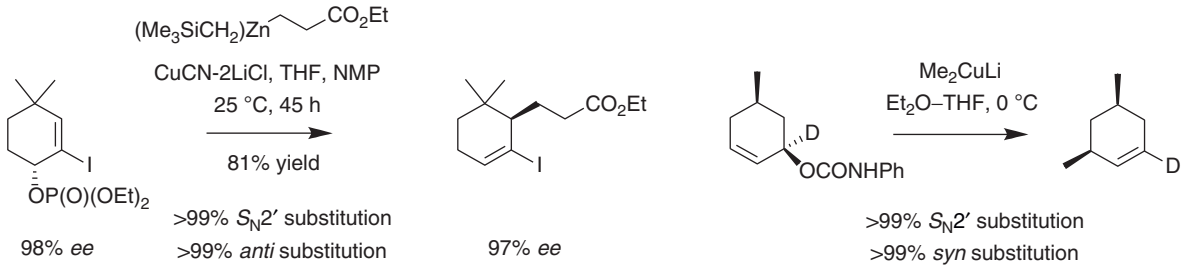


Scheme 12



Addition time	$S_N2':S_N2$	*ee* (%)
40 min	38:62	94
2 h	54:46	95
4 h	83:17	96

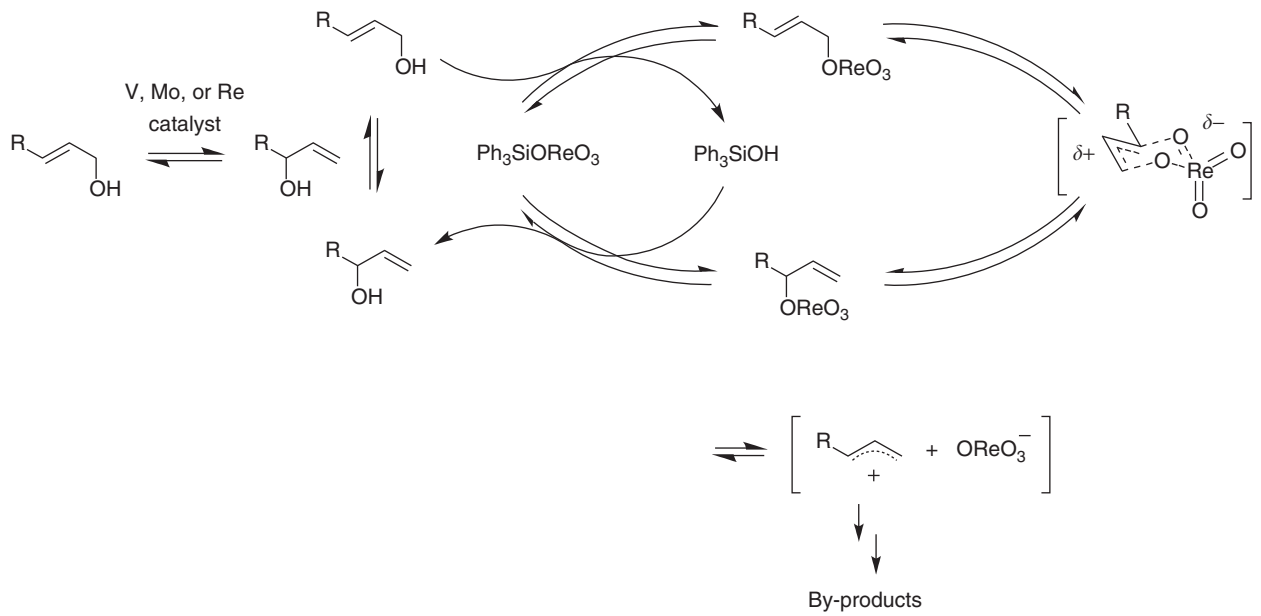
Scheme 13



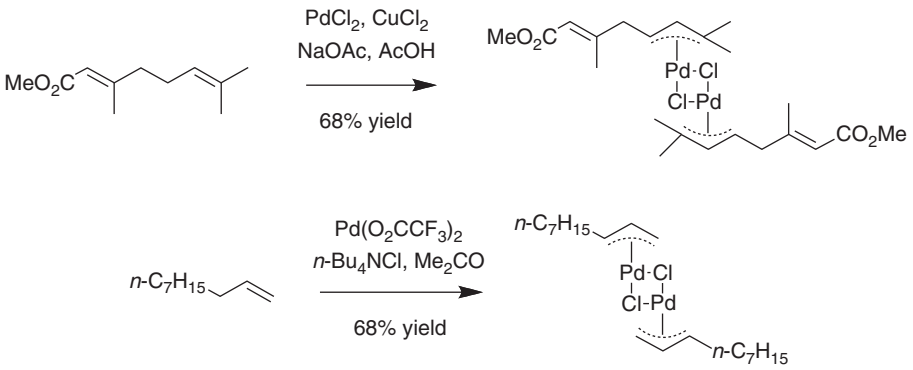
Scheme 14

The vast majority of methods in this area are based on palladium catalysis. One broad approach to allylic C–H functionalization is the oxidative formation of π-allyl palladium intermediates from unactivated alkenes. Some of the early demonstrations of this concept are the efficient formation of *p*-allylpalladium compounds from simple alkenes and a stoichiometric amount of palladium (II) trifluoroacetate or $PdCl_2$ (Scheme 16).[47]

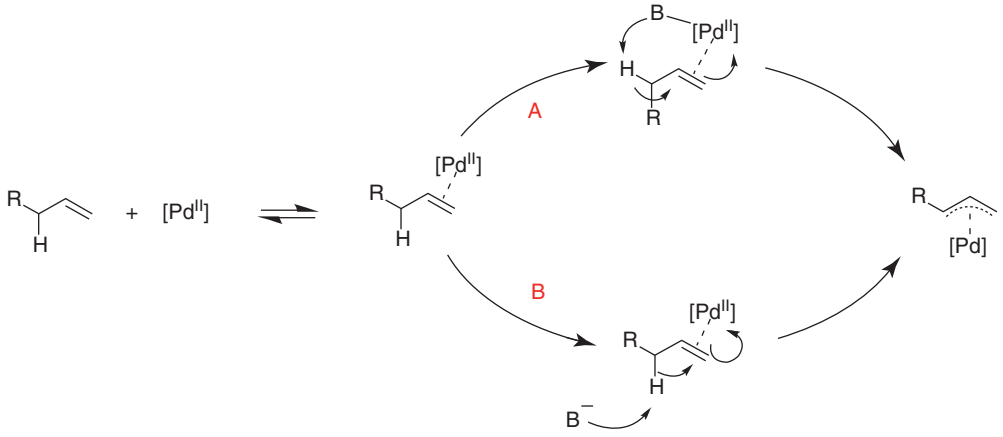
Initial rapid π-complexation of palladium(II) source to the alkene is followed by slow deprotonation. Experimental evidence from mechanistic studies points to two alternatives for this crucial step. In the first one, deprotonation occurs by an intramolecular pathway whereby a ligand on the palladium center serves as the base (Scheme 17, path **A**).[48] The second alternative involves removal of the proton by an external base present in the reaction medium (Scheme 17, path **B**).[49] Since the early discovery of allylic oxidation of cyclohexene to 2-cycohexen-1-yl acetate catalytic in palladium using benzoquinone as the terminal oxidant, expanding the scope to other alkenes has been complicated by competitive Wacker oxidation and other processes. Subsequently, it was found that the reaction course can be influenced in a powerful way by modifying ligands on palladium in the original



Scheme 15



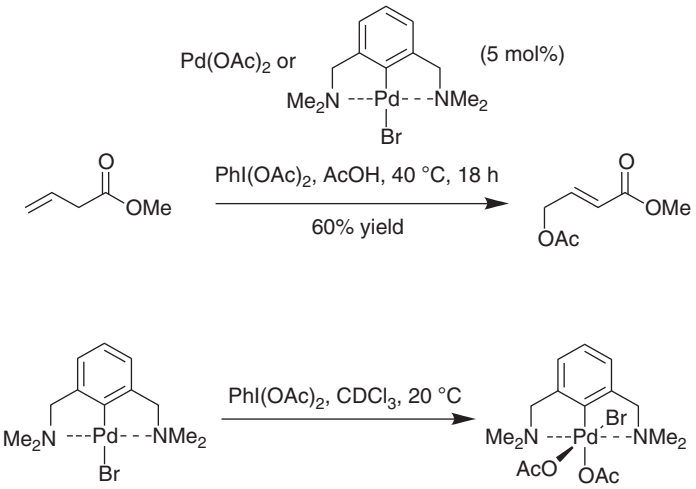
Scheme 16



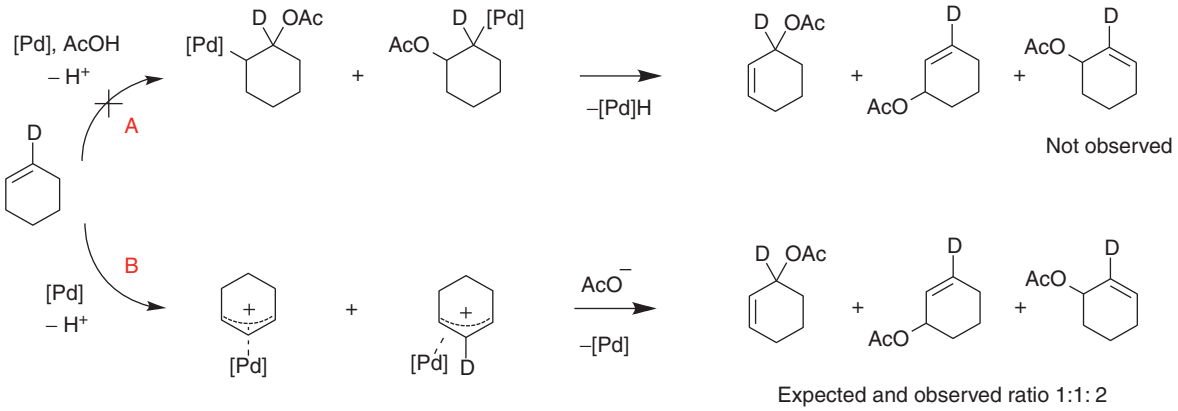
Scheme 17

palladium(II)-benzoquinone system.[50] Specifically, sulfoxide ligands were found to favor the formation of π-allylpalladium species rather than electrophilic addition to the double bond, giving rise to a number of allylic C–H functionalization processes.[51]

Another effective approach to favoring C–H functionalization in lieu of electrophilic addition using palladium catalysis is switching to the Pd(IV)/Pd(II) from Pd(II)/Pd(0) catalytic cycle (Scheme 18).[52–54] It has been found that hypervalent iodine reagents are excellent terminal oxidants for this purpose. Several experiments confirm that these reagents can readily oxidize Pd(II) to Pd(IV) in different species including Pd-pincer complexes such as those shown in Scheme 18.[54,55] Deuterium labeling studies for acetoxylation of cyclohexene unequivocally support a palladium C–H insertion pathway and rule out an alternative acetoxy-palladation pathway to the oxidation product (path **A** vs. path **B**, Schemes 19 and 20).[54]



Scheme 18

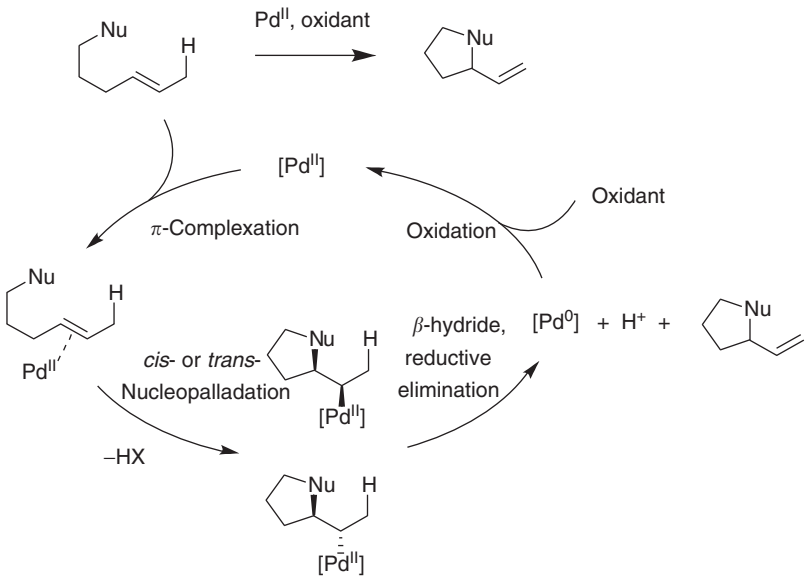


Scheme 19

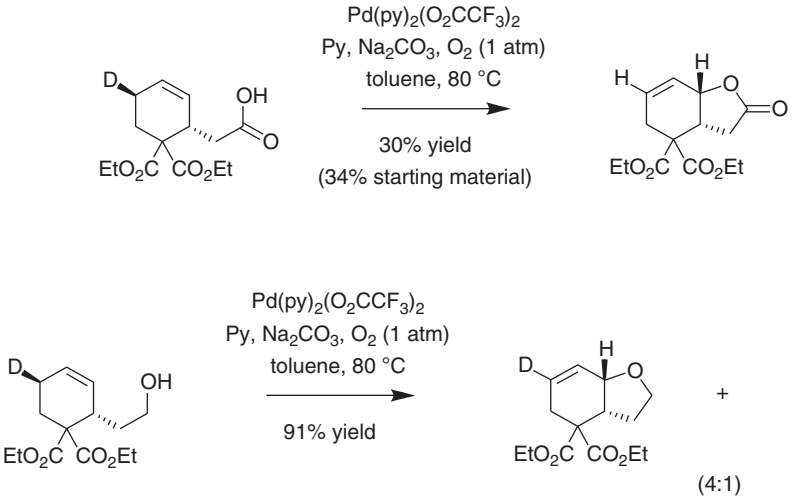
Despite this observation, acetoxy-palladation and other nucleopalladation reactions do represent another broadly feasible approach to the formal C–H functionalization of alkenes.[56] The general catalytic cycle for intramolecular allylic functionalization illustrating this approach is outlined in Scheme 20. The initial π-complexation of the Pd(II) catalyst is followed by an electrophilic addition to the double bond, which can give products of *cis*- or *trans*-nucleopalladation. In certain cases, regioselective β-hydride elimination will take place giving the observed product of allylic functionalization with the transposition of the double bond. The initially formed Pd(II)–H species will undergo a reductive elimination to Pd(0) product, which needs to be reoxidized by a stoichiometric oxidant to complete the catalytic cycle.

Several oxypalladation reactions have been shown to occur by a *cis*- or *trans*-selective pathway.[56] Intramolecular allylic oxidation of the deuterium-labeled cyclohexene derivative incorporating a carboxy group has been found to afford only the product consistent with a *trans*-oxypalladation pathway (Scheme 21).[57] In contrast, the corresponding substrate where the carboxy group is reduced to the primary hydroxy group under identical conditions exclusively affords the products resulting from *cis*-oxypalladation.[57]

A related intramolecular allylic amination reaction with a tosylsulfonamide substrate followed the course suggestive of *cis*-aminopalladation with a variety of palladium catalysts with the exception of the *N*-heterocyclic carbine (NHC)-modified catalyst



Scheme 20



Scheme 21

(IMes)Pd(O_2CCF_3), which gave a mixture of products derived from *cis*- and *trans*-aminopalladation (Scheme 22). When the tosyl group on nitrogen in this substrate was replaced with a nosyl group, lowering the pKa of the NH bond, the products of *cis*-palladation were observed with all catalytic systems studied.[58]

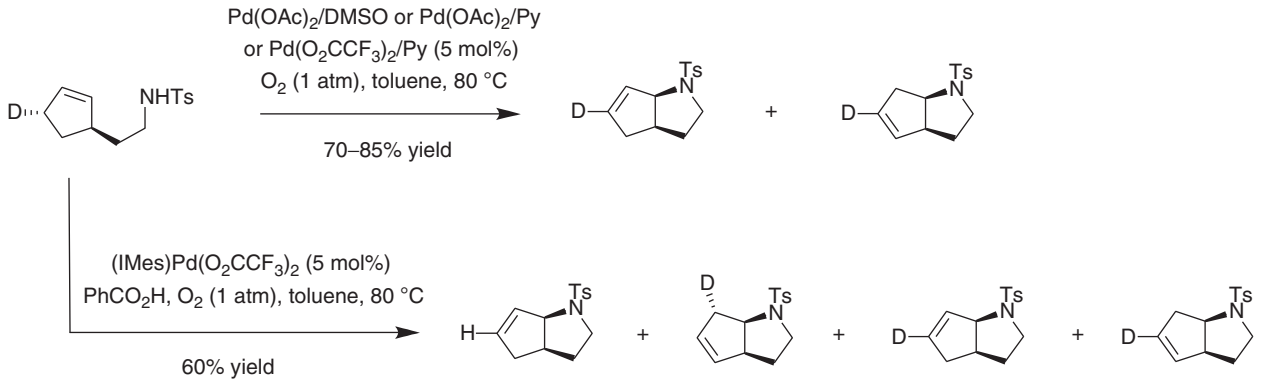
The Pd(II)-catalyzed allylic transposition of trichloroacetimidates follows a different regiochemical course of aminopalladation (Scheme 23).[59] Although formally a [3,3]-sigmatropic rearrangement, the reaction has been postulated to follow a cyclization-induced rearrangement mechanism. Following a complexation of the palladium(II) catalyst to the alkene, a 6-*endo trans*-aminopalladation takes place. The resulting intermediate then undergoes a fragmentation to another Pd-alkene complex, which dissociates to the observed allylic transposition product.

In a copper-catalyzed allylic C–H activation/trifluoromethylation reaction of terminal alkene, the authors proposed Heck-like insertion and elimination process, which was further supported by computation studies. Experimental studies ruled out the radical or π-allyl copper intermediates (Scheme 24).[60]

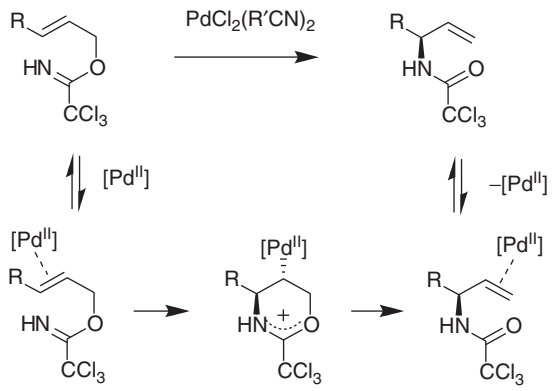
Multiple strategies for allylic C–H functionalization are being actively pursued, and this area of research is experiencing a rapid expansion with a promise to make a substantial impact on the efficiency of organic synthesis.

6.16.2.5 Radical Allylation

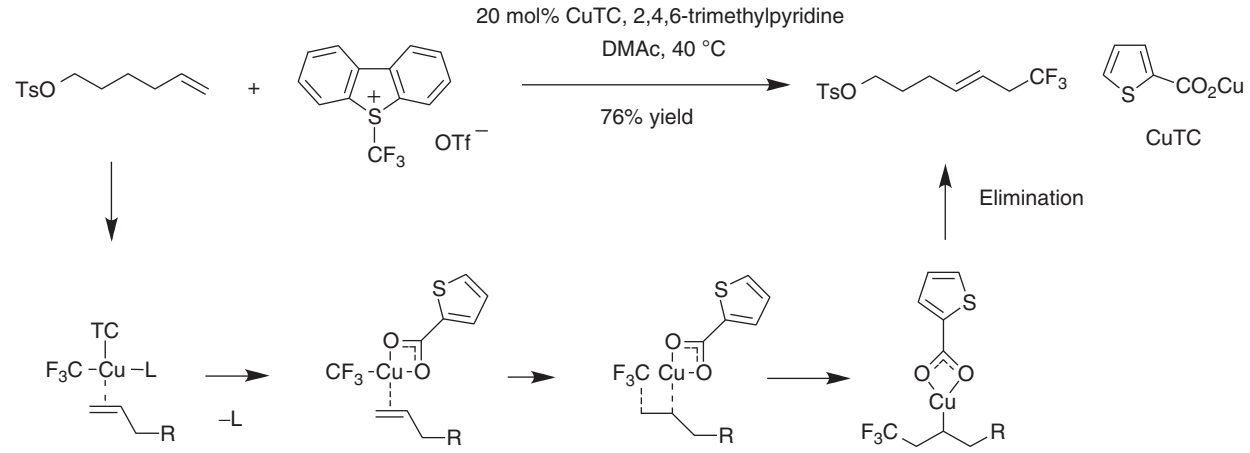
Reactions based on radical reactivity present another rich mechanistic rubric for allylic substitutions. These reactions can follow a general pathway exemplified by allylation of catecholboranes with allylsulfones illustrated in Scheme 25. This is a radical



Scheme 22



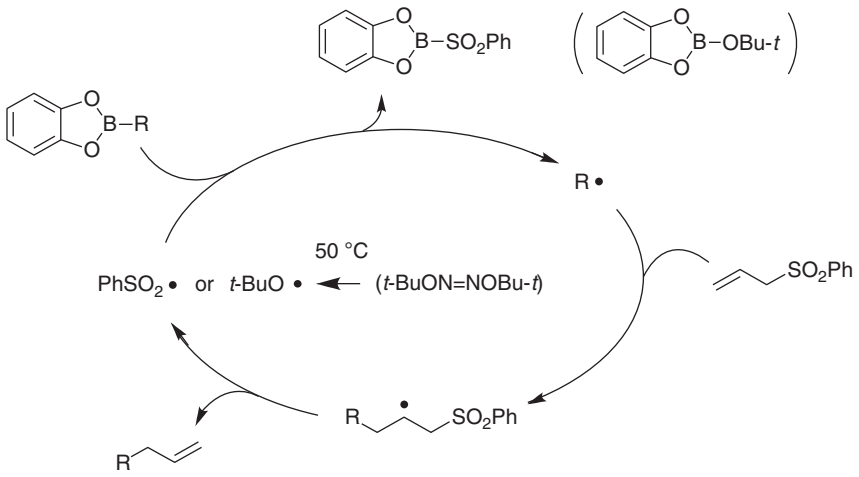
Scheme 23



Scheme 24

addition–elimination pathway, whereby a radical generated from catecholborane, in this case, adds to allyl phenyl sulfone, and the intermediate carbon-centered radical expels a stable arylsulfenyl radical giving the allylation product in a chain process.[61] Allylstannanes and allyl(tristrimethylsiyl)silanes are other commonly used reagents for allylation via a similar radical chain mechanism.[62,63]

An alternative mechanism based on atom transfer radical addition (ATRA) has been proposed for certain reactions involving allyltrimethylsilane. For example, derivatives of α-halo carboxylic acids undergo highly stereoselective Lewis acid-mediated radical allylations with allyltrimethylsilane in the presence of triethylborane as an initiator (Scheme 26a).[64,65] The initially generated



Scheme 25

radical adds to allylsilane at the terminal carbon of the double bond (Scheme 26c). A halogen atom from the substrate is then transferred to this radical, giving the addition product and regenerating the original radical species. The addition product, β-halosilane, is unstable and fragments to the allylation product on isolation or purification through elimination of the halotrimethylsilane. An evidence for this mechanism is provided by the isolation and characterization of the labile ATRA product when α-phenylseleno esters as substrates are used instead of α-haloesters. It has been proposed that two competing transition states account for diastereocontrol in the Lewis acid-mediated radical allylation of β-alkoxy-α-halo esters (Scheme 26b).[64a] Both the semioccupied *p*-orbital is orthogonal to the alkoxy substituent, which is essential for high diastereoselectivity. *Anti*-approach of the allylsilane reagent relative to the R-group is preferred to the *syn*-approach eclipsing the R-group.

6.16.2.6 Ene-Type Reactions

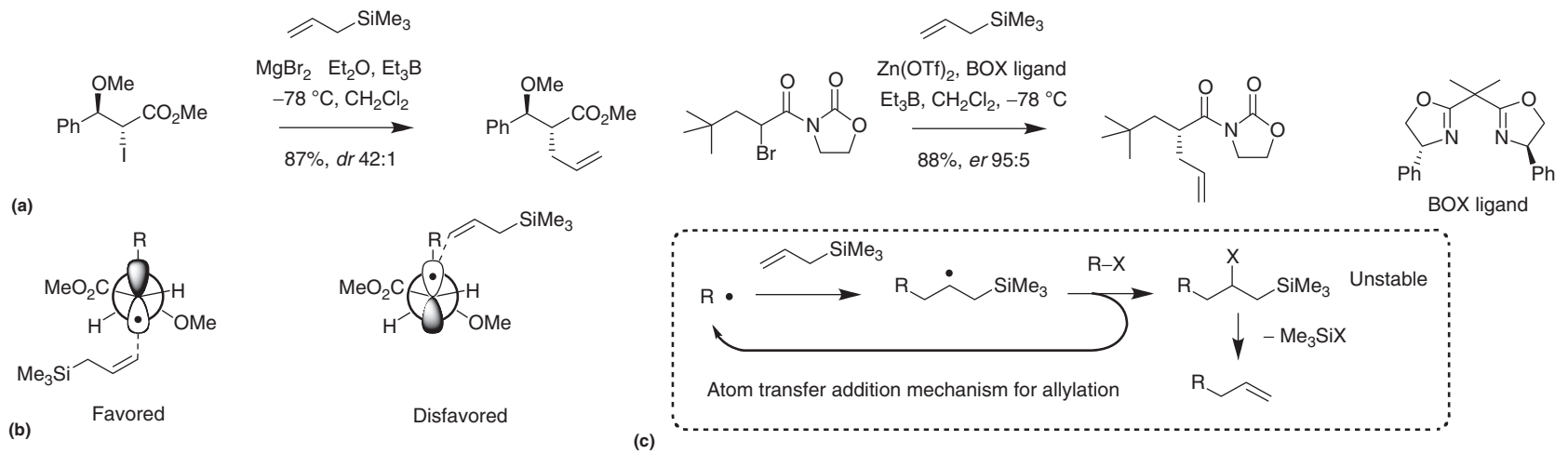
Ene reactions constitute another approach to allylic substitutions formally representing allylic C–H functionalization.[66] Reactions in this class combine alkenes with eneophiles and necessarily occur with allylic rearrangement (Scheme 27). The ene reaction has a broad scope giving best results with electron-defficient hetero-enophiles participating in these synthetically useful transformations.[67] The mechanism of the ene reactions has been the subject of intense investigations that produced interesting controversies. In particular, most recent studies concentrate on the mechanism of the hetero-ene reaction with singlet oxygen,[68] triazolinediones,[69] and nitroso compounds.[70] Many mechanistic continuum proposed for ene reactions include concerted pericyclic and three stepwise paths: diradical, zwitterionic, or a polar pathway such as aziridine *N*-oxide path (ANO) for the nitroso-ene reaction.

Lewis acid-catalyzed ene reaction with carbonyl enophiles has become an important method with many diverse applications in organic synthesis.[66a] Both intramolecular and intermolecular variants of this process have been extensively used. It is generally accepted that the mechanism of Lewis acid-catalyzed carbonyl ene reactions involves either a two-step process with a zwitterionic intermediate or a concerted mechanism with a highly polarized asymmetrical transition state (Scheme 28). In most cases it has been difficult to distinguish between these two mechanistic pathways, however, the consensus appears to be that most Lewis acid-mediated ene reactions of carbonyl compounds are stepwise. For thermal ene reactions the mechanism is influenced by the nature of the substrate and reaction conditions, and evidence for concerted mechanism for some reactions[71] and stepwise mechanism involving diradical intermediates[72,73] for others has been found. Interest in the investigation of a mechanistic picture of ene reactions continues.[74]

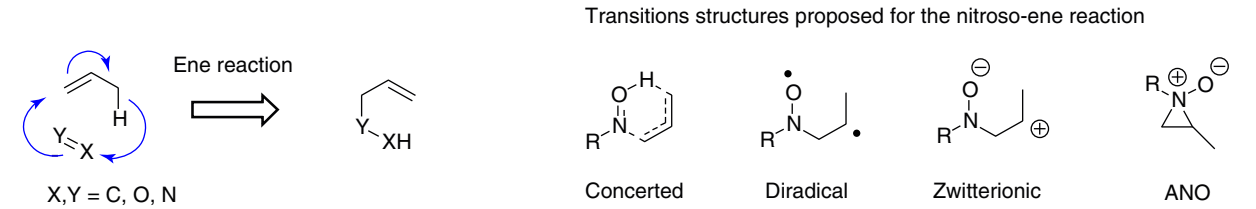
A computational and experimental mechanistic investigation of the rarely utilized aryne-ene reaction, along with a study of its scope and an elegant application in the total synthesis of the alkaloid (±)-crinine has been reported (Scheme 29).[75] Facile cyclization of ene-benzyne intermediate generated from a bromoarene by the action of lithium diisopropylamide (LDA) at room temperature afforded an advanced polycyclic intermediate in good yield as a single diastereomer, which was converted to crinine in eight steps. A Lewis acid-catalyzed ene reaction was used to assemble the remaining ring of the alkaloid.

6.16.2.7 Sigmatropic Rearrangement

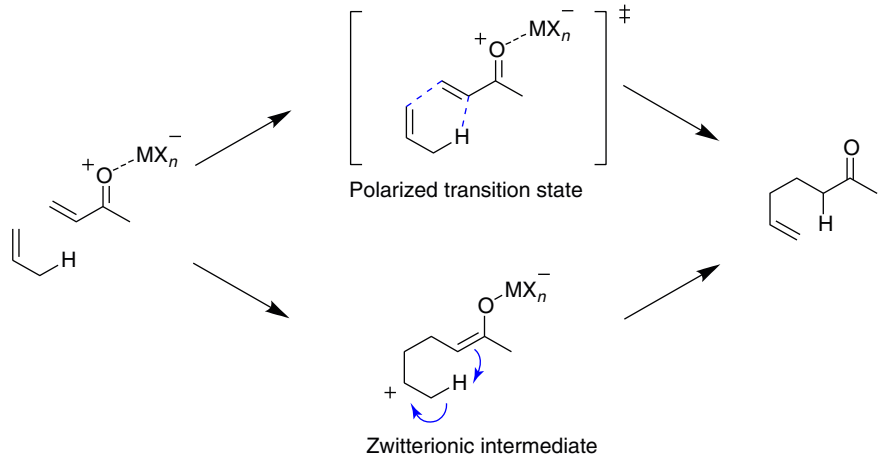
Processes based on sigmatropic rearrangements constitute an especially broad and general collection of methods for allylic rearrangement.[76] By definition, these are intramolecular processes. Nevertheless, sigmatropic transpositions are characterized by broad functional group compatibility and relatively predictable outcomes, and thus have been successfully incorporated in many


(a)
OMe
Ph
CO2Me
I
SiMe3
MgBr2 Et2O, Et3B
–78 °C, CH2Cl2
87%, dr 42:1
OMe
Ph
CO2Me
(b)
R
MeO2C
H
H
OMe
Me3Si
Favored
R
SiMe3
MeO2C
H
H
OMe
Disfavored
(c)
SiMe3
Zn(OTf)2, BOX ligand
Et3B, CH2Cl2, –78 °C
88%, er 95:5
Br
O
O
N
O
BOX ligand
Ph
Ph
R •
SiMe3
R
SiMe3
R–X
X
R
SiMe3
Unstable
– Me3SiX
R
Atom transfer addition mechanism for allylation

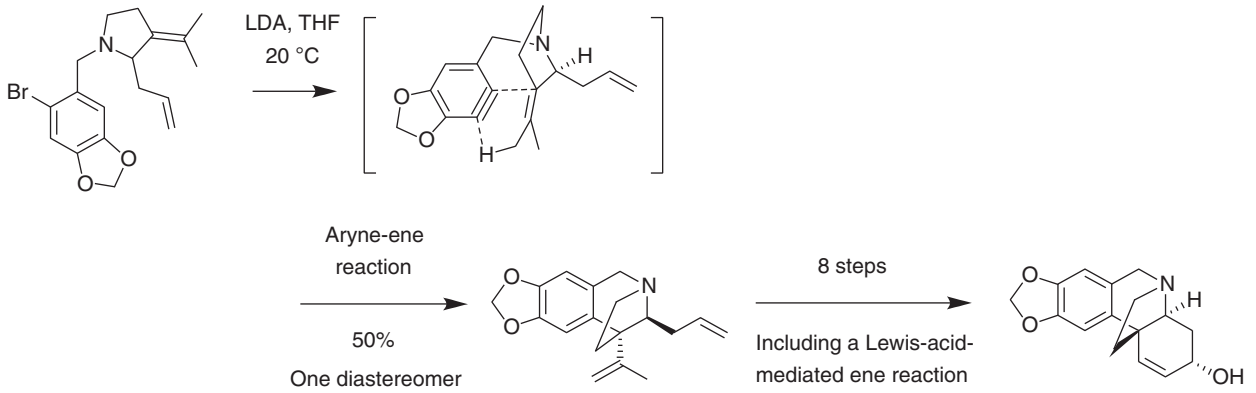
Scheme 26



Scheme 27



Scheme 28

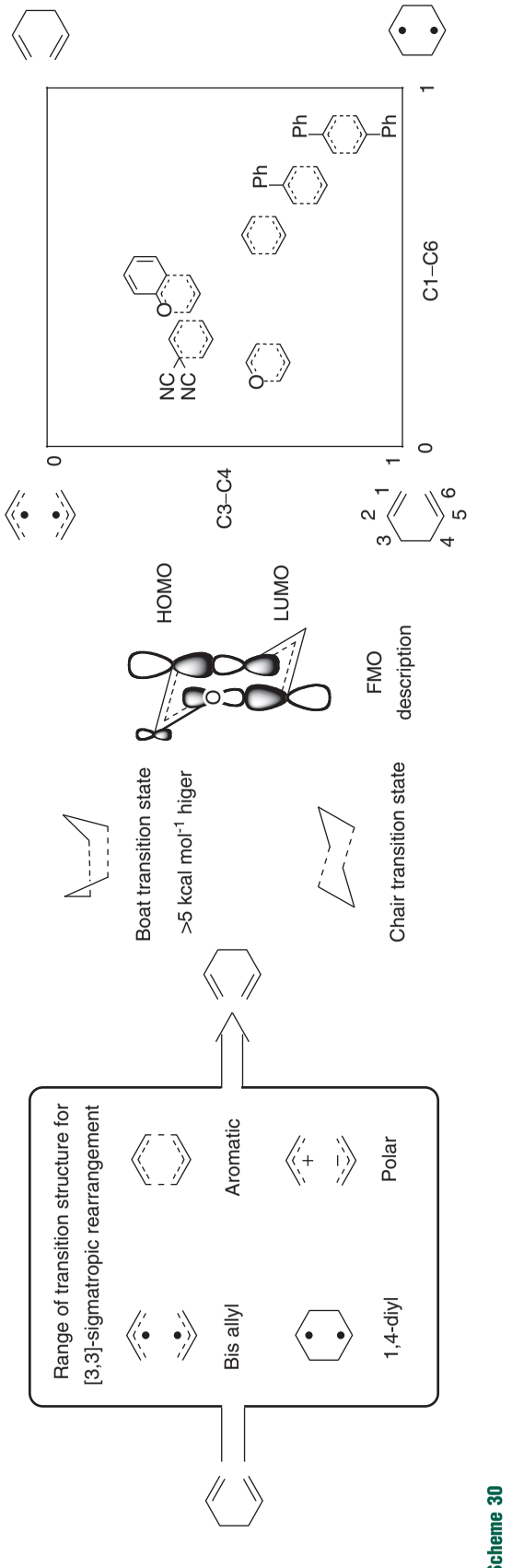


Scheme 29

multistage tandem and domino reactions enabling powerful refunctionalizations with concomitant allylic substitution. High level of stereochemical transmission is another hallmark of sigmatropic rearrangements.

Since their discovery, the mechanism of sigmatropic rearrangements has been the subject of intense investigations and controversies.[77] For the prototypical all-carbon [3,3]-sigmatropic rearrangement of 1,5-hexadiene, the Cope rearrangement,[78] the debate converged on two possibilities, one involving a biradical pathway[79] and another a concerted cyclic pathway with an aromatic transition state.[80] The current consensus is the concerted cyclic aromatic transition state for the Cope rearrangement of 1,5-hexadiene and many related rearrangements such as the Claisen rearrangement. Classic studies with *meso*- and *rac*-3,4-dimethylhexa-1,5-diene demonstrated that the chair-like transition state is the preferred path, which is favored over the alternative boat transition state by 5.7 kcal mol^{-1}.[81]

The mechanism and the rate of [3,3]-sigmatropic rearrangements are affected drastically by substitution and inclusion of charges and heteroatoms within the parent 1,5-hexadienyl system (Scheme 30).[82] The More O'Ferrall–Jencks diagram has been used as a convenient graphic representation of the mechanistic landscape for a range of sigmatropic rearrangements. The *bis* allyl

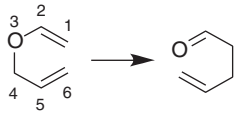

Range of transition structure for
[3,3]-sigmatropic rearrangement
Bis allyl
Aromatic
1,4-diyl
Polar
Boat transition state
>5 kcal mol-1 higer
Chair transition state
HOMO
LUMO
FMO
description
C3–C4
C1–C6
NC
NC
Ph
Ph
Ph
0
1
0
1
1
2
3
4
5
6

Scheme 30

and 1,4-diyl intermediates serve as extremes, where C3–C4 bond-breaking is either leading or lagging formation of the C1–C6 bond.[83] The extent of bond formation or bond scission is shown on the axes. As could be expected, radical-stabilizing substituents at positions C1, C3, C4, and C6 shift the mechanism toward the *bis* allyl radical extreme, whereas substitution-stabilizing radicals at C2 and C5 increase the 1,4-diyl character of the transition state.[77,83] It has been pointed out, however, that the More O'Farrel-Jencks diagram fails to account for the cyclically delocalized nature of the allowed pericyclic transition state.[84] Another level of qualitative understanding of the [3,3]-sigmatropic rearrangement can be derived from the simple frontier molecular orbital (FMO) description of the Claisen rearrangement, for example, as a bonding interaction between the highest occupied molecular orbital (HOMO) of an oxallyl anion and lowest unoccupied molecular orbital (LUMO) of allyl cation, or between the SOMOs of the corresponding oxallyl and allyl radicals.[85] Theoretical analysis of multidimentional bonding changes in sigmatropic rearrangements remains a challenging area of continued research.[86]

Some of the most widely used variants of [3,3]-sigmatropic transposition are the Claisen, the Ireland–Claisen rearrangement,[87] aza-Cope rearrangement, and oxy-Cope rearrangement; the latter two are examples of a phenomenon known as charge-accelerated sigmatropic transposition.

Experimental values for substituent effects on the rate of Claisen rearrangement normalized to the rate of the parent allyl vinyl ether (AVE) system are shown in **Scheme 31**. The influence of the cyano group at each position has been measured.[88] Rate acceleration has been observed at positions C2, C4, and, to a lesser extent, C5. The rearrangement rate decreased slightly for the 2-cyano derivative, with a stronger deceleration for the 6-cyano derivative. A similar effect was observed for other π-acceptor substituents. Thus, 2-methoxycarbonyl substitution at C2 results in a 52-fold rate enhancement, whereas no reaction is observed at 100 °C for the 6-methoxycarbonyl analog.[89]



Substituent	1-CN	2-CN	4-CN	5-CN	6-CN	2-CO_2Me	2-CO_2^-	2-CH_3	4-OMe	5-OMe	2-$OSiMe_3$
Rate relative to allyl vinyl ether	0.90	111	270	15.6	0.11	52	24	13	96	0.025	3×10^6

Scheme 31

The accelerating effect of electron-donors at C1 has been reported for oxyanoin,[90] amino,[91] fluoro,[92] and methyl groups.[93] Quantitative data for the effect of methoxy substitution at C4, C5, and C6 reveal rate enhancement at C4 and C6 by a factor of 96 and 9.5, respectively, and a notable 40-fold deceleration for the 2-methoxyallyl vinyl ether (C5 substitution).[94] An especially powerful rate acceleration is observed for the Ireland–Claisen rearrangement, which is characterized by the presence of a 2-trimethylsiloxy group. In this case, a 9 kcal mol^{-1} decrease in activation energy relative to AVE has been reported, corresponding to rate constant increase by a factor of 3×10^6.[95]

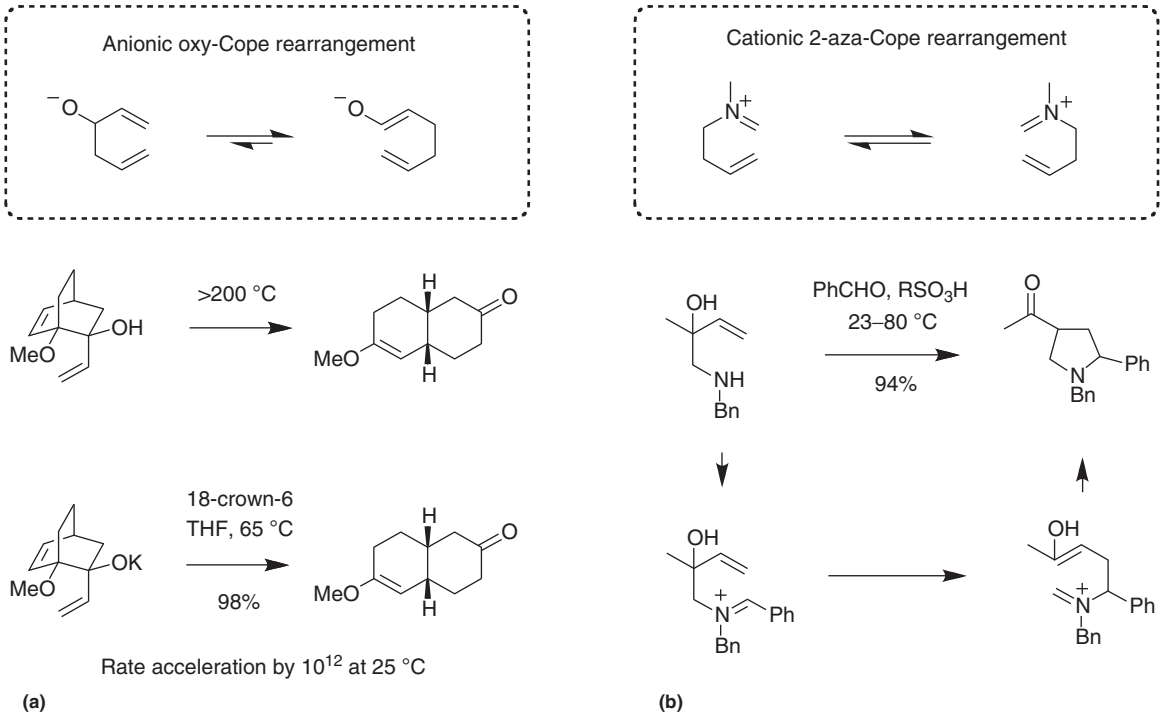
Based on available experimental data, the following generalizations can be made for the effect of substituents on the rate of Claisen rearragement. Electron-donating groups at positions C1, C2, C4, and C6 increase the rate of the rearragement, with a particularly strong effect for C2 substitution. Electron-donating groups at C5 position lower the rate, and the effect is notably stronger for π-donors. Electron-acceptor groups at C2, C4, and C5 positions exert a positive influence on the reaction rate, while slightly lowering the rate at the C1 and, to a greater extent, C6 positions. Theoretical analysis of the substituent effect on Claisen rearrangement using density functional theory (DFT), *ab initio* calculations, and other methods provides calculated values consistent with these observations, indicating the intermediacy of polarized transition states with a greater degree of bond-breaking.[96]

The anionic oxy-Cope and aza-Cope rearrangements are examples of charge-accelerated sigmatropic rearrangements with demonstrated synthetic utility. For the anionic oxy-Cope rearrangement, rate accelerations by over 10^{12} have been observed under strongly ionizing reaction conditions (**Scheme 32a**).[97] The effect has been largely attributed to charge delocalization in the transition state, which is absent in the starting material, and the associated weakening of the C3–C4 bond.[98] Another powerful rate enhancement, that by a factor of approximately 10^{10}, has been observed in cationic 2-aza-Cope rearrangements, which takes place at temperatures 100–200 °C lower than rearrangements of uncharged hydrocarbon counterparts (**Scheme 32b**).[99]

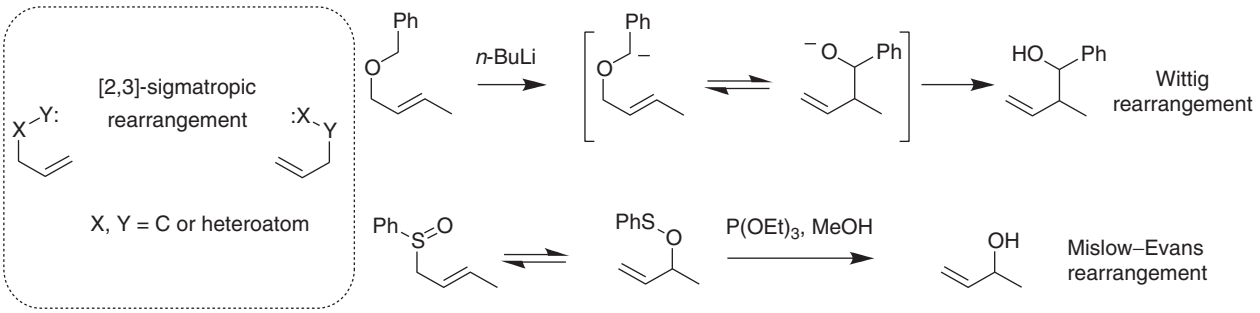
Many other types of sigmatropic rearrangement reactions have been developed and studied, especially for systems containing heteroatoms.[100] Some of the most common of these are based on [2,3]-sigmatropic reorganization, examples of which are the 2,3-Wittig rearrangement[101,102] and Mislow–Evans rearrangement (**Scheme 33**).[103] 1,3-Transpositions have also been used in reactions leading to allylic rearrangement products.[104]

6.16.2.8 Mechanistic Diversity of Allylic Transpositions

It is clear that allylic transposition reactions can take place through an astoundingly broad array of mechanistic pathways. Allylic transposition has served as a valuable probe in understanding organic reaction mechanisms. For many, several mechanisms are operative concurrently and their relative contribution can be shifted in one direction or the other by varying the substitution pattern of the substrate, the nature of the reagent, or reaction conditions. It is not surprising therefore that reactions featuring allylic substitution constitute a significant portion of organic chemistry, and new valuable methodologies continue to be developed at an impressive pace.



Scheme 32



Scheme 33

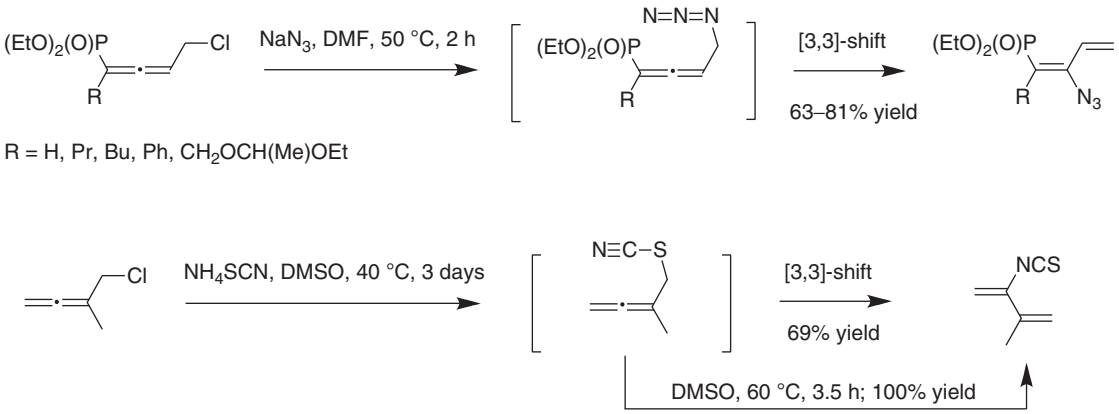
6.16.3 Heteroatom Transpositions

6.16.3.1 1,3-Halogen-to-Nitrogen Transpositions

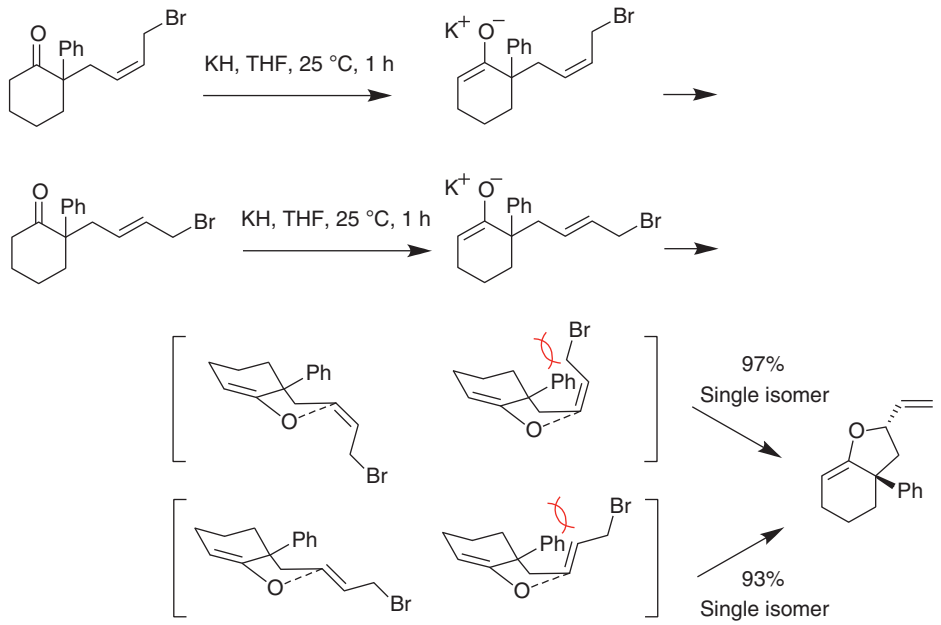
Since 2000, there have only been a few reports of displacement of allylic halides with nitrogen nucleophiles taking place with allylic transposition. The normally expected course of reaction is a direct S_N2 substitution. Examples in Scheme 34 demonstrate cases of formal S_N2' processes following a two-step mechanism beginning with a direct S_N2 substitution with azide or thiocyanate followed by a [3,3]-sigmatropic transposition, affording 2-azido-1,3-dienes or allenyl isothiocyanates as products, respectively, in good or excellent yields.[105,106] In the latter example, 4-thiocyano-3-methyl-1,2-butadiene can be isolated. Its sigmatropic transposition is complete within 3.5 h at 60 °C in quantitative yield.

6.16.3.2 1,3-Halogen-to-Oxygen Transpositions

Direct S_N2' substitutions of allylic halides with oxygen nucleophiles are rare and can be complicated by low regioselectivity. Substitution at the least sterically hindered position is normally preferred. High preference for allylic substitution can be expected in intramolecular reactions forming small or medium-size rings, however, in these cases allylic halides are often unstable and cyclize spontaneously on formation *in situ*. An example in Scheme 35 illustrates an intriguing example of such a process where a



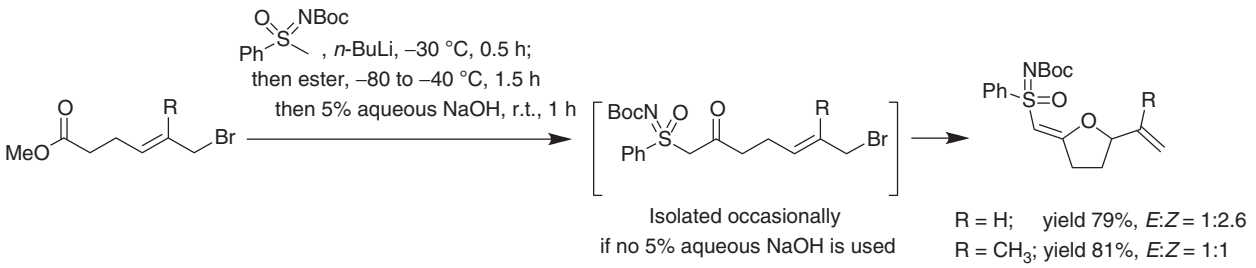
Scheme 34



Scheme 35

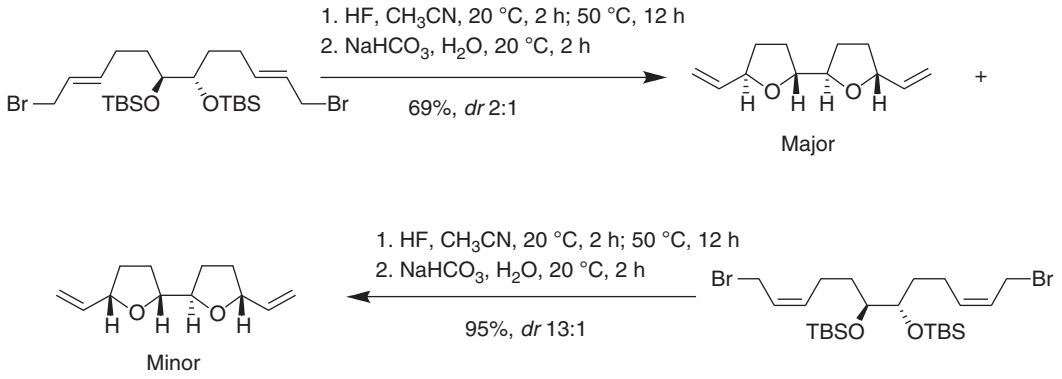
potassium enolate engages in an intramolecular S_N' displacement of an allylic bromide, efficiently forming a cyclic allylic enol ether.[107,108] The reaction is highly diastereoselective, and the configuration of the product is not influenced by the geometry of the double bond in the allylic bromide. The stereochemical course of the reaction can be readily understood on the basis of simple conformational analysis of the transition structures (Scheme 35).

A related process was reported for α-sulfoximino ketones formed *in situ* from esters containing an allylic bromide subunit (Scheme 36).[109] Little stereocontrol for the enol ether double bond configuration was observed, and occasionally an α-sulfoximino ketone that failed to undergo cyclization was isolated as a major product if the final basic aqueous quench was omitted.



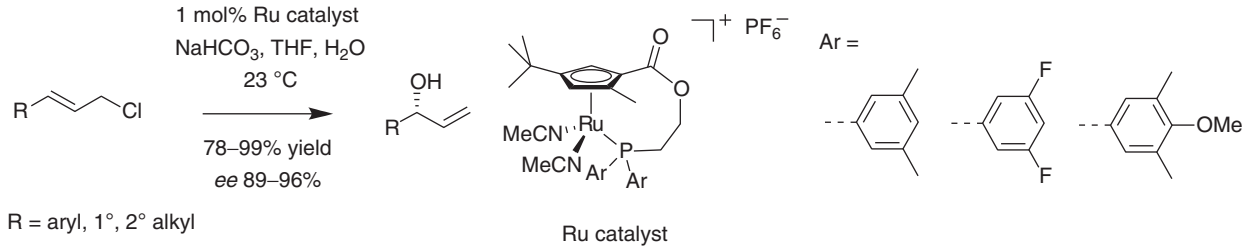
Scheme 36

A bidirectional allylic displacement of bromide with a hydroxy group has been utilized in the synthesis of a C2-symmetrically linked tetrahydrofuran (THF) fragment of acetogenins (Scheme 37). A considerably higher yield and diastereocontrol was observed for the cyclization of the *Z*-allylic bromide, which delivered the two diastereomeric products in 95% yield and 13:1 selectivity favoring the C2-symmetrical product. The first tetrahydropyran ring is formed partially on desilylation with aqueous HF in acetonitrile. Additional heating at 50 °C for 12 h is necessary to complete the first cyclization. Notably, closure of the second cyclic ether required a separate treatment with sodium bicarbonate.[110]



Scheme 37

Few metal-mediated allylic halogen displacements have been developed. In a rare example of enantioselective catalytic substitution with water, secondary allylic alcohols have been generated from primary allylic chlorides in the presence of the chiral ruthenium catalyst. Although the aryl substituent on the phosphine center in the catalyst needs to be tuned for each type of substrate, catalysts with the three aryl groups shown in Scheme 38 give excellent enantioselectivity covering the scope of substrates that includes cinnamyl chlorides (R=Ar), as well as aliphatic allylic chlorides where the R-group is either a primary or a secondary alkyl group. The presence of a primary *tert*-butyldiphenylsilyl ether is tolerated. The yield in this enantioselective hydrolysis reaction is generally high for the reported set of substrates.[111]

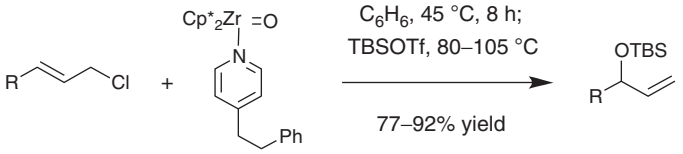


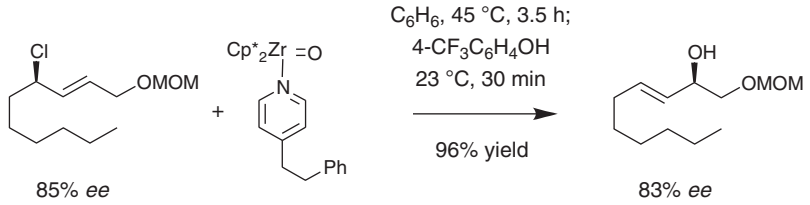
Scheme 38

A regioselective displacement of an allylic chloride with oxygen has been observed with zirconium oxo compounds incorporating a pyridine ligand. These substitution reactions, which require a stoichiometric amount of the zirconium reagent, take place with outstanding regioselectivity in favor of S_N2'-substitution. The products are isolated after silylation of the initially produced zirconium alkoxide with a trialkylsilyl triflate. An excellent suprafacial transfer of chirality was observed with chiral allylic chloride shown in Scheme 39. In this reaction, the allylic alcohol was isolated in excellent yield and almost complete retention of chirality on treatment of the intermediate zirconium alkoxide with 4-(trifluoromethyl)phenol. A coordination of the zirconium reagent to the chloro group was suggested as a rationale for the observed stereochemical outcome.[112]

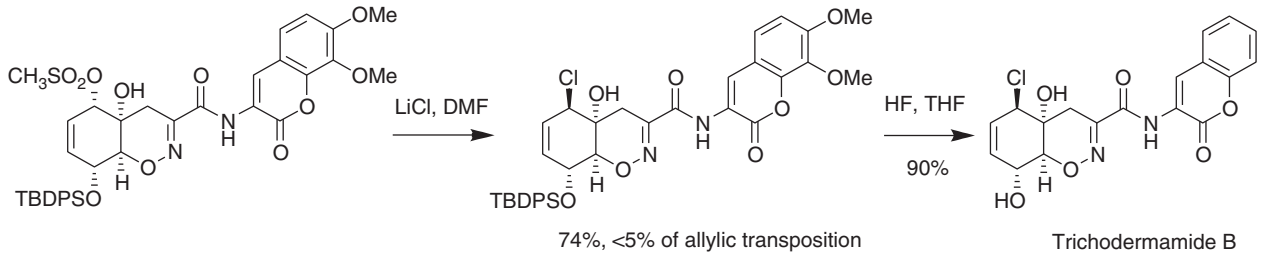
6.16.3.3 1,3-Oxygen-to-Halogen Transpositions

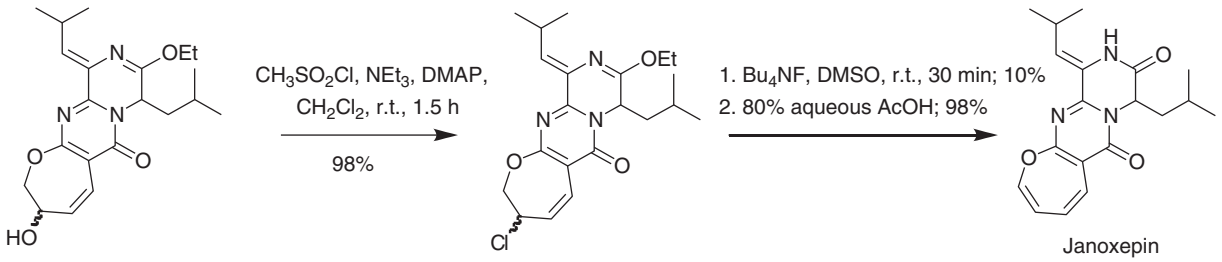
The majority of substitutions of allylic hydroxy groups and their derivatives with halides occur as typical nucleophilic displacements, which tend to give products of direct substitution rather than S_N' products. An example of this selectivity was observed in the total synthesis of trichodermamide B (Scheme 40).[113] With many allylic alcohols, chlorides can be expected to be major products on tosylation or related alkylsulfonation reactions with sulfonyl chlorides, because the chloride anion produced during sulfonation displaces the newly introduced allylic sulfonyl group *in situ*. The final stages of the total synthesis of janoxepin exemplify this transformation, in which the allylic chloride is obtained rapidly from the cyclic allylic alcohol in a nearly

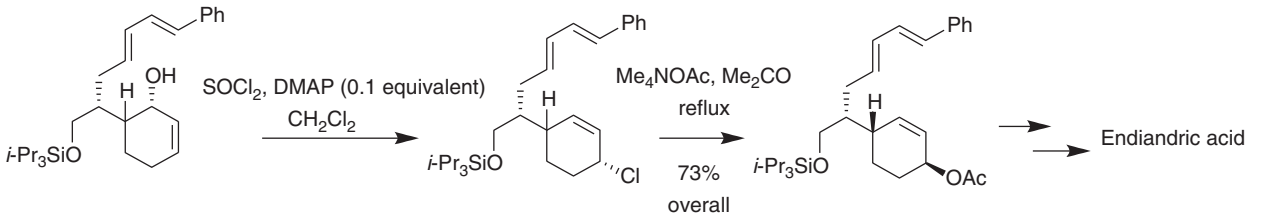


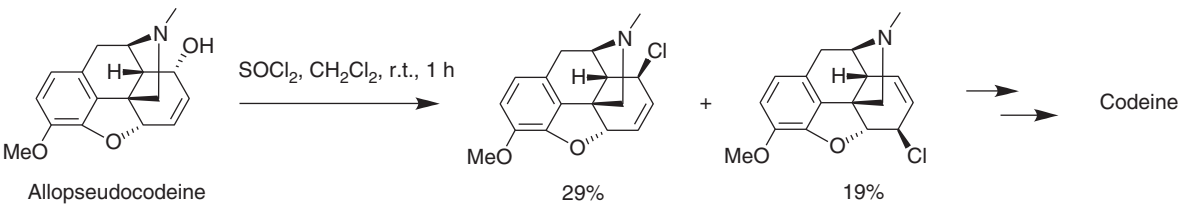


Scheme 39





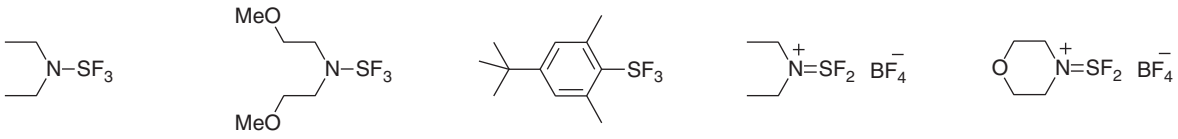




Scheme 40

quantitative yield on treatment with CH_3SO_2Cl.[114] Thionyl chloride has been used traditionally as the reagent of choice to ensure a high degree of selectivity in favor of allylic transposition, however, the outcome is often less predictable than desired. In the total synthesis of endiandric acid, the difficult allylic transposition took place in >73% yield and high regio- and stereoselectivity to give the product of allylic substitution with retention of configuration.[115] The reaction, however, is often more complicated and dependent on reaction conditions and, to a greater extent, the structure of substrate. This is illustrated in the total synthesis of codeine reported in 2011.[116] When allopseudocodeine was treated with thionyl chloride, a nearly equimolar mixture of regioisomeric products was produced with retention of configuration. Examples of clean S_N2-type substitutions with inversion of configuration with thionyl chloride are also known.[117]

Many allylic 1,3-oxygen-to-halogen transpositions reported in the literature produce allylic fluorides or chlorides, whereas clear unambiguous examples of S_N' transpositions leading to allylic bromides or iodides are very rare. Allylic fluorodehydroxylations have been performed with established reagents such as (diethylamino)sulfur trifluoride (Et_2NSF_3, DAST) and *bis*(2-methoxyethyl) aminosulfur trifuloride ($(MeOCH_2CH_2)_2NSF_3$, Deoxofluor), as well as the newer reagents iodine pentafluoride – triethylamine hydrofluoride mixture (IF_5:Et_3N:HF 1:1:3),[118] 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead),[119] diethylaminodifluorosulfinium tetrafluoroborate (XtalFluor-E), and morpholinodifluorosulfinium tetrafluoroborate (XtalFluor-M, **Scheme 41**).[120] Of these, applications employing DAST are prevalent.



Scheme 41

A study aimed at the synthesis of fluorinated cyclic *β*-amino acid derivatives provides a direct comparison of the performance of DAST, Deoxyfluor, and Fluolead in allylic fluorination of diastereomeric functionlalized cyclohexenols (**Scheme 42**).[121] For both stereoisomers, Fluolead afforded no fluorodehydroxylation products and instead induced ring-closure to the cyclic carbamate. Application of DAST and Deoxofluor gave similar results. With the all-*cis* isomer, direct substitution was observed giving an equimolar mixture of stereoisomers in good yields. However, the substrate epimeric at the *α*-position with respect to the ester group gave the product of allylic transposition with retention of configuration predominantly. The product of direct S_N2 substitution was the minor component of the mixture for both reagents. Based on the stereochemical evidence, the results were rationalized by considering the S_N1-type mechanism for the all-*cis* isomer, and a switch to a combination of the S_Ni' (for the major product, transition structure shown) and S_N2-type mechanisms for its epimer.[121]

Fluorination with allylic transpositions can be accomplished in a more complex process using NHC redox-neutral catalysis and an electrophilic source of fluorine (**Scheme 43**). The substrates in this reaction are esters and carbonates derived from *γ*-hydroxy enals, which produce *α*-fluoro-*β*,*γ*-unsaturated esters. The reaction occurs via a Breslow-type zwitterionic intermediate, which undergoes a preferential electrophilic fluorination with $FN(SO_2Ph)_2$ at the *α*-position on the less hindered *α*-face of the dienolate.[122]

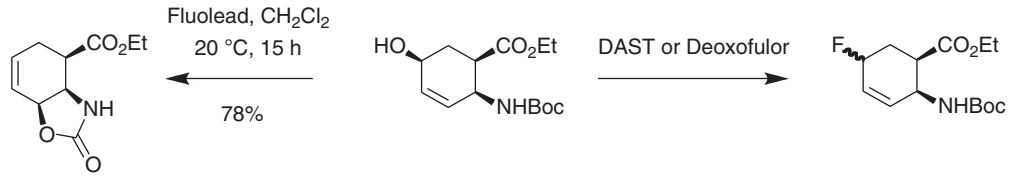
Metal-catalyzed allylic fluorinations reported thus far tend to give products of direct substitution with no allylic transposition. Both palladium- and iridium-catalyzed processes afford allylic fluorides from allylic *p*-nitrobenzoates or trichloroimidates, respectively; however, no preference for allylic transposition has been demonstrated.[123,124]

A rare example of a conversion of secondary allylic alcohol to a primary allylic bromide has been observed during the course of the total synthesis of (+)-morusimic acid B.[125] Phosphorous tribromide is the reagent used in this moderately regioselective reaction that afforded a 2:1 ratio of isomers favoring allylic transposition. The outcome of this reaction can be readily understood based on steric hindrance grounds for an S_N2'-type process.

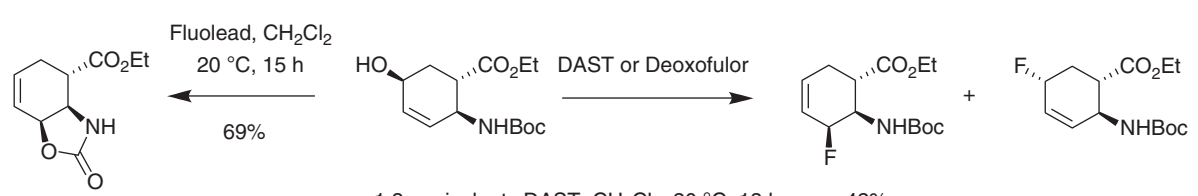
6.16.3.4 1,3-Oxygen-to-Nitrogen Transpositions

Allylic displacement of oxy-substituents with nitrogen-based groups is a powerful approach to the synthesis of functionalized amines. A classic early realization of this approach is a thermal or catalytic 1-aza-3-oxa-Cope rearrangement of allylic imidates (Overman rearrangement).[126] A highly enantioselective rearrangement of allylic trichloroacetimidates has been challenging likely due to competitive complexation of trichloroacetimidate to palladium. This challenge has been overcome by employing cobalt oxazoline palladacycle (COP) catalysts (**Scheme 44**).[127] Initially the efficacy of the COP catalysts has been shown for *N*-aryl imidates, and the scope was extended to the more versatile allylic trichloroacetimidates. The second-generation monomeric COP-hfacac and COP-acac catalysts offer the advantage of improved solubility in a broader range of organic solvents while preserving the high enantioselectivity and chemical yields.[127b]

Thermal and palladium-catalyzed rearrangements of analogous substrates such as allylic imidodiazophospholidines,[128] allylic phosphorimidates,[129] and 2-allyloxypyridines[130] have also been described.

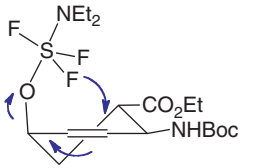


1.3 equivalents DAST, CH_2Cl_2, 20 °C, 13 h: yield 55%, *dr* 1:1
1.5 equivalents Deoxyfluor, CH_2Cl_2, 20 °C, 13 h: yield 63%, *dr* 1:1



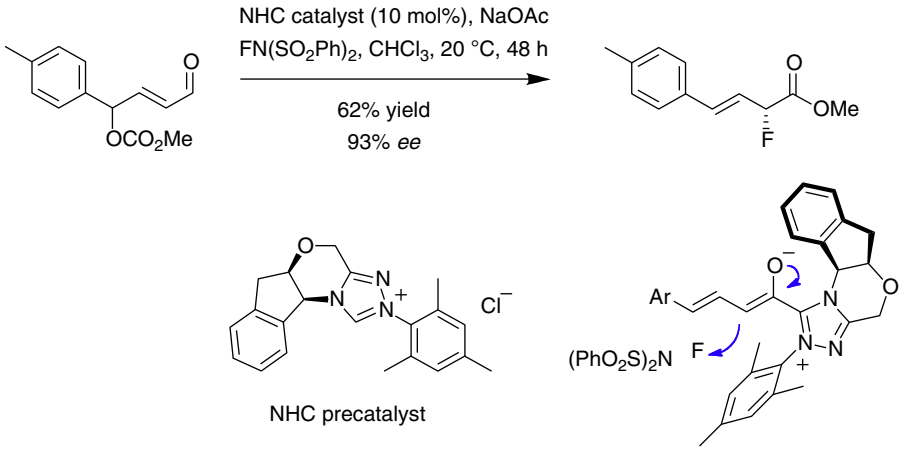
1.3 equivalents DAST, CH_2Cl_2, 20 °C, 13 h: 42%
1.5 equivalents Deoxyfluor, CH_2Cl_2, 20 °C, 13 h: 41%

31%
27%



Transition structure leading to the major product

Scheme 42



Scheme 43

Similar rearrarrangements of allylic *N*-aryl trifluoroimidates have been developed, offering the advantages of high enantioselectivity, functional group tolerance, and facile removal of the *N*-trifluoroacetate group for the amine deprotection (Scheme 45). One approach utilizes a novel palladacyclic precatalyst, PPFIP-Cl, which is converted to its more active, oxidized paramagnetic Pd (III) variant in the presence of silver salt additives.[131] Another approach is based on counteranion-directed palladium catalysis, where a [1,1'-binaphthalene]-2,2'-diol (BINOL)-derived phosphate serves as a chiral counterion. Analysis of the mismatched catalyst system, the (R)-Pd and (S)-TRIP-Ag, confirmed that the chiral phosphate rather than the chiral palladacycle is the primary enantio-directing component in the rearrangement reaction.[132]

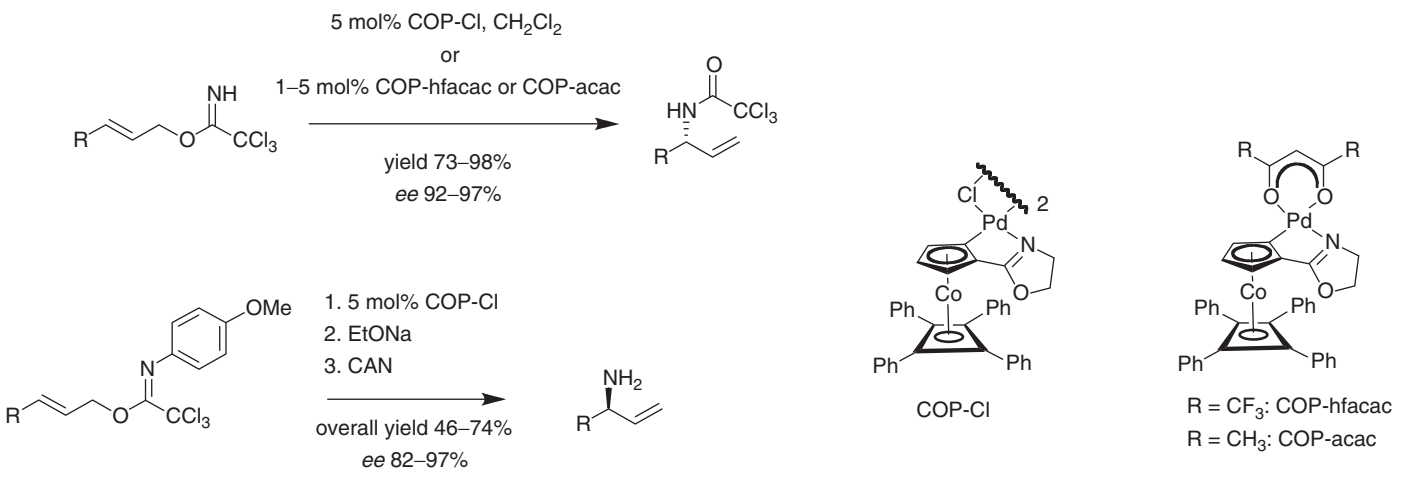
A related, practical method for O→N allylic substitution is the [3,3]-sigmatropic transposition of allylic cyanates to allylic isocyanates (Scheme 46).[133] A major advance in the synthetic utility for this reaction was realized through improved preparation of allylic cyanates by *in situ* dehydration of allylic carbamates.[134] Two reagent systems for this purpose have been developed originally; one uses trifluoromethanesulfonic anhydride, and the other CBr_4-PPh_3 system. Allylic cyanates are unusually reactive and the [3,3]-sigmatropic transpositions typically occur under mild conditions at temperatures below 0 °C.

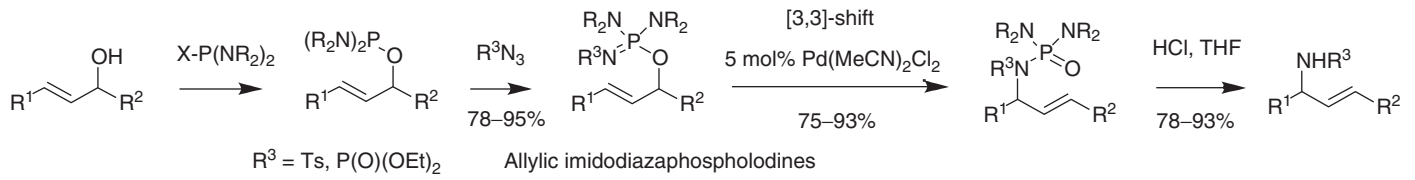
Iridium-catalyzed allylic amination has emerged as a powerful general approach to the asymmetrical synthesis of branched allylic amines from primary allylic alcohol derivatives (Scheme 47). The scope of the amine source is broad, and aliphatic amines,[135] aromatic amines,[136] trifluoroacetamide,[137] imides,[138] sulfonamides,[138,139] and ammonia[140] are all suitable nitrogen donors, giving branched allylation products with high regioselectivity, yield, and generally high enantioselectivity exceeding 90% in most cases studied. Chiral phosphoramidite ligands constructed from BINOL and C_2-symmetrical *bis*(1-arylethyl)amines[141] have proven to be the ligands of choice in forming the active catalytic species by cyclometallation from the iridium precatalyst $[(1,5\text{-cyclooctadiene (COD)})IrCl]_2$.[36]

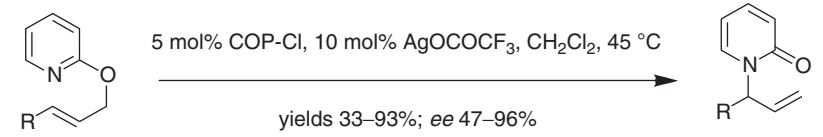
A few examples of acyclic allylic transpositions catalyzed by gold(I) compounds have been reported (Scheme 48). Allylic *N*-tosylcarbamates have been shown to provide allylic *N*-tosylamines by an effective decarboxylative transposition, which is believed to occur by a cyclization-induced rearrangement mechanism similar to that proposed for Pd-catalyzed Overman rearrangement.[142] The catalyst is a combination of AuCl and AgOTf, and water was found to be a suitable solvent for certain substrates. A similar catalytic system without silver trifluoromethanesulfonate is also an effective catalyst for rearrangement of allylic trichloroacetimidates.[143]

Ring-forming direct displacements of unfunctionalized hydroxy groups with amines, amides, carbamates, or sulfonamides provide a direct route to pyrrolidines and piperidines (Scheme 49). This process is characterized by a high level of chirality transfer when chiral allylic alcohols are used.[144] It is not clear whether the *Z*-configuration of the allylic double bond is required for efficient chirality transfer. Catalytic asymmetrical version of this reaction has also been developed for achiral substrates, allowing access to the five- and six-membered heterocycles in practical levels of enantioselectivity and excellent yields.[145] A more active catalytic system for similar transformation utilizes $CpRu(MeCN)_3PF_6$ as precatalyst with pyridine-based chiral ligand Cl-Naph-PyCOOAll. The reactions are typically complete within 3 h at 100 °C with 1 mol% of the catalyst, giving cyclization products in high yields and enantiomeric excess (*ee*) with different classes of substrate, including aliphatic and aromatic carbamates, sulfonamides, and imides.[146] In another ring-forming process, a palladium-catalyzed cascade reaction provides *cis*-substituted isoindolines from arylboronic acids and aromatic imines bearing an allylic acetate moiety at the *ortho*-position.[147] The reaction is believed to proceed through an initial Pd-assisted nucleophilic addition of arylboronic acid to the *N*-tosylimine, forming a Pd amide intermediate, which then continues via aminopalladation of the proximal double bond. The product formation is complete following *β*-acetoxy elimination, forming a palladium acetate by-product returned to the catalytic cycle.

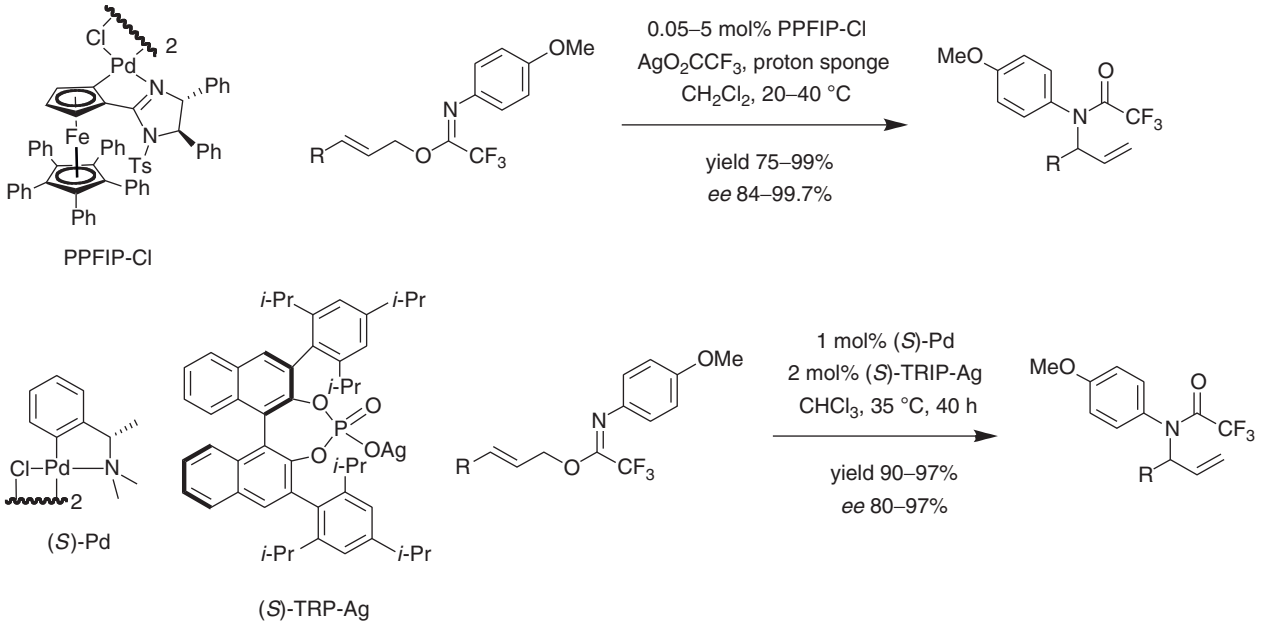
Illustrative applications of oxygen-to-nitrogen allylic transpositions in the synthesis of natural products are shown in Scheme 50. A highly stereoselective thermal Overman rearrangement has been employed for the installation of the sole stereocenter in alkaloids (−)-antofine and (−)-cryptopleurine. An essentially complete transfer of chirality was noted for this reaction, the product of which was used divergently to complete the synthesis of both alkaloids.[148] A Pd-catalyzed displacement of acetate with an amide group has


5 mol% COP-Cl, CH2Cl2
or
1–5 mol% COP-hfacac or COP-acac
yield 73–98%
ee 92–97%
1. 5 mol% COP-Cl
2. EtONa
3. CAN
overall yield 46–74%
ee 82–97%
COP-Cl
R = CF3: COP-hfacac
R = CH3: COP-acac
R = primary, secondary alkyl, containong ether, ester, amine, amide functional groups

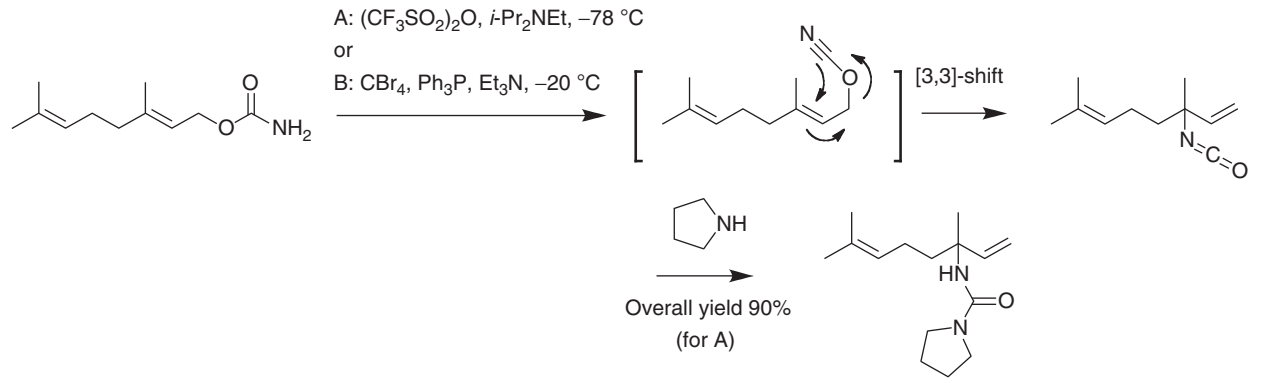

X-P(NR2)2
R3N3
78–95%
[3,3]-shift
5 mol% Pd(MeCN)2Cl2
75–93%
HCl, THF
78–93%
R3 = Ts, P(O)(OEt)2
Allylic imidodiazaphospholodines


5 mol% COP-Cl, 10 mol% AgOCOCF3, CH2Cl2, 45 °C
yields 33–93%; ee 47–96%

Scheme 44



Scheme 45



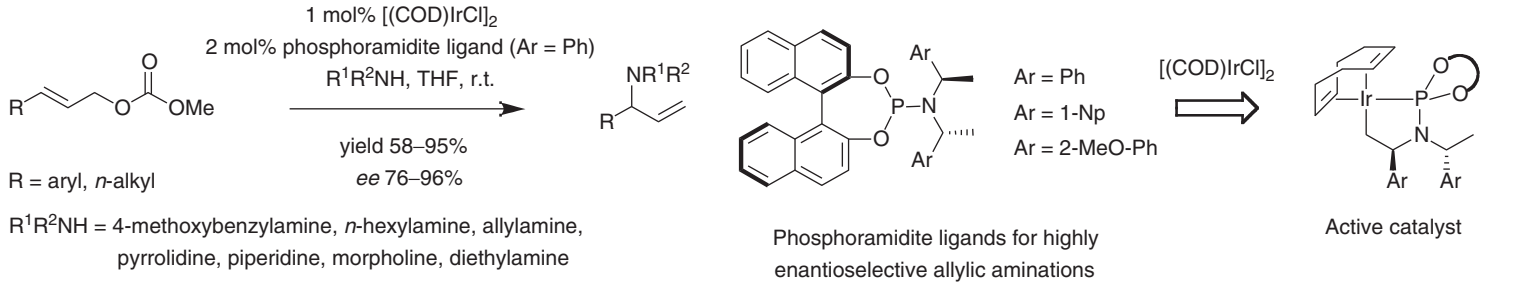
Scheme 46

been used with a complex substrate during the preparation of derivatives of ascomysin. Ascomycin is a therapeutically important immunomodulatory macrolactam produced by *Streptomyces hydroscopicus* var. *ascomyceticus*. A π-allyl palladium complex is presumably a reactive intermediate in this process. The displacement reaction was developed by Novartis chemists to access derivatives of actomysin with a modified pipecolic acid subunit for drug development purposes.[149] The diastereocontrol at the C6 position was found to be low (~1:1). An application of two consecutive thermal trichloroacetimidate rearrangements in the synthesis of anti-influenza agent A-315675 has been described.[150] Both processes occur with high diastereocontrol affording the allylic diamide product in 63% overall yield. A similar thermal tandem trichloroimidate rearrangement approach has been used in an elegant enantioselective synthesis of the oroidin alkaloid (–)-agelastatin.[151]

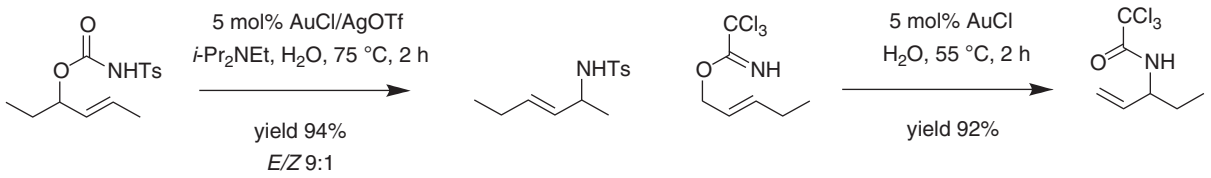
It appears that the more established methods such as the thermal Overman rearragement and allylic cyanate rearrangement are dominant among examples in total synthesis applications. Incorporating other methods for the conversion of allylic alcohols and their derivatives to allylic amines, especially by asymmetrical catalysis, into synthesis design is still rare. This gap creates unique opportunities for synthesis planning and has a potential to increase efficiency in the synthesis of nitrogen-containing natural products and other complex molecules of interest.

6.16.3.5 1,3-Oxygen-to-Oxygen Transpositions

This important and broad subclass of allylic transpositions amounts to isomerization of allylic alcohols and their derivatives. In general terms, these transpositions can offer strategic refunctionalizations during synthesis planning and execution, provide the


1 mol% [(COD)IrCl]2
2 mol% phosphoramidite ligand (Ar = Ph)
R1R2NH, THF, r.t.
yield 58–95%
ee 76–96%
R = aryl, n-alkyl
R1R2NH = 4-methoxybenzylamine, n-hexylamine, allylamine, pyrrolidine, piperidine, morpholine, diethylamine
Ar = Ph
Ar = 1-Np
Ar = 2-MeO-Ph
[(COD)IrCl]2
Phosphoramidite ligands for highly enantioselective allylic aminations
Active catalyst
1 mol% [(COD)IrCl]2
2 mol% phosphoramidite ligand (Ar = Ph)
ArNH2, THF, r.t.
yield 58–95%
ee 72–95%
R = aryl, n-alkyl
4 mol% active catalyst (Ar = Ph)
100 equivalents NH3, THF, 30 °C; HCl
yields 49–73%
ee 97–99%
R = aryl, TrOCH2, n-heptyl, 1-cyclohexenyl

Scheme 47



Scheme 48

basis for the development of methods for enantioselective synthesis of allylic alcohols and ethers, and suggest various strategies for the synthesis of heterocycles containing ether linkages. Several methods for direct one-step oxygen-to-oxygen transposition have been developed providing an economical alternative to multistep heteroatom manipulations used previously.

Most methods for catalytic allylic oxygen transpositions found in the current literature utilize palladium, iridium, ruthenium, and rhenium compounds as catalysts. Recently, gold-catalyzed ring-forming allylic ether formations directly from free allylic alcohols have been added to this group. In addition, there are examples of iron- and zirconium-mediated as well as uncatalyzed processes falling in this category of reactions.

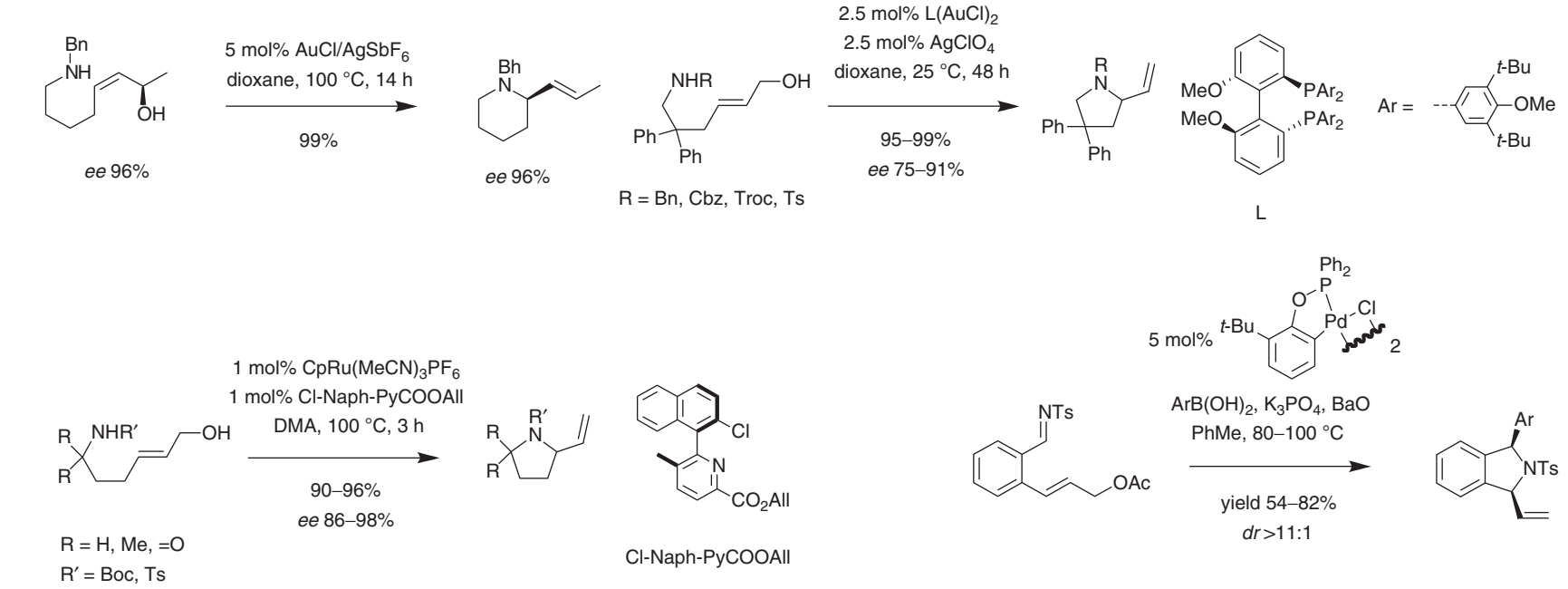
Several distinct approaches to palladium-catalyzed transpositions of allylic alcohol derivatives have been described. Among these are *O*-allylation reactions of trichloroacetimidate derivatives of 2-alken-1-ols with carboxylic acids and phenols (**Scheme 51**). These reactions generally take place with exceptionally high branched-to-linear ratios of products. For the reactions of (*Z*)-allylic trochlroacetimidates with carboxylic acids[152] and phenols,[153] the catalyst $[(R_p,S)\text{-COP-OAc}]_2$ or its enantiomer has been found to be optimal for high enantioselectivity. For the *O*-allylation with (*E*)-allylic trichloroacetimidates-forming aryl ethers, amidate complex $[(R_p,S)\text{-COP-NHCOCCl}_3]_2$ or its enantiomer are preferred.[154] Future directions in developing square planar palladacyclic catalysts for these transformations are advancing the structural design of catalysts and improving versatility of their enantioselective synthesis. The overall goals are to improve accessibility and allow for a facile screening of analogs for optimal enantioselectivity with a broad range of oxygen nucleophiles.[155]

Palladium-catalyzed asymmetrical allylic alkylation of phenols using ligands depicted in **Scheme 52** have been shown to occur at the more substituted position of the allylic system, giving products of 1,3-transposition with carbonates derived from primary allylic alcohols. Regioselectivity is typically in excess of 90% with unhindered phenols, although occasionally a higher fraction of linear products is observed. Enantioselectivity in the range of 60–90% was achieved with a limited set of substrates in the initial studies.[156] (*E*)- and (*Z*)-allylic carbonates afford complementary stereochemical outcomes, suggesting the recognition of the same enantiotopic face by the chiral palladium catalysts, and conservation of the double bond geometry in the π-allyl intermediate. Improved enantioselectivity is observed in the intramolecular variant of the phenol allylic alkylation, which circumvents the problem of regiocontrol.[157] Disubstituted and trisubstituted allylic carbonates with the *E*-configuration of the double bond afforded the cyclization products with consistently good enantioselectivity. A substantially larger gap in enantioselectivity depending on the degree of double bond substitution was observed for (*Z*)-allylic carbonates. Palladium-catalyzed cyclization of disubstituted allylic carbonates (R=H, **Scheme 52**) generally showed low enantioselectivity in the range of 18–57%. In contrast, trisubstituted (*Z*)-allylic carbonates ($R=CH_3$, **Scheme 52**) gave cyclic products with fully substituted carbon centers in excellent enantioselectivity of 95–98%. This methodology was inspired by and successfully exploited in the synthesis of natural chromans and chromanols such as vitamin E, calanolides A and B, and cardioprotective agent MDL-73404.[156,157] Additional applications of this method involve sequential catalytic reactions with Ru and Pd catalysts in a two-catalyst one-pot synthesis of nitrogen and oxygen heterocycles.[158]

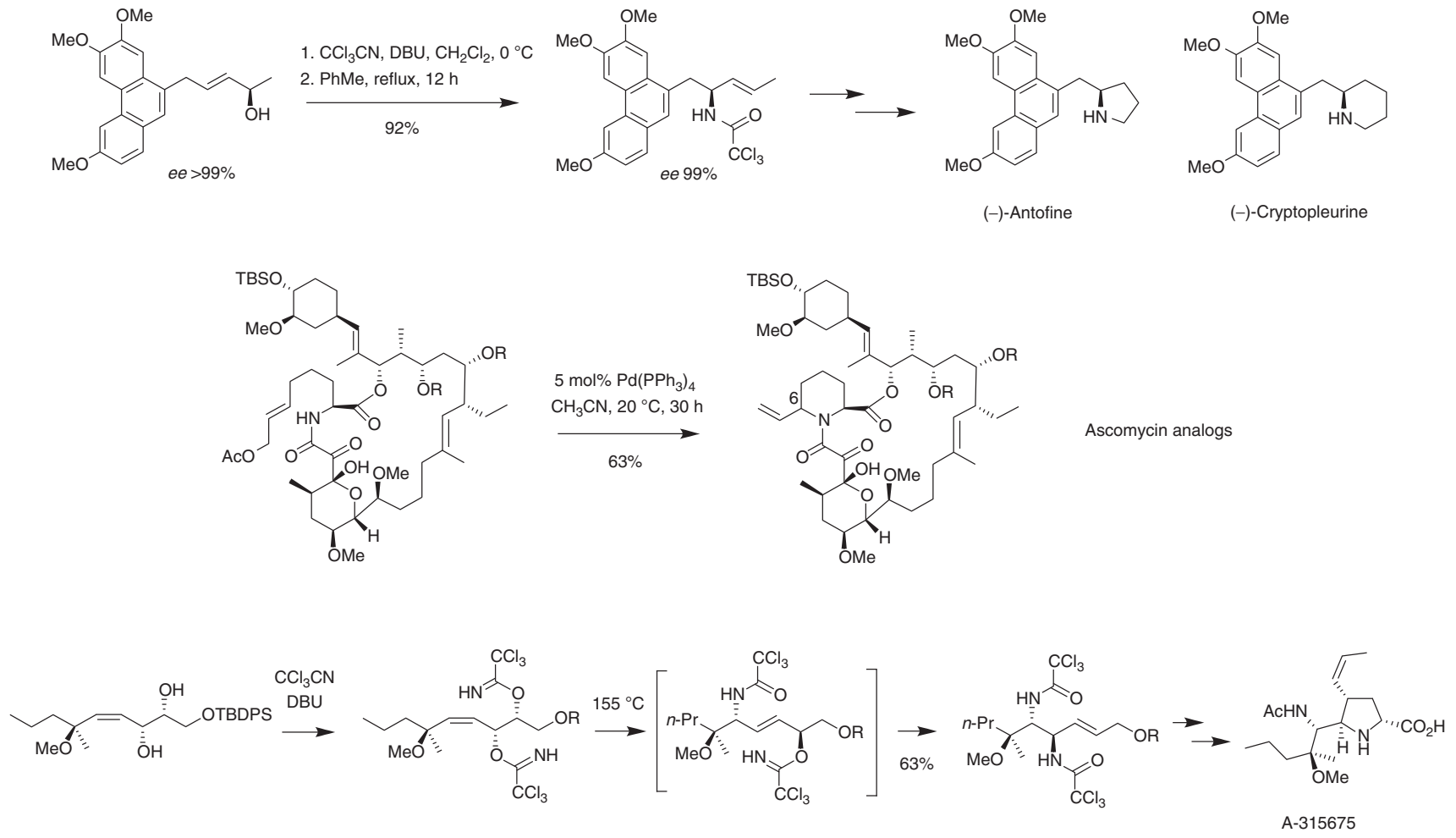
In a reaction sequence comprising two consecutive transition metal-catalyzed processes, a rhodium-catalyzed conjugate addition is followed by a palladium-catalyzed intramolecular allylic alkylation in the synthesis of butyrolactones (**Scheme 53**).[159] The substrates are readily available from Meldrum acid. After the conjugate addition, the lactone formation is initiated by a ring-closure onto the carbonyl group of the Meldrum's acid fragment, which possesses sufficient nucleophilicity for intramolecular allylic alkylaton with the intermediate π-allylpalladium complex. After the fragmentation with a loss of acetone, the acylketene intermediate is intercepted with ethanol giving rise to the fully substituted γ-butyrolactone product in good yield and excellent diastereocontrol.

Several other ring-forming processes based on palladium-catalyzed allylic alkylation of oxygen nucleophiles have been described. Formation of oxazolines and isoxazolidines from allylic benzamides and homoallylic hydroxylamines, respectively, can be efficiently accomplished (**Scheme 54**). Allylic benzamide substrates have been prepared enantioselectively in a few steps from amino acids. Their cyclization could be accomplished under straightforward reaction conditions with $Pd[PPh_3]_4$ as the catalyst via the intermediacy of the π-allylpalladium complex.[160] The formation of isoxazolidines from homoallylic hydroxylamine has been shown to have a higher preference for the *trans*-substituted product under the cyclization-induced Pd(II) mechanism ($Pd(OAc)_2$, LiCl) than under the Pd(0) regime ($Pd(OAc)_2$, dppe) involving π-allylpalladium chemistry, although the chemical yields are comparable for both pathways.[161]

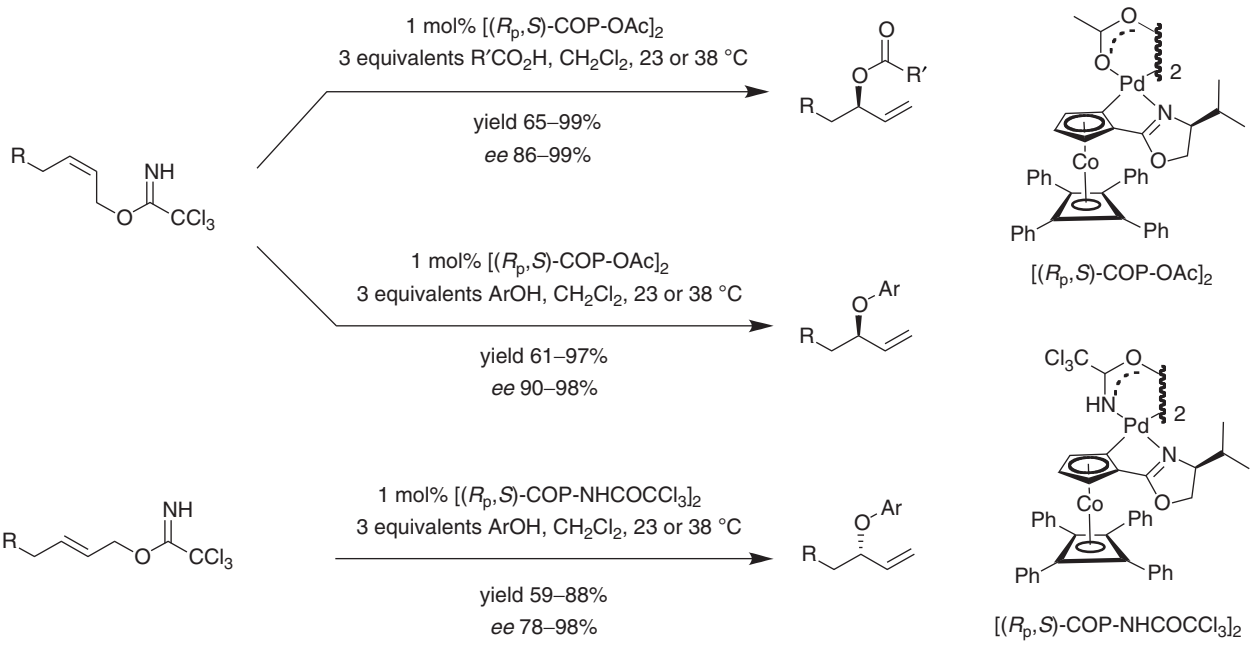
The capacity of palladium catalysis in effecting allylic oxygen transpositions has been exploited in developing selective methods for the synthesis of 1,2- and 1,3-diol subunits found in many important polyketide natural products. One method capitalizes on the use of alkylborates as a transient functional group that provides an oxygen nucleophile for the intramolecular allylic displacement (**Scheme 55**).[162] Unprotected 1,2- and 1,3-diols can be formed if boric acid is used as the reagent, whereas


Bn
NH
OH
ee 96%
5 mol% AuCl/AgSbF6
dioxane, 100 °C, 14 h
99%
Bh
N
ee 96%
NHR
OH
Ph
Ph
R = Bn, Cbz, Troc, Ts
2.5 mol% L(AuCl)2
2.5 mol% AgClO4
dioxane, 25 °C, 48 h
95–99%
ee 75–91%
R
N
Ph
Ph
MeO
MeO
PAr2
PAr2
L
Ar =
t-Bu
OMe
t-Bu
1 mol% CpRu(MeCN)3PF6
1 mol% Cl-Naph-PyCOOAll
DMA, 100 °C, 3 h
90–96%
ee 86–98%
R
NHR′
OH
R
R = H, Me, =O
R′ = Boc, Ts
R′
N
R
R
Cl
N
CO2All
Cl-Naph-PyCOOAll
5 mol%
Ph2
P
O
Pd
Cl
t-Bu
2
ArB(OH)2, K3PO4, BaO
PhMe, 80–100 °C
yield 54–82%
dr >11:1
NTs
OAc
Ar
NTs

Scheme 49


OMe
MeO
OH
MeO
ee >99%
1. CCl3CN, DBU, CH2Cl2, 0 °C
2. PhMe, reflux, 12 h
92%
OMe
MeO
HN
O
CCl3
MeO
ee 99%
OMe
MeO
HN
MeO
(–)-Antofine
OMe
MeO
HN
MeO
(–)-Cryptopleurine
TBSO
MeO
OR
OR
HN
O
AcO
OH
OMe
O
H
OMe
5 mol% Pd(PPh3)4
CH3CN, 20 °C, 30 h
63%
TBSO
MeO
OR
OR
6
N
O
OH
OMe
O
H
OMe
Ascomycin analogs
OH
OTBDPS
MeO
OH
CCl3CN
DBU
CCl3
HN
O
OR
MeO
O
NH
CCl3
155 °C
CCl3
HN
O
n-Pr
OR
MeO
HN
O
CCl3
63%
CCl3
HN
O
n-Pr
OR
MeO
HN
O
CCl3
AcHN
CO2H
H
N
H
OMe
A-315675

Scheme 50



Scheme 51

trialkylborates provide corresponding allylic ether products with high regioselectivity. However, the conceptual appeal of this method is attenuated by modest yields and low stereocontrol. Using acetals as a covalent linker in the formation of 1,3-diols in a similar approach proved to be notably more effective in achieving high yields and stereoselectivity in preference of *syn*-1,3-diol derivatives.[163] The rapid reversible formation of the α-alkoxyethylate intermediate mediated by potassium hexamethyldisilazide is presumed to set up Curtin–Hammet conditions for the following Pd-mediated allylic cyclization, where the alkoxyethoxide diastereomer leading to the all-*cis* product undergoes the cyclization at a higher rate.

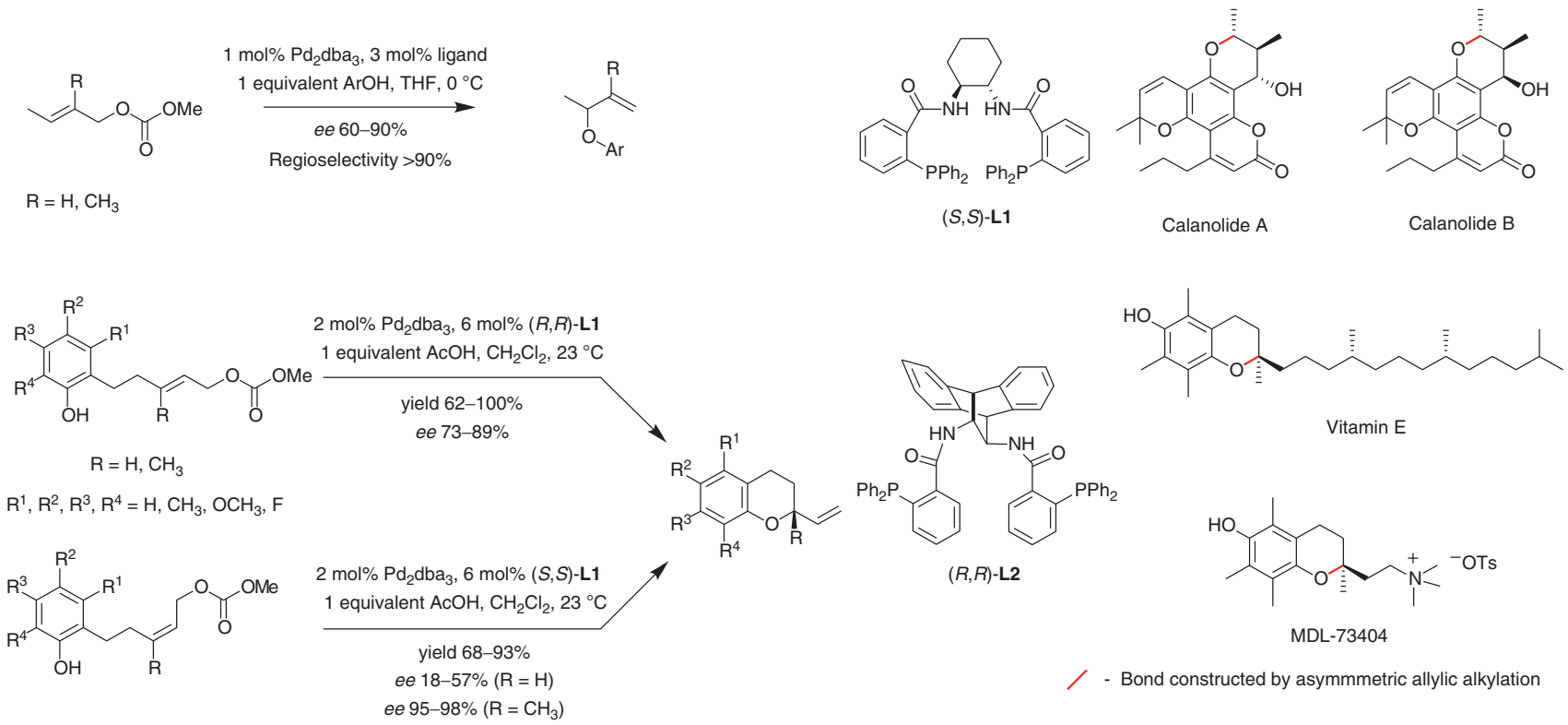
When allylic carbonates are used as substrates in Pd-catalyzed oxygen transpositions, carbon dioxide is typically produced as a by-product. Recently, two reports have described allylic transpositions of acyclic carbonates to rearranged cyclic carbonates of allylic 1,2-diols without the loss of CO_2 (**Scheme 56**). In these reactions, once the π-allylpalladium intermediate is formed, the methoxycarbonate counterion transfers the CO_2 fragment to the allylic hydroxy group. The newly generated alkoxycarbonate undergoes an intramolecular cyclization onto the π-allylpalladium moiety giving the final product. As expected, *trans*-substituted products are generally preferred when secondary alcohols are used as the substrate.[164,165]

The ability of iridium complexes to direct alkylation at the more substituted terminus of the allylic system with high regioselectivity forms the basis of methods for iridium-catalyzed allylic oxygen transposition.[166] Efficient enantioselective allylic *O*-alkylations of aliphatic alcohols have been described (**Scheme 57**). Copper and zinc alkoxides have been found to be optimal reagents in this iridium-catalyzed etherification reaction with *tert*-butyl carbonates derived from primary allylic alcohols.[167] In this reactive system, primary, secondary, and tertiary alcohols have proven to be suitable substrates, although enantioselectivity for the etherification of copper *tert*-butoxide with *tert*-butyl (*E*)-2-buten-1-yl carbonate eroded to 63% *ee* from typically high values obtained for primary and secondary copper alkoxides. Allylic *O*-alkylations of phenols with allylic transpositions have been realized under similar reaction conditions with sodium or lithium phenoxides.[168] One limitation of this reaction is that phenoxides with strongly electron-withdrawing groups such as nitro or cyano show poor reactivity.

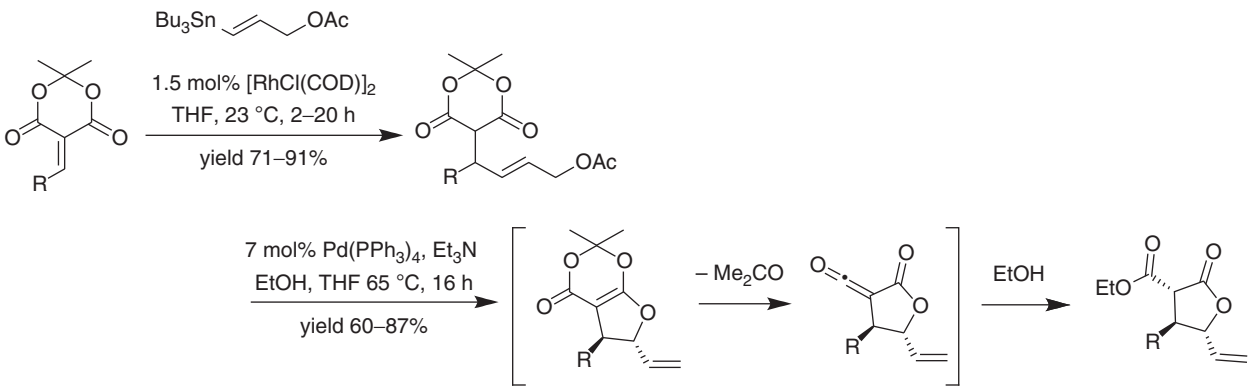
Potassium silanoates have also been used successfully in the iridium-catalyzed transposition of allylic *tert*-butyl carbonates (**Scheme 57**). One of the main benefits of using silanoates as the nucleophile is the facile removal of the silyl group from products, giving an access to transposed allylic alcohols with a free hydroxy group under mild conditions in high enantioselectivity. Although only Et_3SiOK was used in the scope studies, other common silanoates Me_3SiOK, *t*-$BuMe_2SiOK$, and $(i\text{-}Pr)_3SiOK$ are suitable nucleophiles. The enantioselectivity increases with the size of silanoates, whereas the yield decreases.[169]

An improved protocol for a direct allylation of primary, secondary, and tertiary alcohols with allylic acetates has been described. In this protocol, iridium metallacyclic catalyst generated from $[Ir(cod)Cl]_2$ and the chiral BINOL-derived phosphorimidate ligand is used, and potassium phosphate serves as a basic additive, avoiding the need for the preparation of lithium or copper alkoxides. Addition of an alkyne (1-phenylpropyne) was found to be essential to suppress isomerization of the product to enol ether and ensure high yields in the allylic ethers.[170] Similar enantioselective processes using allylic phosphates and $[Ir(cod)Cl]_2$/Ph-PYBOX as a catalyst system with oximes as oxygen nucleophiles have been described.[171]

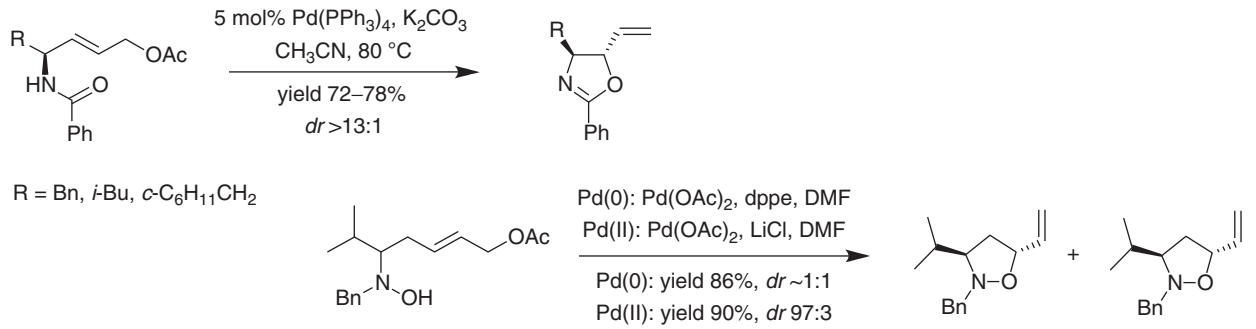
A direct transposition of unmasked allylic alcohols can be catalyzed by high oxidation state oxo complexes of vanadium(V), tungsten(VI), and molybdenum(VI), and has been carried out industrially at temperatures of 130–200 °C for the production of terpenic alcohols.[45] More reactive Mo(VI) and V(V) catalysts that are active at 25 °C have been reported, however, competitive


1 mol% Pd2dba3, 3 mol% ligand
1 equivalent ArOH, THF, 0 °C
ee 60–90%
Regioselectivity >90%
R = H, CH3
(S,S)-L1
Calanolide A
Calanolide B
2 mol% Pd2dba3, 6 mol% (R,R)-L1
1 equivalent AcOH, CH2Cl2, 23 °C
yield 62–100%
ee 73–89%
R = H, CH3
R1, R2, R3, R4 = H, CH3, OCH3, F
(R,R)-L2
Vitamin E
2 mol% Pd2dba3, 6 mol% (S,S)-L1
1 equivalent AcOH, CH2Cl2, 23 °C
yield 68–93%
ee 18–57% (R = H)
ee 95–98% (R = CH3)
MDL-73404
- Bond constructed by asymmmetric allylic alkylation

Scheme 52



Scheme 53



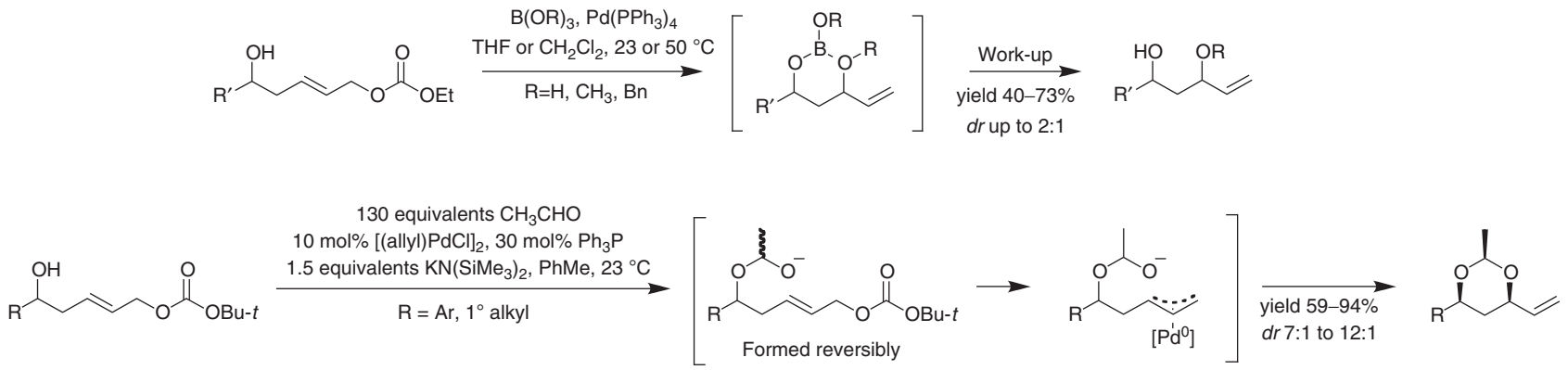
Scheme 54

oxidation of the allylic hydroxy group leads to catalyst deactivation over time. An important advance in the area of direct 1,3-transposition of allylic alcohols appeared with the discovery of highly reactive oxo rhenium(VII) compounds such as $Ph_3SiOReO_3$, which are capable of inducing rearrangements at rates over 100 times greater than that of the molybdenum catalysts.[44] Readily available rhenium(VII) oxide is also a highly active catalyst, and allylic silyl ethers are also suitable substrates for the rhenium-catalyzed transpositions (Scheme 58).

Because the distribution of the isomeric allylic alcohols under the reaction conditions is determined by their relative thermodynamic stability, various methods had to be devised to control regio- and stereoselectivity in these transpositions, most of which focused on rhenium catalysis. Successful strategies used trapping techniques to remove one of the regioisomers, therefore shifting the equilibrium process in its direction (Scheme 58). Reliance on electronic bias in combination with steric effects is among some of the early attempts to influence the distribution of regioisomers.[172] Rearrangement of allylic alcohols bearing an α-aryl group generally favored products with a conjugate double bond. Equilibrium between primary and tertiary allylic alcohols could be directed toward the primary alcohol by selective silylation of the less-hindered primary hydroxy group. Various tethering strategies have been exceptionally effective in directing the rhenium(VII)-catalyzed transpositions. Excellent regiochemical control has been achieved by tethering the allylic system to the (*Z*)-vinylboronate moiety, which forms a cyclic six-membered vinylboronate ester with the transposed silyl ether group.[173] Although the starting material for this process has a relatively unusual structure, it can be prepared in one step by a ruthenium-catalyzed Alder-ene coupling between a homoallylic silyl ether and alkynyl pinacolborate. These substrates are readily available by well-established methods. In another approach that has several related features, structural strain has been used as the regiochemical control factor in the rhenium-catalyzed transposition of cyclic allylic silyl ethers. A substantial, albeit not complete, racemization was observed in this reaction when enantioenriched substrates were employed.[174]

Very high levels of stereo- and regiocontrol have been achieved by fixating the transposed allylic alcohols as acetals or ketals (Scheme 59).[175] The acetal formation is conveniently performed *in situ* and provides access to masked 1,3-diols. The process is characterized by a rapid rearrangement and ketalization at room temperature, followed by a slower isomerization to the thermodynamically more stable diastereomer. Concomitant removal of silyl ether groups is occasionally observed.

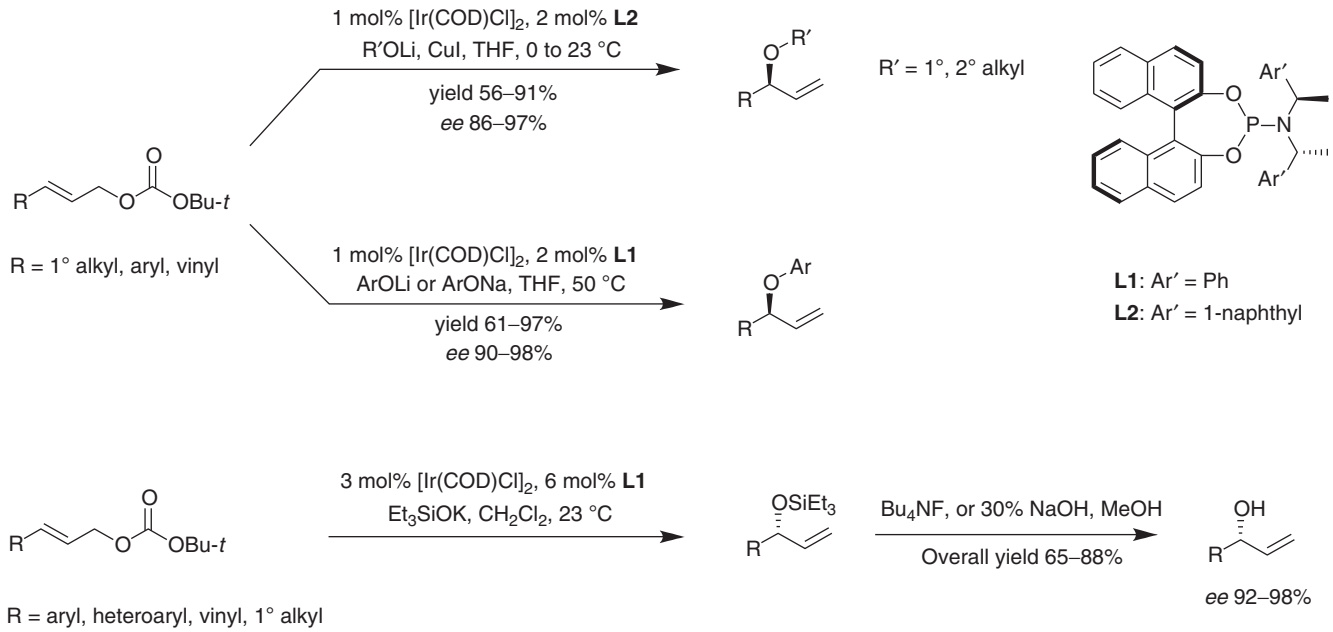
Intramolecular acetalization as a recourse for controlling regio- and stereoselectivity in the rhenium-catalyzed transposition of allylic alcohols has been exploited in a set of reactions in which the acetal or ketal group is incorporated in the substrate. Illustrative examples of this approach are depicted in Scheme 55.[176] Monocyclic, bridged bicyclic, and spirocyclic ketals and acetals are formed in good yields and excellent stereoselectivity. In most cases, this approach obviates the need for predefined stereochemistry in the starting material, potentially offering tactical advantages in synthesis planning.


B(OR)3, Pd(PPh3)4
THF or CH2Cl2, 23 or 50 °C
R=H, CH3, Bn
Work-up
yield 40–73%
dr up to 2:1
130 equivalents CH3CHO
10 mol% [(allyl)PdCl]2, 30 mol% Ph3P
1.5 equivalents KN(SiMe3)2, PhMe, 23 °C
R = Ar, 1° alkyl
Formed reversibly
yield 59–94%
dr 7:1 to 12:1

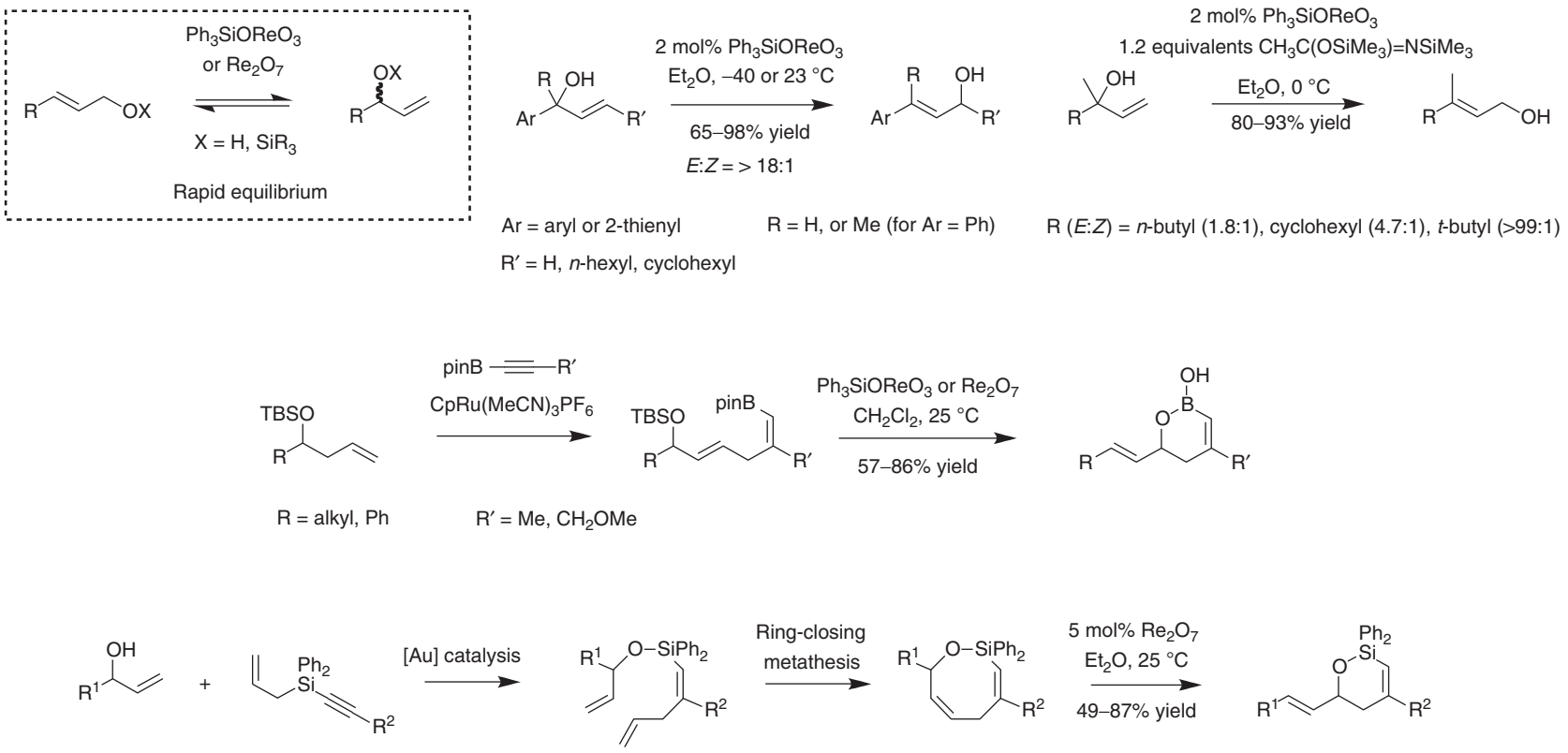
Scheme 55

5 mol% Pd2dba3 CHCl3
20 mol% dppf
dioxane, 50 °C
OH
R
R′
OMe
O
[Pd]
–CH3OH
[PdLn]
From E-allylic methyl carbonates
From Z-allylic tert-butyl carbonates
n-C3H7
n-C3H7
76% yield
60% yield
87% yield
dr 96:4
83% yield
dr 90:10
60% yield
77% yield
92% yield
dr 90:10
61% yield

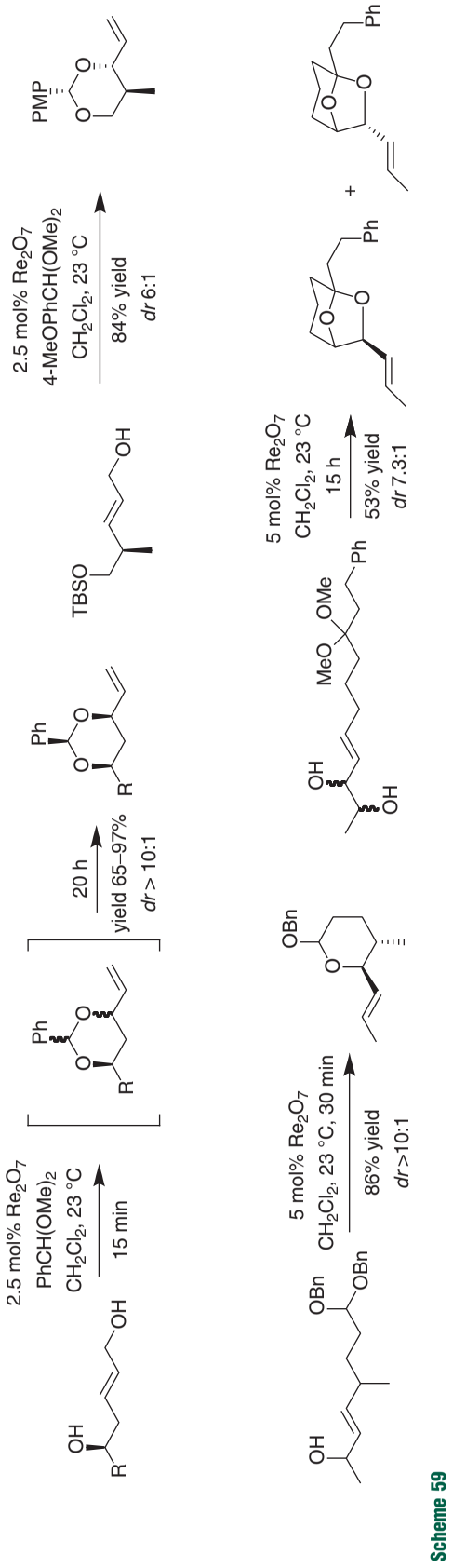
Scheme 56


1 mol% [Ir(COD)Cl]2, 2 mol% L2
R′OLi, CuI, THF, 0 to 23 °C
yield 56–91%
ee 86–97%
R′ = 1°, 2° alkyl
Ar′
P–N
Ar′
1 mol% [Ir(COD)Cl]2, 2 mol% L1
ArOLi or ArONa, THF, 50 °C
yield 61–97%
ee 90–98%
L1: Ar′ = Ph
L2: Ar′ = 1-naphthyl
OBu-t
R = 1° alkyl, aryl, vinyl
3 mol% [Ir(COD)Cl]2, 6 mol% L1
Et3SiOK, CH2Cl2, 23 °C
Bu4NF, or 30% NaOH, MeOH
Overall yield 65–88%
ee 92–98%
R = aryl, heteroaryl, vinyl, 1° alkyl

Scheme 57

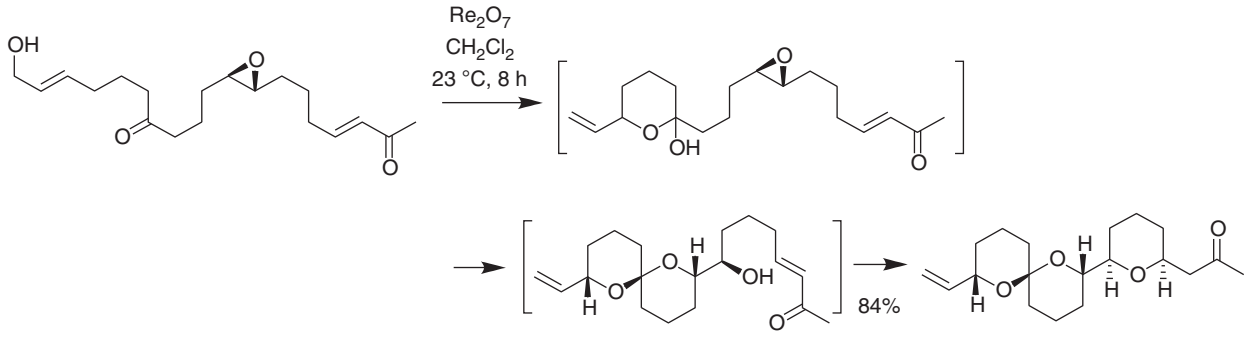

Ph3SiOReO3
or Re2O7
X = H, SiR3
Rapid equilibrium
2 mol% Ph3SiOReO3
Et2O, –40 or 23 °C
65–98% yield
E:Z = > 18:1
Ar = aryl or 2-thienyl
R′ = H, n-hexyl, cyclohexyl
R = H, or Me (for Ar = Ph)
2 mol% Ph3SiOReO3
1.2 equivalents CH3C(OSiMe3)=NSiMe3
Et2O, 0 °C
80–93% yield
R (E:Z) = n-butyl (1.8:1), cyclohexyl (4.7:1), t-butyl (>99:1)
pinB—≡—R′
CpRu(MeCN)3PF6
Ph3SiOReO3 or Re2O7
CH2Cl2, 25 °C
57–86% yield
R = alkyl, Ph
R′ = Me, CH2OMe
[Au] catalysis
Ring-closing
metathesis
5 mol% Re2O7
Et2O, 25 °C
49–87% yield

Scheme 58


2.5 mol% Re2O7
PhCH(OMe)2
CH2Cl2, 23 °C
15 min
20 h
yield 65–97%
dr > 10:1
2.5 mol% Re2O7
4-MeOPhCH(OMe)2
CH2Cl2, 23 °C
84% yield
dr 6:1
5 mol% Re2O7
CH2Cl2, 23 °C
15 h
53% yield
dr 7.3:1
5 mol% Re2O7
CH2Cl2, 23 °C, 30 min
86% yield
dr >10:1

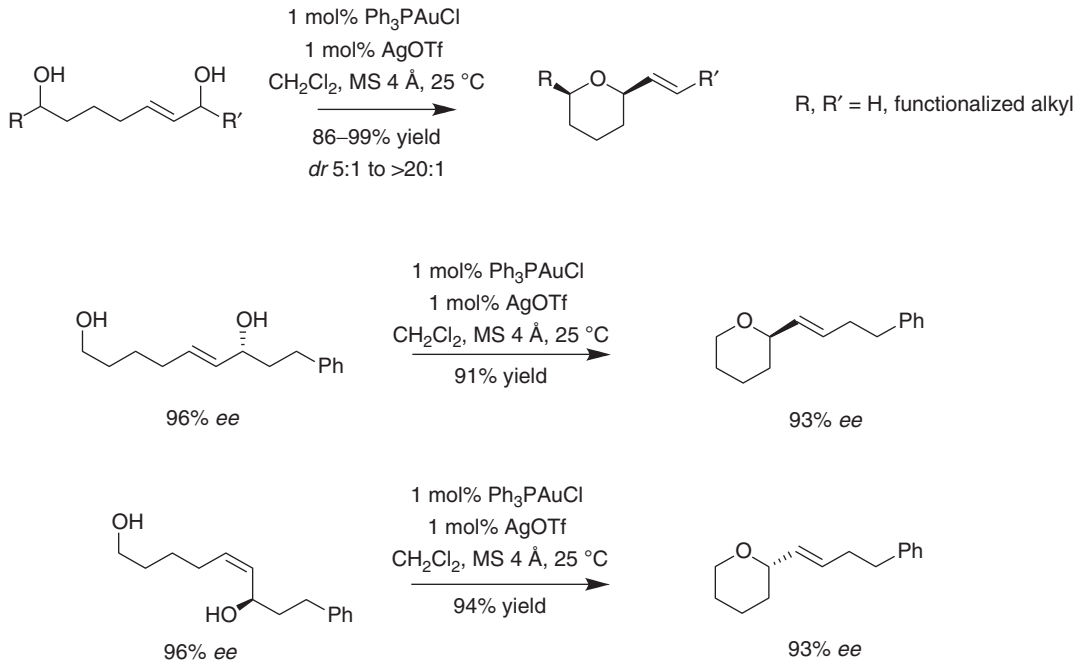
Scheme 59

An example in Scheme 60 illustrates an impressive cascade transformation enabled by the Re-catalyzed allylic alcohol transposition. The secondary allylic hydroxy group resulting from an initial reversible Re-catalyzed rearrangement of the substrate is affixed by an irreversible cyclization onto the epoxide moiety via the hemiketal intermediate. The process is completed by a Michael addition to the unsaturated ketone, giving the polycyclic product with a substantial increase in structural complexity in a very good yield and with complete stereocontrol.[177]



Scheme 60

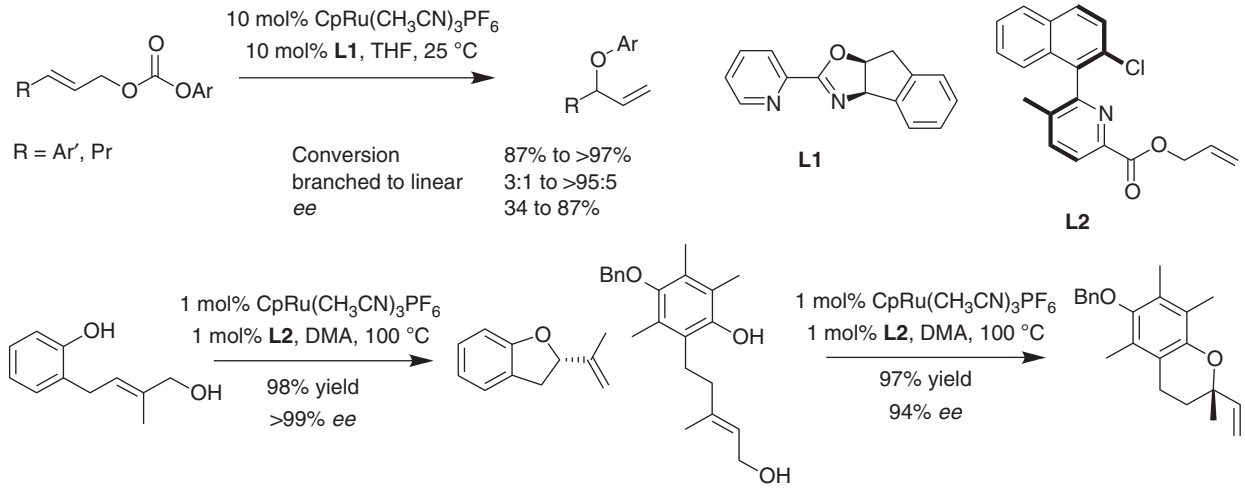
Allylic displacement of a free hydroxy group with oxygen nucleophiles can also be accomplished using gold catalysis (Scheme 61). These transformations are currently limited to cyclization reactions. A simple readily accessible $Ph_3PAuCl/AgOTf$ catalytic system was found to be sufficiently active, with typical experiments requiring 1 mol% of the catalysts at room temperature, with some cyclizations taking place at temperatures as low as −78 °C at which an improved diastereoselectivity is achieved.[178] Subsequent studies with chiral allylic alcohols demonstrated that an excellent 1,3-transfer of chirality is observed in these cyclization reactions.[179] Configuration of the allylic double bond exerts a strong influence on the configuration of the newly formed allylic ether, showing stereochemical complementarity for *E*- and *Z*-isomers of the substrate. The available data are consistent with the displacement of the allylic OH by the incoming hydroxy group occurring on the same face of the allylic system for *E*- and *Z*-isomers. The gold-catalyzed cyclizations of allylic diols displayed very good compatibility with functional groups resident in the substrate, and thus hold strong potential for applications in the synthesis of complex molecules.[180]



Scheme 61

Asymmetrical decarboxylative Ru-catalyzed rearrangement of allylic aryl and alkyl carbonates provides aryl and alkyl ethers at the more substituted position of the allylic system, resulting in allylic oxygen-to-oxygen 1,3-transposition if primary allylic

carbonates are used as the substrate. The levels of regioselectivity in preference of the branched-over linear products are generally moderate, rarely exceeding 9:1 with the catalysts–ligand combination depicted in Scheme 62.[181] Although rather good, enantioselectivity achieved in this process was lower than what could be realized by alternative methods, and is in the range of 30–40% for aryl ethers containing strongly electron-withdrawing groups, and 84–87% *ee* for electron-neutral aryl groups. Enantioselectivity also decreased substantially for aliphatic aryl carbonates (R=Pr, *ee* 60%). Intermolecular variant of this reaction using phenols with methyl, ethyl, or *tert*-butyl primary allylic carbonates is also developed, displaying similar regio- and enantioselectivity. A related decarboxylative aryl ether formation using iron catalyst $Bu_4N[Fe(CO)_3(NO)]$ in the presence of triphenylphosphine was reported.[182]



Scheme 62

A notably higher enantioselectivity was obtained with the same ruthenium precatalyst in the ring-forming dehydration process using an axially chiral pyridine ligand (**L2**, Scheme 62). Five- and six-membered cyclic allylic ethers have been prepared from the cyclization of primary, tertiary, and certain phenolic hydroxy groups. Although the scope is relatively narrow, the products have been obtained in high yields and high enantioselectivity.[183]

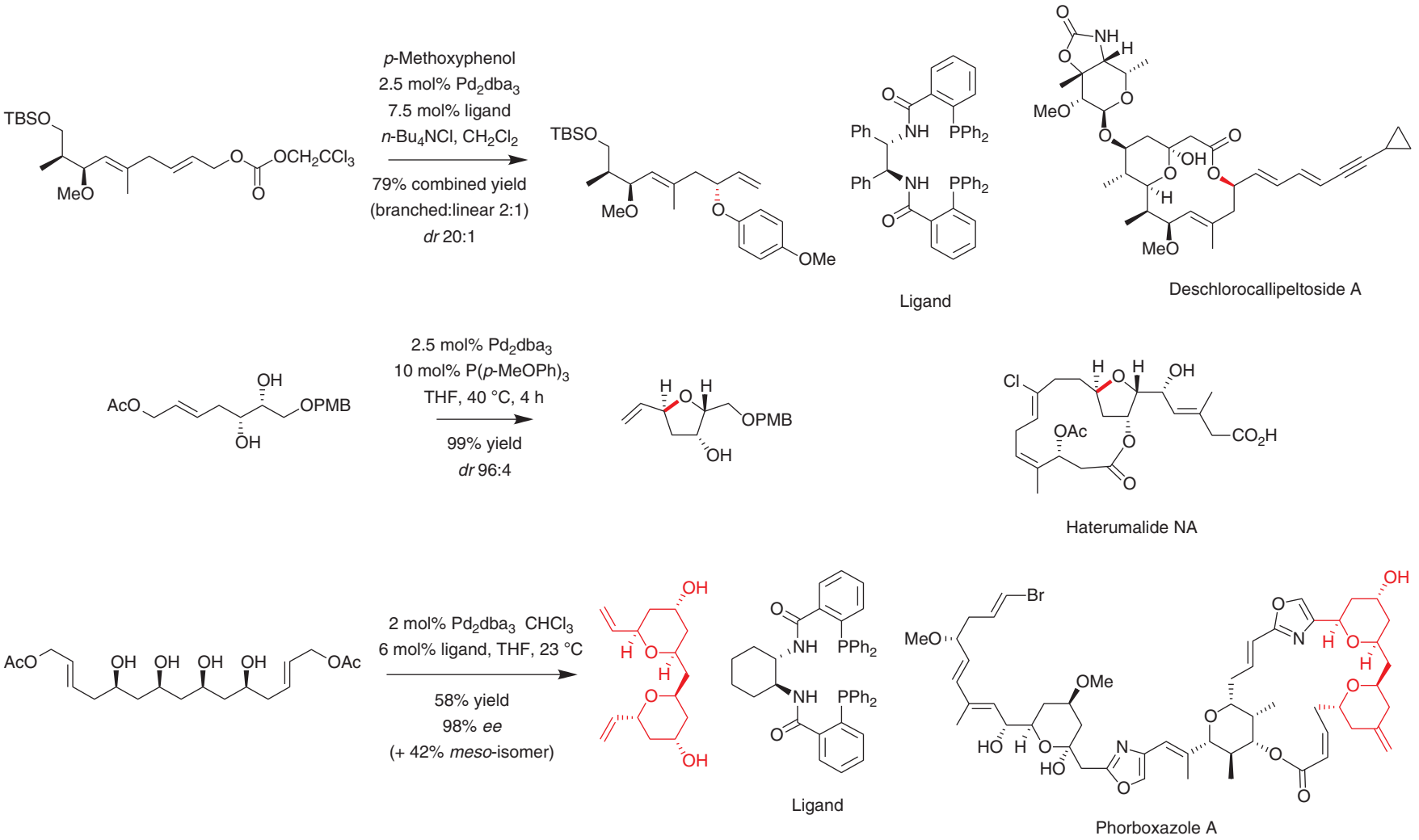
Selected examples of allylic oxygen 1,3-transpositions in the total synthesis of complex molecules are illustrated in Scheme 63. A palladium-catalyzed enantioselective allylic alkylation with *p*-methoxyphenol was exploited at the early stages of the total synthesis of deschlorocallipeltoside A, a complex marine sponge polyketide. The requisite allylic ether group was formed with excellent diastereocontrol albeit with low regioselectivity. The *p*-methoxyphenyl group functioned as a protecting group throughout much of the synthesis, and was effectively removed before macrolactonization in 82% yield.[184]

Palladium-catalyzed formation of cyclic allylic ethers has been used rather extensively in complex molecule synthesis. The THF fragment of haterumalide NA (oocydin A) was assembled by a diastereoselective intramolecular allylation of the allylic acetate with very high *trans*-selectivity. It was discovered that tris(*p*-methoxyphenyl)phosphine is a uniquely effective ligand ensuring high rates and stereoselectivity in this transformation.[185] A similar tetrahydrofural formation was used in the synthesis of a simple marine alkaloid pachastrissamine.[186] A ligand-controlled desymmetrization of allylic acetates appended to the termini of polyol chain was explored for the synthesis of phorboxazoles. Very high enantioselectivity was achieved in these bidirectional cyclizations.[187]

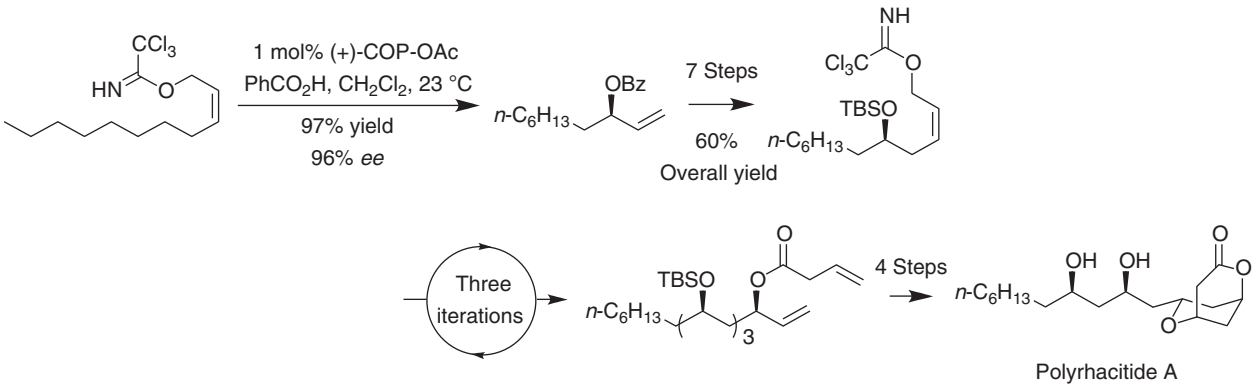
Iterative application of the enantioselective S_N2'-allylation of carboxylic acids with allylic trichloroacetimidates was the basis of the synthesis strategy for the Chinese medicinal ant metabolites polyrhacitides A and B (Scheme 64). Although the length of the reaction sequence for each iteration, seven steps, is relatively high, four of the five stereogenic centers of polyrhacitides have been constructed with high stereocontrol by means of the COP-OAc-catalyzed allylic esterification, demonstrating its synthetic utility in the increasingly complex molecular setting.[188]

Two types of allylic oxygen transposition were applied in the enantioselective total synthesis of (–)-dactylolide, a cytotoxic marine natural product that has attracted considerable interest as synthesis target (Scheme 65).[189] The first process aimed at the formation of the tetrahydropyran subunit of the macrolide by the palladium-catalyzed ligand-directed displacement of the primary allylic carbonate. A good level of diastereocontrol (11:1) was realized in this process, favoring the desired *cis*-substitution in the cyclization product. The product was advanced in five steps to the substrate of the next allylic transposition, in this case the rhenium-catalyzed isomerization to the cyclic boronate ester, setting up the correct functionalization found in the natural product, which was completed after the eventual oxidation of the enone group.

An elegant late-stage rhenium-catalyzed direct allylic alcohol transposition was the centerpiece for the stereoselective assembly of the macrocyclic framework of leucascandrolide (Scheme 65).[190] The unusually stable cyclic macrohemiacetal with the requisite stereochemistry at the C17 position was formed in comparable yields from either the 19*R*- or 19*S*-diastereomer. Aside from


TBSO
MeO
OCH2CCl3
p-Methoxyphenol
2.5 mol% Pd2dba3
7.5 mol% ligand
n-Bu4NCl, CH2Cl2
79% combined yield
(branched:linear 2:1)
dr 20:1
OMe
Ligand
Deschlorocallipeltoside A
AcO
OPMB
OH
2.5 mol% Pd2dba3
10 mol% P(p-MeOPh)3
THF, 40 °C, 4 h
99% yield
dr 96:4
Haterumalide NA
OAc
2 mol% Pd2dba3 CHCl3
6 mol% ligand, THF, 23 °C
58% yield
98% ee
(+ 42% meso-isomer)
Ligand
Phorboxazole A

Scheme 63



Scheme 64

providing practical benefits in the context of the total synthesis, this observation is an early experimental evidence for thermodynamic stereochemical control in the rhenium-catalyzed direct transposition of allylic alcohols.

6.16.3.6 Other Heteroatom Transpositions

The higher order silylcuprate reagent $(PhMe_2Si)_2Cu(CN)Li_2$ was introduced in 1981[191] and found wide application in organic synthesis. However, the requirement for not only two equivalents of $PhMe_2SiLi$, but also stoichiometric amounts of copper cyanide limits its utility, especially for large-scale reactions. It was determined that mixing $Me_2Cu(CN)Li_2$ with $PhMe_2SiZnMe_2Li$, generated *in situ* from Me_2Zn and $PhMe_2SiLi$ in THF at –78 °C, rapidly formed mixed cuprate $(PhMe_2Si)(Me)Cu(CN)Li_2$ via a facile ligand exchange. Furthermore, a variant of this process catalytic in $Me_2Cu(CN)Li_2$ was developed. Thus, treatment of vinyl epoxides with $PhMe_2SiZnMe_2Li$ and 3 mol% of $Me_2Cu(CN)Li_2$ led to the formation of allylsilanes in high yield by an S_N2' displacement of oxygen with silicon (Scheme 66).[192]

A related Cu(I)-catalyzed allylic substitution reaction with *bis*(triorganosilyl)zinc reagents and allylic acetates and carbamates was reported.[193] The reaction with cyclic allylic substrates has been proposed to involve π-allyl copper intermediates. For acyclic allylic substrates, the outcomes were controlled by the formation of both π-allyl and [σ+π]enyl intermediates, depending on the nature of the substrate.

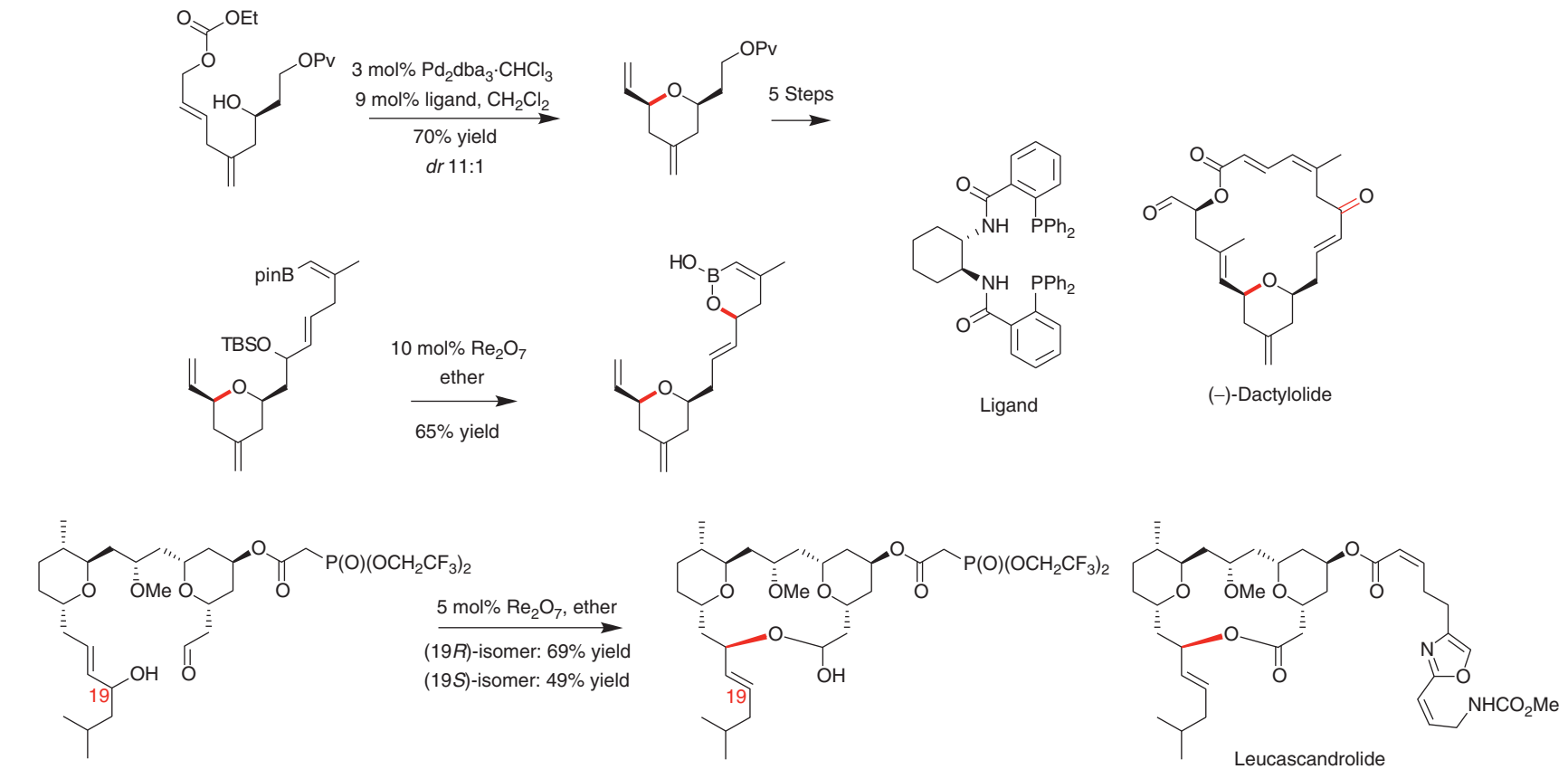
Oxygen-to-boron transposition has been used to access allylic boronates – powerful reagents in preparation of homoallylic alcohols, especially when high enantiocontrol is desired. Palladium-catalyzed borylation of allylic alcohols or the corresponding esters became one of the most powerful protocols for the preparation of allyl boronates, which can be either isolated or used *in situ*. The mild conditions of palladium-catalyzed processes are compatible with a broad array of various functional groups.

A one-pot procedure combining the synthesis of allylic boronates from allylic acetates and their addition to aldehydes and sulfonimines has been described (Scheme 67). The allylboronante formation is catalyzed by Pd_2dba_3 in dimethylsulfoxide (DMSO), and the overall process is characterized by high regio- and stereoselectivity.[194] It was found that the allylation of sulfonimine required the palladium catalyst and afforded the *syn*-diastereomer as the major product, whereas the corresponding reaction with aryl aldehydes took place with *anti*-selectivity. No allyl–allyl homocoupling product was observed, which is a common side-product in this type of transformation.

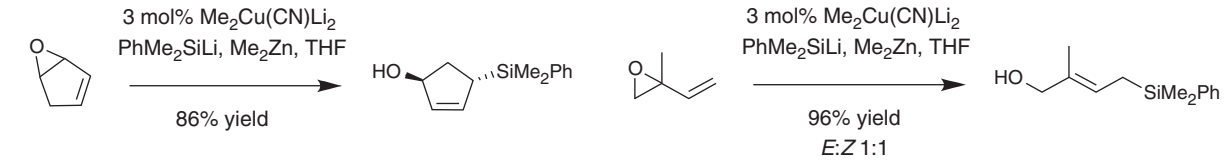
Using chiral diboronates shown in Scheme 67, homoallylic alcohols could be obtained in moderate *ee* of up to 53%.[195] However, employment of chiral diboronates in palladium-catalyzed allylation of sulfonimines only gave racemic products, which suggested that the allylation of imines proceeded via allylpalladium intermediates.

A highly S_N2'-selective boronation reaction of allyl carbonates with *bis*(pinacolato)diboron could be realized using the CuOBu-*t*–xantphos catalytic system.[196] The reaction is stereospecific; optically active allyl carbonates provide chiral allylboronates with a high degree of chirality transfer. The reaction of (*S*,*E*)-methyl oct-3-en-2-yl carbonate and $[B(pin)]_2$ at 0 °C afforded the product in excellent yield and regioselectivity, with S_N2' chirality transfer of more than 97% (Scheme 68). (*Z*,*E*)-Methyl oct-3-en-2-yl carbonate and $[B(pin)]_2$ delivered the allylboronate with complete chirality transfer. Copper(I)-catalyzed asymmetrical enantioselective allylic substitution with *bis*(pinacolato)diboron was developed following this study.[197] The optimal ligand for the process was found to be (*R*,*R*)-QuinoxP*. A number of primary (*Z*)-allylic carbonates could be converted to allylboronates with excellent enantioselectivity. No aryl substituted allyl carbonate was described in the report. The enantioselectivity of the reaction was greatly influenced by the configuration of the double bond in the substrates. For example, (*E*)-methyl (5-phenylpent-2-en-1-yl) carbonate afforded the product in 44% *ee* in high yield, whereas the corresponding reaction of the *Z*-isomer provided the product in 95% *ee*.

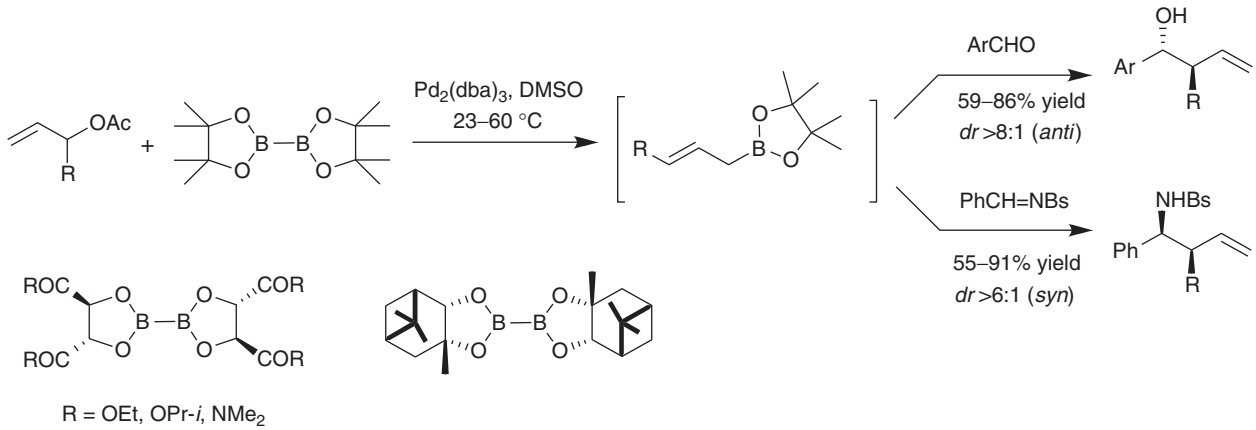
Palladium pincer complexes are a class of well-defined, very stable compounds whose catalytic activities could be modulated by changing the electronic properties of heteroatoms in the side arms (Scheme 69). Allyl alcohols were readily converted to allylboronic acids by the catalysis with SeCSe–palladium catalyst **L1** in the presence of $(Bpin)_2$ ordiboronic acid. The products could either be isolated by converting unstable allyl boronic acids to allyltrifluoroboronates or added *in situ* to electrophiles such as aldehydes and imines. The application of the SCS-catalyst **L2** led to a considerably faster reaction albeit slightly decreased yields.[198]


OEt
OPv
HO
3 mol% Pd2dba3·CHCl3
9 mol% ligand, CH2Cl2
70% yield
dr 11:1
OPv
5 Steps
NH
PPh2
NH
PPh2
Ligand
(–)-Dactylolide
pinB
TBSO
10 mol% Re2O7
ether
65% yield
HO
B
P(O)(OCH2CF3)2
OMe
OH
19
5 mol% Re2O7, ether
(19R)-isomer: 69% yield
(19S)-isomer: 49% yield
N
NHCO2Me
Leucascandrolide

Scheme 65



Scheme 66



Scheme 67

A strong influence of solvent on regioisomer distribution has been observed in the one-pot synthesis of homoallylic alcohols from free allylic alcohols and aldehydes catalyzed by palladium pincer complex **L2** (Scheme 69).[199] In the presence of methanol, the expected branched products were isolated. However, the absence of methanol resulted in the formation of linear products. Presumably, when methanol is available, the initial adduct between the allylboronate and aldehyde undergoes a rapid methanolysis releasing the product. When methanol is not available, the initial adduct undergoes another addition to an aldehyde, eventually leading to oxonia-Cope sigmatropic rearrangement followed by hydrolysis to the linear homoallylic alcohol.

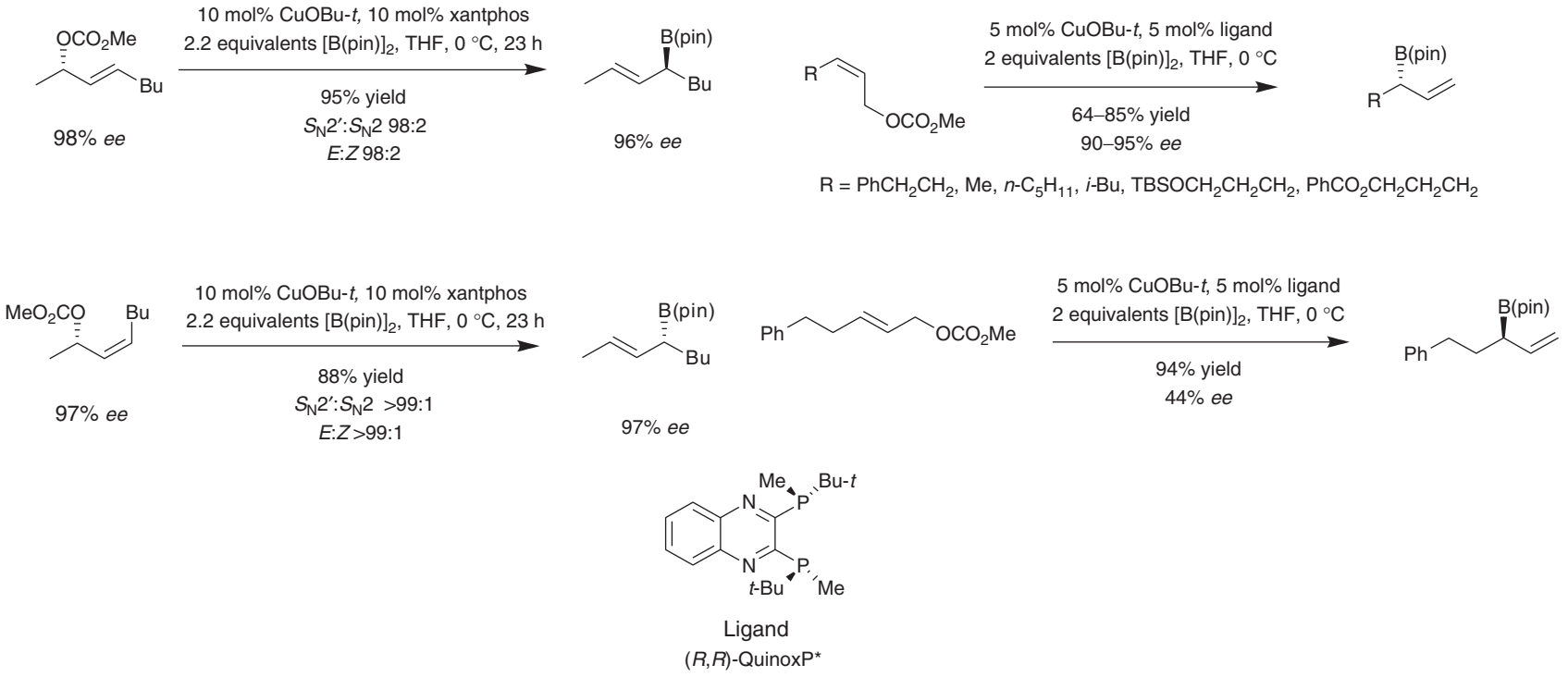
Direct conversion of allylic alcohols to allylsilanes and allylboronates can be achieved with cationic palladium complex $Pd(MeCN)_4(BF_4)_2$, although products of the direct S_N2 displacement are preferred. The reactions are conducted with a slight excess of the dimetallic reagents and 5 mol% of the palladium catalyst in DMSO/MeOH without any other additives (Scheme 70).[200,201]

Functionalized allylstannanes constitute an important class of reagents. One of the main challenges of transition metal-catalyzed synthesis of allylstannanes is avoiding further undesired reactivity of the products with the catalyst. The palladium pincer complex possessing strong σ-donor ligands shown in Scheme 71 was found to be effective in the synthesis of allylstannanes.[202] Suitable substrates include allylic chlorides, phosphates, and vinylic epoxides. Products with the C–Sn bond at the least substituted position of allylic system are preferred, irrespective of the structure of the substrate.

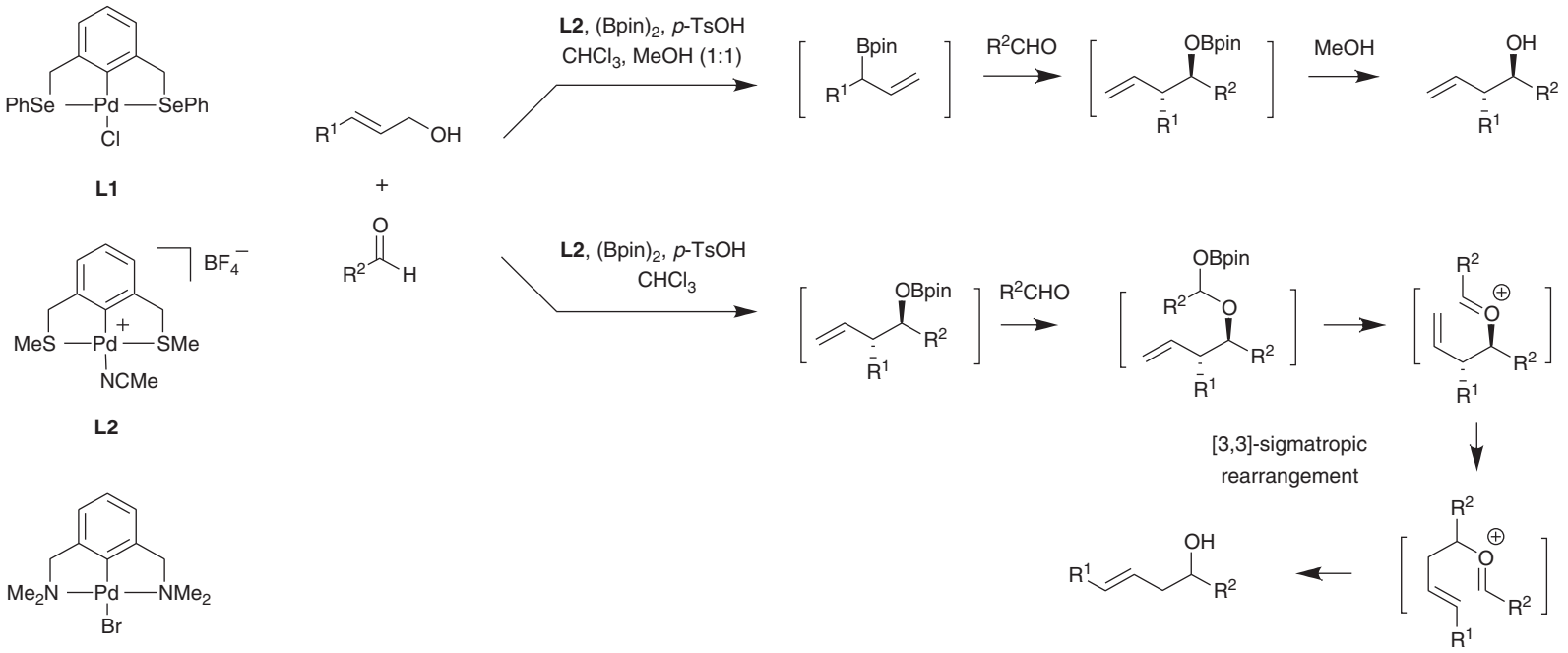
The use of sulfur nucleophiles in transition metal-catalyzed allylic transpositions of allylic alcohol derivatives is relatively rare compared to carbon, nitrogen, and oxygen nucleophiles since sulfur nucleophiles deactivate many catalysts by forming unreactive complexes. Methods have been developed to circumvent this problem: (1) rearrangement of *O*-allylphosphorothioates or phosphonothionates;[203] (2) decomposition of *O*-allyl or *S*-allyl dithiocarbonates;[204] (3) allylic substitution by silylated thiols.[205] However, limitations still remain. The utility of Cp*Ru(cod)Cl as the catalyst for allylic alkylation of thiols has been demonstrated (Scheme 72).[206] In contrast to the previous transformations catalyzed by palladium complexes, both aliphatic and aromatic thiols smoothly afforded the allylated products in moderate-to-excellent yields. A double inversion process was proposed for this ruthenium-catalyzed thiol allylation reaction. The reaction of both linear and branched allylic carbonates shown in Scheme 72 provided regioisomeric products in nearly identical ratios, favoring the linear product, which is in contrast to the ruthenium-catalyzed allylation reactions with carbon or nitrogen nucleophiles.

Palladium-catalyzed asymmetric syntheses of allylic sulfides from allyl carbonates have been described, however, the nucleophiles were still limited to silyl sulfides, *t*-butyl, or aryl sulfides.[207] Only very recently, catalytic asymmetric allylic alkylation of aliphatic thiols was achieved with the monodentate iridium-phosphoramidite complex as illustrated in Scheme 73.[208] In contrast to the allylation of thiophenol, where CsF was important to control the regioselectivity and maintain high yields,[209] the authors found that CsF had little influence on either yield or regioselectivity.

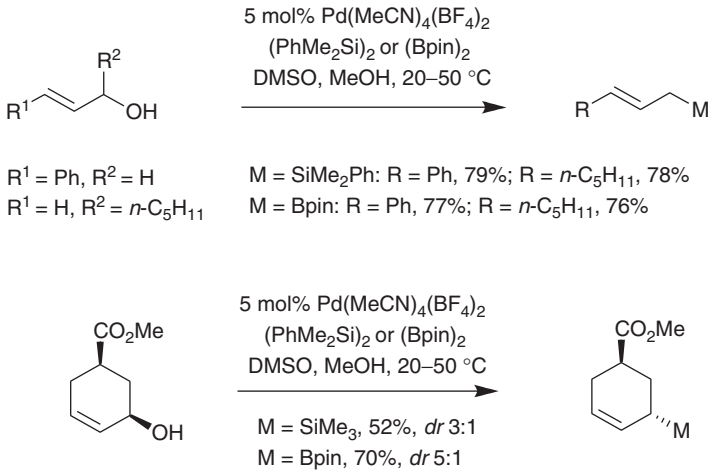
The ruthenium complex $Ru(Cp^*)(\eta^3\text{-}C_3H_5)(MeCN)_2(PF_6)_2$ was shown to efficiently catalyze allylation of aromatic or aliphatic thiols with allylic alcohols (Scheme 74).[210] The atom-economic reaction has wide substrate scope, and in most of the studies substrates achieved full conversion within 1 h. More interestingly, the branched-to-linear ratio of the products could be controlled


OCO2Me
Bu
10 mol% CuOBu-t, 10 mol% xantphos
2.2 equivalents [B(pin)]2, THF, 0 °C, 23 h
95% yield
SN2′:SN2 98:2
E:Z 98:2
98% ee
B(pin)
Bu
96% ee
R
OCO2Me
5 mol% CuOBu-t, 5 mol% ligand
2 equivalents [B(pin)]2, THF, 0 °C
64–85% yield
90–95% ee
B(pin)
R
R = PhCH2CH2, Me, n-C5H11, i-Bu, TBSOCH2CH2CH2, PhCO2CH2CH2CH2
MeO2CO
Bu
10 mol% CuOBu-t, 10 mol% xantphos
2.2 equivalents [B(pin)]2, THF, 0 °C, 23 h
88% yield
SN2′:SN2 >99:1
E:Z >99:1
97% ee
B(pin)
Bu
97% ee
Ph
OCO2Me
5 mol% CuOBu-t, 5 mol% ligand
2 equivalents [B(pin)]2, THF, 0 °C
94% yield
44% ee
B(pin)
Ph
Me
Bu-t
N
P
N
P
t-Bu
Me
Ligand
(R,R)-QuinoxP*

Scheme 68


PhSe
Pd
SePh
Cl
L1
BF4−
MeS
Pd
SMe
NCMe
L2
Me2N
Pd
NMe2
Br
L3
R1
OH
+
O
R2
H
L2, (Bpin)2, p-TsOH
CHCl3, MeOH (1:1)
Bpin
R2CHO
OBpin
MeOH
OH
L2, (Bpin)2, p-TsOH
CHCl3
[3,3]-sigmatropic
rearrangement

Scheme 69



Scheme 70

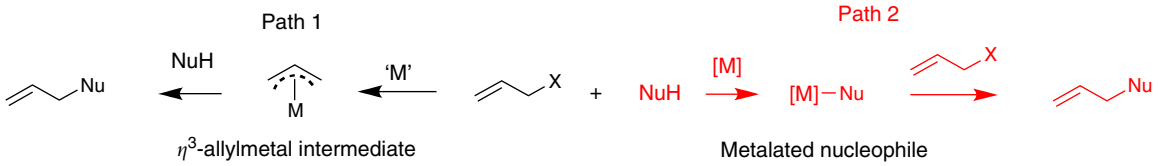
by the reaction time: the reaction of thiophenol with 1-(naphthalen-1-yl)allyl alcohol is complete within 16 min favoring the branched product, which undergoes complete isomerization to the linear product after 8 days.

Direct substitution of allyl alcohols or ethers with diethylphosphorothioic acids under UV irradiation ($\lambda > 300$ nm, dichloromethane (DCM)) afforded allyl phosphorothioic esters in moderate-to-excellent yields (Scheme 75).[211] Control experiments indicated that the UV irradiation was not necessary, although it was found that UV does increase the reaction rate. The reaction with optically active allylic ethers provided nearly racemic products indicating either a cationic or radical mechanism. Allyl phosphorothioate esters readily coupled with Grignard reagents in the absence of transition metal catalysts. Generally, the use of aromatic or alkenylmagnesium halides favored the S_N2-type displacements, whereas S_N2' products were preferred when secondary aliphatic Grignard reagents were used. A control set of reactions with corresponding allylic chlorides or bromides gave either low yield with aryl Grignard reagent or poor regioselectivity with alkyl Grignard reagents.

6.16.4 1,3-Heteroatom-to-Carbon Transpositions

6.16.4.1 Allyl Systems as Electrophiles

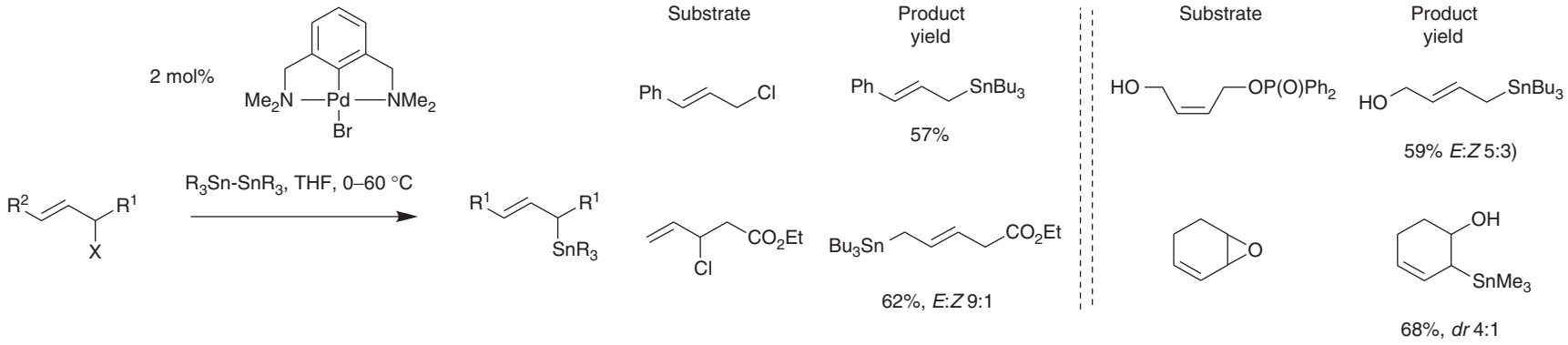
Two general paths for allylic transpositions where allyl systems show electrophilic reactivity can be classified, one involving η^3-allylmetal species, also referred to as π-allylmetal intermediates, and the other involving metallated nucleophiles with allylic halides and related electrophiles directly.



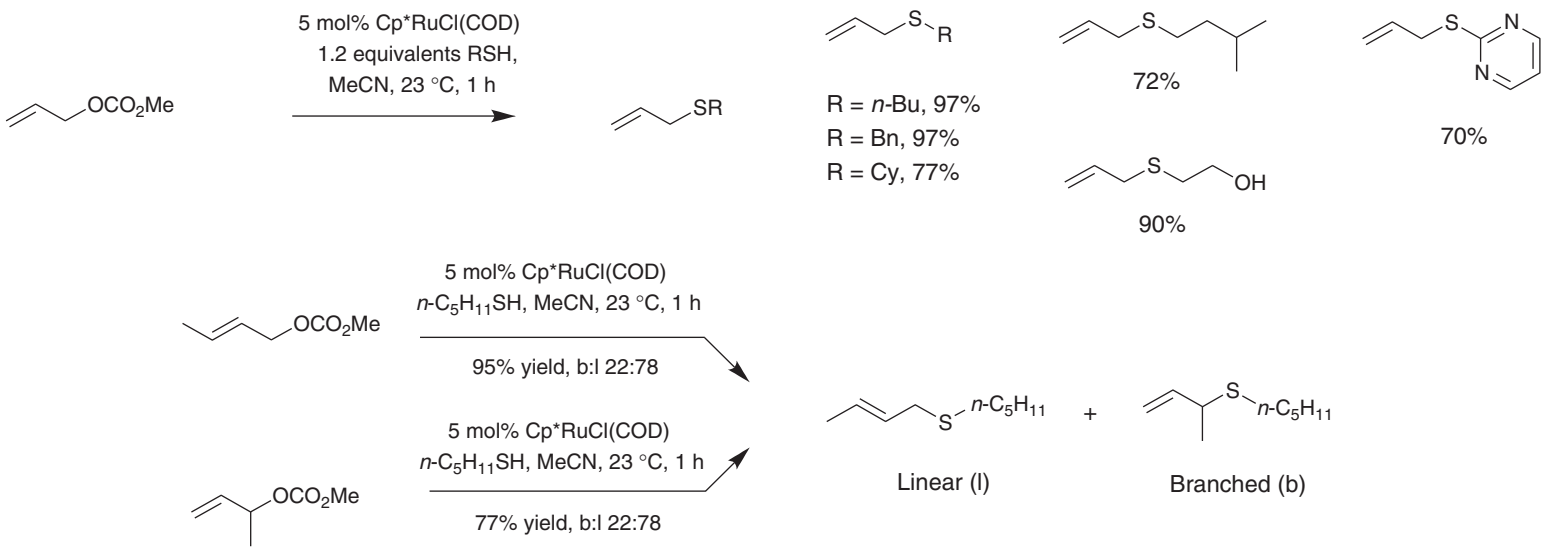
6.16.4.1.1 Transition metal-catalyzed transposition via π-allylmetal intermediates

Carbon–carbon bond forming reactions are the essence of organic synthesis. Therefore, methods for their construction have been in a state of continuous evolution. Transition metal-catalyzed reactions provide powerful strategies for the construction of C–C bonds. Among them, it is fair to say that transition metal-catalyzed allylation reaction has emerged as one of the cornerstone reactions in modern organic synthesis especially with the introduction of its asymmetrical version, often referred to as the asymmetrical allylic alkylation reaction (AAA reaction). The AAA reaction has been extensively studied by numerous research groups using different nucleophiles, designed chiral ligands, and different transition metals. In modern chemistry, both regioselectivity (linear and branched isomers) and stereoselectivity can be effectively modulated by changing the nature of ligands, transition metals, and additives. Due to inherent limitations in space, only selected contributions illustrative of general concepts and new directions have been highlighted in this section.[212,213] Additional emphasis is placed on transformations displaying high S_N2' regioselectivity.

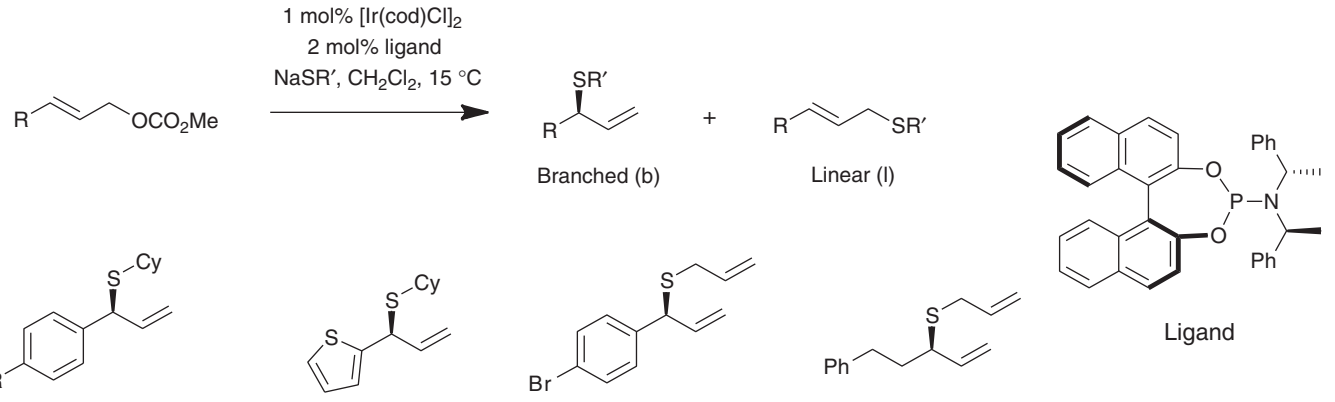
In early studies, allylic acetates were the most commonly used allylic substrates, and nucleophiles were limited to stabilized carbanions. The efforts toward synthesis of alkaloid (–)-huperzine A exemplify an archetypal strategy centered on the palladium-catalyzed double allylation of the β-keto ester with 2-methylene-1,3-propanediol diacetate that was selected by three independent


2 mol%
Me2N—Pd—NMe2
Br
R3Sn-SnR3, THF, 0–60 °C
R2
R1
X
R1
R1
SnR3
Substrate
Product yield
Ph
Cl
Ph
SnBu3
57%
CO2Et
Cl
Bu3Sn
CO2Et
62%, E:Z 9:1
Substrate
Product yield
HO
OP(O)Ph2
HO
SnBu3
59% E:Z 5:3)
O
OH
SnMe3
68%, dr 4:1

Scheme 71


5 mol% Cp*RuCl(COD)
1.2 equivalents RSH,
MeCN, 23 °C, 1 h
OCO2Me
SR
S
R
R = n-Bu, 97%
R = Bn, 97%
R = Cy, 77%
72%
90%
70%
5 mol% Cp*RuCl(COD)
n-C5H11SH, MeCN, 23 °C, 1 h
95% yield, b:l 22:78
5 mol% Cp*RuCl(COD)
n-C5H11SH, MeCN, 23 °C, 1 h
77% yield, b:l 22:78
n-C5H11
Linear (l)
Branched (b)

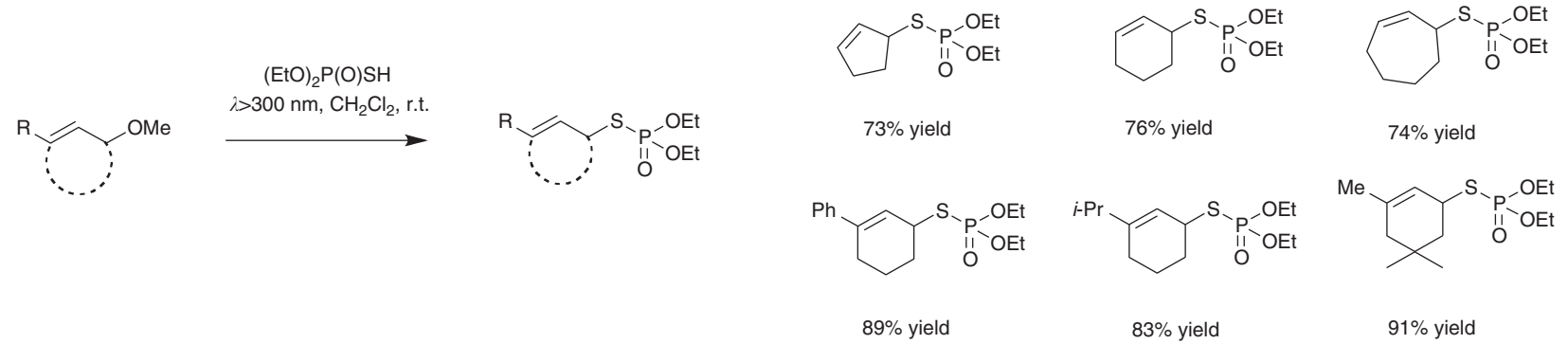
Scheme 72

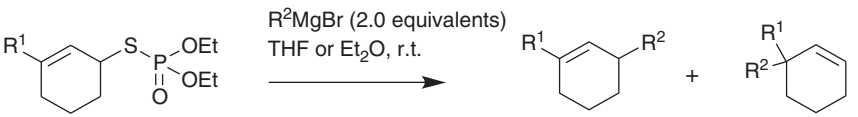

1 mol% [Ir(cod)Cl]2
2 mol% ligand
NaSR′, CH2Cl2, 15 °C
R
OCO2Me
SR′
Branched (b)
+
Linear (l)
Ph
O
P
N
O
Ph
Ligand
S
Cy
R
S
Cy
S
Br
S
Ph
R = H: 72% yield, b:l 91:9, 96% ee
R = OMe, 71% yield, b:l 94:6, 98% ee
74% yield
b:l 86:14
98% ee
60% yield
b:l 94:6
94% ee
34% yield
b:l 77:23
95% ee

Scheme 73

Scheme 74

Time	Conversion, %	b:l
16 min	100	13.0 : 1.0
18 h	100	1.0 : 2.0
41 h	100	1.0 : 5.0
8 d	100	0 : 1.0

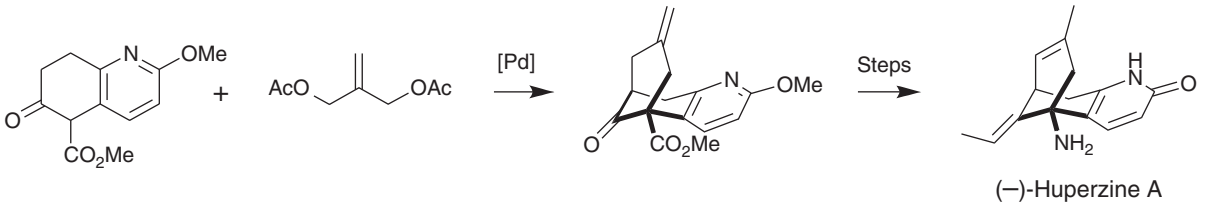




R^1	Grignard reagent	$S_N2:S_N2'$	yield
Me	4-$CF_3C_6H_4$MgBe	>95:5	81%
Me	4-F-C_6H_4MgBr	>95:5	75%
i-Pr	4-F-C_6H_4MgBr	>95:5	70%
4-FC_6H_4	4-F-C_6H_4MgBr	>95:5	70%
Me	$PhC(=CH_2)MgBr$	>95:5	55%
Me	c-C_6H_{11}MgBr	<5:95	81%
Me	c-C_3H_7MgBr	13:87	80%
Me	*i*-PrMgBr	<5:95	86%

Scheme 75

groups (Scheme 76).[214] More recently, less reactive allyl alcohol with a free hydroxy group could be used directly in the presence of *in situ* activators such as boron and titanium compounds.[215]



Scheme 76

Palladium-catalyzed allylic alkylation of *N*-(diphenylmethylene)glycinate with 1-phenyl-2-propenyl acetate produced the linear product with excellent enantioselectivity and good regioselectivity.[216] The reaction was conducted under heterogeneous conditions combining the chiral phosphine ligand and chiral phase transfer catalyst (PTC) indicated in Scheme 77. Azalactones were also used extensively to prepare certain unusual amino acid derivatives. A palladium-catalyzed reaction of linear allylic acetate with azalactone in the presence of a chiral ligand afforded the corresponding linear products in good-to-excellent yields and enantioselectivities.[217] Two years later, by using the identical PTC catalyst and triphenylphosphate as the ligand for Pd, the asymmetric allylation of *N*-(diphenylmethylene)glycinate was realized.[218] Various allylated products were obtained with excellent enantioselectivity and moderate-to-good yields. The reaction of γ-substituted allylic substrates provided the products with high regio- and stereoselectively favoring direct S_N2 substitution products.

Palladium-catalyzed allylic alkylation was also applied to the enantioselective synthesis oxindoles. An all carbon quaternary chiral center at the 3-postion of oxindole was constructed with good enantioselectivity from an indole-derived silyl enol ether. The product was advanced to accomplish the total synthesis of natural product horsfiline (Scheme 77).[219]

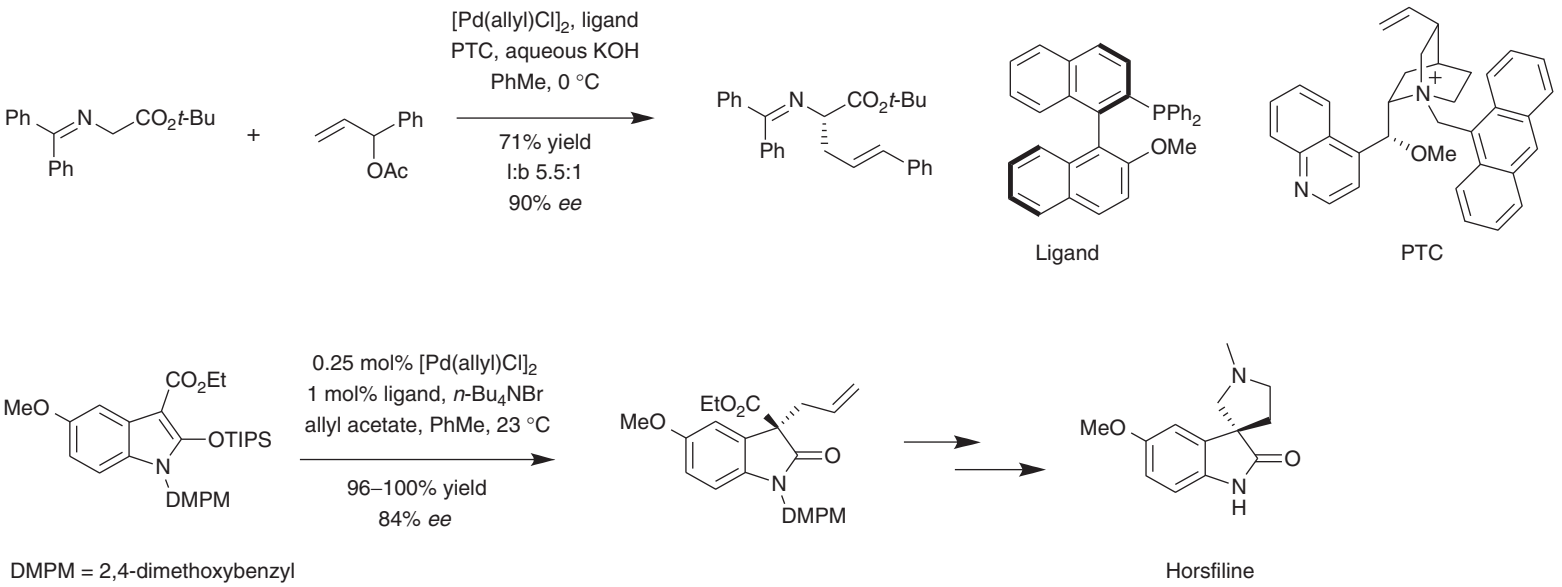
Traditionally, soft nucleophiles whose conjugate acids have pK_a values lower than 20 have been used with allylic acetates or carbonates in palladium-catalyzed allylic alkylation reactions. To overcome this limitation, unstabilized pregenerated lithium, tin, boron, magnesium, or silyl enolates have been exploited.[220] For example, asymmetrical allylation of silyl enolates prepared from α-fluoroketones is a process in which five-, six- and seven-membered α-fluoroketones have been prepared in good-to-excellent yields and excellent stereoselectivity (Scheme 78). Acyclic fluorinated silyl enol ethers gave the corresponding products with lower enantioselectivity.[221]

More recently, the asymmetrical allylic alkylation reaction catalyzed by iridium complexes has been studied intensively due to the generally high levels of regio- and stereoselectivity observed in this process. Similarly to rhodium-catalyzed allylic alkylation, the iridium-catalyzed reaction displays preference for branched products, which is especially important for organic synthesis. In 1997, the first example of efficient iridium-catalyzed allylation of allylic acetates and carbonates with the sodium salt of diethyl malonate was reported.[222] In the same year, the first iridium-catalyzed asymmetrical allylation reaction by using chiral phosphine–oxazoline ligands was accomplished.[223] Chiral phosphoramidite ligands have shown outstanding generality in iridium-catalyzed asymmetrical allylation reactions.[224] In many cases, additives such as tetrahydrothiophene (THT), CuI, and LiCl were necessary in the iridium-catalyzed allylation when carbon nucleophiles were used.[225] During the synthesis of brefeldin analogues, the initial chiral building block was constructed via iridium-catalyzed allylation of malononitrile and the allyl carbonate derivative (Scheme 79).[226] The reaction could be performed on scales up to 40 mmol.

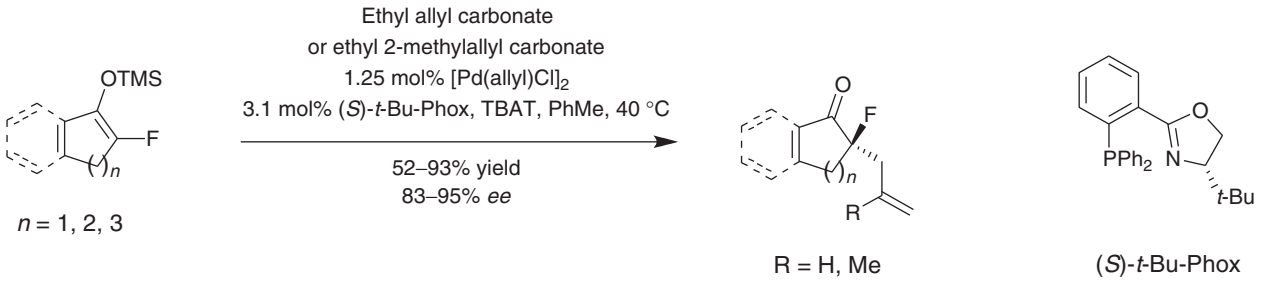
Fluorinated compounds could be prepared stereoselectively using fluorobis(phenylsulphonyl)methane as the nucleophile.[227] A remarkable intramolecular allylic dearomatization of indoles, pyrroles, and phenols was reported, giving products with high diastereoselectivity and enantioselectivity.[228] These studies showed that both spiro[5.4] and spiro[4.4] products could be produced with high stereoselectivity (Scheme 79).[229]

The use of preformed metal enolates is not without drawbacks, usually requiring strongly basic or electrophilic reagents, and occasionally when tin enolates are used, toxic reagents. The generation of enolates by decarboxylation can address these limitations.[230,231] Furthermore, decarboxylative enolization allows for the regiospecific generation of the reactive intermediate. Since in this approach both the nucleophile and allyl–metal species are generated *in situ*, excellent functional group compatibility can be achieved. Currently, the decarboxylative allylic alkylation reaction is among the most frequently used methods for the AAA reaction.[232]

After the initial validation of the palladium-catalyzed decarboxylative allylation in the early 1980s,[233–235] an enantioselective variant of this reaction was developed using Pd_2dba_3 and the chiral *bis*-phosphine ligand shown in Scheme 80.[236] The combination of $Pd_2(dba)_3$ and the chiral ligand effectively catalyzed the decarboxylative rearrangement of allylic β-ketoesters to homoallylic ketones. Generally, the reaction afforded moderate-to-excellent yields of products with 80–99% *ee*. To avoid the regioselectivity problems, substrates with formally symmetrical allylic groups were studied. It was also found that enantioselectivity was quite sensitive to substitution at the α-position: with a tertiary α-carbon the reaction proceeded with low enantioselectivity and virtually no diastereocontrol.


Ph
N
CO2t-Bu
Ph
+
Ph
OAc
[Pd(allyl)Cl]2, ligand
PTC, aqueous KOH
PhMe, 0 °C
71% yield
l:b 5.5:1
90% ee
Ph
N
CO2t-Bu
Ph
Ph
PPh2
OMe
Ligand
N
+
N
OMe
PTC
CO2Et
MeO
OTIPS
N
DMPM
0.25 mol% [Pd(allyl)Cl]2
1 mol% ligand, n-Bu4NBr
allyl acetate, PhMe, 23 °C
96–100% yield
84% ee
EtO2C
MeO
O
N
DMPM
N
MeO
O
N
H
DMPM = 2,4-dimethoxybenzyl
Horsfiline

Scheme 77



Scheme 78

The asymmetric allylic alkylation of simple alkanone derivatives to construct all-carbon quaternary centers via decarboxylation of the corresponding allylic enol carbonates utilizes *P,N*-type ligands, phosphinooxazolines (Phox), for optimal enantioselectivity in the range of 79–92% *ee* (Scheme 81).[237] In subsequent studies, high-throughput ligand screening led to the discovery that an electron-deficient *tert*-butyl Phox ligand exerted the highest control over enantioselectivity.[238] The identity of the solvent had little effect on the outcome, and solvents like THF, benzene, toluene, ether, and ethyl acetate showed similar reactivity and selectivity. The DFT calculation in combination with experimental studies demonstrated that the reaction proceeded via an inner sphere pathway, and the C–C bond formed through a Claisen-type seven-centered transition state. These results are different from the soft enolate asymmetrical allylation reactions, which undergo an external attack of the nucleophile onto the η^3-coordianted palladium complex (Scheme 82).[239]

An asymmetrical decarboxylative palladium-catalyzed allylic alkylation reaction forming α-quaternary and α-tertiary carbon centers was described in 2005 (Scheme 83). Allylic enol carbonates served as the starting material. No apparent racemization of the newly formed α-tertiary chiral center was observed.[240] Intriguingly, it was found that when the corresponding lithium enolate was employed as the nucleophile with the same enantiomer of the chiral ligand, the opposite enantiomer of the product was formed in the reaction.[241] In fact, the palladium-catalyzed AAA reaction of 1-methyl-2-tetralone with allyl acetate was highly sensitive to the choice of base; changing the base from LDA to cesium carbonate showed the preference for the formation of the opposite enantiomer.[242]

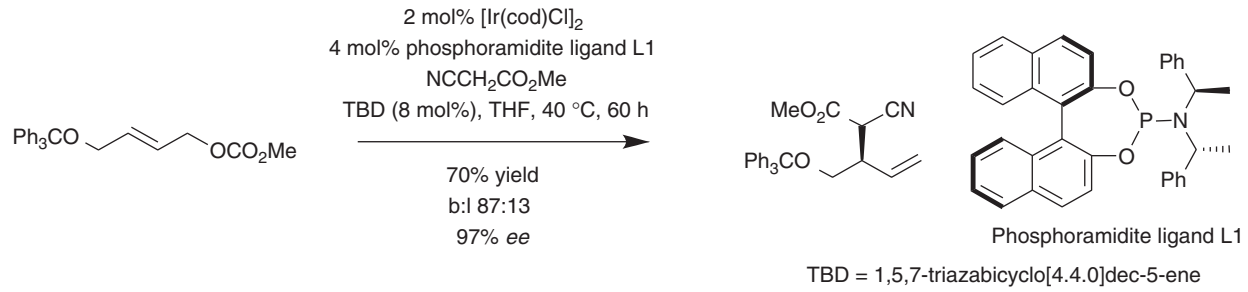
The palladium-catalyzed decarboxylative asymmetric allylic alkylation reaction with allylic enol carbonates is an attractive protocol for the construction of both tertiary and quaternary centers at the α-position of ketones, however, relatively difficult preparation of allylic enol carbonates limits its applications. The palladium-catalyzed decarboxylative allylation with allylic β-ketoesters offers a potentially more practical alternative.[243] In comparison with decarboxylation of allyl enol carbonate, the use of allyl β-ketoester afforded fairly similar results, suggesting that both processes share a common intermediate.

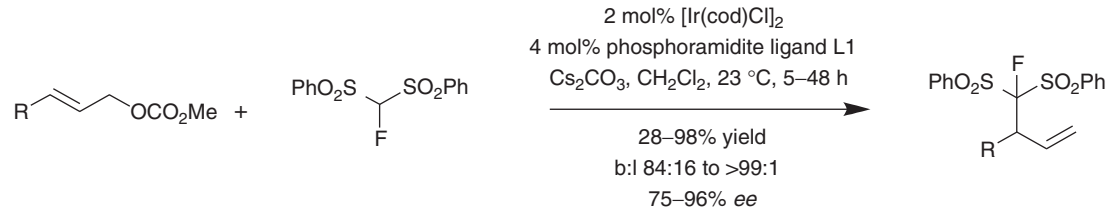
Different variants of Pd-catalyzed double asymmetric allylic alkylation have been described, using two reactive functionalities in the substrates, incorporating either allylic enol carbonates or β-keto esters. High enantioselectivity and good diastereoselectivity were generally observed in these processes. Application of bidirectional double asymmetric allylic alkylation in the total synthesis of complex terpenoid cyanthiwigin F is a powerful illustration of the utility of decarboxylative allylation in enantioselective organic synthesis (Scheme 84).[244]

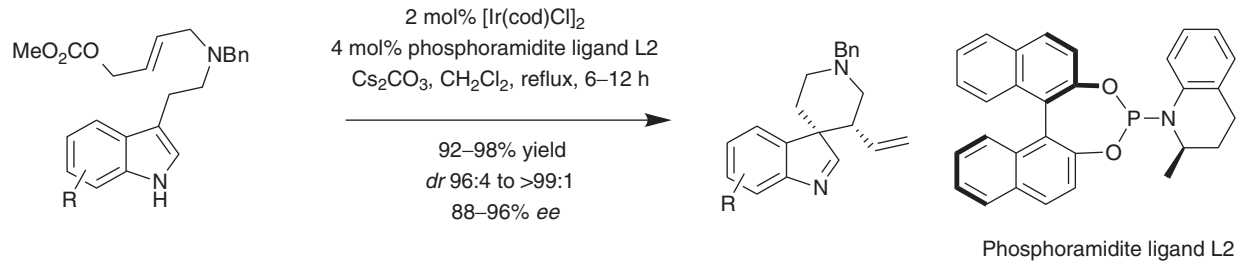
Other funcationalized allylic β-ketoesters have been studied including vinylogous β-ketoesters, α-fluoro-β-ketoesters,[245] α-acetamido-β-ketoesters,[246] and α-carboxyamido-β-ketoesters.[247] Decarboxylative allylation reaction of acyclic substrates is generally more complicated than that of cyclic substrates. In most examples of asymmetric decarboxylative allylic alkylation, the *E*-isomer of the substrate afforded the products with high yields and excellent enantioselectivity, whereas the *Z*-isomers usually gave relatively low yields and enantioselectivity at a considerably slower rate of reaction. One exception is the *Z*-enol carbonates derived from aryl ketones.[248]

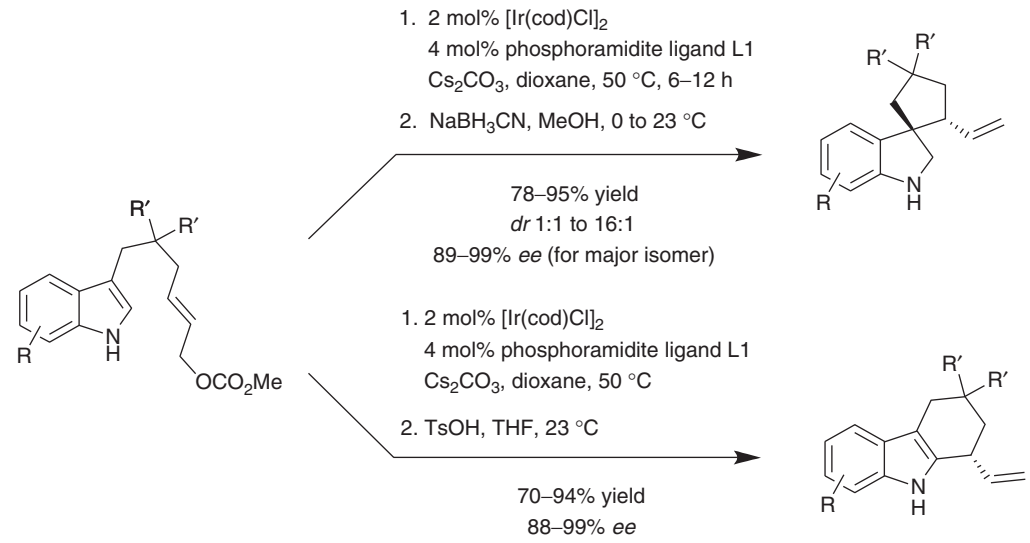
The palladium-catalyzed decarboxylative allylic alkylation favors the products where the new bond is formed at the least substituted center of the allylic system. In a limited set of examples where an asymmetrically substituted allylic system was studied, products of direct S_N2 displacement have been produced preferentially. In contrast, ruthenium- and iridium-catalyzed decarboxylative allylation shows a strong preference for branched allylic products, effectively accomplishing S_N2' allylic displacements with carbon nucleophiles.[249] In 2007, an Ir-catalyzed enantioselective decarboxylative allylation reaction was reported, which showed higher levels of selectivity compared to the corresponding ruthenium-catalyzed reactions. High enantioselectivity and excellent branched-to-linear selectivity was observed with β-ketocinnamates, whereas aliphatic substrates showed slightly reduced enantio- and regioselectivity (Scheme 85).[250]

The putative enolate intermediate generated during the metal-catalyzed decarboxylative allylation process can be trapped *in situ* by a Michael acceptor. Following the initial report that utilized a tethered Michael acceptor,[251] many processes based on this cascade reaction concept have been described. A number of activated Michael acceptors including arylidene malononitriles, arylidene-α-cyano esters, and Meldrum's acid derivatives have been used. In addition, imines,[252] isocyanates,[253] nitrones,[254] activated ketones,[255] and activated cyclopropanes[256] were used as electrophilic acceptors for *in situ* incorporation into the products.

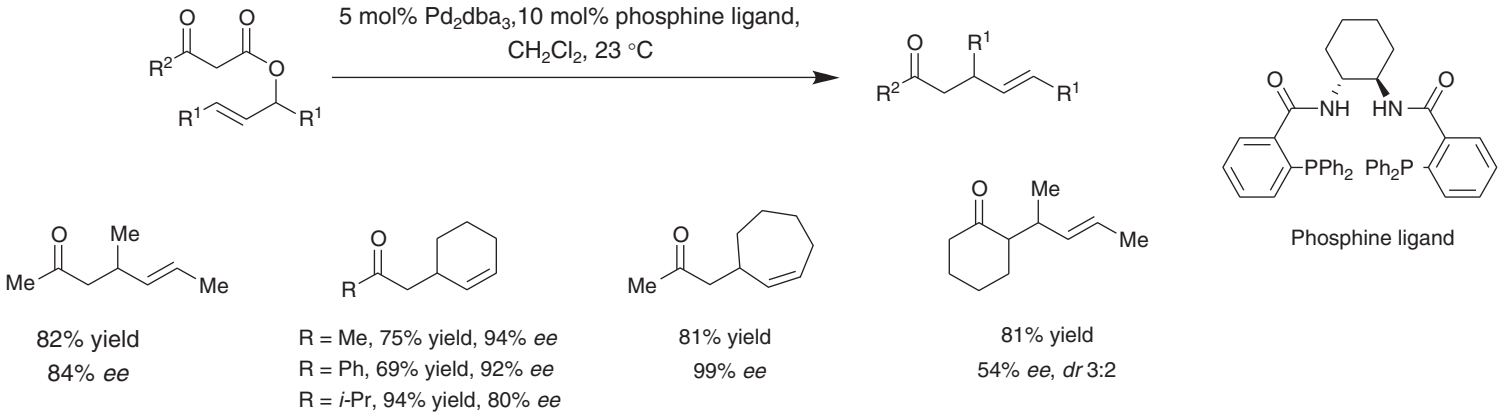

2 mol% [Ir(cod)Cl]2
4 mol% phosphoramidite ligand L1
NCCH2CO2Me
TBD (8 mol%), THF, 40 °C, 60 h
Ph3CO
OCO2Me
70% yield
b:l 87:13
97% ee
MeO2C
CN
Ph3CO
Ph
O
P
N
Ph
Phosphoramidite ligand L1
TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene


R
OCO2Me
+
PhO2S
SO2Ph
F
2 mol% [Ir(cod)Cl]2
4 mol% phosphoramidite ligand L1
Cs2CO3, CH2Cl2, 23 °C, 5–48 h
28–98% yield
b:l 84:16 to >99:1
75–96% ee
F
PhO2S
SO2Ph
R

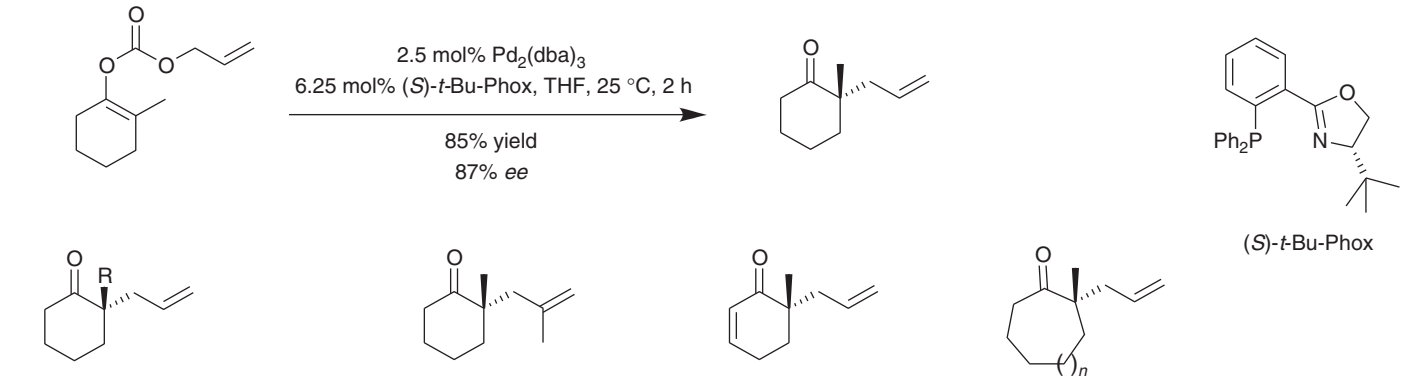

MeO2CO
NBn
R
N
H
2 mol% [Ir(cod)Cl]2
4 mol% phosphoramidite ligand L2
Cs2CO3, CH2Cl2, reflux, 6–12 h
92–98% yield
dr 96:4 to >99:1
88–96% ee
Bn
N
R
N
O
P
N
O
Phosphoramidite ligand L2


1. 2 mol% [Ir(cod)Cl]2
4 mol% phosphoramidite ligand L1
Cs2CO3, dioxane, 50 °C, 6–12 h
2. NaBH3CN, MeOH, 0 to 23 °C
78–95% yield
dr 1:1 to 16:1
89–99% ee (for major isomer)
R′
R′
R
N
H
OCO2Me
1. 2 mol% [Ir(cod)Cl]2
4 mol% phosphoramidite ligand L1
Cs2CO3, dioxane, 50 °C
2. TsOH, THF, 23 °C
70–94% yield
88–99% ee

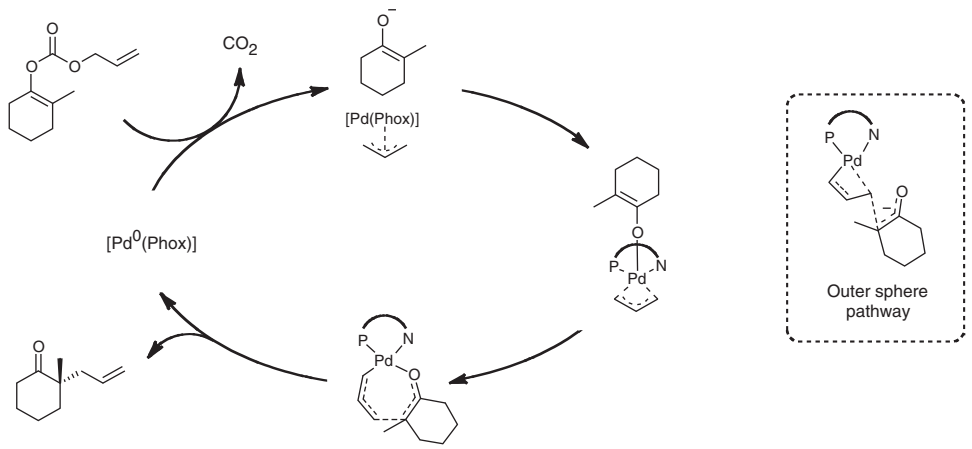
Scheme 79


5 mol% Pd2dba3,10 mol% phosphine ligand,
CH2Cl2, 23 °C
Phosphine ligand
82% yield
84% ee
R = Me, 75% yield, 94% ee
R = Ph, 69% yield, 92% ee
R = i-Pr, 94% yield, 80% ee
81% yield
99% ee
81% yield
54% ee, dr 3:2

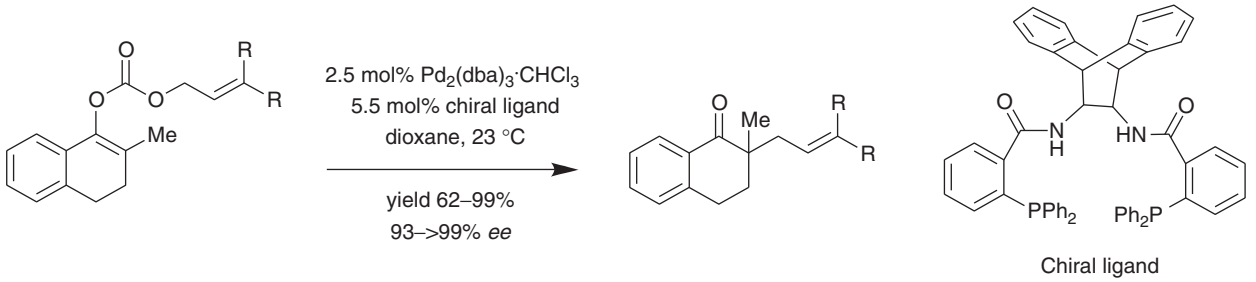
Scheme 80


2.5 mol% Pd2(dba)3
6.25 mol% (S)-t-Bu-Phox, THF, 25 °C, 2 h
85% yield
87% ee
Ph2P
N
O
(S)-t-Bu-Phox
R = Et, 96% yield, 92% ee
R = t-Bu, 55% yield, 82% ee
R = Bn, 96% yield, 85% ee
R = (CH2)3OBn, 87% yield, 88% ee
89% yield
91% ee
91% yield
89% ee
n = 1, 81% yield, 87% ee
n = 2, 96% yield, 79% ee

Scheme 81



Scheme 82



Scheme 83

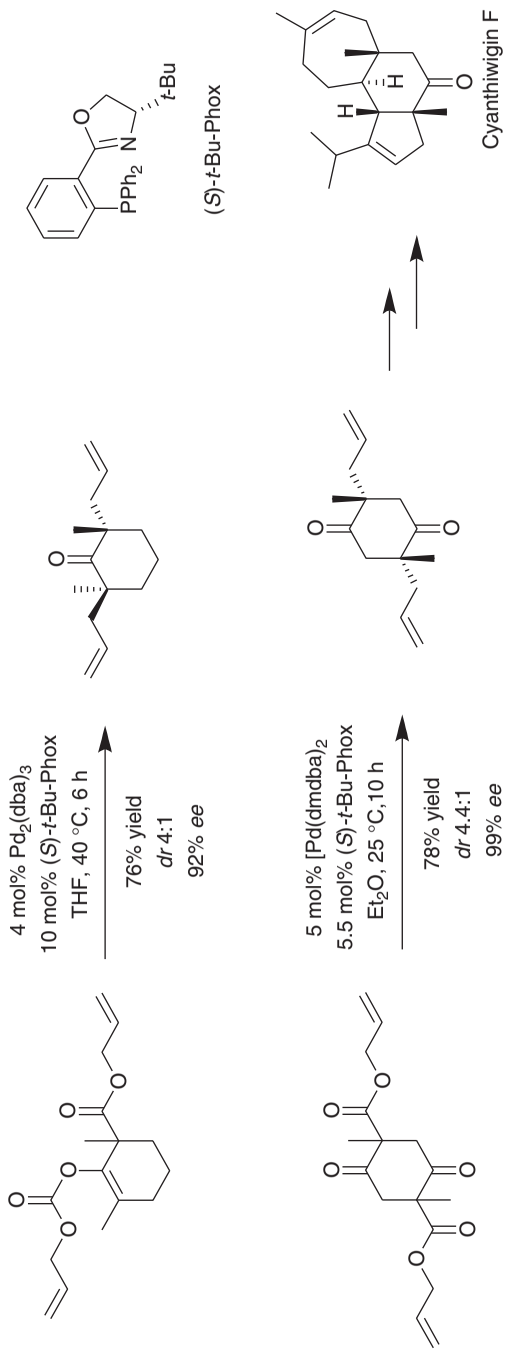
With arylidene malonitriles, the S_N2 versus S_N2' regioselectivity in the decarboxylative allylation could be controlled by the choice of transition metal catalyst (Scheme 86).[257] In the presence of $[Pd(PPh_3)_4]$, the linear product is formed with high regioselectivity. When the ruthenium catalyst $Cp_*Ru(bpy)Cl$ is used, high preference for the branched product of S_N2'-type substitution is realized.

In the studies of the palladium-catalyzed decarboxylative allylation of γ-methylidene-δ-valerolactones in the presence of methyl acrylate, an unexpected formation of a spiro[2.4]heptane product was observed,[258] which appeared to result from the nucleophilic attack at the central carbon atom in the (η^3-allyl)palladium intermediate.[259] Further studies indicated that the use of 2,2'-bis (diphenylphosphino)-1,1'-binaphthalene (BINAP) or dppf instead of PPh_3 did not significantly change product selectivity. In the presence of phosphites such as $P(OMe)_3$, $P(OiPr)_3$, the yield of the spiro[2.4]heptane product was enhanced, albeit the diastereoselectivity remained moderate (Scheme 87).

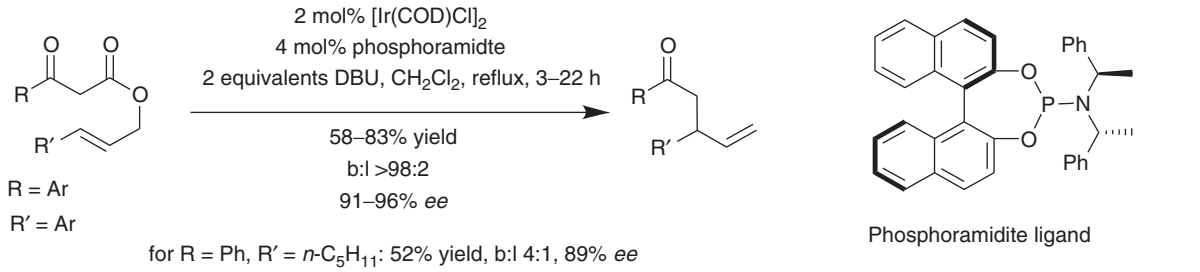
The decarboxylative allylic alkylation reaction has proven to be a generally useful method in organic syntheses, with many examples demonstrating its superiority to alternative allylic alkylation methods. Due to the mildness of the reaction conditions, typically requiring only mild reaction conditions with reactive intermediates generated *in situ* at low concentration, a wide range of functional groups can be tolerated. Since the reacting groups are in proximity, the desired allylation typically is faster than competing processes. Recent studies indicate that α-cyanoacetate,[260] nitronates,[261] α-hetero/electron-deficient aryl acetates,[262] α-ketimine acetate,[263] α-sulfonyl acetates[264,265] can successfully undergo decarboxylative allylic alkylation reaction.

An unusual decarboxylative allylation where the nucleophilic counterpart is generated by retro-aldol reaction has been described (Scheme 88).[266] In this transformation, the bicyclo[3.2.0]heptanone substrate is prepared by a photocycloaddition of ethylene to allyl enol carbonate derived from cyclopenta-1,3-dione precursor. Under the palladium catalysis, the initial fragmentation results in a retro-aldol reaction giving seven-membered enolate intermediates, which undergo allylic alkylation delivering the final products in excellent yield and enantioselectivity in the formation of the quaternary chiral center when the simple allyl group is introduced. With methallyl group introduction, a less hindered chiral catalyst (*S*)-*i*-Pr-Phox was required for reactivity, leading to a substantially lower enantioselectivity.

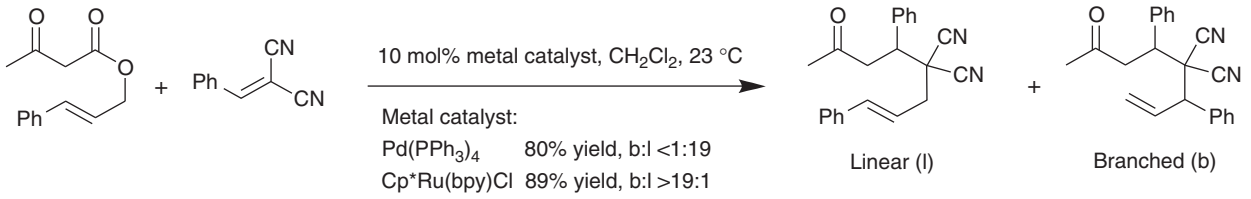
2-Trimethylsilylmethyl-2-propen-1-yl acetate has proven to be a uniquely powerful reagent for catalytic synthesis of carbocyclic compounds (Scheme 89).[267] The catalytic cycle is initiated by the formation of the zwitterionic π-allyl palladium intermediate by an oxidative addition of the active Pd° complex to the allylic actetate followed by nucleophilic desilylation by the *in situ*-generated acetate anion. Nucleophilic addition of the carbanionic complex to an electron-deficient alkene followed by ring-closure via an intramolecular allylic alkylation completes the formal [3+2] cycloaddition of trimethylenemethane (TMM). Based on the same


4 mol% Pd2(dba)3
10 mol% (S)-t-Bu-Phox
THF, 40 °C, 6 h
76% yield
dr 4:1
92% ee
5 mol% [Pd(dmdba)2
5.5 mol% (S)-t-Bu-Phox
Et2O, 25 °C, 10 h
78% yield
dr 4.4:1
99% ee
(S)-t-Bu-Phox
Cyanthiwigin F

Scheme 84



Scheme 85



Scheme 86

concept, a series of palladium-catalyzed TMM [2n+3] cycloaddition reactions for the synthesis of medium-size rings was developed.[268]

With a disubstituted electron-deficient alkene, the [3+2] TMM cycloaddition with the *E*-isomer favored the *trans*-adduct, whereas with the *Z*-isomer, the *cis*-product formed stereospecifically (**Scheme 90**).[269] The method enabled the completion of the total synthesis of brefeidin A.[270] The reaction with trisubstituted electron-deficient alkenes also showed excellent stereoselectivity.

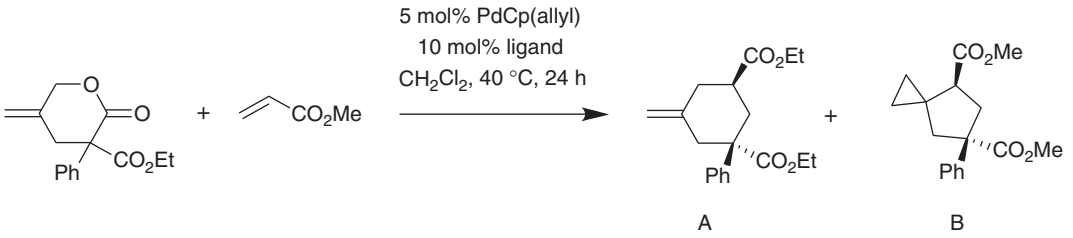
A general catalytic asymmetric TMM cycloaddition reaction enabled by a chiral phosphoramidite ligand was first reported in 2006. The reaction gave moderate-to-good yields and enantioselectivities for all cyclopentane products. Excellent stereocontrol with respect to *trans:cis* selectivity was observed (>19:1).[271] This method was further extended to the preparation of highly substituted carbocycles.[272] The development of new ligands was critical, and it was found that introducing 2-naphthenyl group into the cyclic phosporamidite ligand, as shown in **Scheme 91**, gave the best results. Due to the highly efficient stereoinduction by the phosphorimidiate ligand, it was possible to elevate the reaction temperature, increase its rate, and at the same time maintain high levels of enantioselectivity.

Evaluation of 3-cyano-3-acetoxy-2-trimethylsilylmethyl-1-propene revealed that unsaturated acylpyrroles were suitable substrates (**Scheme 92**). Unsaturated acylpyrroles are an attractive group of acceptors due to their versatility for further transformations. All reported substrates gave products with excellent diastereo- and enantioselectivity. The observed sense of regioselectivity could be explained by oxidative addition and desilylation that gives the expected zwitterionic allylpalladium species in which the anion is distal to nitrile group. Subsequently, the allylpalladium complex translocates to the thermodynamically favored distal position by π-σ-π isomerization placing the negative charge in proximity to the nitrile group.

Direct catalytic allylation of unactivated aldehydes and ketones is often complicated by side reactions such as competitive aldol condensation. A successful example of the direct intermolecular α-allylation reaction of aldehydes was accomplished by using a combination of transition-metal and enamine catalysis (**Scheme 93**).[273] The carbonyl group was activated by forming an enamine intermediate with pyrrolidine. Concurrently, allyl acetate formed an active allylpalladium species in the presence of the palladium catalyst. In addition to pyrrolidine, other cyclic and acyclic secondary amines have been shown to catalyze the direct allylation reaction albeit with lower yields. Presently, attempts to achieve the asymmetrical allylation by using chiral secondary amines or chiral phosphine ligands have given either low yield or low enantioselectivity.

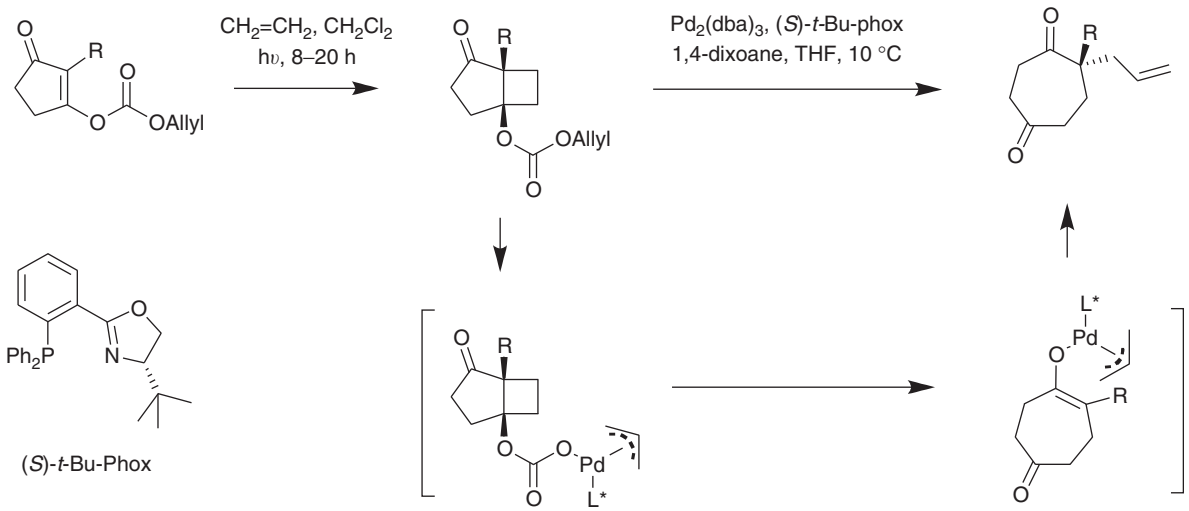
Following seminal studies on palladium-catalyzed direct α-allylation of carbonyl compounds with *N*-benzyl allylamine,[274] a method utilizing chiral phosphoric acids to induce asymmetry in palladium-catalyzed allylation of *N*-benzhydryl allylamine with aldehydes was developed (**Scheme 94**).[275] Oxidative addition of enammonium phosphate provides a cationic π-allylpalladium complex and an enamine, which are noncovalently tethered by a chiral phosphate counteranion. Nucleophilic attack of enamine on the π-allylpalladium complex gives, after hydrolysis, the α-alkylated aldehyde. Aldehydes with all-carbon quaternary stereogenic centers at the α-position have been formed in moderate-to-good yield with generally excellent enantioselectivity.

Subsequent studies demonstrated that allylic alcohols could be used directly in the aldehyde allylation reactions catalyzed by palladium and amines (**Scheme 95**). Elevated acidity of the medium due to the presence of the phosphoric acid catalyst facilitated the formation of the reactive π-allylpalladium species formed directly from unactivated allylic alcohols with a free hydroxy group. Simple allylic amines rather than diphenylmethylamine have been used initially in the allylation reaction.[276] A mixture of allyl alcohol and 2-phenylpropanal in the presence of TRIP (**Scheme 94**) and $Pd(PPh_3)_4$ produced the allylation product with very low enantioselectivity. The low enantioselectivity was attributed to the poor *E*/*Z* selectivity in the formation of the enamine intermediate. Accordingly, the structure of the amine was found to have a significant impact on the enantioselectivity, and the optimal



Ligand	Yield of A (*dr*)	Yield of B (*dr*)
PPh_3	29% (83:17)	64% (75:25)
BINAL	14% (81:19)	55% (78:22)
dppf	16% (81:19)	29% (81:19)
$P(OMe)_3$	4%	93% (65:35)
$P(OPr\text{-}i)_3$	5%	86% (79:21)

Scheme 87



Scheme 88

conversion and enantioselectivity was obtained with 40 mol% of diphenylmethylamine. The final treatment with aqueous hydrochloric acid is needed to ensure complete hydrolysis of the initially formed imine to the aldehyde.

In comparison to the aforementioned nucleophilc allylic alkylation, the palladium-catalyzed cross-coupling of allylic electrophiles with organometallic reagents is somewhat less developed. Within this class of reactions, boronic acids are in some cases more attractive as the organometallic counterpart compared to the classic copper-based reagents, which require strongly nucleophilic organometallic precursors such as organomagnesium, organolithium, or organozinc compounds.[277] Along these lines, a regioselective allyl–aryl coupling reaction between allylic acetates and arylboronic acids was described in 2008.[278] This reaction is characterized by excellent S_N2' selectivity as demonstrated by employing regiocomplementary substrates (Scheme 96). The reaction is proposed to proceed via Heck-type C═C bond insertion followed by β-acetate elimination.[279] A related palladium-catalyzed coupling of arylboronic acids with allylic phenyl ethers was reported.[280] The reaction was conducted in water as the environmentally benign solvent in the presence of 2% of nonionic amphiphile PTS (Scheme 96). With 3-aryl-propen-1-yl phenyl ethers the reaction afforded linear products predominantly, whereas branched products were formed preferentially when aliphatic allylic 3-alkyl-propen-1-yl phenyl ethers were used.

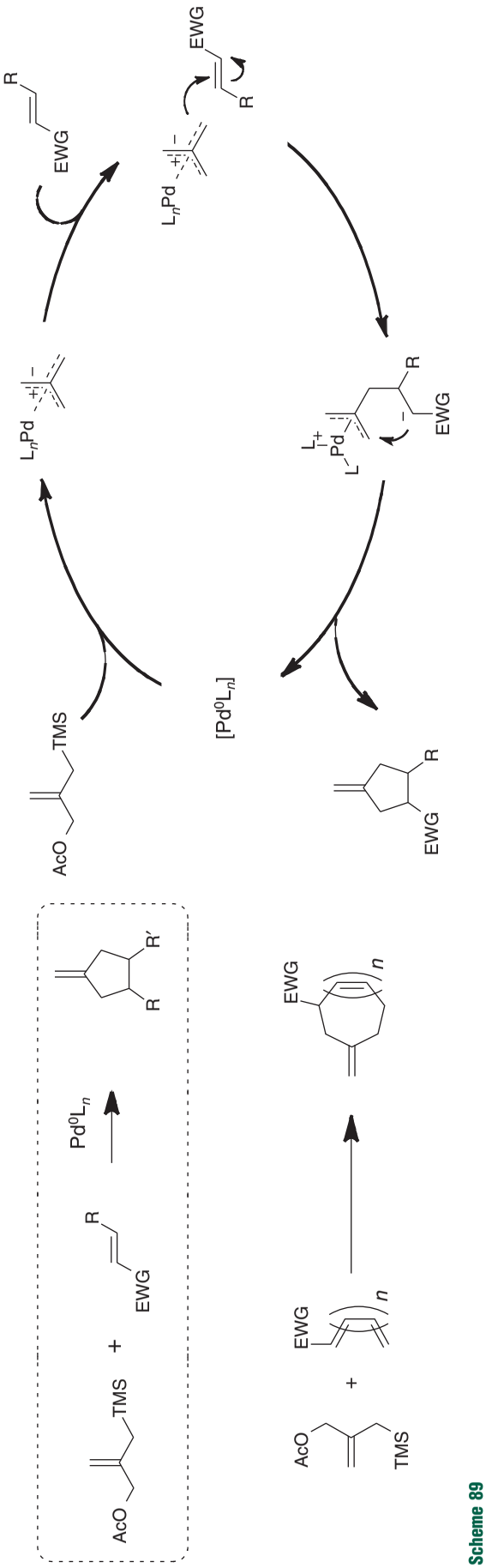
Rhodium-catalyzed allylic cross-coupling of aryl boronic acids and arylzinc bromides has also been investigated. A $RhCl_3$-catalyzed direct cross-coupling reaction of cinnamyl alcohol with various aryl- and vinylboronic acids in ionic liquid medium has been described (Scheme 97).[281] The rhodium-catalyzed reaction of optically active allyl carbonates with arylzinc bromides gave S_N2 displacement products in good yield with inversion of configuration (Scheme 97). The resulting product was advanced to (*S*)-ibuprofen via Ru-catalyzed oxidative cleavage of the terminal alkene.[282]

A rhodium-catalyzed allylic displacement within a cyclic system accomplishes an enantioselective synthesis of highly substituted cyclohexenes.[283,284] The asymmetric ring-opening (ARO) of oxabicyclic alkenes with organoboronic acids and the $[Rh(COD)Cl]_2$/PPF-P-*t*-Bu catalyst system afforded the products in the presence of water and base. Reactions of arylboronic acids bearing a substituent at the *ortho*-position (2-chloro- or 2-methyphenylboronic acid) gave no expected ring-opening products (Scheme 98).

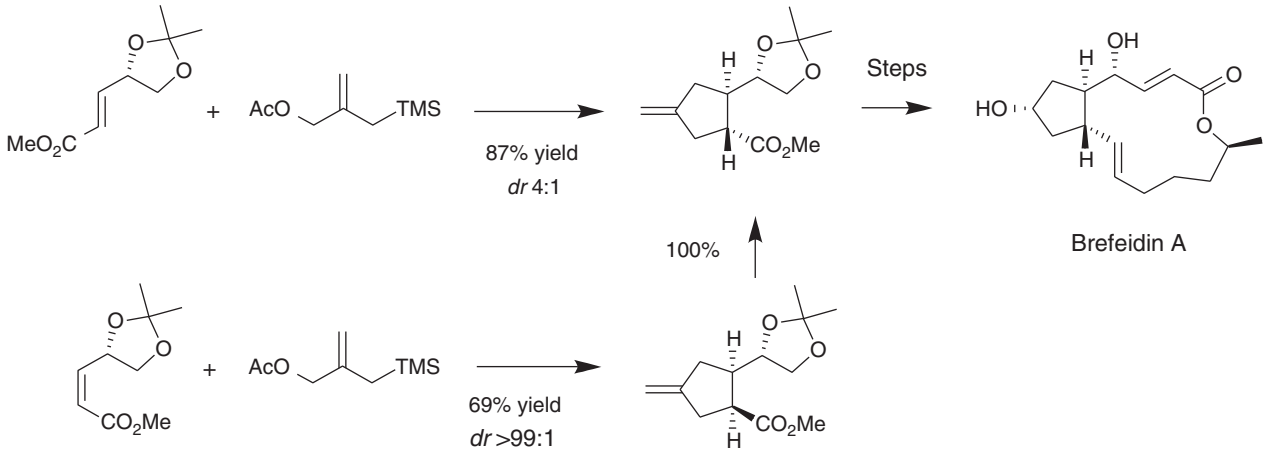
The use of a nickel/Pybox catalytic system allowed for an efficient asymmetric cross-coupling of racemic secondary allylic chlorides and organozinc reagents with generally good-to-excellent enantioselectivity and S_N2-type regioselectivity.[285] This methodology was the centerpiece of an efficient enantioselective total synthesis greatly of fluvirucine A_1, where key steps are the nickel/Pybox-catalyzed asymmetrical coupling of racemic allylic chlorides (Scheme 99).

In 2010, a palladium-catalyzed allyl–allyl cross-coupling reaction was reported.[286] With monodentate ligand PPh_3, the reaction formed the linear products selectively. However, the regioselectivity of this reaction was sensitive to the 'bite angle' when bidentate ligands were used. Generally, ligands with small 'bite-angle' such as dppe, dppp, afforded substitution products with high regioselectivity in preference of branched isomers. When chiral ligand 2,2′-bis(difurylphosphino)-6,6′-dimethoxybiphenyl [(*R*)-MeO-furyl-BIPHEP] was employed, the allyl–allyl cross-coupling products were formed with high regio- and stereoselectivity. The linear and the corresponding internal racemic *tert*-butyl carbonates as the starting materials gave identical products. For the aliphatic 3-alkyl-2-propen-1-yl *tert*-butyl carbonates, the selectivity could be improved by slecting (*R*,*R*)-$QuinoxP_*$ as the ligand. All-carbon quaternary centers could also be constructed by the cross-coupling of 3,3-disubstituted allylic *tert*-butyl carbonates with allylboronates (Scheme 100).[287]

Recently, a palladium-catalyzed cross-coupling of allylic silanolate salts with arylhalides has been developed. Mechanistic studies with stereodefined substrates provided support for an intramolecular *syn* S_E' process.[288]


AcO
TMS
R
EWG
Pd^0L_n
R'
R
EWG
n
AcO
TMS
+
EWG
n
$[Pd^0L_n]$
L_nPd
R
EWG
L_nPd
EWG
R
R
EWG
L_nPd
AcO
TMS

Scheme 89



Scheme 90

6.16.4.1.2 Copper-catalyzed processes

Copper-catalyzed enantioselective allylic substitution reactions using organometallic nucleophiles and allylic electrophiles is a powerful approach to creating useful enantioenriched materials for organic synthesis, including those incorporating quaternary chiral centers.[289,290] This is especially true for processes displaying a high preference for S_N2' substitution, and substantial progress has been achieved in developing methods capable of exerting a great degree of control over regio- and stereoselectivity. The typically high regiocontrol in preference of S_N2' substitution is one of the most appealing features of copper catalysis in allylic displacements.

The first example of enantioselective catalytic substitution employed a chiral arenethiolatocopper(I) complex with Grignard reagents.[291] Although only moderate enantioselectivity was observed, this reaction paved the way for other copper-catalyzed asymmetrical allylic substitution reactions. Copper, as well as silver complexes were found to efficiently catalyze allylic substitution with organomagnesium, organozinc, triorganoaluminum, and other reagents.

6.16.4.1.2.1 Copper-catalyzed nucleophilic addition of diorganozinc reagents

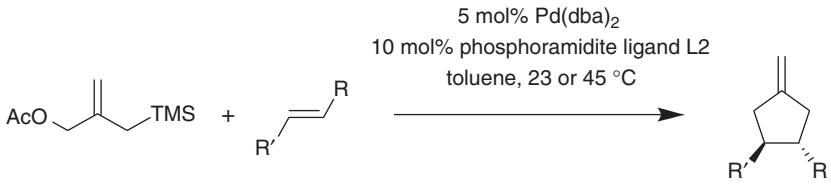
Organozinc reagents are among the most widely used reagents in the asymmetrical allylic substitution reaction. Currently five major classes of ligands have been developed in this field, namely, chiral amines, chiral phosphorus-based ligands, chiral sulfonamides, peptide-based ligands, and stabilized chiral *N*-heterocyclic carbenes.

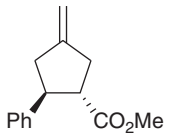
Allylic substitution reactions using diorganozinc compounds in combination with copper(I)-complexes modified by ferrocene-derived chiral amines are among the first Cu-catalyzed asymmetrical allylic substitutions.[292] An improvement in enantioselectivity was realized by using a C_2-symmetrical amine ligand and polymeric methylaluminum oxide (MAO).[293] Kinetic studies had shown that the stereoselectivity of the reaction was time-dependent; the *ee* values gradually decreased with time. The authors speculated that the time-dependent stereoselectivity was due to the increasing concentration of RZnCl. Independent addition of RZnCl confirmed its strong negative effect on enantioselectivity. The addition of excess of MAO, which is known to be a strong zinc chloride scavenger, greatly improved the enantioselectivity by shifting the equilibrium toward the diorganozing reagent and lowering the concentration of RZnCl (Scheme 101).

A combinatorial ligand-screening approach assisted in identifying effective peptide-based compounds for copper-catalyzed asymmetrical allylic substitution with allylic phosphates.[294,295] The peptides containing 2-pyridinylmethylimino, 6-isopropoxy-2-pyridinylmethylimino, and 2-hydroxy-1-naphthylmethylimino groups proved to be especially effective.

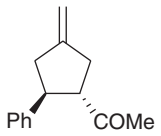
Chiral phosphoroamidites have proven to be another highly useful class of ligands for the copper(I)-catalyzed allylic substitution reactions. The desymmetrization of cyclic *meso* bisphosphates and allylic substitution of vinyloxiranes are but a few examples of their utility (Scheme 102).[296–298]

The efficacy of chiral functionalized *N*-heterocyclic carbenes (NHCs) in S_N2'-selective allylic substitution has been demonstrated with allylic phosphate groups with dialkylzinc reagents.[299] Initial experiments with the chiral imidazolidinium chlorides required relatively high catalyst loading (10 mol%) to maintain acceptable levels of enantioselectivity. Eventually, silver-NHC precatalysts (**L1**, **L2**, Scheme 103) were evaluated, resulting in a significantly lower NHC loading of 1 mol% while maintaining good-to-excellent enantioselectivity in the allylic substitution reaction affording products with chiral tertiary and quaternary stereocenters. The activity of the NHC ligands in which the phenolic hydroxy group is replaced with a methoxy group is substantially diminished. Mechanistic studies confirmed that the active catalyst is generated by transmetallation of the silver-NHC precatalysts with $CuCl_2{\cdot}2H_2O$, and the catalytic activity of the Cu–NHC complexes was validated independently. The development of the second-[300] and third-generation catalysts was essential to broaden the scope of both substrate and the organozinc reagent. For example, the second-generation Ag–NHC complex (**L2**, Scheme 103) showed greater versatility especially with sterically hindered dialkylzinc compounds. Catalytic synthesis of chiral allylic silanes could be achieved with (3-silyl)allyl phosphates as the

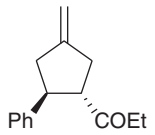




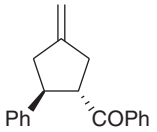
97% yield
90% *ee*



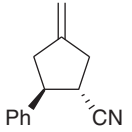
91% yield
98% *ee*



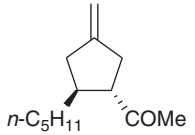
72% yield
83% *ee*
(with L1 at –23 °C)



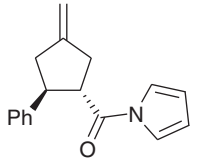
83% yield
80% *ee*
(with L1 at –23 °C)



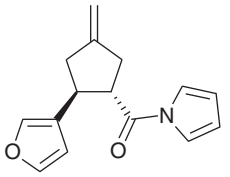
98% yield
92% *ee*



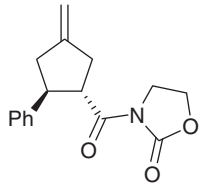
80% yield
95% *ee*



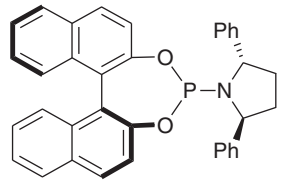
80% yield
91% *ee*



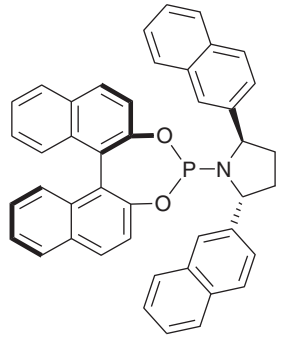
99% yield
86% *ee*



94% yield
84% *ee*

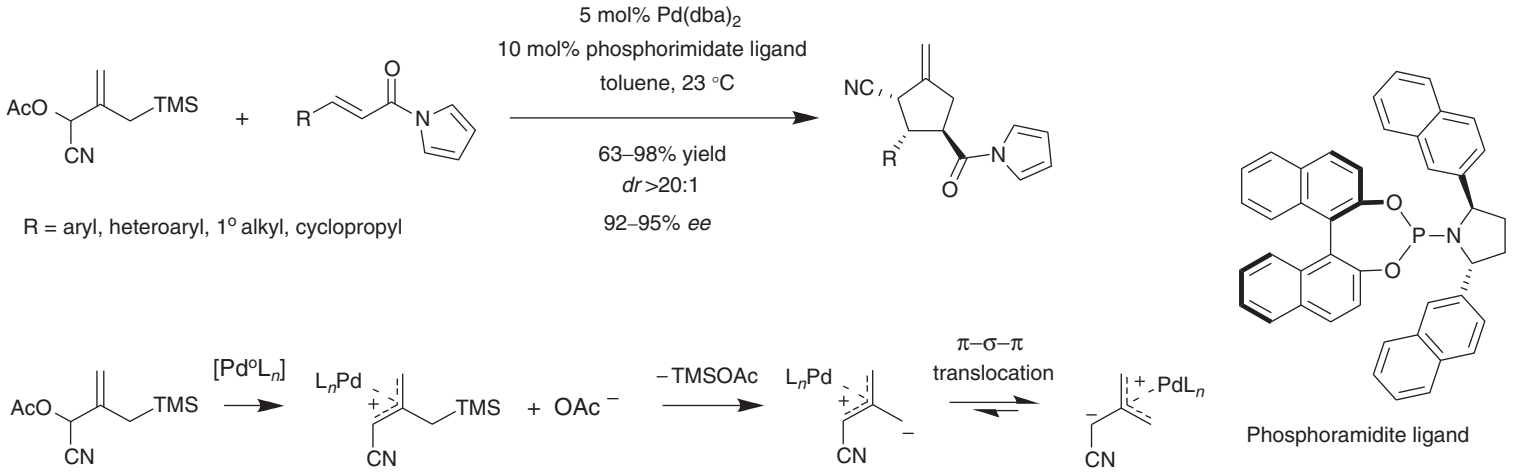


Phosphphoramidite ligand L1

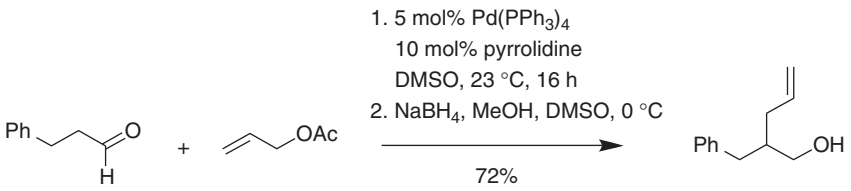


Phosphphoramidite ligand L2

Scheme 91


AcO
TMS
CN
+
R
O
N
5 mol% Pd(dba)2
10 mol% phosphorimidate ligand
toluene, 23 °C
63–98% yield
dr >20:1
92–95% ee
NC
R
N
O
R = aryl, heteroaryl, 1° alkyl, cyclopropyl
[Pd°Ln]
LnPd
TMS
CN
+ OAc −
−TMSOAc
π–σ–π
translocation
PdLn
O
P
N
O
Phosphoramidite ligand

Scheme 92



Scheme 93

substrates.[301] With certain substrates, the second-generation precatalyst showed better results than the third-generation precatalyst with diarylzinc reagents. Copper-free NHC-catalyzed allylation with diorganozinc and trialkylaluminum reagents has also been described.[302] Chiral Zn- and Al-based *N*-heterocyclic carbene complexes, which were postulated to serve as the catalytically active species in the absence of copper additives, have been isolated and characterized by X-ray crystallographic analysis.

6.16.4.1.2.2 Copper-catalyzed nucleophilic addition of Grignard and organolithium reagents

A variety of compounds have been introduced as ligands for copper-catalyzed allylic substitution reactions utilizing organomagnesium (Grignard) and organolithium reagents, examples of which are illustrated in Scheme 104. Copper thiolate catalysts are among the early successes in this field.[303] Moderate enantioselectivity was achieved with TADDOL-based phosphite ligands in the asymmetric substitution of allylic halides and acetates with simple Grignard reagents.[304] Subsequently, phosphoramidite ligands proved to be superior in their ability to control enantioselectivity.[305] The optimal results were achieved with methoxy-substituted phosphoramidite ligand **L1** (Scheme 104) in the S_N2' substitution of primary allylic chlorides with various Grignard reagents.[306] The scope of this effective Cu(I)-phosphoroamidite ligand system was further expanded to allylic substitution reaction of various di- and trisubstituted allylic chlorides[307] and 1,4-dihalo-2-butenes.[308]

In 2010, a new class of NHC ligands bearing a diphenyl imidazoline core and a flexible functionalized *N*-benzylic substituent was introduced (**L1**, Scheme 105). The imidazolium salts serving as precursors to these NHC ligands were found to catalyze the asymmetric allylic substitution with Grignard reagents in the absence of copper salt, albeit at lower reaction rates.[309] The same type of NHC ligands were utilized for asymmetric allylic substitution reactions of γ-chloro-α,β-unsaturated esters in another study (**L2**, Scheme 105).[310] Furthermore, the corresponding Cu(I)-catalyzed reaction provided the opposite enantiomer.

Application of the ferrocene-based amino diphosphine ligands resulted in the excellent regio- and stereoselectivity in the allylic substitution of allylic bromides with organomagnesium reagents.[311] With 3-chloro-1-propen-1-yl boronates as the substrates, a successful synthesis of enantioenriched α-substituted allylboronates was achieved. The copper(I) 2-thiophenecarboxylate-phosphoroamidite catalytic system in combination with Grignard reagents was used in this transformation.[312]

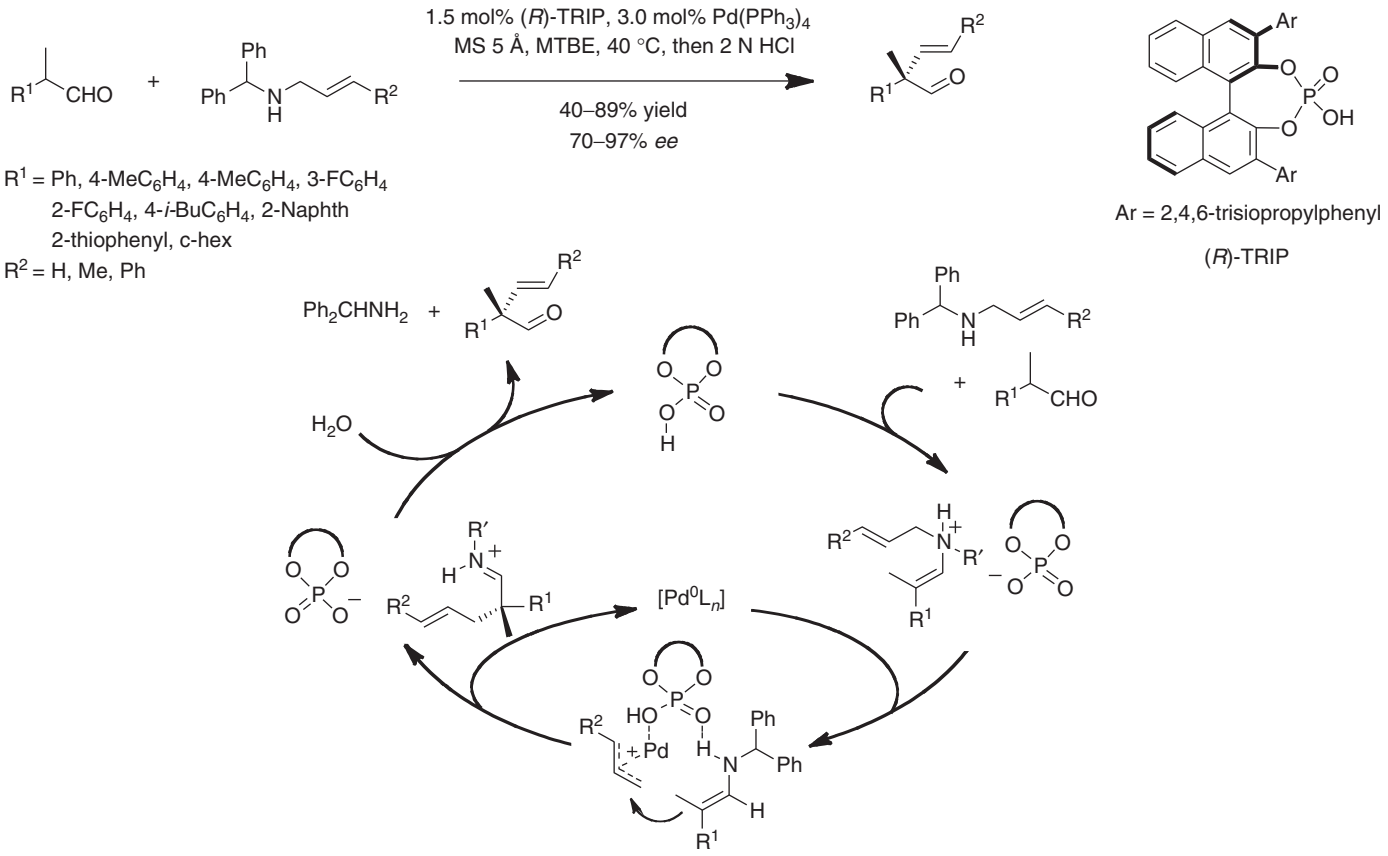
Organolithium compounds are among the classic and the most useful reagents in organic synthesis. Nevertheless, the exceptionally reactive, strongly basic nature of these reagents limits their application in asymmetric synthesis, especially in the development of catalytic enantioselective transformations.[313] In spite of these challenges, several enantioselective allylic substitution reactions with organolithium compounds catalyzed by chiral copper complexes have been described (Scheme 106). The chiral complex produced from copper(I) bromide-dimethyl sulfide adduct and chiral diphosphine Taniaphos served as the catalyst for allylic S_N2' displacments of allylic bromides with RLi reagents in DCM.[314] Kinetic studies indicated that the active species is a reactive chiral monoalkyl copper–phosphine complex. A strong solvent effect was observed for this reaction. A solvent with poor coordinating properties gave enhanced enantioselectivity. The source of copper(I) species had little effect on yield or selectivity. An important technical aspect of this reaction is the requirement for the slow addition of the organolithium reagent, indicating a rapid substoichiometric process with efficient copper/ligand recovery rather than a true catalysis.

With Taniaphos as the chiral ligand, the reaction of simple allylic bromides with primary alkyllithium reagents gave the products with good regio- and stereoselectivity (Scheme 106). With allylic chlorides, phosphoroamidite *ent*-**L1** gave the optimal results. The use of secondary organolithium reagents or trisubstituted allyl bromides required phosphoramidites **L2** and **L3** to obtain higher selectivity.

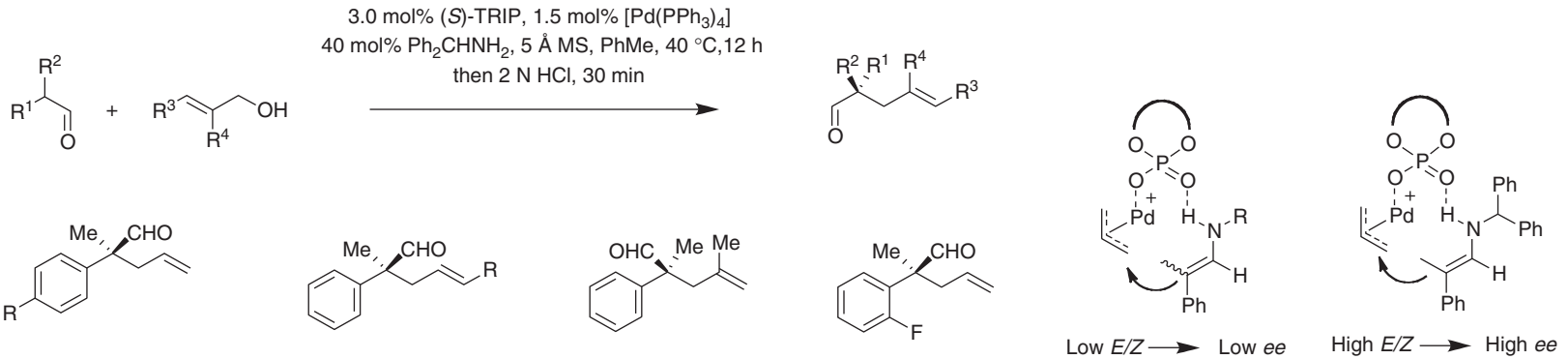
6.16.4.1.2.3 Copper-catalyzed nucleophilic addition of organoaluminum and boronate reagents

The chiral phosphoramidite ligands repeatedly mentioned in this chapter have been used in copper-catalyzed allylic substitution reactions with organoaluminum reagents as the nucleophilic counterpart. Generally, modest enantioselectivity has been realized to date.[315]

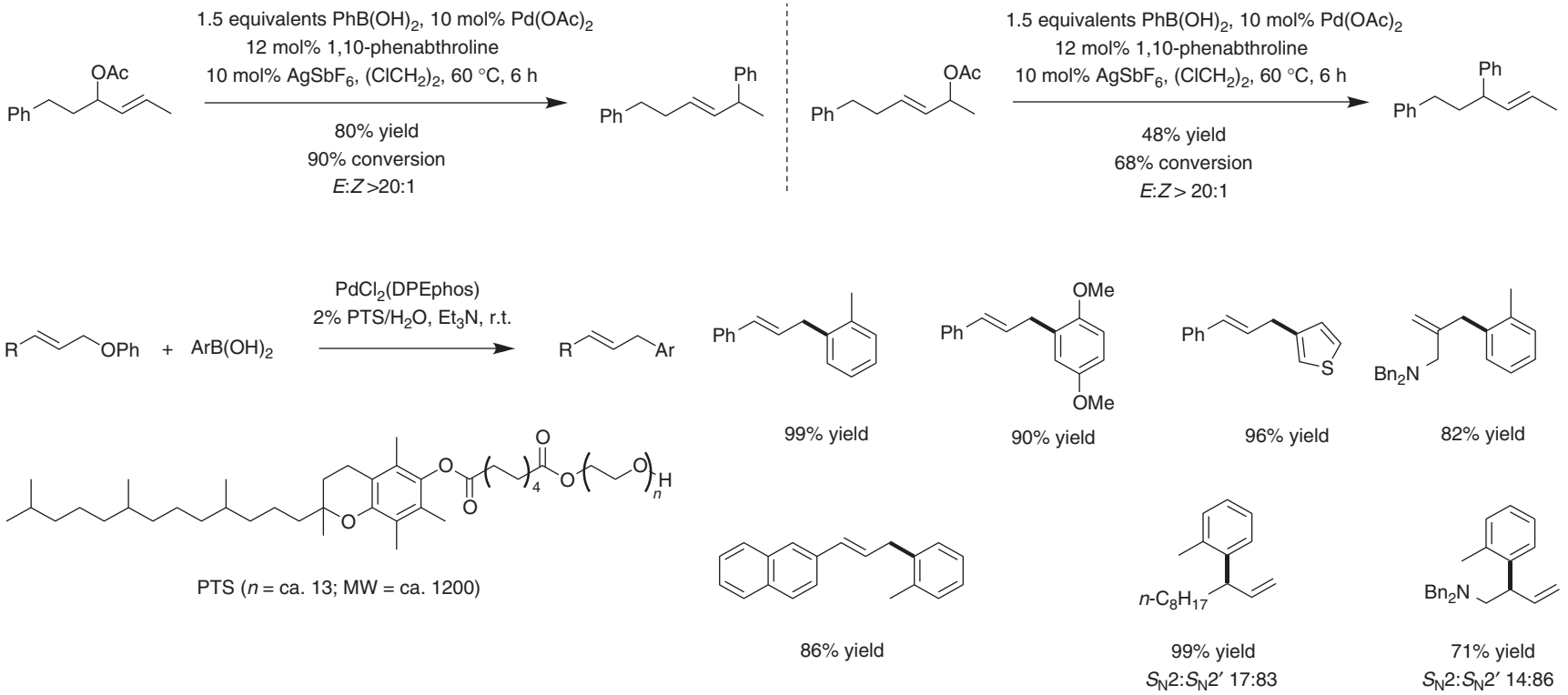
A catalytic asymmetric allylic substitution reaction with vinylaluminum reagents was described, in which the reagent is generated *in situ* by hydroalumination of terminal alkynes with diisobutylaluminum hydride (Scheme 107).[316] The requisite chiral catalyst was generated from $CuCl_2{\cdot}2H_2O$ and an NHC-derived silver complex. The chiral *N*-heterocyclic carbene contained a 2-arenesulfonic acid fragment as a part of its design. One limitation of the original version of the reaction is that aluminum reagents derived from arylalkynes and enynes were contaminated with substantial amounts of alkynyl aluminum by-products, leading to competitive substitution with the alkynyl reagents. In the presence of $NiCl_2(PPh_3)_2$, the hydroalumination proceeded smoothly and with high regioselectivity (85 to >98% terminal:internal selectivity), solving this problem.[317] Aryl- and heteroarylaluminum reagents produced *in situ* from the corresponding organolithium reagents and dialkylaluminum chlorides are also


1.5 mol% (R)-TRIP, 3.0 mol% Pd(PPh3)4
MS 5 Å, MTBE, 40 °C, then 2 N HCl
40–89% yield
70–97% ee
R1 = Ph, 4-MeC6H4, 4-MeC6H4, 3-FC6H4
2-FC6H4, 4-i-BuC6H4, 2-Naphth
2-thiophenyl, c-hex
R2 = H, Me, Ph
Ar = 2,4,6-trisiopropylphenyl
(R)-TRIP
Ph2CHNH2
H2O
[Pd0Ln]

Scheme 94


3.0 mol% (S)-TRIP, 1.5 mol% [Pd(PPh3)4]
40 mol% Ph2CHNH2, 5 Å MS, PhMe, 40 °C,12 h
then 2 N HCl, 30 min
R = Me, 94% yield, 99.6% ee
R = OMe, 95% yield, 94% ee
R = Ph, 98% yield, 92% ee
R = Cl, 98% yield, 90% ee
R = Ph, 96% yield, 88% ee
R = Me, 66% yield, 88% ee
95% yield
88% ee
94% yield
92% ee
Low E/Z
Low ee
High E/Z
High ee

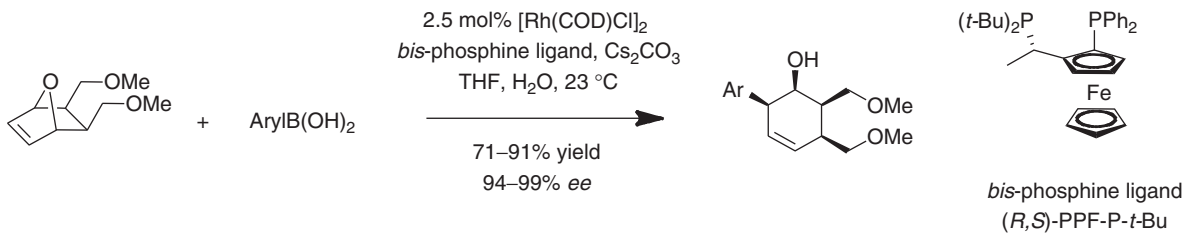
Scheme 95


1.5 equivalents PhB(OH)2, 10 mol% Pd(OAc)2
12 mol% 1,10-phenabthroline
10 mol% AgSbF6, (ClCH2)2, 60 °C, 6 h
80% yield
90% conversion
E:Z >20:1
1.5 equivalents PhB(OH)2, 10 mol% Pd(OAc)2
12 mol% 1,10-phenabthroline
10 mol% AgSbF6, (ClCH2)2, 60 °C, 6 h
48% yield
68% conversion
E:Z > 20:1
PdCl2(DPEphos)
2% PTS/H2O, Et3N, r.t.
PTS (n = ca. 13; MW = ca. 1200)
99% yield
90% yield
96% yield
82% yield
86% yield
99% yield
S_N2:S_N2′ 17:83
71% yield
S_N2:S_N2′ 14:86

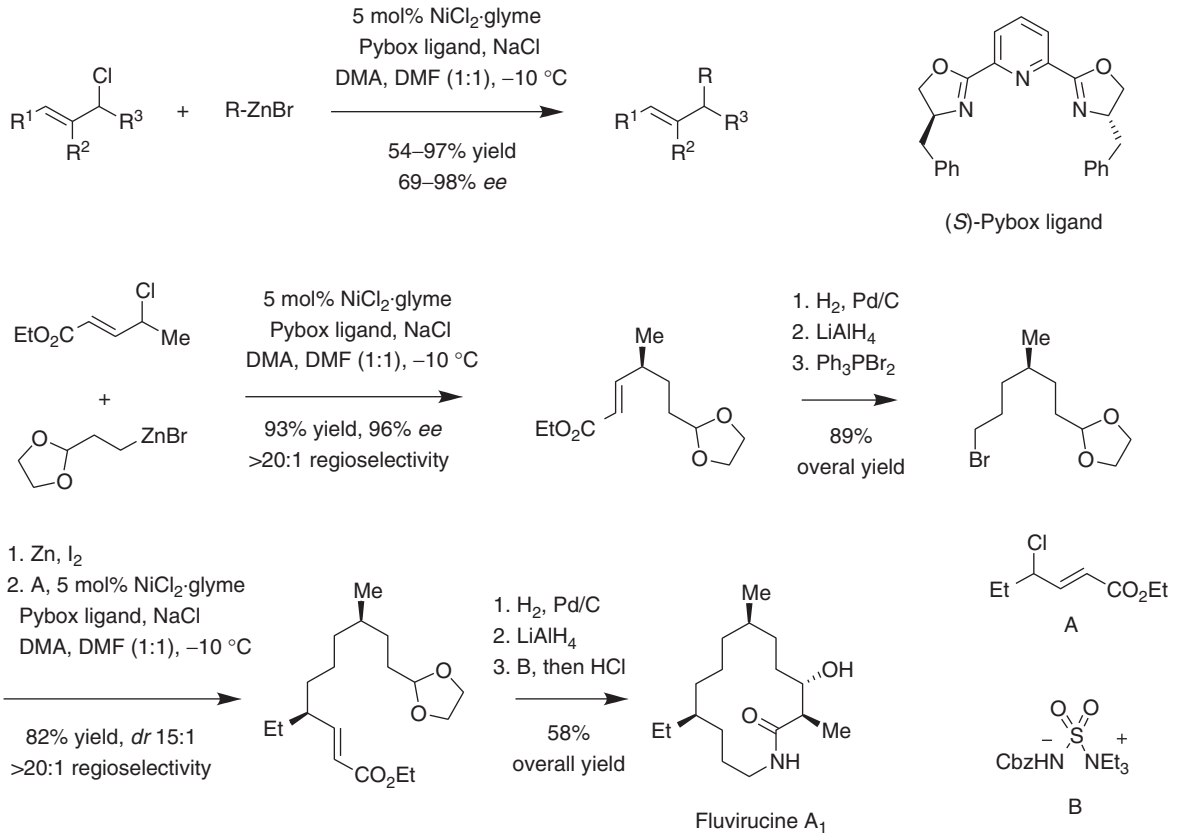
Scheme 96

RhCl3·xH2O, Cu(OAc)2
ArB(OH)2
ionic liquid, 50 °C
33–78% yield
Ph
OH
Ph
Ar
OCO2Me
Me
95% ee
TpRh(C2H4)2
4-t-BuC6H4ZnBr
LiBr, dba, Et2O, 0 °C
90% yield
t-Bu
Me
95% ee
RuCl3, NaIO4,
CCl4, MeCN, H2O
74% yield
t-Bu
Me
CO2H

Scheme 97



Scheme 98

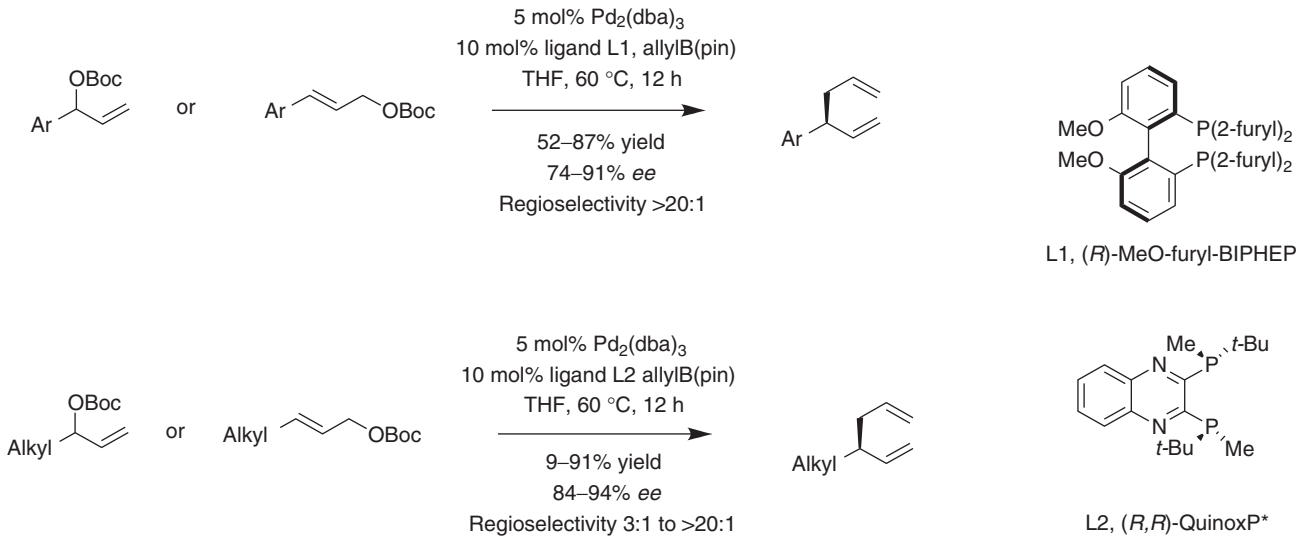


Scheme 99

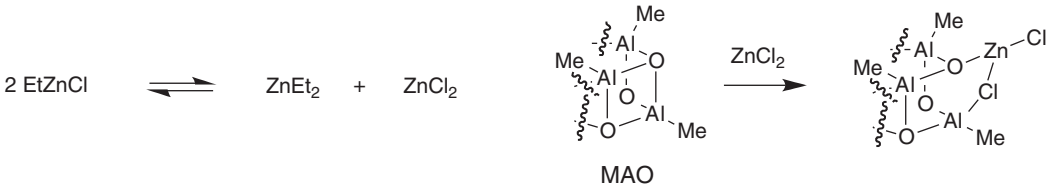
suitable nucleophiles.[318] For high enantioselectivity, lithium and magnesium salts formed on transmetallation must be removed by filtration.

Alkynylaluminum reagents can be generated cleanly from terminal alkynes and diisobutylaluminum hydride in the presence of 5 mol% of triethylamine.[319] Capitalizing on this process, a catalytic enantioselective displacement of allylic phosphates with alkynes has been developed (**Scheme 108**). A rather broad scope of this reaction allows for incorporation of functional groups while maintaining good selectivity.[320]

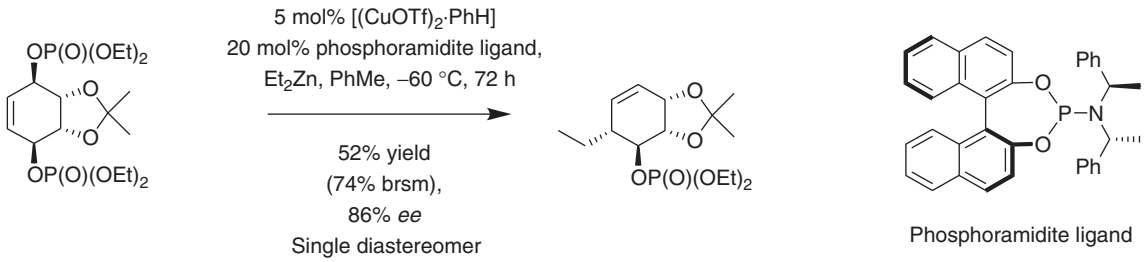
Examples of copper-catalyzed allylic substitution with organoboronates as nucleophiles are limited. In 2010, a copper-catalyzed S_N2'-selective allylic substitution reaction of arylboronates with allylic phosphates was disclosed.[277] The reaction of chiral cyclic and acyclic allylic phosphates with the *Z* configuration afforded products with high level of chirality transfer. Products with the *E* configuration of the double bond were formed with good selectivity. However, the use of acyclic substrates with the *E*-double bond resulted in moderate *E*/*Z* selectivity. The addition of a small amount of H_2O and 3 equivalents of KO*t*Bu was critical. In the same year, an S_N2' substitution of allylic chlorides with arylboronates catalyzed by copper–NHC complexes was described.[321] Moderate-to-excellent S_N2' regioselectivity was observed. Application of the chiral NHC ligand bearing a free hydroxyl group enabled an asymmetric version of the Cu(NHC)-catalyzed substitution (**Scheme 109**).[322] Studies indicated that both regio- and enantioselectivity in this reaction were highly sensitive to the structure of the metal alkoxide additive.


OBoc
Ar
or
Ar
OBoc
5 mol% Pd2(dba)3
10 mol% ligand L1, allylB(pin)
THF, 60 °C, 12 h
52–87% yield
74–91% ee
Regioselectivity >20:1
Ar
MeO
MeO
P(2-furyl)2
P(2-furyl)2
L1, (R)-MeO-furyl-BIPHEP
OBoc
Alkyl
or
Alkyl
OBoc
5 mol% Pd2(dba)3
10 mol% ligand L2 allylB(pin)
THF, 60 °C, 12 h
9–91% yield
84–94% ee
Regioselectivity 3:1 to >20:1
Alkyl
Me
t-Bu
N
P
N
P
t-Bu
Me
L2, (R,R)-QuinoxP*

Scheme 100



Scheme 101



Scheme 102

Copper-catalyzed enantioselective coupling of allylic phosphates and commercially available allenylboronic pinacolates resulted in the formation of products containing tertiary and quaternary chiral centers. It was found that the sulfonate group in the chiral NHC ligand **L1** (Scheme 110) was essential for the high S_N' selectivity. The reaction using monodentate NHC ligands or even bidentate NHC ligands bearing a free hydroxyl group (cf. **L2**, Scheme 110) resulted in the formation of linear products.[323]

Alkylboranes generated from terminal alkenes with 9-BBN could participate in the allyl–alkyl coupling in the presence of catalytic copper(I).[324] A ligand was not necessary for this transformation although the presence of a base such as KOBu-*t* was required. No reaction took place when secondary alkylborane reagents were used. The reaction of cyclic or (*Z*)-acyclic allylic secondary phosphates gave the products with high regio- and *Z*/*E*-selectivity. The products with the E geometry of the double bond were preferred. The *Z*/*E* selectivity was significantly lower when (*E*)-allylic phosphates were used, although high S_N' selectivity was preserved.

6.16.4.1.3 Claisen and related sigmatropic rearrangements

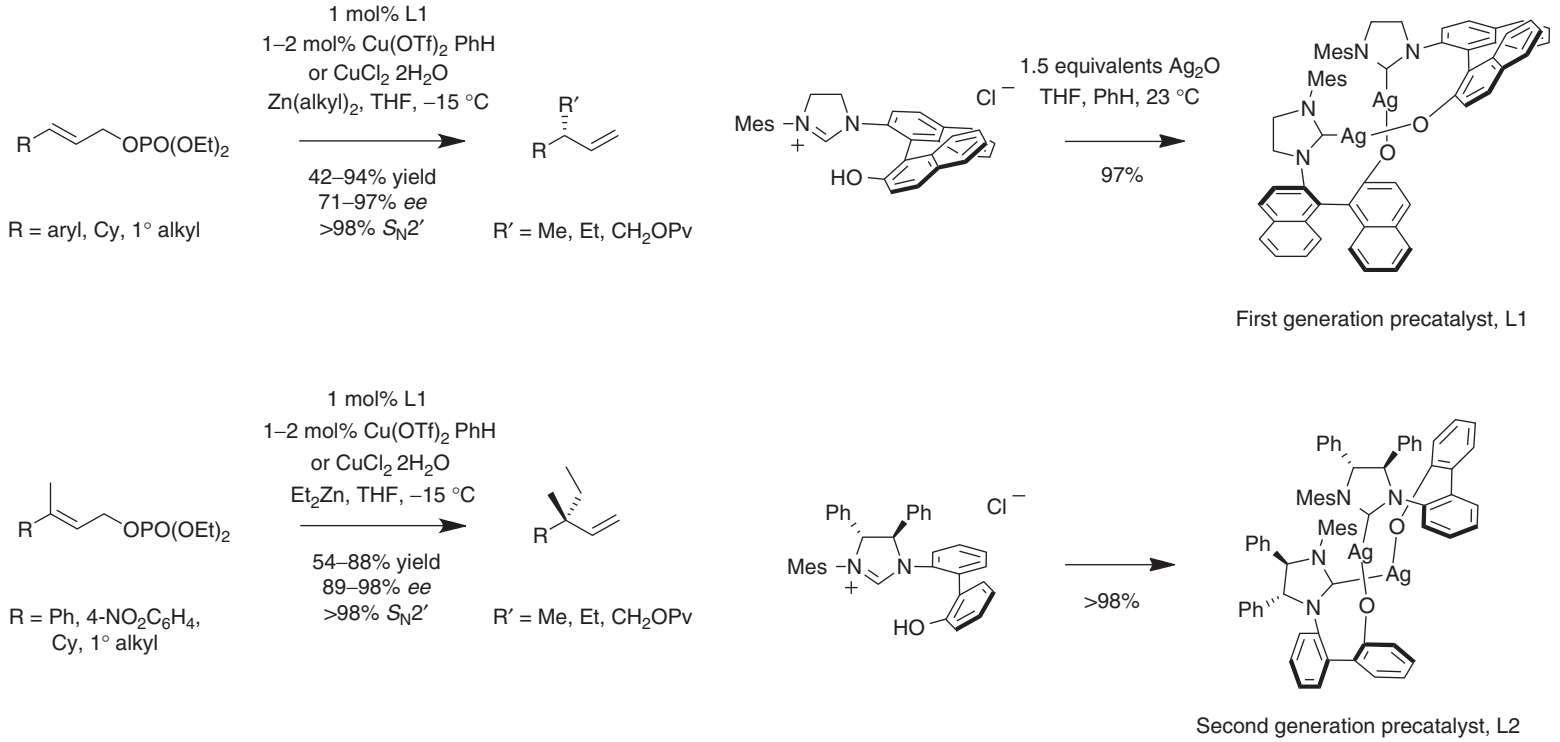
Since its discovery over a century ago, the Claisen rearrangement has found extensive application in organic synthesis.[325] Its significance reaches across the field of organic chemistry from the understanding of fundamental aspects of chemical reactivity, to the design of modern synthetic methods and applications in complex molecule synthesis. Several new classic variants of Claisen rearrangement were introduced, including Carroll rearrangement, Eschenmoser rearrangement, Johnson rearrangement, Ireland–Claisen rearrangement and metallo-Claisen rearrangement,[326] and the list continues.[327,328] This section will focus on new developments after 1990s, with a particular emphasis on the stereochemical control and some illustrative applications in organic synthesis.

Generally, the stereochemical outcome of the Claisen rearrangement could be reliably predicted. A chair-like transition state is predominant in acyclic systems. When $R^2 \neq H$ (Scheme 111), the energy difference between the two alternative chair conformations in the transition state will result in the selective formation of products with the *E* configuration of the double bond.

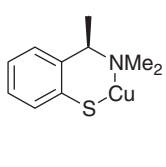
The situation with transition states in the Claisen rearrangement of cyclic system is more complicated. For example, the (*E*)-silyl enol ether generated from 1-cyclohexen-3-yl propionate undergoes a preferential rearrangement via a chair-like transition state (TS) because of the strong eclipsing interaction in the boat-like TS between the methyl group and the allylic endocyclic methylene within the cyclohexene ring (Scheme 112).[329] In the absence of the eclipsing interaction, as is the case with the (*Z*)-enolate, the preferred TS adopts the boat-like conformation in avoidance of the unfavorable interaction of the OTBS substituent and the cyclohexenyl ring. In the Ireland–Claisen reaction of the allylic lactone shown in Scheme 113, only the *E*-enolate could be formed, and the product necessarily arises from a boat transition state because the chair-like transition state is not available in this strained system.[330]

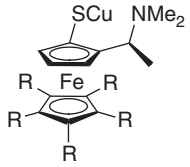
The course of the [3,3]-sigmatropic rearrangement can be manipulated by the choice of reaction parameters. Under thermal conditions in the presence of weakly acidic 2,6-dimethylphenol, the *anti*-product is produced selectively presumably through a chair-like transition state. However, in the presence of a palladium(II) catalyst, the *syn*-product is formed, presumably through a boat-like transition state stabilized by complexation with palladium (Scheme 114).[331]

Either substrate or reagent control has been realized for a variety of asymmetrical reactions that capitalize on the power of the Claisen rearrangement for the reaction design. However, the number of successful examples is still very limited, and the


1 mol% L1
1–2 mol% Cu(OTf)2 PhH
or CuCl2 2H2O
Zn(alkyl)2, THF, –15 °C
R
OPO(OEt)2
R′
42–94% yield
71–97% ee
>98% SN2′
R = aryl, Cy, 1° alkyl
R′ = Me, Et, CH2OPv
Mes
N
HO
Cl –
1.5 equivalents Ag2O
THF, PhH, 23 °C
97%
MesN
Ag
O
First generation precatalyst, L1
1 mol% L1
1–2 mol% Cu(OTf)2 PhH
or CuCl2 2H2O
Et2Zn, THF, –15 °C
54–88% yield
89–98% ee
>98% SN2′
R = Ph, 4-NO2C6H4,
Cy, 1° alkyl
R′ = Me, Et, CH2OPv
Ph
>98%
Second generation precatalyst, L2

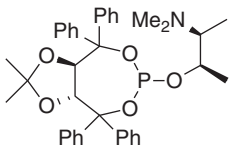
Scheme 103



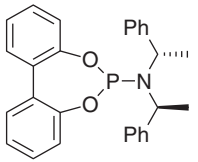


R = H, Me, Ph

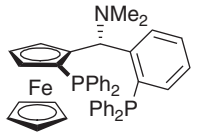
Copper thiolate catalysts

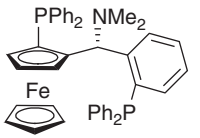


TADDOL phosphites



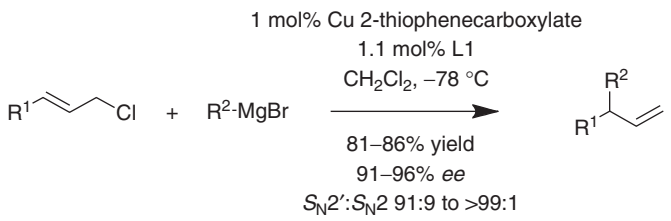
Phosphoramidites



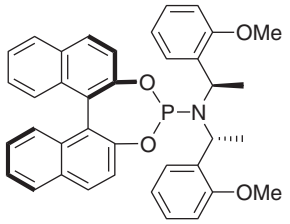


(R,R_p)-Taniaphos

Ferrocenyl phosphine ligands

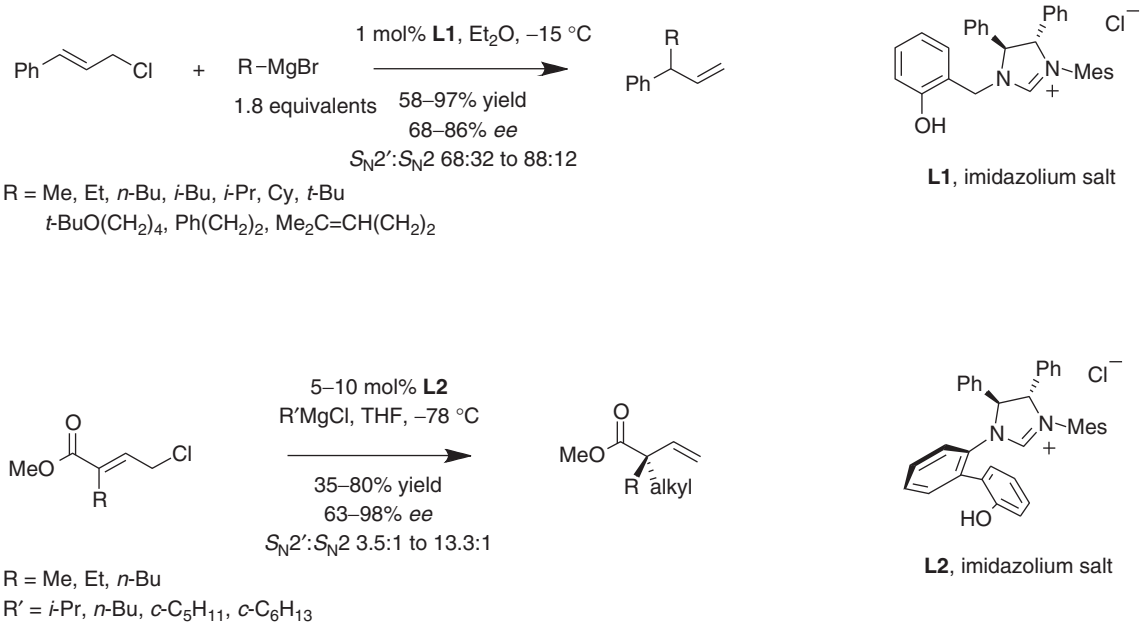


R^1 = Ph, 4-MeC_6H_4, *c*-Hex
R^2 = Et, 3-butenyl, 4-pentenyl



L1, phosphoramidite ligand

Scheme 104



Scheme 105

asymmetric catalytic version of the Claisen rearrangement remains an underdeveloped and challenging area in synthetic methodology.

6.16.4.1.3.1 Diastereoselective [3,3]-rearrangement

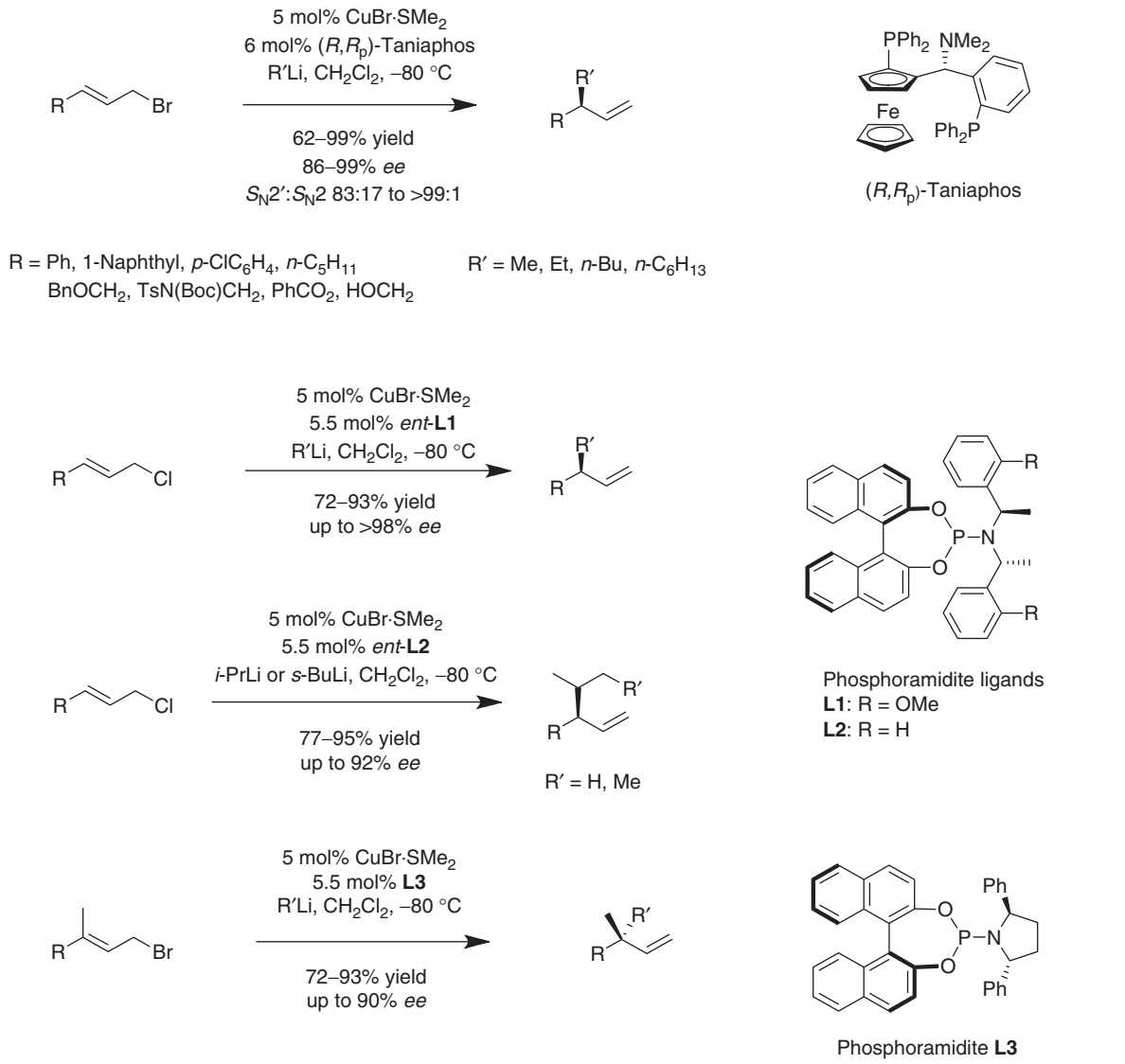
The enatioselective construction of the cyclic allylic aryl ether by a palladium-catalyzed etherification of methyl 1-cyclohexen-3-yl carbonate sets the stage for the diastereoselective Claisen rearragement. The Claisen rearrangement is catalyzed by $Eu(fod)_3$, giving the product in excellent yield and enantioselectivity (Scheme 115).[332]

The key problem in the Ireland–Claisen rearrangement of α-branched allylic esters is poor stereoselectivity in the enolization step, which translates into the poor diastereoselectivity observed after the [3,3]-sigmatropic rearrangement (Scheme 116).

To circumvent this problem, a chelating group to direct the enolization process has been introduced into the acyl group of the substrate. High diastereoselectivity of 94:6 favoring the *syn* diastereomer has been obtained in the Ireland–Claisen rearrangement of allylic mandelates by using $(Ipc)_2BOTf$ for enolizations (Scheme 117).[333] Presumably, the chelated (*Z*)-boron enolate is formed. The apparent limitation of this method is that only substrates bearing a directing group are suitable in this approach. In 2005, a silylene transfer to α,β-unsaturated ester with the intermediate formation of the (*Z*)-silyl enolate followed by its Ireland–Claisen rearrangement has been described. The rearrangement products are formed with excellent diastereoselectivity (Scheme 118).[334]

Recently, a general method for stereoselective enolization of acyclic α,α-disubstituted esters was developed requiring no reliance on chelating groups. The concept is based on the stereochemical match between the stereodefined substrate and the chiral lithium amide.[335] Application of Koga-type lithium amides resulted in a highly stereoselective formation of α,α-disubstituted enolates (Scheme 119), where the sense of selectivity could be switched by inverting the configuration of either the ester or the chiral amide. In contrast to enantioselective enolizations of prochiral ketones, no LiCl additive was needed for high stereoselectivity, simplifying the experimental protocol. The utility of this methodology in a demanding setting was demonstrated with a complex allylic ester in the context of the enantioselective total synthesis of marine natural product pinnatoxin A.[336] The adjacent congested quaternary and tertiary stereocenters of the target structure were assembled by this procedure.

Incorporation of a chiral auxiliary at various positions in the substrate is another way to control the stereoselectivity in the Claisen rearrangement. Chiral sulfinyl groups have been used successfully in directing the stereochemical course of the Claisen rearrangement.[337] The stereochemistry of the rearrangement depicted in Scheme 120 is controlled by the favorable π-π stacking interaction between the two phenyl substituents in the substrate. The 'outside' orientation of the methyl group is preferred in the alternative chair-like transition structures, leading to the observed configuration of the new stereogenic centers in the major product.[338] A chiral oxazolidinone fragment enables a highly diastereoselective Claisen rearrangement of ketene hemiaminal derivatives (Scheme 121). The substrate is conveniently generated *in situ* by acid-catalyzed addition of allylic alcohols to readily available chiral ynamides derived from oxazolidinones. The preferred conformation of the transition structure aims to minimize dipole–dipole and steric interactions.[339]



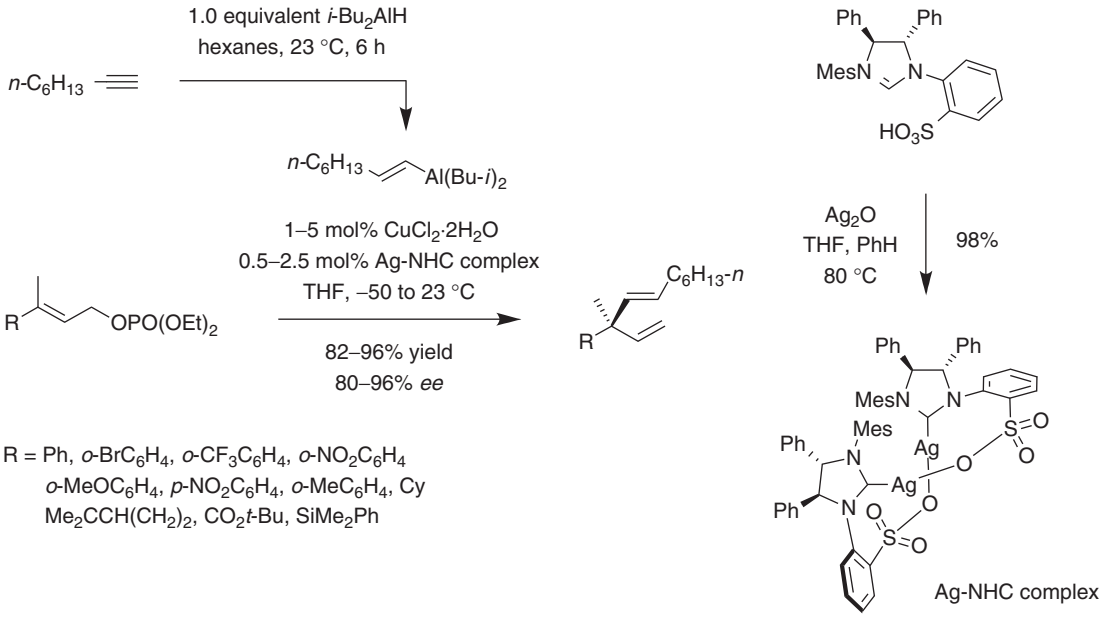
Scheme 106

6.16.4.1.3.2 Enantioselective [3,3]-rearrangements

Stoichiometric reagent control using chiral boron halides as depicted in Scheme 122 was developed for some of the early examples of enantioselective Ireland–Claisen rearrangement of achiral allylic ester. Both *Z*- and *E*-enolates could be accessed by proper choice of base. The ligands on the boron atom provided a chiral environment for the sigmatropic rearrangement.[340] A related boron reagent was developed for the enantioselective aromatic Claisen rearrangement of allyl *ortho*-hydroxyphenyl ethers. A five-membered cyclic intermediate was proposed to rationalize the observed enantioselectivity (Scheme 123).[341]

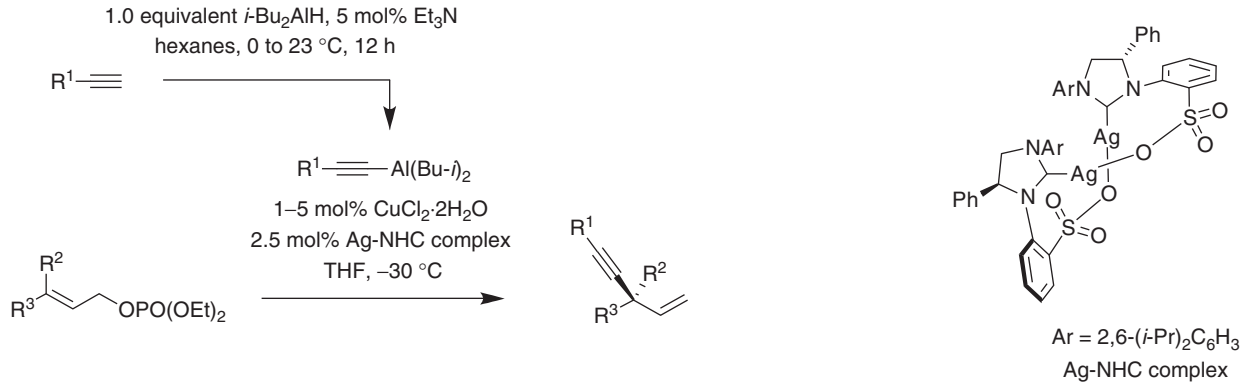
The effect of a wide range of chiral Lewis acidic reagents, including aluminum,[342] magnesium,[343] copper,[344] scandium,[345] and palladium[346] compounds, on the asymmetrical Claisen rearrangement has been investigated. An aza-Claisen rearrangement on *N*-acyl-*N*-allyl morpholinium salts in the presence of catalytic titanium tetrachloride was described in 1999.[347] The substrate was prepared by acylation of *N*-allyl morpholine derivatives with α-alkoxyacetyl chlorides *in situ*. Two years later, a catalytic asymmetrical version was realized by the use of the chiral magnesium complex (Scheme 124). Acid chlorides bearing strongly coordinating α-alkoxy substituents were important for high enantioselectivity. The reaction afforded products with all-carbon quaternary stereocenters at the β-position with a high level of enantiocontrol. One limitation was that two to three equivalents of the chiral magnesium complex were necessary due to the high rate of the background rearrangement.[343]

A method based on dual catalysis with a ruthenium complex and a Lewis acid for asymmetrical formal Claisen rearrangement was disclosed in 2010.[348] A ruthenium complex was chosen as the catalyst because of its strong bias for branched product in allylic substitution reactions. The chiral transition metal catalyst is conveniently generated *in situ* from $[CpRu(CH_3CN)_3]PF_6$ and aminoindanol-derived ligand shown in Scheme 125. No reaction was noted in the absence of triphenyl borate. A competitive formation of the [1,3] transposition product was observed.

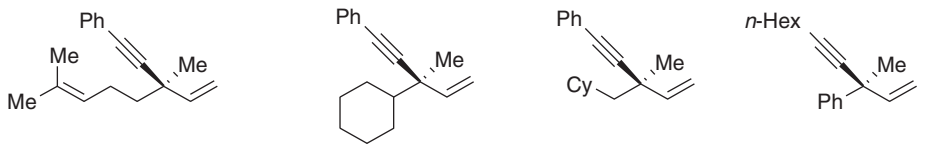


R = Ph, *o*-BrC_6H_4, *o*-$CF_3C_6H_4$, *o*-$NO_2C_6H_4$
o-$MeOC_6H_4$, *p*-$NO_2C_6H_4$, *o*-MeC_6H_4, Cy
$Me_2CCH(CH_2)_2$, CO_2t-Bu, $SiMe_2Ph$

Scheme 107



Ar = 2,6-(*i*-$Pr)_2C_6H_3$
Ag-NHC complex

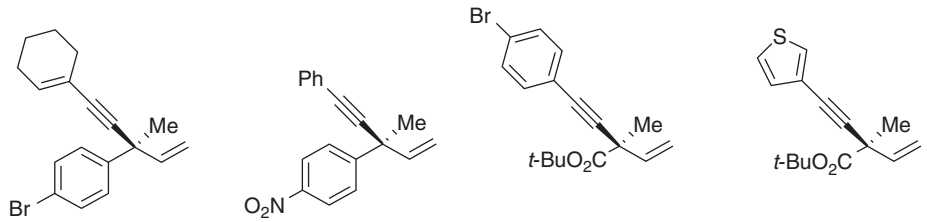


92% yield
86% *ee*

91% yield
84% *ee*

78% yield
88% *ee*

88% yield
92% *ee*



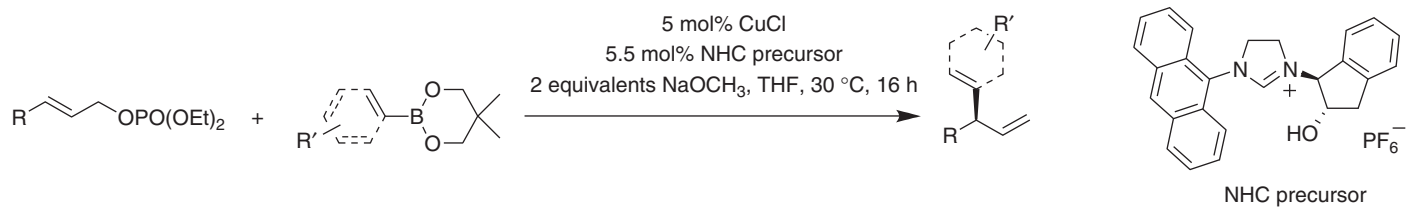
91% yield
>98% *ee*

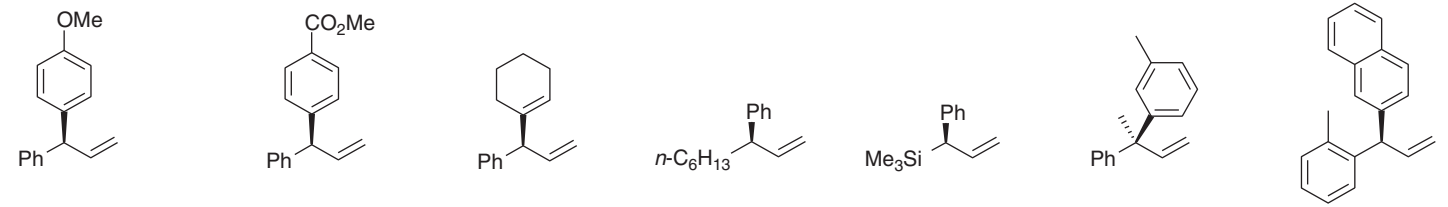
77% yield
84% *ee*

91% yield
96% *ee*

96% yield
96% *ee*

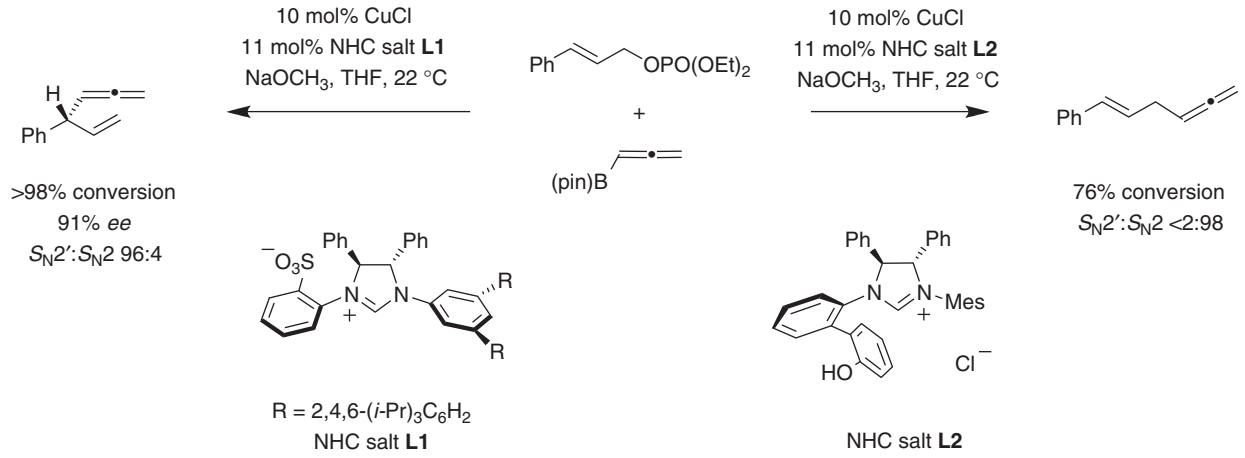
Scheme 108



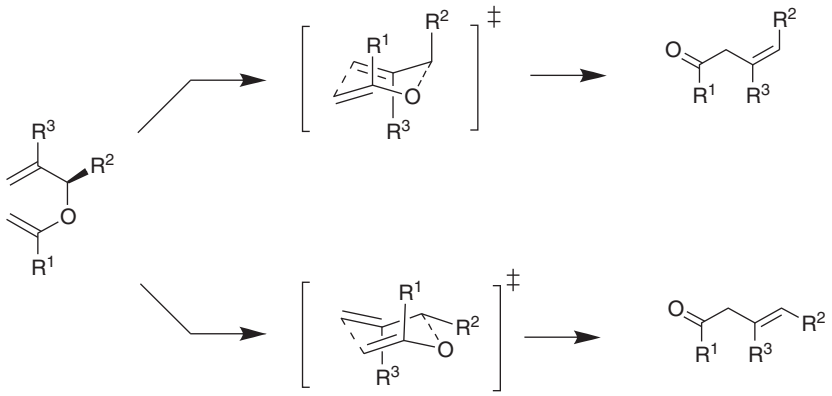


92% yield	89% yield	84% yield	87% yield	74% yield	89% yield	84% yield
92% *ee*	91% *ee*	73% *ee*	68% *ee*	84% *ee*	90% *ee*	96% *ee*
S_N2':S_N2 99:1	S_N2':S_N2 96:4	S_N2':S_N2 99:1	S_N2':S_N2 99:1	S_N2':S_N2 99:1	S_N2':S_N2>9 9:1	S_N2':S_N2 99:1

Scheme 109



Scheme 110



Scheme 111

A hydrogen bond donor catalyst based on guanidine was successfully developed for the asymmetrical Claisen rearrangement of *O*-allylic *α*-ketoesters (Scheme 126).[349] The catalyst was designed to mimic chorismate mutases, a group of enzymes that catalyzes the biological [3,3]-sigmatropic rearrangement of chorismate to prephenate. Computational studies indicate that the guanidinium catalyst lowers the free energy of the rearrangement by approximately 3.6 kcal/mol, thereby accelerating the rate of the rearrangement by a factor of 250.

6.16.4.1.3.3 [2,3]-Sigmatropic rearrangements

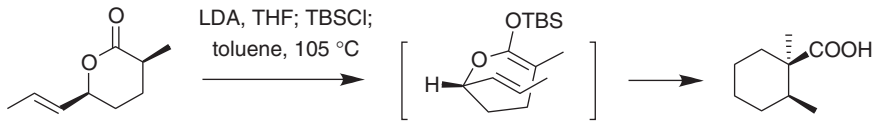
Another class of rearrangements important in synthetic chemistry is the [2,3]-sigmatropic, or Wittig rearrangement. In the classic version of the process, a strong base is needed to generate the reactive carbanion by metallation of moderately acidic substrates or by lithium-tin exchange (Scheme 127).[350] More recently, transition metal catalysis provided alternative means for the generation of intermediates capable of [2,3]-sigmatropic transposition under mild reaction conditions. Overall, the reactive ionic intermediates can be accessed in two general ways: (1) allylation of the substrate with an allylic electrophile followed by deprotonation with a mild base, which will generate the reactive zwitterionic intermediate whose facile [2,3]-sigmatropic rearrangement will lead to products, and (2) direct formation of the zwitterionic intermediate by a transition metal-catalyzed reaction of nucleophilic substrate and diazo compounds. Rhodium, copper, and ruthenium catalysts have been typically used in the latter approach.

An elegant entry into the [2,3]-sigmatropic rearrangement was described in 2011.[351] The reaction is based on palladium-catalyzed allylic amination with tertiary *α*-amino esters. Ammonium ylide formation in the presence of cesium carbonate was followed by an efficient [2,3]-sigmatropic rearrangement giving products in good yields and diastereoselectivity. When a camphorsultam was used as a chiral auxiliary, high levels of asymmetric induction were achieved (Scheme 128).

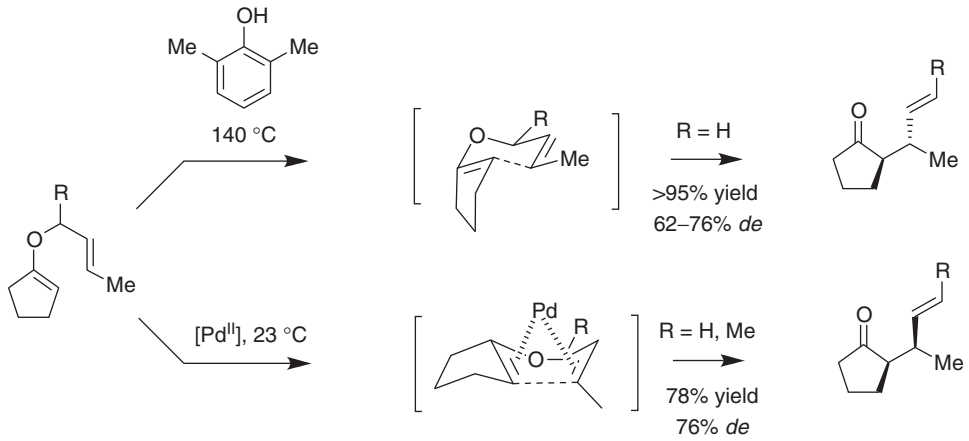
Compounds of certain transition metals, namely, rhodium, ruthenium, and copper, are able to effectively catalyze decomposition of diazo compounds to extrude nitrogen and form electrophilic metal carbene species. In the presence of substrates bearing a nucleophilic heteroatom, metal carbenes readily form reactive zwitterionic species.[352,353] If the catalyst remains associated with the newly formed ylide, asymmetrical induction may be observed in the subsequent transformation. Even if the dissociation of the metal does occur, an enantioselective transformation may still ensue if the free ylide is configurationally stable.

LDA, THF
TBSCl
OTBS
O
O
E-enolate
Chair-like
transition structure
preferred
H
CO2TBS
40%
+
H
CO2TBS
7%
O
X
Chair-like TS
X = OTBS
LDA, TBSCl
HMPA/THF
OTBS
Boat-like
transition structure
preferred
H
CO2TBS
27%
+
H
CO2TBS
9%
O
X
Boat-like TS

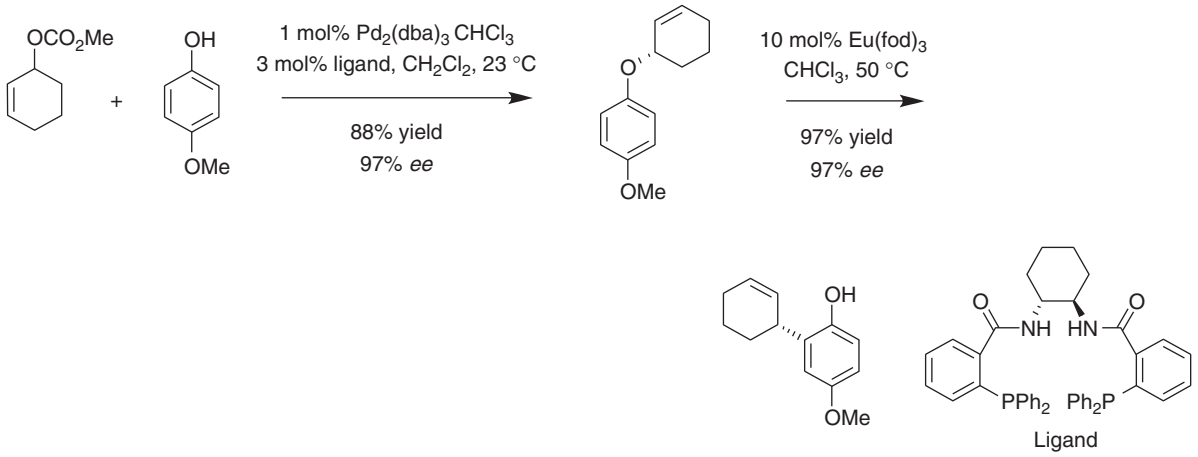
Scheme 112



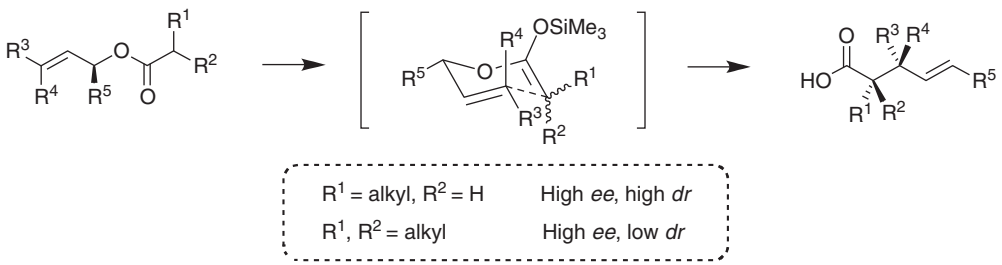
Scheme 113



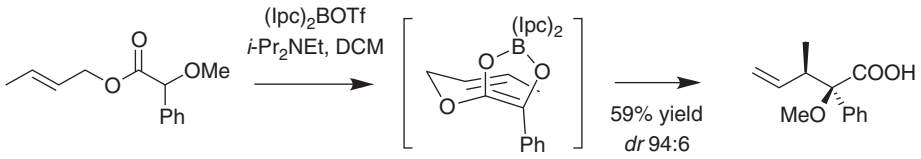
Scheme 114



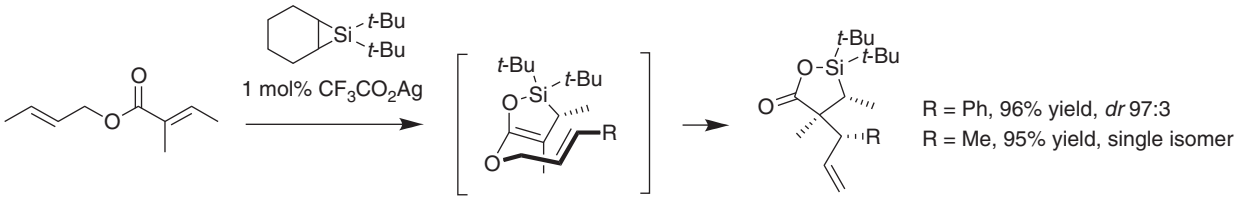
Scheme 115



Scheme 116



Scheme 117



Scheme 118

If the free ylide is configurationally unstable, the asymmetrical induction is unlikely after decomplexation of the chiral metal complex (Scheme 129).[352b,354]

In the elegant total synthesis of (+)-griseofulvin reported in 1991, the key transformation is a rhodium-catalyzed oxonium ylide formation followed by [2,3]-Wittig rearrangement affording the requisite benzofuranone structure (Scheme 130).[355] During the total synthesis of the cladienllin family of natural products, a rhodium- and copper-catalyzed ring-formation based on the [2,3]-rearrangement was investigated (Scheme 130). Treatment of the starting diazo compound with $Cu(hfacac)_2$ (hfacac = 1,1,1,5,5,5-hexafluoroacetylacetonato) resulted in the formation of the expected nine-membered ether rings in excellent yield, although the undesired *Z*-isomer was produced as the major product. Temperature had little effect on the *E*/*Z* selectivity, and changing the solvent resulted in mixtures of the isomers with the *Z*-isomer as the major product. Rhodium catalysts bearing a large counterion favored the desired *E*-isomer. The reaction catalyzed by $Rh_2(O_2CCPh_3)_4$ gave the best selectivity.[356]

The first catalytic enantioselective oxonium yilde [2,3]-rearrangement using a novel chiral rhodium(II)-catalyst was reported in 1992.[357] Subsequently, a copper-catalyzed ylide formation from diazo compounds followed by [2,3]-rearrangement in the presence of chiral diimine ligands was described.[358] The use of $Rh_2(4S\text{-MEOX})_4$ as the catalyst ensured excellent enantioselectivity in the ylide formation/rearrangement process, at the same time minimizing the extent of the competitive cyclopropanation (Scheme 131).[359] Different diastereomers are formed preferentially when $Rh_2(OAc)_4$ and $Rh_2(4S\text{-MEOX})_4$ are used as catalysts, with the chiral catalyst giving a notably lower yield.

The ylide formation/[2,3]-rearrangement cascade reaction has been extended to the synthesis of macrocyclic ethers (Scheme 132).[170] The copper-catalyzed 10-membered ether ring-formation in the presence of the chiral *bis*(oxazoline) ligand (BOX ligand) was characterized by high chemoselectivity (8:1 ratio of ether formation product to the cyclopropanation product), although low yield and moderate enantioselectivity were observed. The same reaction attempted with $Rh_2(4S\text{-MEOX})_4$ catalyst did not provide the macrocyclic product.

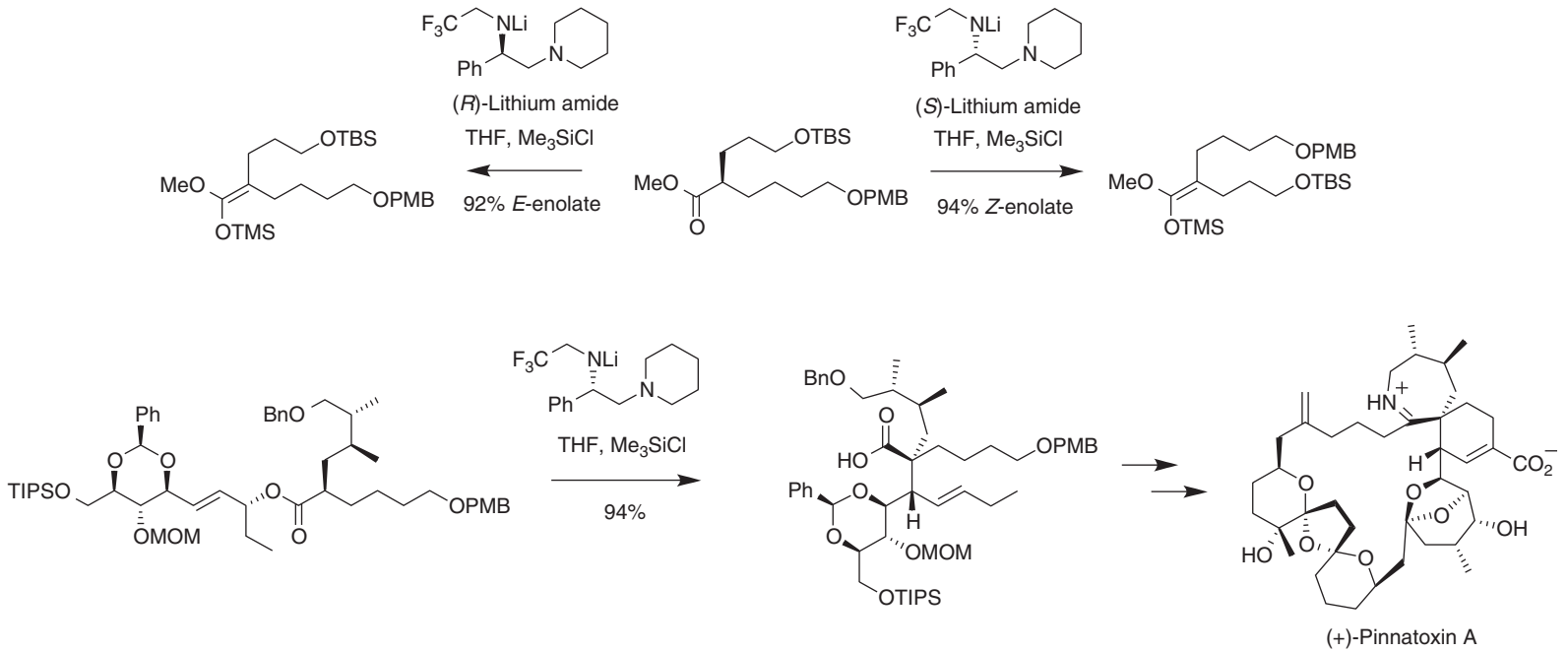
An intriguing entry into the core structure of zaragozic acid by intramolecular ylide formation/[2,3]-rearrangement was accomplished using a chiral rhodium catalyst.[360] The product in this desymmetrization reaction was formed with rather low *ee*.

More recently, the synthesis of medium-size unsaturated oxygen heterocycles from vinyl oxiranes and oxetanes has been investigated (Scheme 133).[361] The approach is based on copper-catalyzed ylide formation from diazo esters followed by intramolecular formal [2,3]-transposition. The reaction with α-arylvinyl oxiranes was characterized by poor yields due to competitive deoxygenation producing 2-aryl-1,3-butadiene as the major product. The side reaction was suppressed when the corresponding oxetanes were used as starting materials. Notably, no competing cyclopropanation was observed. The yield in the formation of the five- and seven-membered products was substantially higher, reaching 86% for diethyl diazomalonate, which has also provided the terahydrofuran with high regioselectivity.

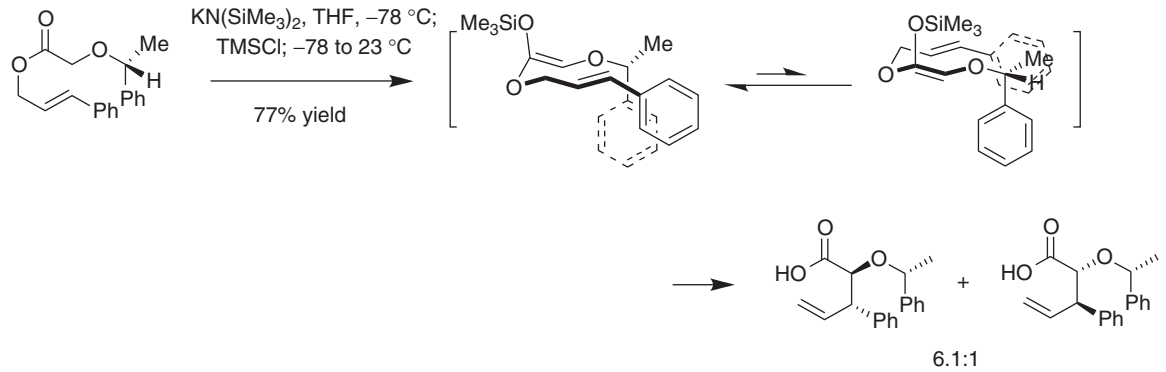
In addition to allylic ethers, allylic amines, thioethers, and iodides form ylides on treatment with diazo compounds in the presence of a metal catalyst. These ylides subsequently undergo efficient [2,3]-sigmatropic rearrangements. The spiro ammonium ylide illustrated in Scheme 134 formed by an intramolecular copper-catalyzed process undergoes a transposition to give the isomeric bicyclic products.[362] The product with the azabicyclo[5.3.0]decanone ring system resulting from the [2,3]-transposition is formed preferentially.

Ruthenium porphyrin complex [Ru(II)(TTP)(CO)] was effective in catalyzing the sulfonium and ammonium ylide formation (Scheme 135).[363] The electron-rich iron complex $Bu_4N[Fe(CO)_3(NO)]$ promotes efficient carbene transfer reactions.[364]

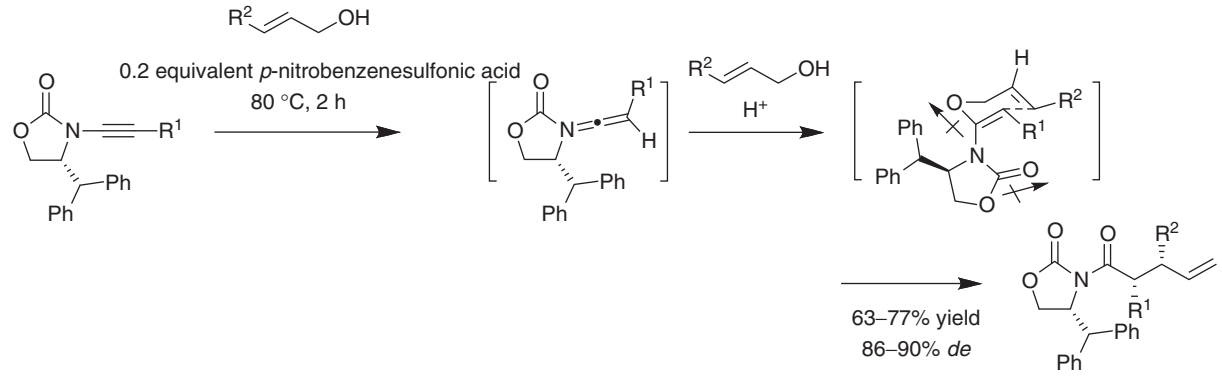
A remarkable enantioselective synthesis of α-iodoesters by a formal insertion of ethyl diazoacetate into allyl iodide has been developed (Scheme 136). The reaction gave the best yield of 62% and enantioselectivity of 69% with $CuPF_6$/BOX as the catalyst system. The corresponding reaction with rhodium as catalyst [$Rh_2(4S\text{-MEOX})_4$, $Rh_2(4R\text{-MEOX})_4$, and $Rh_2(4S\text{-MPPIM})$] afforded the product in 12–15% yields, and the only detectable by-product is the dimer formed from the carbene.[170] The reaction presumably takes place through the intermediacy of a rarely encountered iodonium ylide.


F3C
NLi
Ph
N
(R)-Lithium amide
THF, Me3SiCl
92% E-enolate
(S)-Lithium amide
THF, Me3SiCl
94% Z-enolate
OTBS
MeO
OPMB
OTMS
O
OPMB
OTBS
TIPSO
OMOM
BnO
Ph
THF, Me3SiCl
94%
HO
H
OTIPS
HN+
CO2−
OH
(+)-Pinnatoxin A

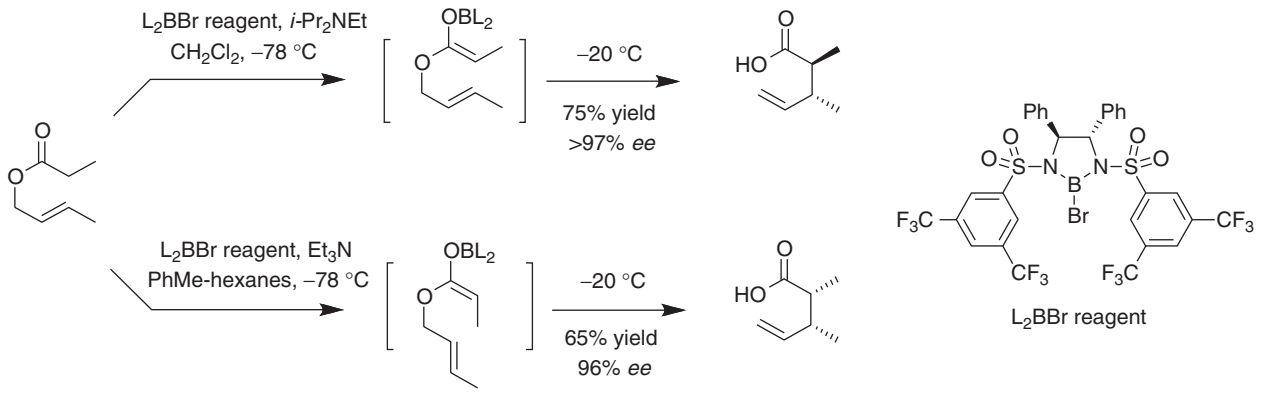
Scheme 119



Scheme 120



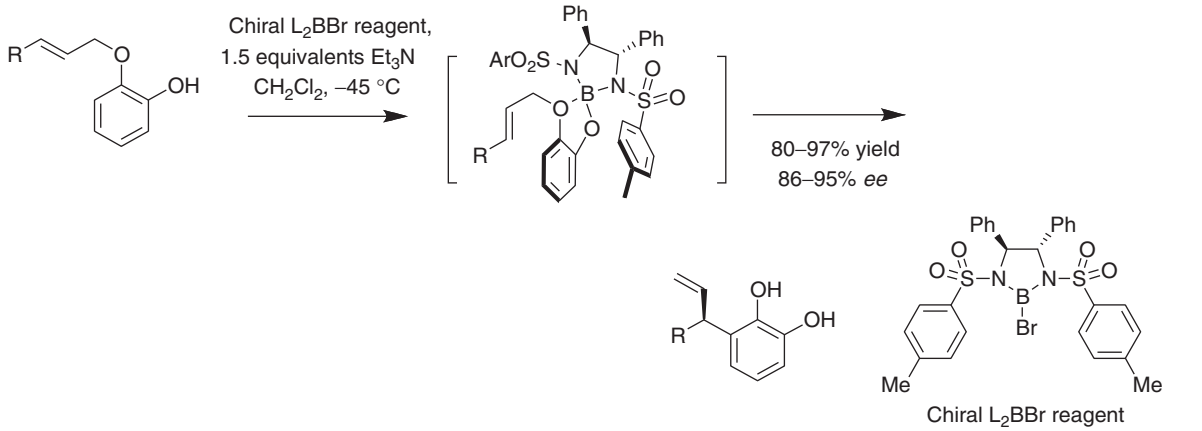
Scheme 121



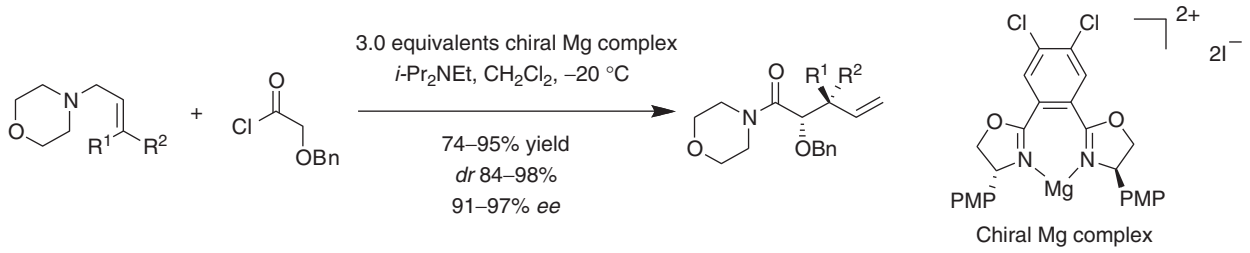
Scheme 122

6.16.4.2 Allyl Systems as Nucleophiles

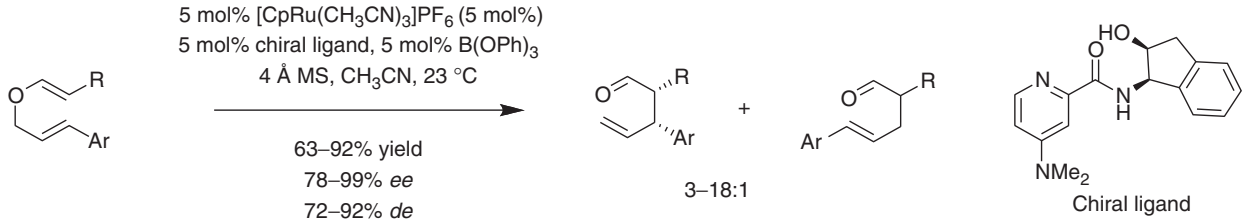
Enantioselective addition of allylmetal reagents to carbonyl compounds is one of the most broadly utilized methods in asymmetrical organic synthesis.[365] The addition of isolable allylboron and allylsilane compounds to aldehydes and ketones is among the first examples of such reactions.[366] Following these seminal discoveries, many new reagents and methods have been developed, with the asymmetrical nucleophilic allylation dominating the attention of modern synthetic methodology.



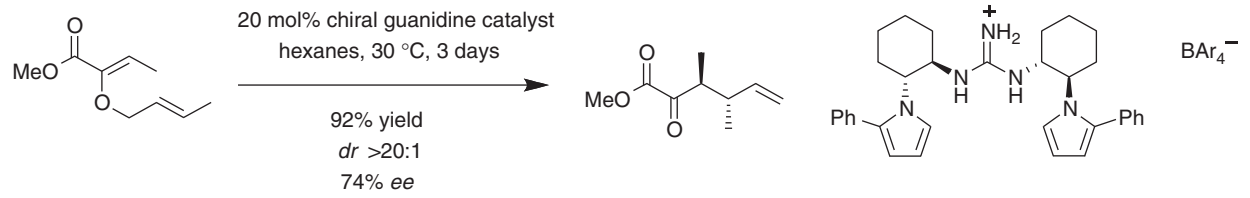
Scheme 123



Scheme 124



Scheme 125



Scheme 126

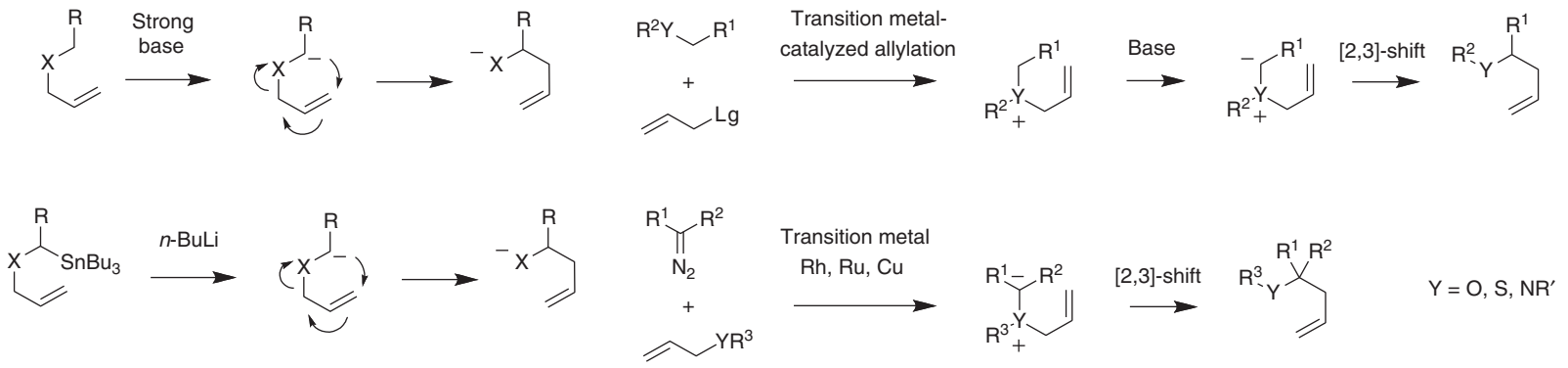
6.16.4.2.1 Allylation with allylboron reagents

A variety of stoichiometric chiral allylboron reagents for asymmetrical addition to carbonyl compounds have been developed over the past four decades, a selected group of which is illustrated in Scheme 137.[367–372] These compounds have shown great utility for a variety of specific applications.

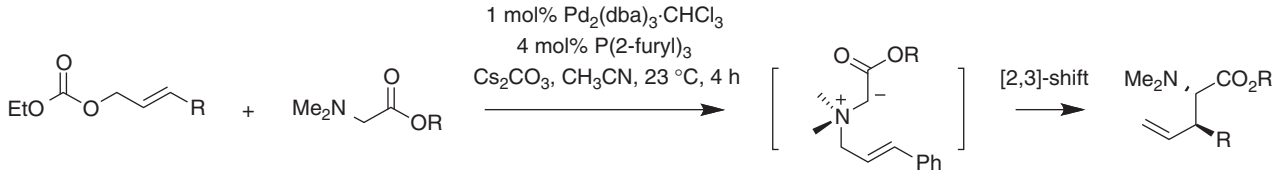
Among more recent developments, it has been demonstrated that Lewis acids have a beneficial effect on the reactivity in the allylboronate addition to aldehydes, enhancing the rate of the allylation reaction and increasing the regio- and stereoselectivity in

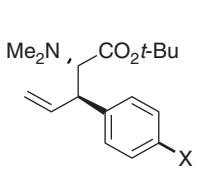
Classic [2,3]-Wittig rearrangement

Transition-metal catalysis strategies for entry into the [2,3]-sigmatropic rearrangements

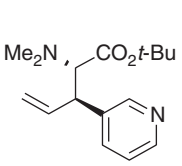


Scheme 127

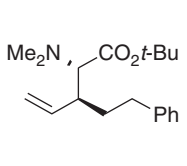




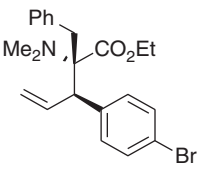
X = H, 87% yield, *dr* 9:1
X = Br, 89% yield, *dr* 7:1
X = F, 87% yield, *dr* 7:1
X = OMe, 84% yield, *dr* 9:1



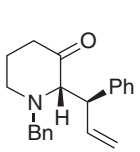
76% yield
dr 5:1



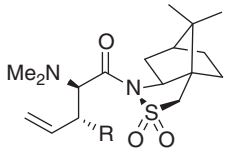
83% yield
dr 9:1



90% yield
dr 7:3

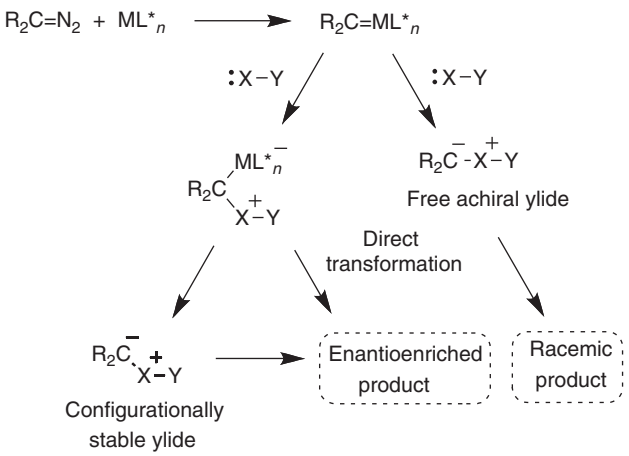


80% yield
dr 4:1

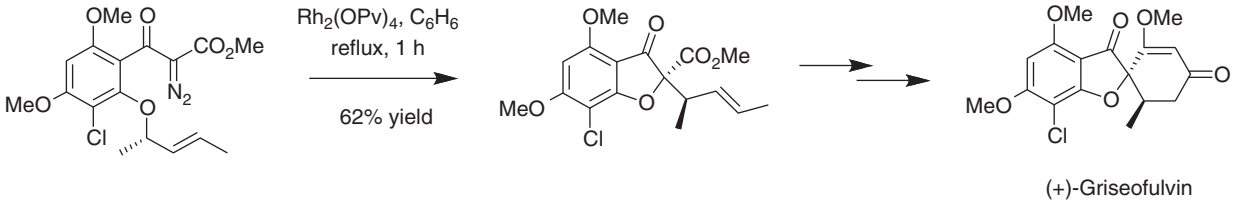


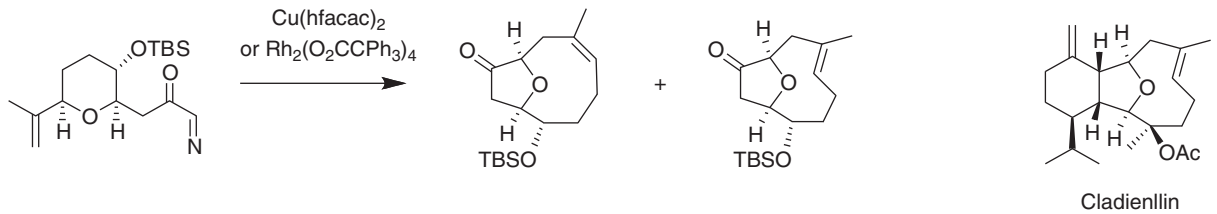
R = H, 89% yield, *dr* 20:1
R = Me, 97% yield, *dr* 20:2:1:0
R = Ph, 96% yield, *dr* 22:2:1:0

Scheme 128

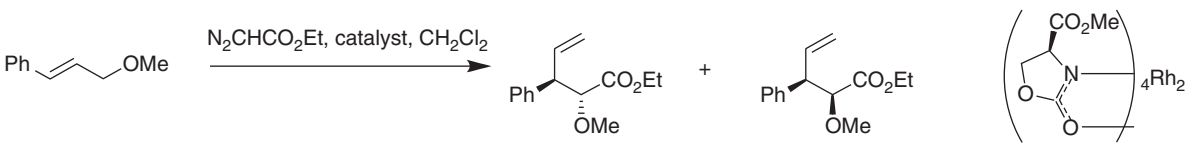


Scheme 129





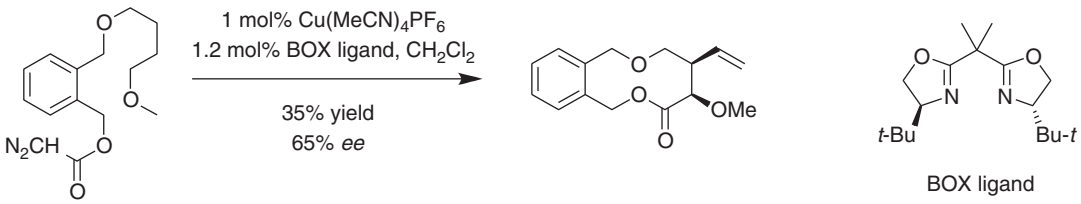
Scheme 130



Metal catalyst	Yield	Product ratio (*ee*)
$Rh_2(OAc)_4$	63%	83 : 17
$Rh_2(4S\text{-MEOX})_4$	37%	15 (95% *ee*) : 85 (98% *ee*)

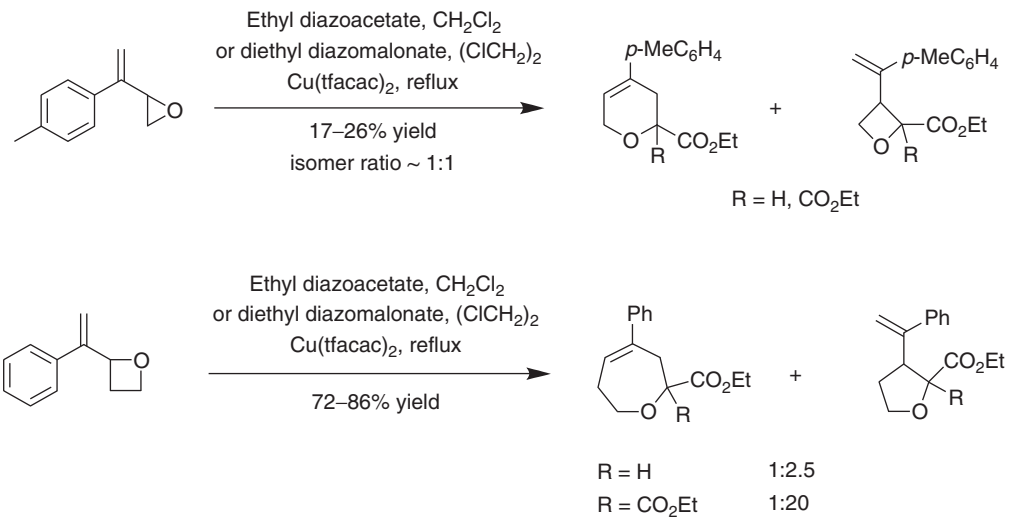
$Rh_2(4S\text{-MEOX})_4$

Scheme 131

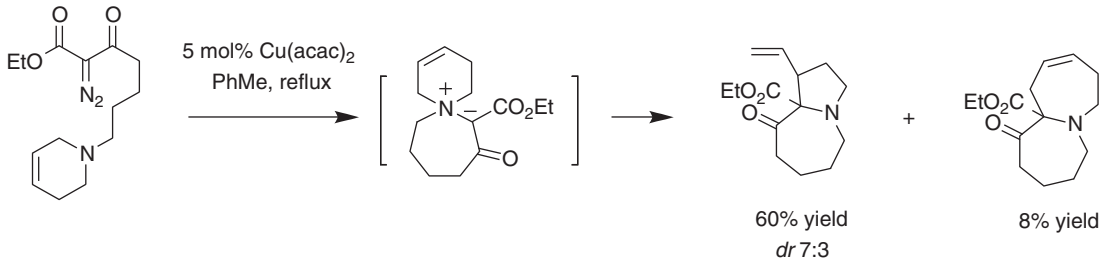


BOX ligand

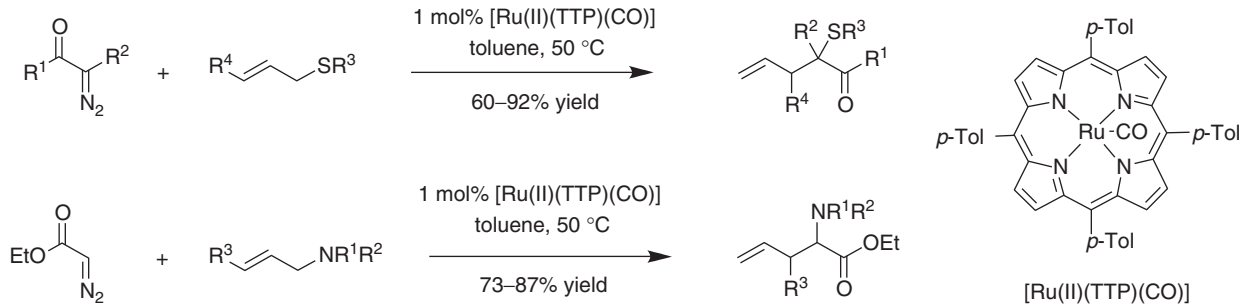
Scheme 132



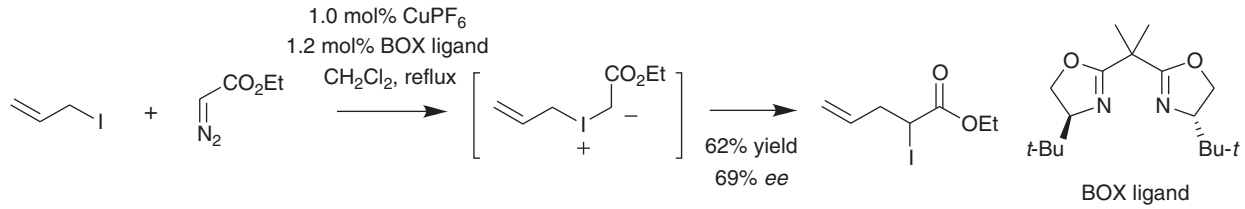
Scheme 133



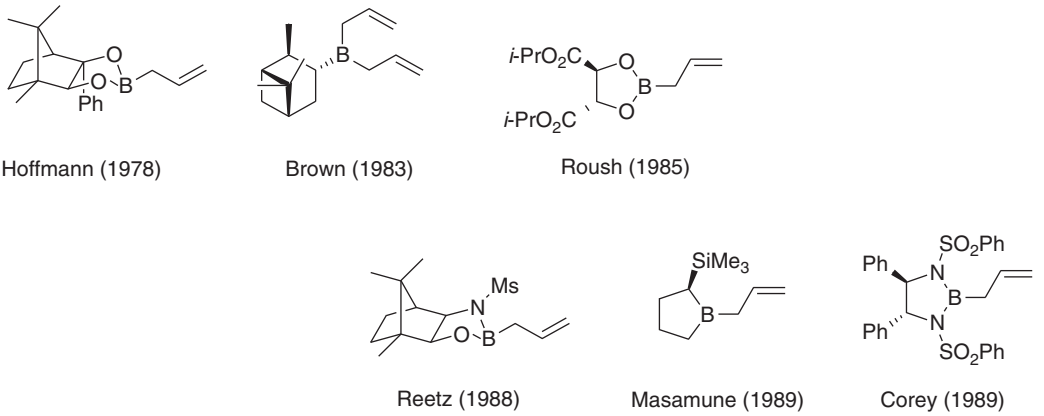
Scheme 134



Scheme 135

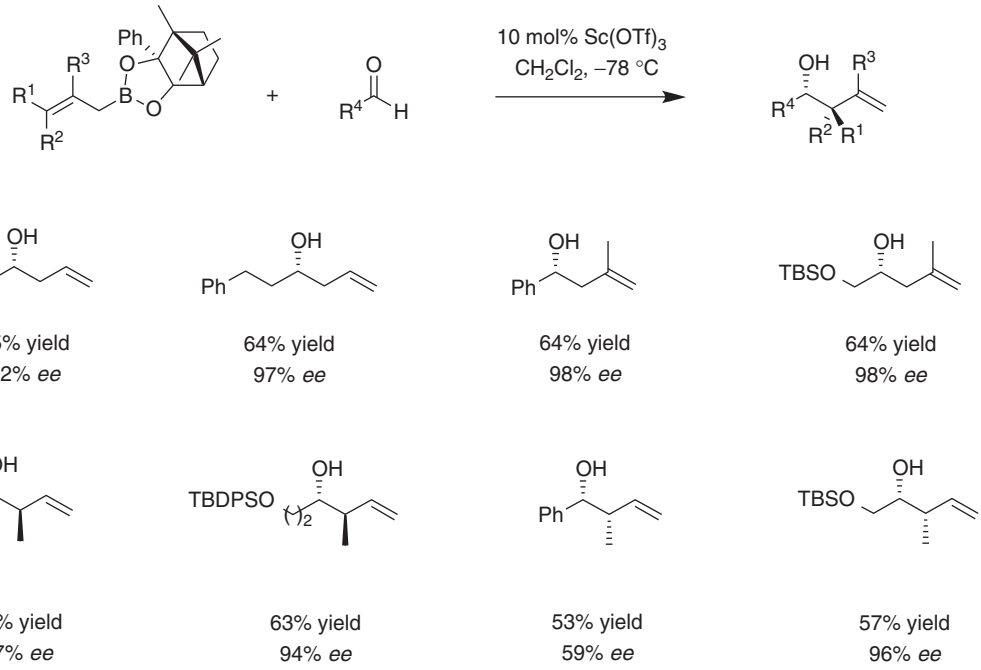


Scheme 136



Scheme 137

the synthesis of homoallylic alcohols (Scheme 138).[373] This modification has proven to be particularly useful for multisubstituted allyl boronates, which otherwise display lower reactivity and selectivity.[374]

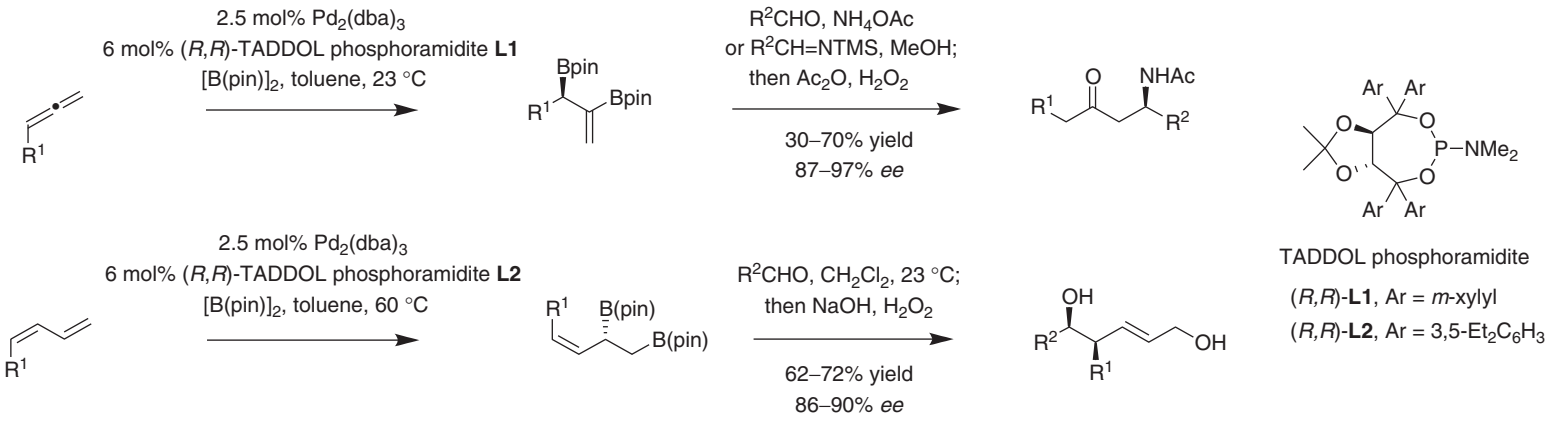


Scheme 138

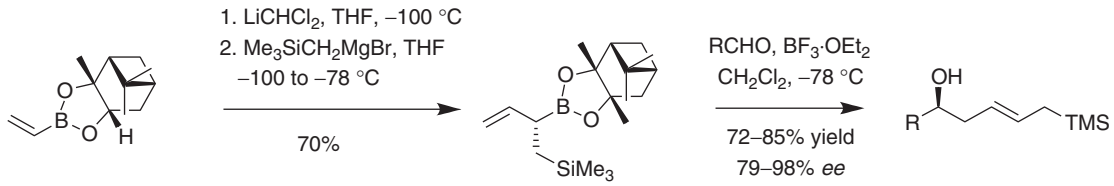
Transition metal complexes of palladium and platinum catalyze asymmetric diboronation of allenes and 1,3-dienes in the presence of chiral TADDOL-derived phosphoroamidites (Scheme 139).[375] The allylic boronates have been prepared with high stereoselectivity. Subsequent allylation with imines or aldehydes provided, after oxidation, homoallylic amines or alcohols, respectively, with excellent chirality transfer.

A chiral boronate containing a (trimethylsilyl)methyl substituent at the α-position has been prepared by a homologation protocol entailing a sequential treatment of the chiral vinylboronate precursor with $LiCHCl_2$ and Me_3SiCH_2MgBr (Scheme 140).[376] The reaction is thought to proceed through a 1,2-B migration and an S_N2 substitution with Grignard reagent. The reagent has been advanced *in situ* by the addition to an aldehyde, giving the homoallylic alcohols in excellent yield and enantioselectivity. The product contains an (E)-allylic silane moiety, which potentially can be used for an additional nucleophilic allylation.

In addition to the aforementioned stoichiometric reagents for the asymmetrical nucleophilic addition of allylmetal reagents, the number of methods based on asymmetric catalysis is continuously growing. Chiral derivatives of zinc, indium,[377] copper, nickel, and BINOL[378] were found to be effective in asymmetric allylation of carbonyl compounds with achiral allylboron reagents.


2.5 mol% Pd2(dba)3
6 mol% (R,R)-TADDOL phosphoramidite L1
[B(pin)]2, toluene, 23 °C
R1
Bpin
Bpin
R2CHO, NH4OAc
or R2CH=NTMS, MeOH;
then Ac2O, H2O2
30–70% yield
87–97% ee
O
NHAc
R1
R2
2.5 mol% Pd2(dba)3
6 mol% (R,R)-TADDOL phosphoramidite L2
[B(pin)]2, toluene, 60 °C
R1
B(pin)
B(pin)
R2CHO, CH2Cl2, 23 °C;
then NaOH, H2O2
62–72% yield
86–90% ee
OH
OH
R2
R1
Ar
Ar
O
O
P–NMe2
O
O
Ar
Ar
TADDOL phosphoramidite
(R,R)-L1, Ar = m-xylyl
(R,R)-L2, Ar = 3,5-Et2C6H3

Scheme 139



Scheme 140

A chiral diamine-zinc fluoride catalytic system was used in an effective asymmetrical allylation of activated hydrazono esters with achiral allyl pinacol boronates.[379] A transmetallation to an active allylzinc intermediate was suggested for the reaction pathway, with chirality being induced via a tight six-membered metallacycle adopting a chair-like conformation in the transition state (Scheme 141).[380]

Copper derivatives have been found to be effective catalysts for addition of allylic boronates to carbonyl compounds and imines. For example, allylic pinacolboronates add to ketimines in the presence of catalytic amounts of $La(OPr\text{-}i)_3$ and $CuF_2 \cdot PPh_3$.[381] Asymmetrical allylation of ketones was realized using chiral phosphine ligands in combination with copper catalysts.[382] In the presence of 1–5 mol% of a readily accessible NHC–Cu complex, homoallylic amines could be prepared from allylboronates and phosphinoylimines with high stereoselectivity (Scheme 142).[383] The C_1-symmetrical imidazolinium salts used in this reaction have been prepared on a multigram scale in four steps from commercially available materials. The addition of 2 equivalents of methanol in this carefully engineered reaction is crucial. Less than 5% conversion was observed in the absence of methanol.

A nickel-catalyzed allylation of conjugated dienals with allylic boronates has been investigated (Scheme 143).[384] In the absence of the transition metal catalyst, the reaction of allylboronates with sorbic aldehyde gave the (*E*,*E*)-isomer of the product with >95% conversion after 15 h in THF at room temperature. Interestingly, the corresponding reaction catalyzed by $Ni(cod)_2$ and PCy_3 was complete within 40 min and gave the (*E*,*Z*)-isomer as the sole product. Using the chiral TADDOL-derived phosphoramidite as the ligand, the (*E*,*Z*)-isomer was produced in 75% *ee* with high (*E*,*Z*):(*E*,*E*) selectivity in 71% yield.

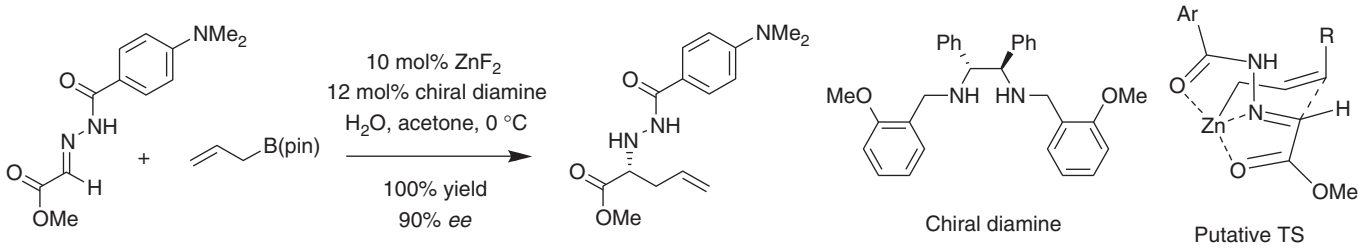
6.16.4.2.2 Allylation with allylsilane reagents

In 2002, the preparation of the chiral allyl silane reagent shown in Scheme 144 was reported. The allylsilane is readily available from (1*S*,2*S*)-pseudoephedrine and allyltrichlorosilane. The reaction of the chiral allylsilane with aliphatic aldehydes cleanly produces homoallylic alcohols with good-to-excellent enantioselectivity. The reagent is stable and can be stored for long periods of time without notable decomposition. Isolation and purification of products is experimentally simple and typically involves only an acidic extractive work-up, giving the products with >90% purity.[385] A variety of chiral allylsilane reagents could be accessed from the simple precursor by cross-metathesis with Grubbs' second-generation catalyst.[386] Continued efforts have been devoted to developing new chiral allylsilane reagents or modified reaction conditions to address limitations uncovered during synthetic application of these reagents.

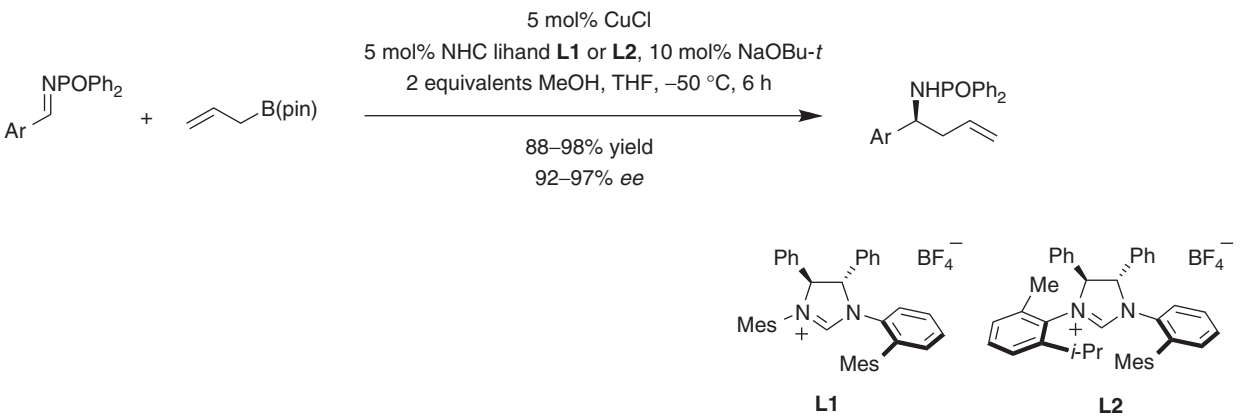
A chiral allylsilane reagent prepared from *bis*(4-bromobenzyl)cyclohexane-1,2-diamine (Scheme 145) has shown excellent efficiency in allylation of simple aliphatic aldehydes, giving products in high yields and excellent enantiopurity by a simple reaction protocol. A limitation was revealed due to poor reactivity of these reagents with even mildly hindered or unsaturated aldehydes. A solution to this problem was developed through the assistance of Lewis acid catalysis. In the presence of Lewis acids, the reactivity of the allylsilane reagents was greatly enhanced. Scandium triflate proved to be the optimal catalyst, increasing not only yields but also enantioselectivity. Some representative examples presented in Scheme 145 describe efficient synthesis of functionalized allylic alcohols catalyzed by scandium triflate; no reactivity without this reagent was observed in each case.[387] In a related approach, this class of chiral allylsilanes has also shown utility in the synthesis of homoallylic amine derivatives by stereoselective addition to hydrazones and imines.[388]

A cascade aldol-allylation reaction using highly engineered (enoxy)allylsilane reagents and aldehydes has been demonstrated to be effective in assembling polyketide building blocks (Scheme 146).[389] The advantage of using these reagents is that the aldehyde oligomerization is minimized. Oligomerization is a typical problem in aldol coupling with aldehydes because the product itself is an aldehyde, creating chemoselectivity issues. With the (enoxy)allylsilane reagent, the aldehyde formed *in situ* is removed by the intramolecular allylation with good diastereocontrol.

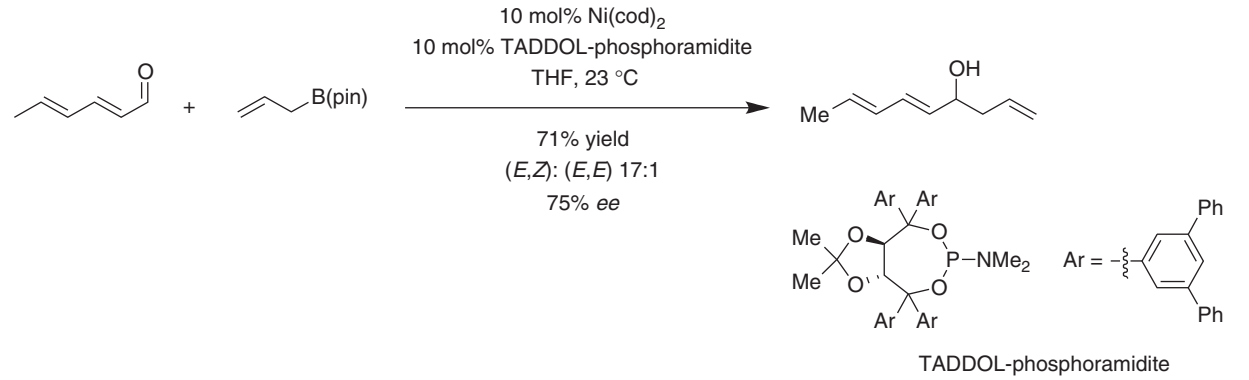
Chiral Lewis bases have been used to develop asymmetric addition of allylsilanes to aldehydes. With a stoichiometric amount of the simple monomeric phosphoramide depicted in Scheme 147, addition of allylic trichlorosilanes to benzaldehyde afforded the homoallylic alcohols in a good yield. Although only moderate enantioselectivity was achieved, high diastereoselectivity in the reaction supported a closed chair-like transition state. The reaction with a catalytic amount of the phosphoramide afforded 40% yield of the allylic alcohol with slightly lower enantioselectivity.[390] Mechanistic studies provided evidence supporting a pathway with a transition state incorporating two molecules of the phosphoramide. As a result, a series of bidentate chiral ligands were prepared (Scheme 147). Systematic investigations found that tether length of five methylene units gives optimal stereocontrol.[391] Chiral phosphoramide additives derived from proline and a chiral formamide have also been investigated.[392]


NMe2
O
NH
N
O
H
OMe
+
B(pin)
10 mol% ZnF2
12 mol% chiral diamine
H2O, acetone, 0 °C
100% yield
90% ee
NMe2
O
NH
HN
O
OMe
Ph
Ph
MeO
NH
HN
OMe
Chiral diamine
Ar
R
NH
O
Zn
N
H
O
OMe
Putative TS

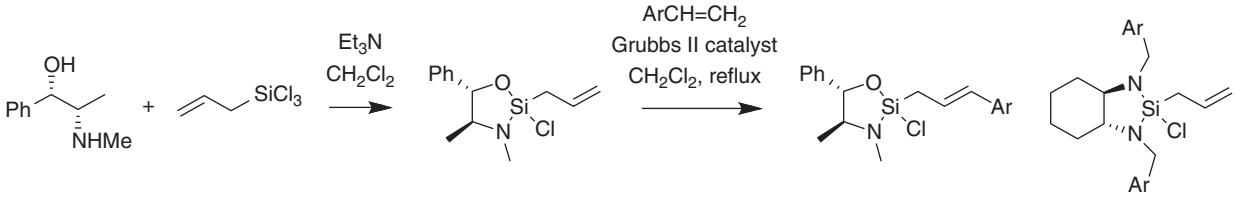
Scheme 141



Scheme 142



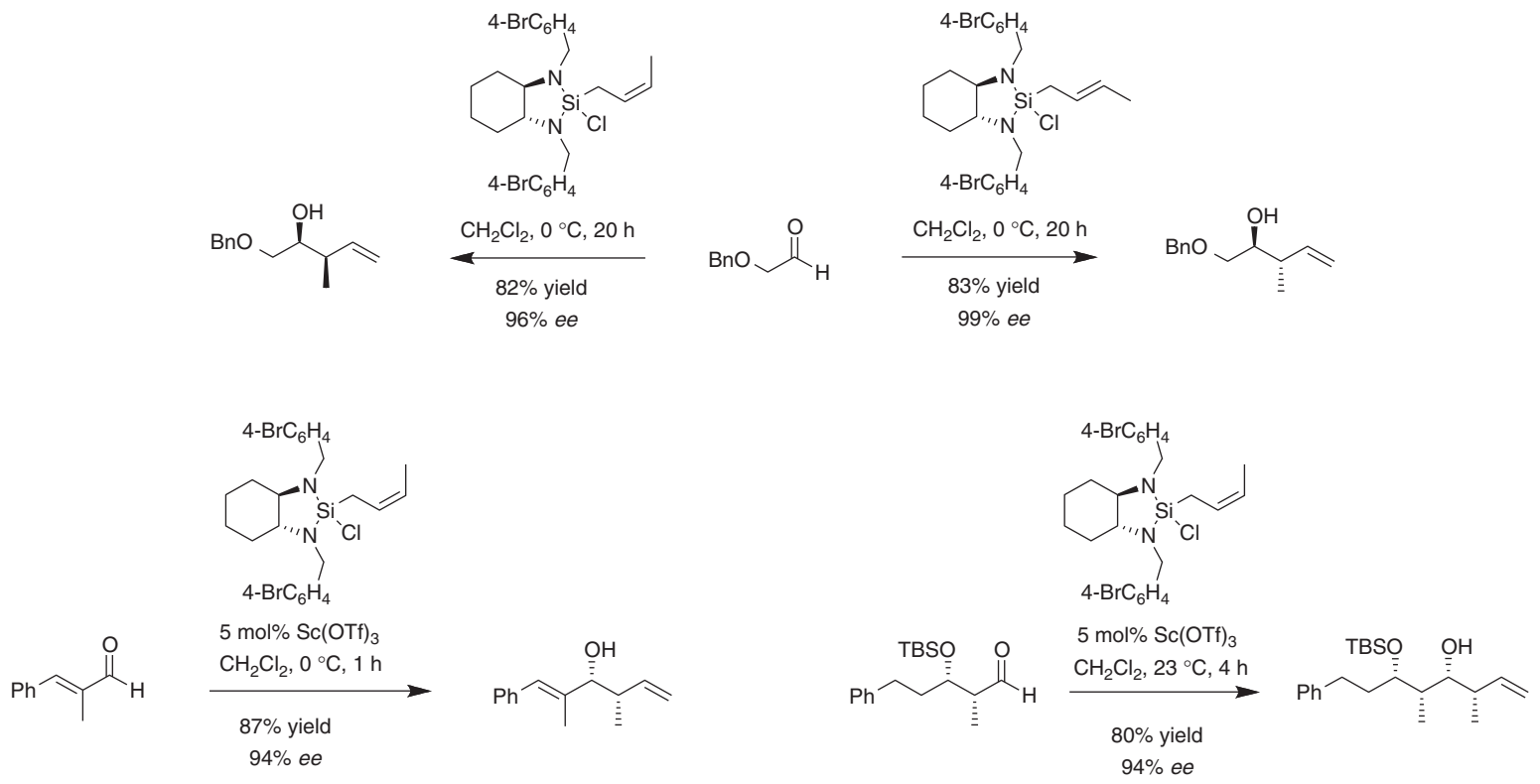
Scheme 143



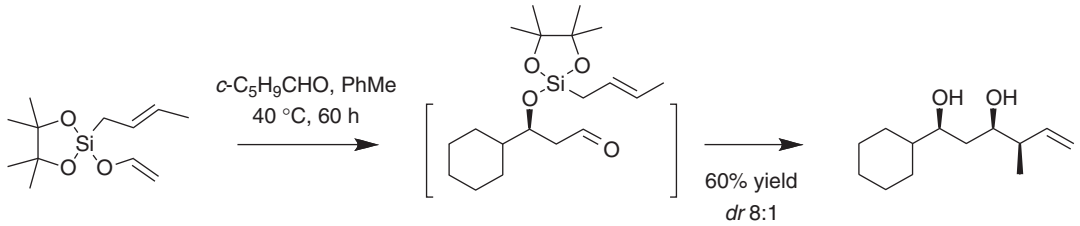
Scheme 144

Chiral *N*-oxides have become an important class of highly potent Lewis base catalysts for allylation with allylsilanes. In the presence of 10 mol% of the *bis*-quinoline-derived chiral *N*-oxide **L1** (Scheme 148), the reaction of benzaldehyde with (*E*)-2-butenyltrichlorosilane gave the alcohol in excellent enantioselectivity in moderate yield.[393] The bipyridine-derived catalysts were found to have a much higher catalytic activity. Generally high yields and good-to-excellent enantioselectivities could be achieved with only 0.01–0.1 mol% loading of the catalyst. The high reactivity can be attributed to the π-π stacking of the phenyl group at the 6,6′-position in **L2** with the aryl group of the aromatic aldehydes.[394]

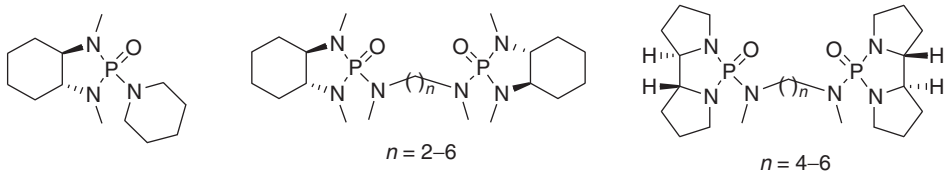
The success achieved with the chiral *N*-oxide catalysts in the addition of allylsilanes to aldehydes encouraged the development of new structural variants of these compounds, a selection of which is depicted in Scheme 149. During these studies with the *bis*-pyridyl structural motif,[395] an intriguing discovery was made that the mono-*N*-oxide **L2** (Scheme 149) showed excellent catalytic activity, whereas enantioselectivity observed with the corresponding *bis*-*N*-oxide **L1** was rather low. The addition of one equivalent of tetrabutylammonium iodide further enhanced the catalyst activity, allowing the reaction temperature to be raised to –65 °C without a loss in enantioselectivity. Compounds (+)-**L3** and (–)-**L3** are an enantiomeric pair of atropisomers, which slowly interconvert in solution. The configurational stability of these compounds in the solid state is reasonably high. Allylation of benzaldehyde with allyltrichlorosilane in the presence of (+)-**L3** affords the product in 98% *ee*, whereas the opposite enantiomer is produced with (–)-**L3**. Other active catalysts (L4, (+)-MENTHOX, Scheme 149) have resulted from the continuous efforts in this area.[396]


4-BrC6H4
N
Si
Cl
N
4-BrC6H4
BnO
OH
CH2Cl2, 0 °C, 20 h
82% yield
96% ee
BnO
O
H
CH2Cl2, 0 °C, 20 h
83% yield
99% ee
BnO
OH
Ph
O
H
5 mol% Sc(OTf)3
CH2Cl2, 0 °C, 1 h
87% yield
94% ee
Ph
OH
TBSO
O
H
5 mol% Sc(OTf)3
CH2Cl2, 23 °C, 4 h
80% yield
94% ee
TBSO
OH

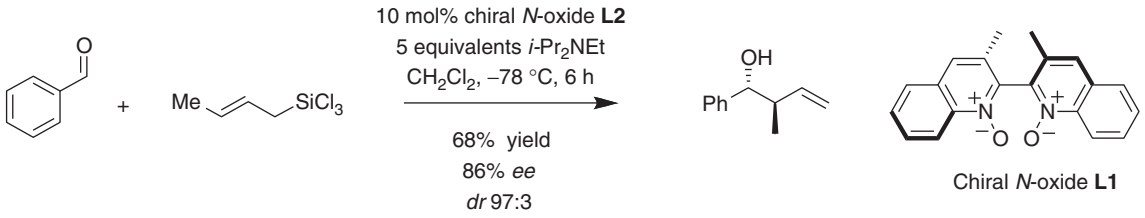
Scheme 145

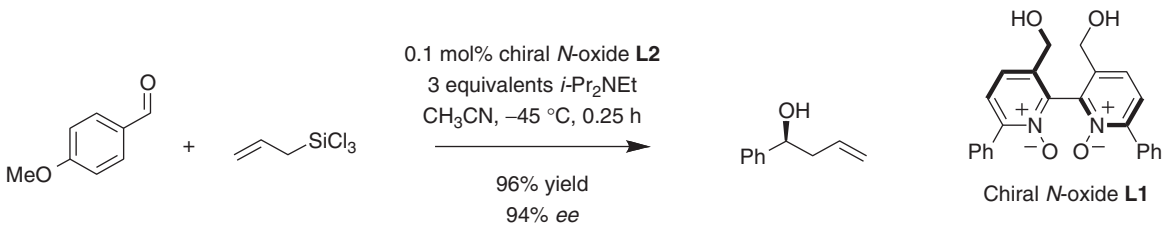


Scheme 146

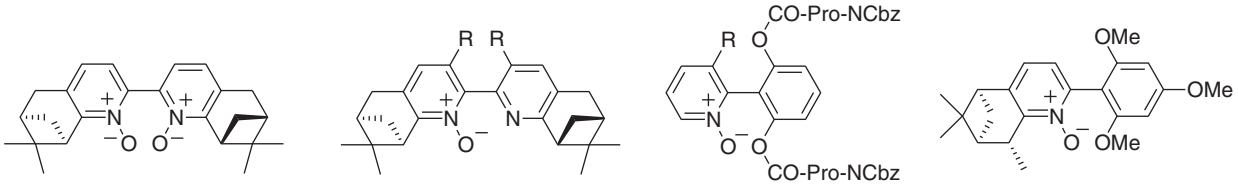


Scheme 147





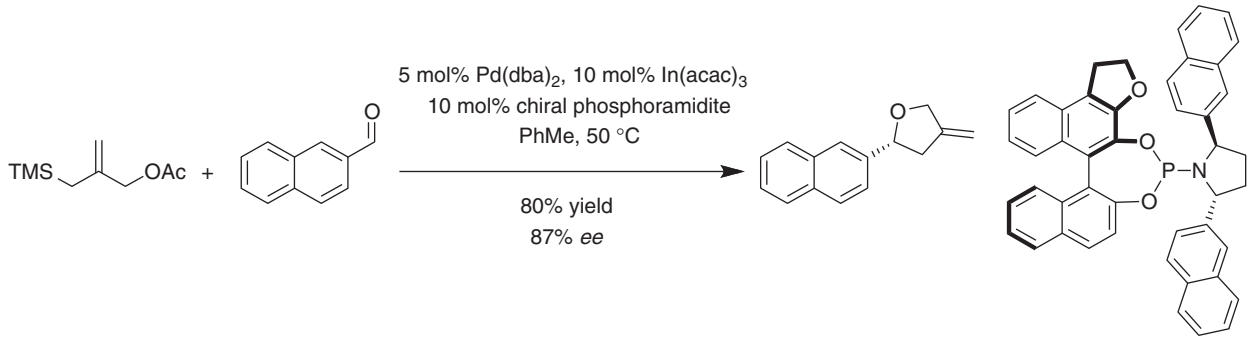
Scheme 148



Scheme 149

An allylation of imines with tetraallylsilane under the catalysis of a chiral (η3)-allylpalladium dimer was reported in 2004.[397]

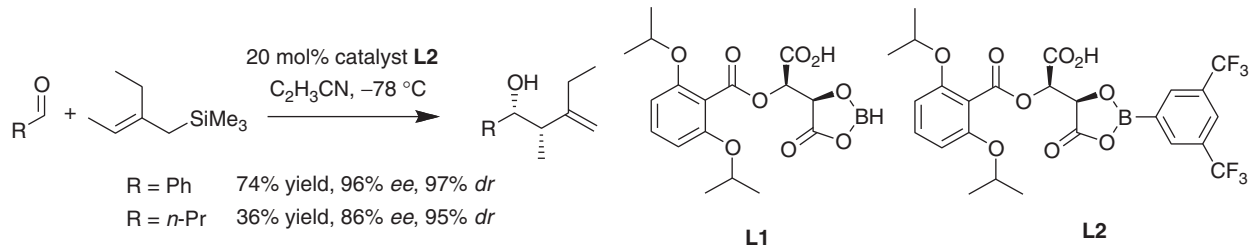
In 2011, an asymmetric TMM cycloaddition with 3-acetoxy-2-trimethylsilylmethyl-1-propene and aldehydes in the presence of the chiral phosphoramidite ligand was developed (Scheme 150).[398] The electron-rich ligand, which is capable of stabilizing the η^3-allylpalladium intermediate, is essential to achieve a good chemical yield. In some cases, the addition of a Lewis acid to activate the aldehyde significantly increases the yields. The asymmetrical TMM allylation approach has also been used with imines.[399,400]



Scheme 150

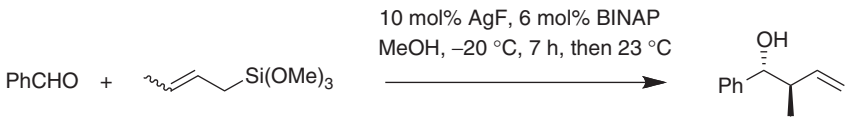
Application of chiral Lewis acid catalysts for enantioselective addition of allylsilanes and other allylmetal reagents to aldehydes is another prolific area of research.[401] Many types of catalytic systems have been described for this purpose, including chiral boronates,[402] titanium–BINOL complexes,[403] silver–phosphine complexes,[404] as well as copper and zinc compounds.[405]

Dioxaborolanone derivatives **L1** and **L2** shown in Scheme 151 catalyze allylation of aldehydes with trimethylallylsilanes and provide the products in generally moderate yields and good enantioselectivity, favoring the *syn* adducts. The 3,5-*bis*(trifluoromethyl)phenylboronic acid derivative **L2** showed enhanced chemical yields and enantioselectivity.[402]

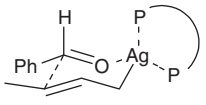


Scheme 151

The addition of 2-buten-1-yltrimethoxysilanes to benzaldehyde in the presence of AgF-BINAP catalyst system provided the products with high *anti*-selectivity regardless of the geometric purity of the silane reagent (Scheme 152). Nuclear magnetic resonance (NMR) spectroscopic studies indicated the rapid disappearance of 2-butenyltrimethoxysilane upon the addition of AgF and BINAP, suggesting a transmetallation mechanism. It was not clear why the high *anti*-selectivity is dominant regardless of the configuration of the crotylsilane. As a rationalization, the authors hypothesized that the rate of E/Z isomerization for the intermediate 2-buten-1-ylsilver reagent exceeds that of its addition to aldehydes.[406]



E:*Z* (for the silane)	Yield	*ee*	*dr*
17:83	77%	96%	92:8
>99:1	82%	94%	94:6
55:45	99%	94%	93:7



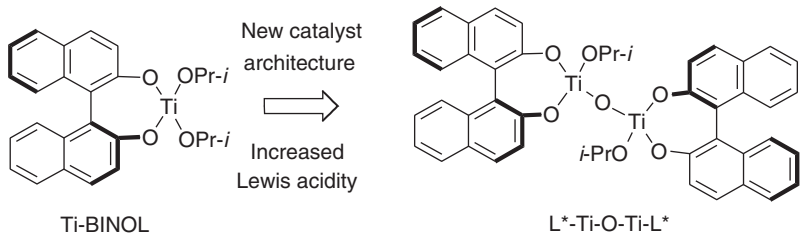
Putative TS

Scheme 152

6.16.4.2.3 Allylation with allylstannane reagents

A combination of titanium(IV) isopropoxide and BINOL is one of the most efficient catalytic systems for the addition of allylstannane reagent to aldehydes.[407] The efficiency of this process can be augmented by the addition of 4-(trifluoromethyl) phenylboroxin, which serves to activate the Lewis acid catalyst in a concept referred to as 'Lewis acid-assisted Lewis acid catalysis,' or LLA.[408]

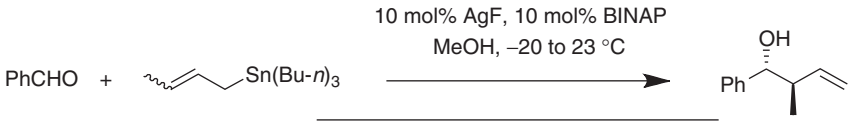
Inspired by strong Lewis acidity of Al-O-Al unit found in methylalumoxane (MAO) and *bis*(dimethylaluminum) oxide, a modification of the original titanium(IV)-BINOL catalyst led to the new catalyst architecture, the binaphthoxyl *bis*-Ti oxide (L*-Ti-O-Ti-L*) catalyst shown in Scheme 153. The catalyst showed a significant improvement in both reactivity and enantioselectivity for the addition of tributylallylstannane to aldehydes. The reaction of octanal and allyltributyltin in the presence of 10 mol% of the modified L*-Ti-O-Ti-L* catalyst in CH_2Cl_2 at 0 °C gave 85% yield of the product with 99% *ee*, whereas the original titanium-BINOL catalyst gave only 14% yield of the product with 81% *ee*.[409] A positive nonlinear effect was found by correlating the enantiopurity of homoallylic alcohol with the *ee* value for BINOL.



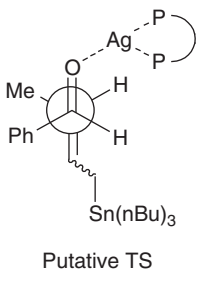
Scheme 153

Another titanium-based catalyst has been prepared by mixing BINOL, $TiCl_2(OiPr)_2$, and two equivalents of allyltributyltin. The catalyst was capable of accelerating the addition of tetraallyltin to ketones with moderate enantioselectivity.[410] The enantioselectivity was greatly enhanced by the use of BINOL-Ti($OiPr$)$_4$ catalyst prepared *in situ* without removal of the released isopropanol,[411] and the *ee* of the product from the allylation reaction of 3-methylacetophenone and tetraallyltin increased from 51% to 73%. After addition of 20 equivalents of isopropanol, the *ee* value of the product increased further to 96%.[412] Additional investigation established that asymmetrical allylation of ketones could be performed under 'solvent-free' conditions if the catalyst is generated with a 1:2 stoichiometry for Ti($OiPr$)$_4$ and BINOL and an additional 3 equivalents of isopropanol. The reaction provided tertiary homoallylic alcohols in excellent yields and similar or slightly lower enantioselectivity compared to the same reaction performed with DCM as the solvent.[413]

Other metal complexes including silver,[417] zirconium,[414] chromium,[415] tin(IV),[416] and indium[418,419] have been investigated for allylation with allylstannanes. Analogously to a similar reaction with allylsilanes, the AgF-BINAP-catalyzed addition of 2-buten-1-yltributylstannane with benzaldehyde produced the product with the *anti*-configuration preferentially. The diastereoselectivity was unaffected by the configurational impurity of the stannane reagent.[417] In contrast to the reaction with 2-buten-1-yltrimethoxysilane, no transmetallation was observed when 2-buten-1-ylstannane was treated with an equimolar amount of AgF and BINAP. Thus, an antiperiplanar transition state was proposed for the unusual *anti*-selectivity (Scheme 154).

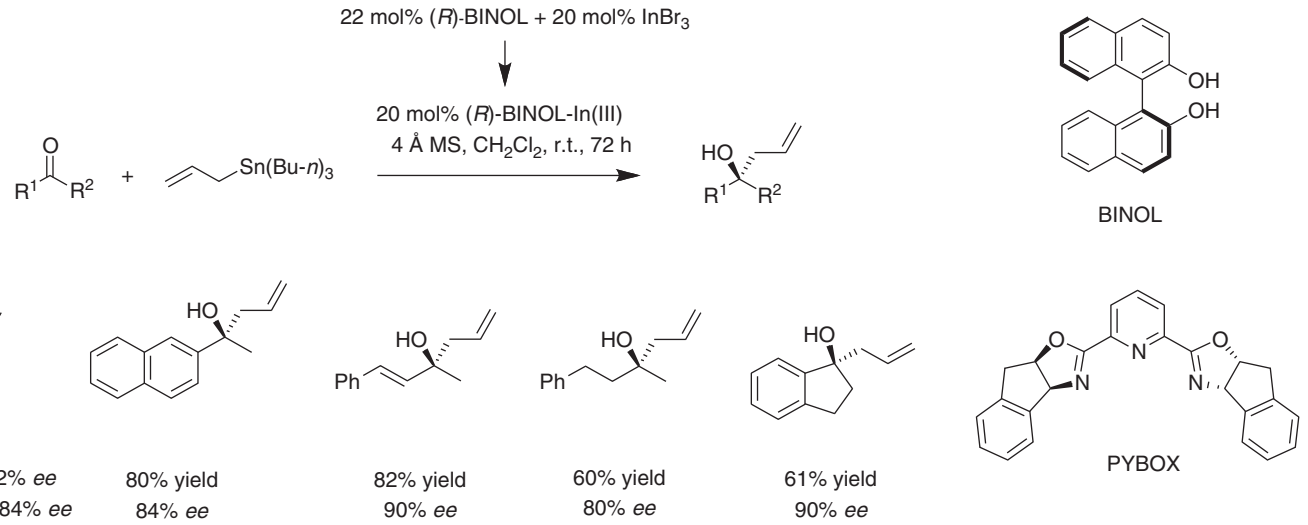


E:*Z* (for the reagent)	Yield	*ee*	*dr*
95:5	56%	94%	85:15
2:98	72%	91%	85:15
47:53	45%	94%	85:15



Scheme 154

Coordination compounds of indium are a newer class of Lewis acid catalysts that is receiving an increasing attention. Some of the main advantages of indium complexes are the sustained catalytic activity in the presence of water and low toxicity. Several indium complexes have been probed for the asymmetrical addition of allylstannanes to carbonyl compounds. Application of the BINOL-$InCl_3$ system gave a higher enantioselectivity in comparison to the PYBOX-$InCl_3$ system (Scheme 155). It is noteworthy that PYBOX and BINOL ligands could be recovered in high yields by a simple work-up protocol or chromatography on silica gel.[418] An allylindium-BINOL adduct has been hypothesized to be the actual active catalytic species. The addition of water before the formation of the allylindium-BINOL adduct resulted in poor yields and no enantioselectivity. A related chiral BINOL–$InBr_3$ complex has been successfully applied to allylation of ketones. Generally, homoallylic alcohols were obtained with good enantioselectivity.[419] More importantly allyltributylstannane could be used in contrast to many other catalytic systems that require more active allylation reagents such as tetraallylstannane (Scheme 155).

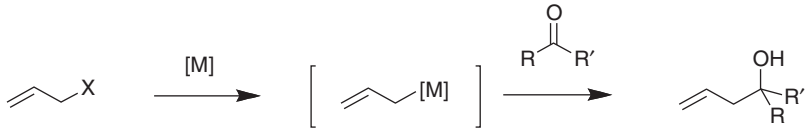

22 mol% (R)-BINOL + 20 mol% InBr3
20 mol% (R)-BINOL-In(III)
4 Å MS, CH2Cl2, r.t., 72 h
Sn(Bu-n)3
BINOL
PYBOX
R = Ph, 74% yield, 82% ee
R = pTol, 41% yield, 84% ee
80% yield
84% ee
82% yield
90% ee
60% yield
80% ee
61% yield
90% ee

Scheme 155

The use of other transition metals such as platinum,[420] palladium,[421] and rhodium[422] as catalysts in the asymmetric nucleophilic allylation of carbonyl compounds has also been investigated. The mode of activation for these metal complexes is either by a Lewis acid binding to the carbonyl group or through the formation of allylmetal intermediates.

6.16.4.2.4 *Allylation with other* in-situ*-generated allylmetal reagents*

Barbier-type addition reaction of allyl halides to carbonyl compounds in the presence of stoichiometric or catalytic metal reagents involves the intermediacy of allylmetal species formed *in situ* (Scheme 156). This strategy avoids the isolation of sensitive or potentially toxic organometallic reagents and simplifies experimental operations. Currently, the most common metals employed for this type of transformation are chromium, indium, and iridium.



Scheme 156

The chromium(II)-mediated coupling between allyl halides and aldehydes was initially reported in 1977.[423] The chromium(II) reagent was prepared by the treatment of $CrCl_3$ with 0.5 equivalent of lithium aluminum hydride in THF. In 1986, the significance of nickel additives for the smooth generation of allylchromium intermediates was demonstrated. The reaction became a reliable transformation for organic synthesis and now is known as the Nozaki–Hiyama–Kishi (NHK) reaction.[424] By the addition of a stoichiometric amount of manganese and Me_3SiCl additives, the amount of toxic chromium salts could be reduced to a catalytic loading. On the basis of these findings, a chromium-catalyzed asymmetrical allylation of aldehydes with the salen–Cr(II) complex was described in 1999 (Scheme 157).[425]

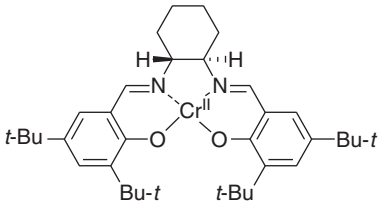
A chiral ligand derived from (2*R*,5*S*)-bicyclo[2.2.1]heptane-2,5-diamine (DIANANE) in combination with chromium(III) chloride showed an improved enantioselectivity of up to 92% *ee* (Scheme 157).[426] A chiral tethered *bis*-(8-quinolinolato) chromium catalyst (TBOX-Cr(III)) was introduced in 2006.[427] The use of allyl bromides was necessary with this catalyst because the pinacol coupling of the carbonyl counterpart was dominant as the major reaction pathway when allyl chlorides were used. A very high enantioselectivity of up to 99% *ee* was achieved with the TBOX catalyst. Tridentate *bis*(oxazoline) ligands Car-BOX and the nonsymmetrical ligand Bn-*t*-Bu-BOX have also shown a synthetically useful levels of enantiocontrol.[428,429] Peptide-based ligands for the NHK reaction have been studied, showing enantioselectivity reaching 95% *ee* for certain substrates.[430] A class of sulfonamide-based oxazoline ligands (sulfonamide-BOX) for the asymmetrical NHK reaction has been developed.[431] Further investigation with these sulfonamide-BOX ligands demonstrated that 2-haloallylation can be performed efficiently with high enantioselectivity when 2-haloallyl bromides are used. Furthermore, the high crystallinity of the ligand allowed its efficient recovery in a pure form.

Indium metal in the powder form has been shown to readily insert into allyl halides to form allylindium species in DMF or THF.[432] These reagents generated *in situ* have been used as allylation reagents with carbonyl compounds. The indium-mediated allylation reaction has been also successfully conducted in water.[433] As a benchmark reference, the corresponding reaction of acetophenone and allylbromide in the presence of metallic zinc gave only an 18% yield. Currently, indium-mediated reactions, including allylation reaction, have received considerable attention due to advantages of using indium over other metals. In comparison with organolithium and organomagnesium reagents, organoindium compounds have relatively low activity. Thus, they display greater functional group tolerance and are compatible with halide, nitro, ester, and even hydroxy groups. Due to high tolerance of water, it is not necessary to conduct indium-mediated reactions under strictly oxygen-free or anhydrous conditions (Scheme 158).

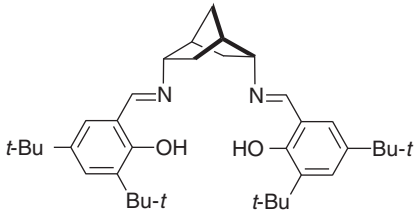
The structural characteristics of organoindium species involved in the allylation of aldehydes remain a subject of debate. Several structures have been proposed. Although modern techniques such as NMR, mass spectrometry, and X-ray crystallography have been used extensively to determine the structure of allylindium intermediates, no consensus has been reached. In a recent review, allylindium dihalide ($allylInX_2$) and diallylindium halide [$(allyl)_2InX$] were proposed as the most likely candidates for active species in the allylation reaction.[434] Nevertheless, the lack of clear understanding of the structure of these reagents has not prevented their broad application in synthetic organic chemistry. In addition to aldehydes and ketones, other functionalized carbonyl compounds including those with acidic or reactive groups have been exploited in the indium-mediated allylation reaction. α-Ketoacid,[435] acyl chlorides[436] and α-ketonitriles[437] have been employed as substrates using aqueous reaction conditions (Scheme 159).

α,β-Unsaturated aldehydes and ketones are also suitable substrates. In the presence of a stoichiometric amount $InCl_3$ the allylation gave the 1,2-addition products exclusively (Scheme 160).[438] The allylation of quinones by allylindium species in DMF is also feasible. The reaction of *p*-benzoquinone and allyl bromide in the presence of indium delivered the product quantitatively. The subsequent [3,3]-sigmatropic rearrangement in the presence of silver oxide afforded α-allylated quinone.[439]

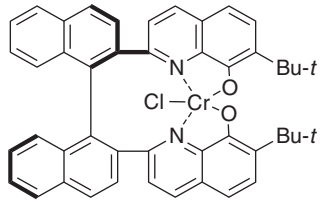
The indium-mediated allylation of carbonyl compounds has been performed with a catalytic amount of indium in the presence of a stoichiometric terminal reducing agent (Scheme 161).[440] Good yields of homoallylic alcohols have been reached



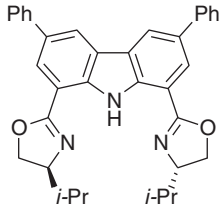
Cr(II) salen complex
up to 89% *ee*



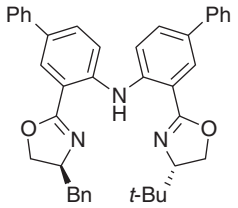
DIANANE-derived ligand
up to 92% *ee*



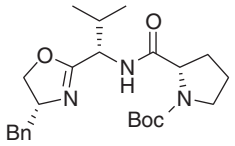
TBOX-Cr(III) catalyst
up to 99% *ee*



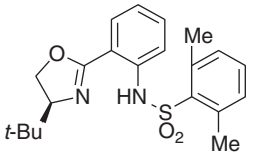
Car-BOX
up to 96% *ee*



Bn-*t*-Bu-BOX
up to 91% *ee*

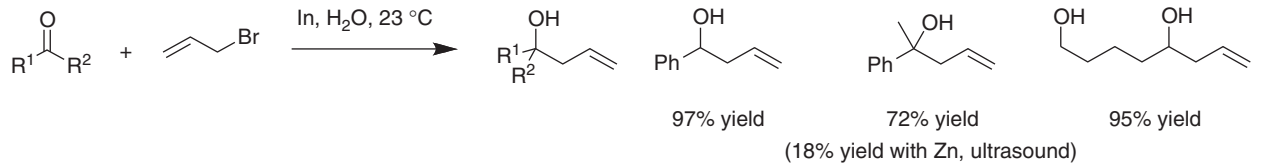


Peptide-based ligand
up to 95% *ee*

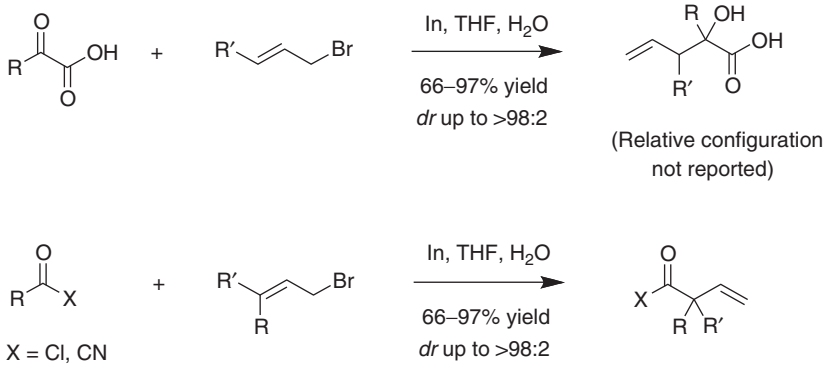


Sulfonamide-BOX ligand
up to 97% *ee*

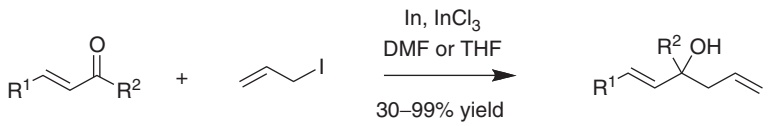
Scheme 157

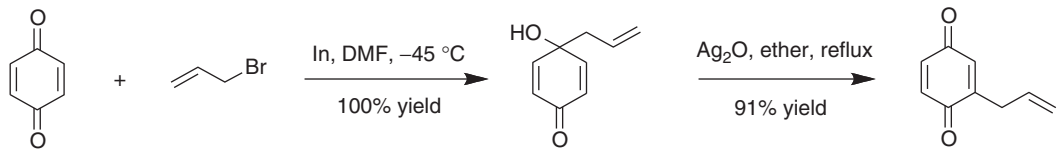


Scheme 158

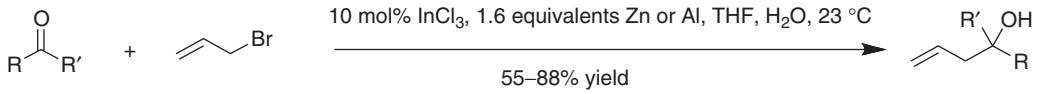


Scheme 159





Scheme 160

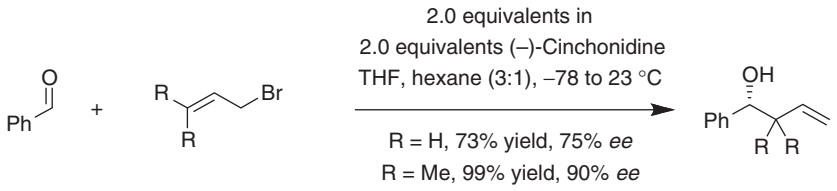


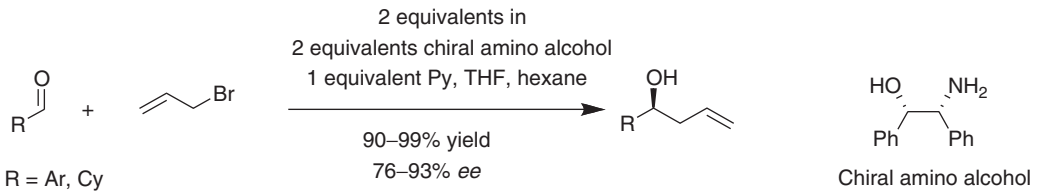
Scheme 161

with 10 mol% of indium trichloride and 1.6 equivalents of zinc or aluminum. The presence of water has been found to be essential to minimize side-reactions.

There are only a few examples of indium-mediated asymmetric allylation reactions of carbonyl compounds. The possible reasons are that the reaction usually requires a stoichiometric amount of indium and, perhaps more importantly, the poorly understood structure of the allylindium reagent. The current examples usually require a stoichiometric amount of chiral ligands.

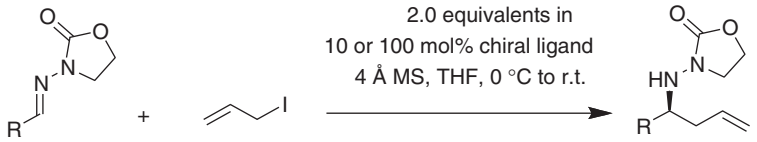
An example of enantioselective indium-mediated allylation of benzaldehyde using (–)-cinchonidine or (+)-cinchonine as chiral promoters was described in 1999 (Scheme 162).[441] Moderate-to-good yields and up to 90% *ee* were achieved. DCM can be used as the solvent due to the low basicity of organoindium reagents. The allylation of 2,2,2-trifluoromethyl phenyl ketone delivered the corresponding product in 70% *ee*. However, the reaction of unactivated ketones and heteroaromatic aldehydes afforded the products with poor enantioselectivity. Another example of the asymmetrical version of the indium-mediated allylation reaction utilizes 2 equivalents of a chiral amino alcohol as the enantiodirecting agent. The reaction required the addition of pyridine to achieve high yields and enantioselectivity (Scheme 162).[442]



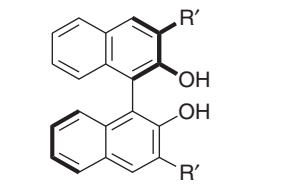


Scheme 162

The indium-mediated allylation of *N*-aryl imines derived from aromatic aldehydes in the presence of (+)-cinchonine only gave moderate *ee* (22–44% *ee*) in excellent yields.[443] With a benzaldehyde-derived hydrazone as the substrate, catalytic amounts of chiral BINOL ligands could be used (**Scheme 163**). This is the first example of a successful use of a catalytic amount of a chiral additive in the indium-mediated allylation reaction. However, with hydrazones derived from aliphatic aldehydes, the enantioselectivity was substantially reduced when 10 mol% of the chiral reagent was used instead of 100 mol% (**Scheme 163**).[444] Further investigations led to the discovery of a more effective trifluoromethylsulphone-substituted BINOL ligand. Generally excellent yields and enantioselectivity could be achieved with hydrazones derived from aromatic aldehydes.[445]

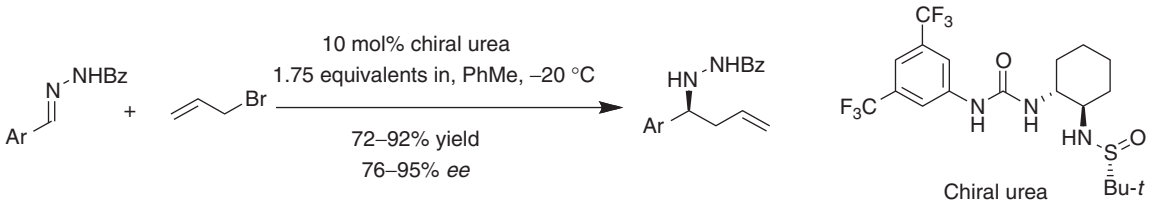


R	**L1** (10 mol%)	**L1** (100 mol%)	**L2** (10 mol%)
Ph	77%, 70% *ee*	72%, 84% *ee*	95%, 88% *ee*
2-ClC_6H_4	67%, 91% *ee*	50%, 97% *ee*	95%, 97% *ee*
2-furyl	70%, 70% *ee*	65%, 91% *ee*	97%, 90% *ee*
$PhCH_2CH_2$	73%, 34% *ee*	61%, 92% *ee*	93%, 74% *ee*

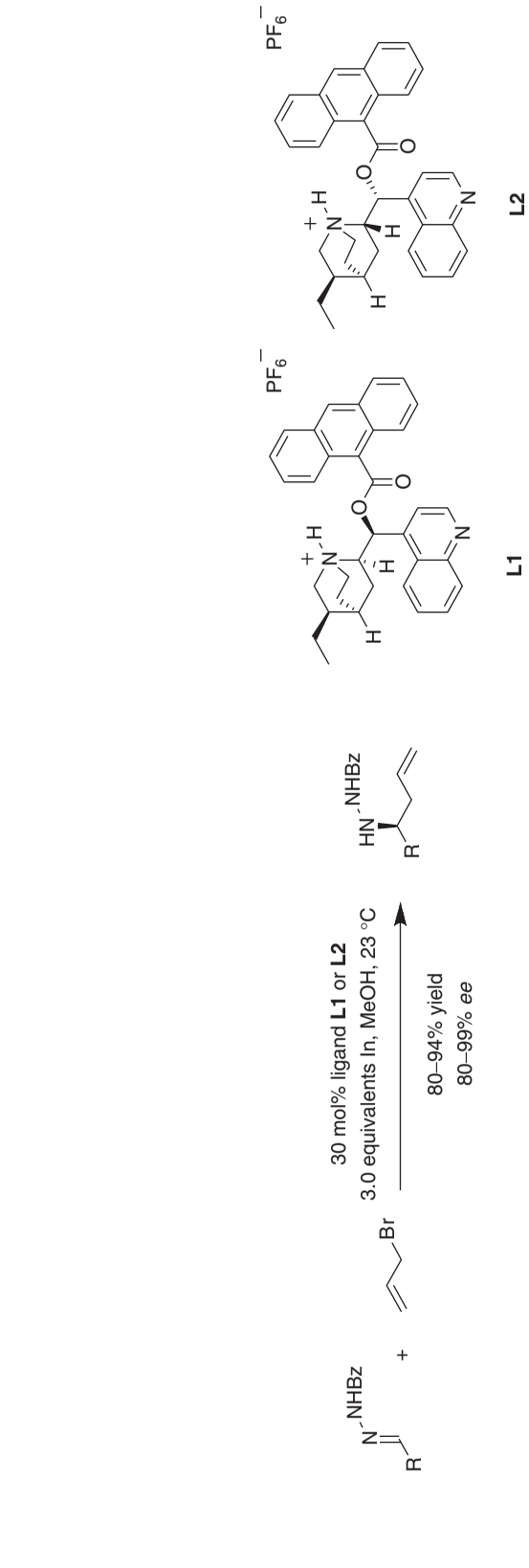


Scheme 163

Chiral urea ligands have been used in the indium-mediated addition of allyl haldes to *N*-acylhydrazones.[446] The chiral urea shown in **Scheme 164** was uniquely effective in providing excellent enantioselectivity, whereas for several other analogs the maximum enantioselectivity reached 52% *ee*. The enantioselectivity and the yield of this reaction, however, were sensitive to



Scheme 164

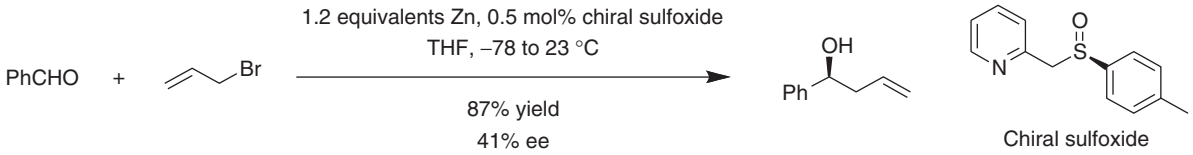

PF6−
L2
PF6−
L1
30 mol% ligand L1 or L2
3.0 equivalents In, MeOH, 23 °C
80–94% yield
80–99% ee
NHBz
Br
NHBz
R

Scheme 165

reaction parameters such as the source of the metallic indium and the stirring rate. At higher stirring rate, the rapid formation of allylindium species resulted in higher yields but somewhat reduced enantioselectivity.

The use of protonated cinchona alkaloid-derived additives for enantioselective additions of allylindium reagents to related *N*-acylhydrazones of aliphatic and aromatic aldehydes has been described (Scheme 165).[447] These reactions were conducted in methanol at room temperature. The relatively low basicity of allylindium reagents was compatible with the presence of tertiary ammonium salts. Decreasing the loading of the chiral additive **L1** (Scheme 165) from 30 mol% to 20 mol% resulted in significant deterioration of enantioselectivity from 99% *ee* to 30% *ee*, with a further decrease to 8% *ee* at 10 mol% of **L1**. This nonlinear phenomenon was attributed to a concentration-dependent shift in equilibrium between the protonated and dissociated amine species. The opposite sense of enantioselectivity was realized with the epimeric additive **L2** (Scheme 165).

Zinc- and tin-mediated asymmetric allylation of carbonyl compounds have been investigated. Moderate enantioselectivity was achieved with the chiral sulfoxide additive shown in Scheme 166.[448] Saccharose and β-cyclodextrin have also been examined in the zinc- and tin-promoted allylation reaction with a varying degree of success.[449]



Scheme 166

Palladium-catalyzed asymmetric allylation of carbonyl compounds with allylic acetates in the presence of diethyl zinc or directly with allylic alcohols in the presence of triethylborane have been developed (Scheme 167). These methods are based on umpolung of electrophilic π-allylpalladium intermediates, which are generated initially.[450] It has been shown that both allylic alcohols and their 2-THF and 2-THP derivatives could be used for allylation of aldehydes in the presence of a palladium catalyst and excess of diethyl zinc, although poor diastereoselectivity is typical.[451] The asymmetrical version of this reaction was first reported in 2004, although only a very limited scope of substrates was investigated.[452] By the use of chiral monodentate spirophosphite **L2** as a ligand, both the substrate scope and enantioselectivity were greatly improved.[453] Initially, a transmetallation process where an allylzinc or allylborane reagent was formed was proposed. Further studies revealed that the active allylation reagent is an η^1-allylpalladium species, which were generated from η^3-allylpalladium species in the presence diethyl zinc or triethyl borane.[454,455]

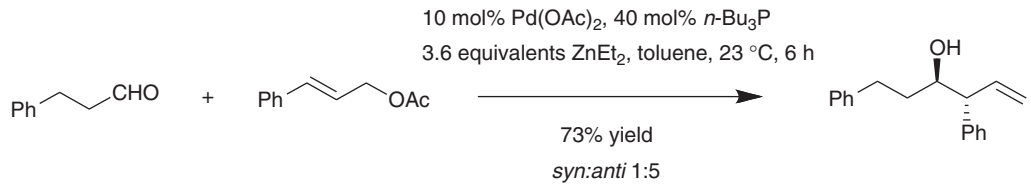
More recently, an iridium-catalyzed dehydrogenative allylation of benzylic alcohols with allylic acetates has been described. Subsequently, the dehydrogenative allylation of aliphatic alcohols and allylation of aldehydes have been realized (Scheme 168). In the presence of *m*-nitrobenzoic acid and Cs_2CO_3, the iridium/BINAP-catalyzed allylation reaction of benzylic alcohols and allyl acetate provided homoallylic alcohols with excellent enantioselectivity. By the addition of isopropanol, aldehydes could be converted to homoallylic alcohols generally with a higher enantioselectivity when (–)-TMBTP is used as a chiral ligand.[456] On the basis of mechanistic studies, the reaction of diols, activated ketones, and α-methyl allyl acetate have been further investigated and generally excellent stereoselectivities in the allylation processes have been achieved.[457]

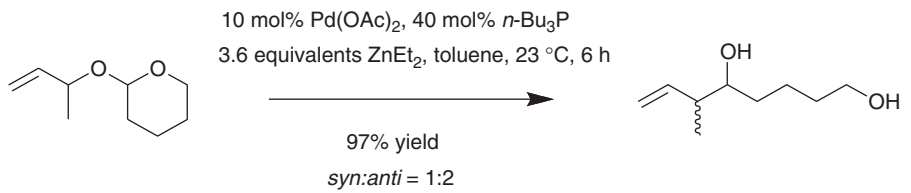
Titanium-mediated direct coupling of imines with allylic alcohols is an effective method for the synthesis of homoallylic amines with high diastereoselectivity.[458] Complexation of imines with low-valent titanium reagent affords an intermediate azametallacyclopropane (Scheme 169). Ligand exchange of the azametallacyclopropane with lithium allyloxide followed by a formal metallo-[3,3]-rearrangement delivers the homoallylic titanium amide, which gives the final product on hydrolysis.

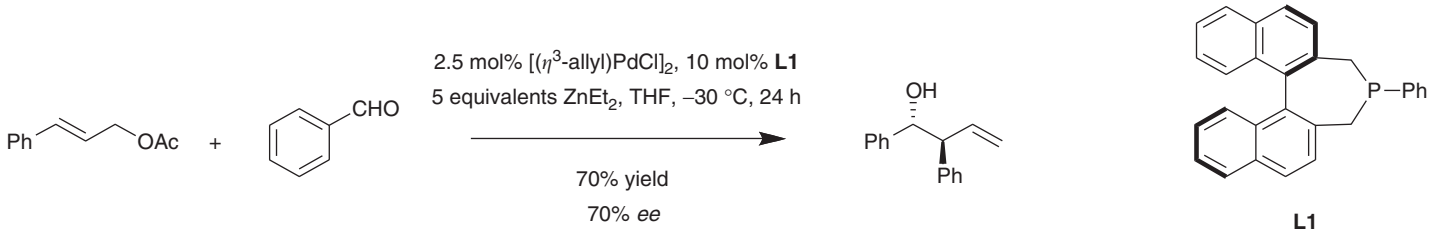
When vinyldimethylchlorosilane is used as the reaction partner, the reaction efficiently affords the silyl ether, which on Tamao oxidation smoothly delivers the corresponding alcohol (Scheme 170).[459] Stereo-defined skipped dienes can be synthesized efficiently by the titanium-mediated coupling of allenic or allylic alcohols with alkynes. The utility of this effective cross-coupling has been demonstrated in the elegant total synthesis of *ent*-phorbasin C.[460]

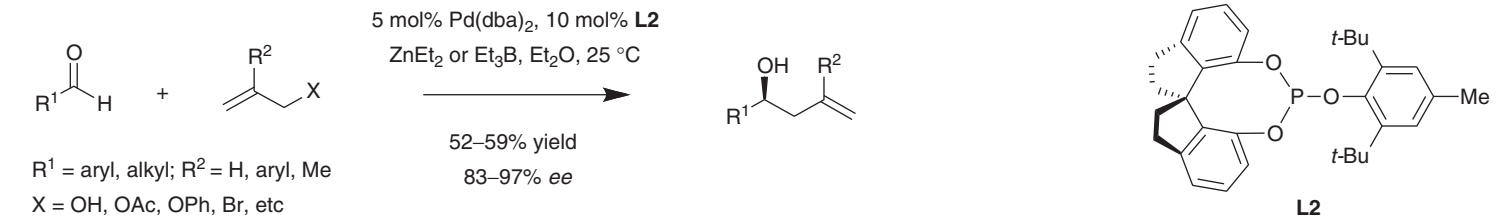
6.16.5 Concluding Remarks

As can be concluded from the material in this chapter, allylic transpositions can be accomplished by a multitude of methods under an astonishing variety of mechanistic regimes, some of which may be rather complex. Although our goal was to provide a broad picture of recent advances in allylic transpositions, many were not included, especially reductive processes forming a carbon–hydrogen bond and isomerizations of unsubstituted allylic or propargyllic systems. It is clear, however, that the unique features of the allylic system that has fostered reaction development during the past many decades will continue to promote the development of new methods in the future.

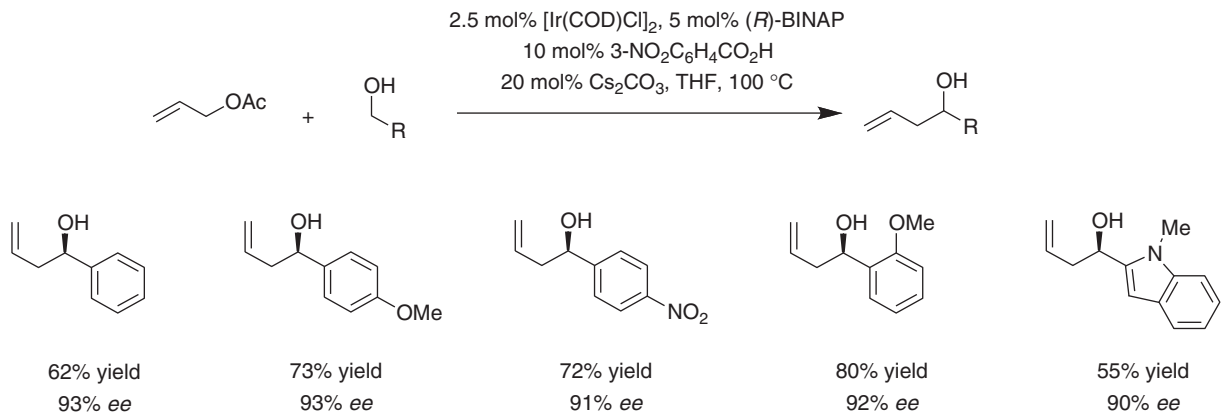

10 mol% Pd(OAc)2, 40 mol% n-Bu3P
3.6 equivalents ZnEt2, toluene, 23 °C, 6 h
Ph
CHO
+
Ph
OAc
OH
Ph
Ph
73% yield
syn:anti 1:5


10 mol% Pd(OAc)2, 40 mol% n-Bu3P
3.6 equivalents ZnEt2, toluene, 23 °C, 6 h
O
O
OH
OH
97% yield
syn:anti = 1:2

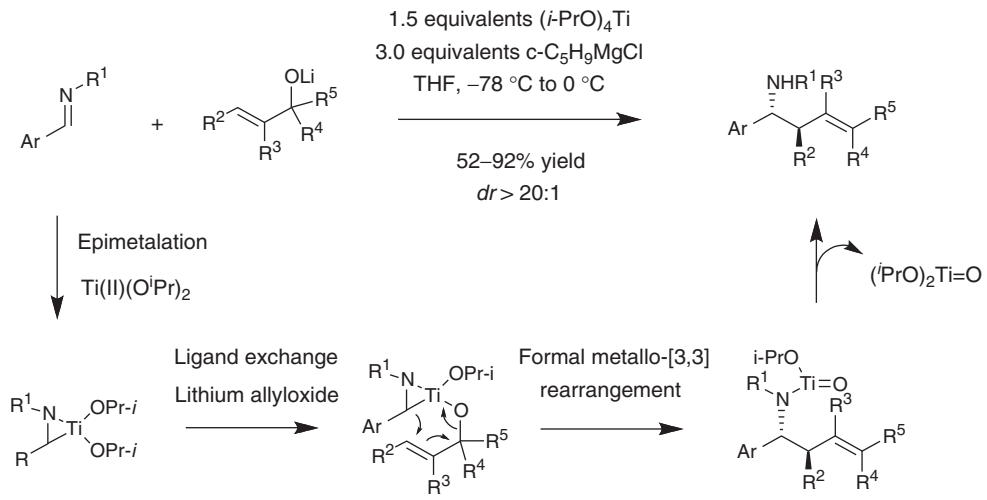

2.5 mol% [(η3-allyl)PdCl]2, 10 mol% L1
5 equivalents ZnEt2, THF, –30 °C, 24 h
Ph
OAc
+
CHO
OH
Ph
Ph
70% yield
70% ee
P—Ph
L1


5 mol% Pd(dba)2, 10 mol% L2
ZnEt2 or Et3B, Et2O, 25 °C
O
R1
H
+
R2
X
OH
R2
R1
52–59% yield
83–97% ee
R1 = aryl, alkyl; R2 = H, aryl, Me
X = OH, OAc, OPh, Br, etc
t-Bu
O
P
O
Me
O
t-Bu
L2

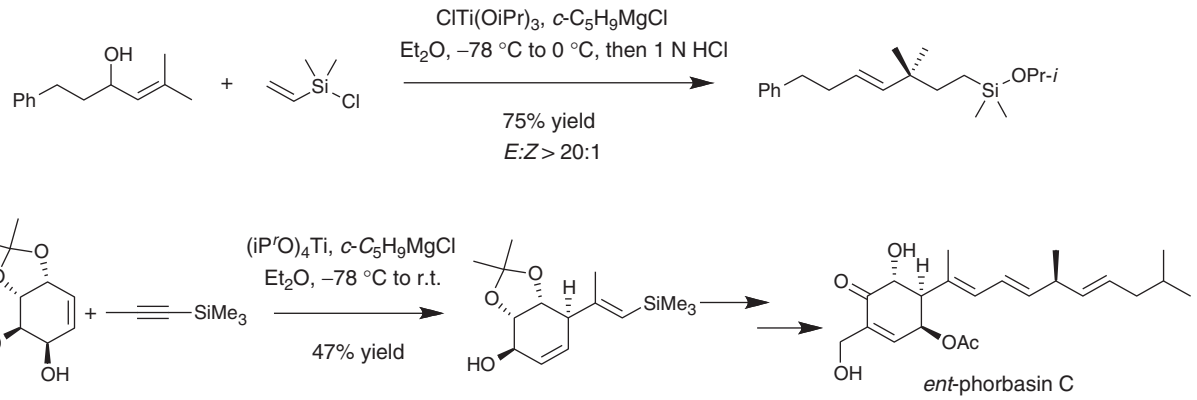
Scheme 167



Scheme 168



Scheme 169



Scheme 170

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6.17 Polonovski- and Pummerer-type Reactions and the Nef Reaction

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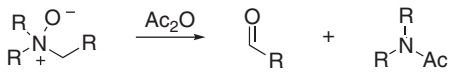
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This chapter is a revision of the previous edition chapter by David S. Grierson, Henri-Philippe Husson, Vol. 6, pp 909–947, © 1991, Elsevier Ltd.

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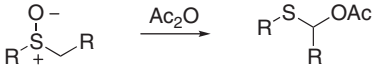
6.17.1 Introduction

As initially reported, the Polonovski, Pummerer, and Nef reactions all involve the transfer of oxidation from a heteroatom to the adjacent carbon.[1] In the Polonovski reaction, for example, an amine *N*-oxide reacts with acetic anhydride to give an aldehyde and an acetamide (equation 1).[2] The key intermediate in this reaction is a nitrogen-stabilized carbocation (iminium ion), and a rich body of research has featured Polonovski-initiated iminium ion cascades. Depending on the substrate and conditions used to effect the Polonovski reaction, a variety of alternative products are seen, ranging from Grob-like fragmentations to iminium ion additions. Alternative reaction conditions, particularly those that use different reagents, such as silylating and selenating reagents to activate the *N*-oxide oxygen, have broadened the scope and increased the selectivity of the reaction.



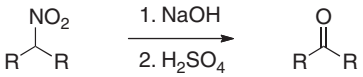
(1)

The Pummerer reaction involves a sulfoxide with acetic anhydride to give α-acetoxy sulfides (equation 2). The range of conditions under which Pummerer-like reactions occur has grown significantly in recent years, and the reaction has been applied to the synthesis of a broad range of structures, particularly heterocycles. Like the Polonovski reaction, the intermediacy of a heteroatom-stabilized carbocation (in this case, a thionium ion) opens the reaction to a wide range of Pummerer-initiated reaction sequences, from fragmentation reactions to thionium ion additions. In comparison with the Polonovski reaction, a wider range of methods are used to generate the stabilized carbocation Pummerer reaction intermediate, some starting from sulfides rather than sulfoxides, and thus the definition of the Pummerer reaction has expanded accordingly.



(2)

Although Nef reported several foundational reactions, such as the reaction of alkyne anions with aldehydes or ketones and the reaction of acyl chlorides with isocyanides, this chapter focuses on the reaction of nitroalkanes to afford carbonyl compounds (equation 3).[3] Under classic conditions, the reaction sequentially subjects a nitroalkane to strongly basic and acid conditions. Accordingly, significant effort has been invested in developing milder conditions that expand the scope of the reaction, and the value of the reaction is demonstrated by the application of these milder conditions to a variety of synthetic intermediates.[4,5] The key intermediate for the Nef reaction is either the *aci* tautomer or the nitronate salt, and methods that either oxidize or reduce these intermediates seek to facilitate the hydrolysis to give the carbonyl products.



(3)

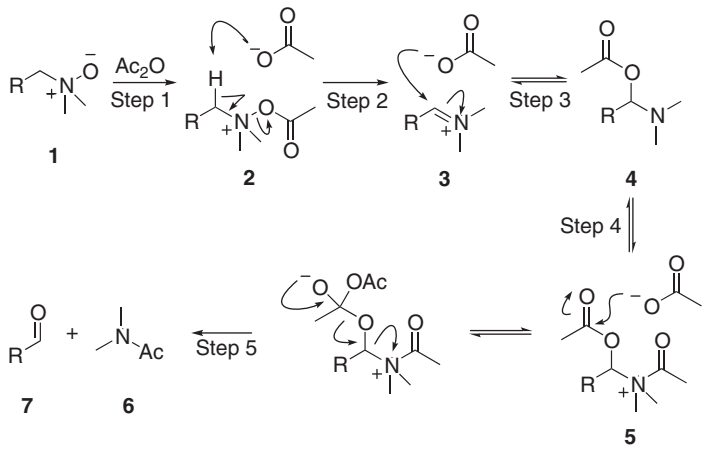
This chapter focuses on reported developments in each of the reactions that have appeared since the previous installment of this series.[1] In many cases, seminal work is referenced either to provide context for the new discoveries or to provide completeness to the coverage. In no cases is this chapter an exhaustive review of the reaction; rather, illustrative examples are used to provide a sense of the scope and limitation of each reaction.

6.17.2 The Polonovski Reaction

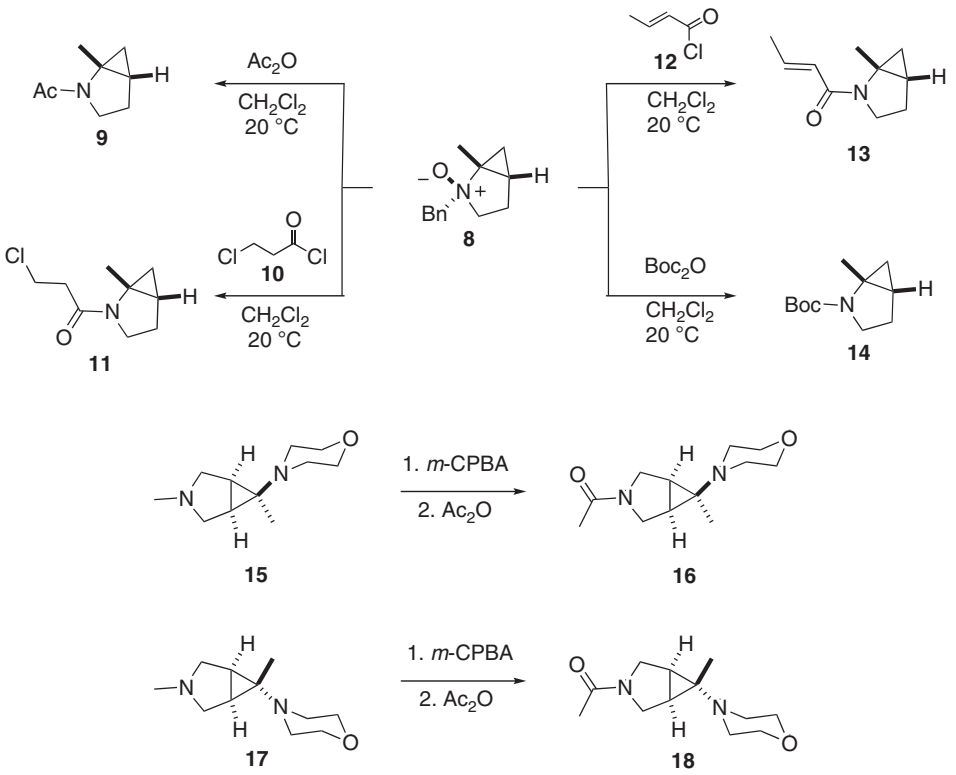
6.17.2.1 Mechanism

In principle, the classic Polonovski reaction can involve five elementary steps.[1,2] The initial step involves the activation of an amine *N*-oxide, **1**, with an electrophile, such as acetic anhydride, to give acyloxyammonium ion **2** (Scheme 1). Elimination of acetate ion provides iminium ion **3** to which the acetate ion adds, affording α-acyloxyamine **4**. Reaction of amine **4** with a second equivalent of anhydride produces a second ammonium ion, **5**. Finally, acetate-initiated fragmentation furnishes acetamide **6** and aldehyde **7**. The course of the reaction depends on the specific conditions and the substrate structure. For example, the second step involving proton removal and cleavage of the N–O bond often occurs through an asynchronous concerted E2 mechanism, although evidence for a more stepwise $E1_{cb}$ mechanism exists. The $E1_{cb}$ mechanism is observed when an electron-withdrawing group facilitates deprotonation (*vide infra*). Additionally, the equilibrium between **3** and **4** depends on the nucleofugacity of the leaving group, nucleophilicity of the counter ion, and the acidity of the solution. Accordingly, various methods have been developed to influence the reaction mechanism.

A variety of anhydrides and acid chlorides effect the Polonovski reaction. For example, the reaction of amine *N*-oxide **8** with acetic anhydride provided the expected acetamide **9** in 75% yield (Scheme 2).[6] Similarly, exposing **8** to acid chloride **10** produced **11** in 88% yield, and the reaction with acid chloride **12** afforded **13** in 68% yield. Dicarbonates also initiate the Polonovski reaction. For example, Boc_2O reacted with **8** to give **14** in 97% yield. Similarly, diamine **15** was reacted with *m*-CPBA followed by



Scheme 1

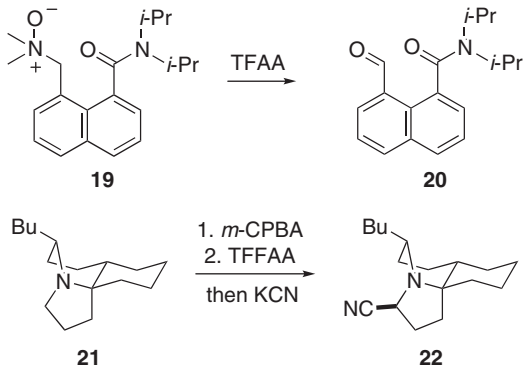


Scheme 2

Ac_2O to give **16** in 63% yield, and diamine **17** gave **18** in 63% yield under similar conditions.[7] It should be noted that analogous piperidine derivatives failed to provide the corresponding amides, probably because of the increased strain associated with the intermediate exocyclic iminium ion.[8]

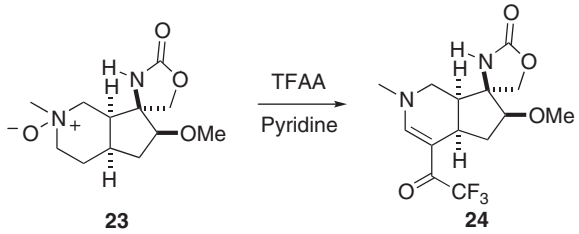
In contrast, Potier's use of trifluoroacetic anhydride (TFAA) to initiate the Polonovski reaction favors the iminium ion,[9] and this links the chemistry of amine *N*-oxides to the rich chemistry of iminium ions. Consequently, the Polonovski–Potier reaction has seen significant use in the synthesis of nitrogen-containing molecules.

Other common variants involve diversion of a reactive intermediate to other reaction paths. Exposure of **19** to Polonovski–Potier conditions, for example, afforded aldehyde **20** after an aqueous workup, although only in 40% yield (**Scheme 3**).[10,11] In a synthetic route to lepodiformines A and B, amine **21** was oxidized by the action of *m*-CPBA and the crude *N*-oxide was reacted with TFAA followed by KCN to provide aminonitrile **22** in 85% yield.[12]



Scheme 3

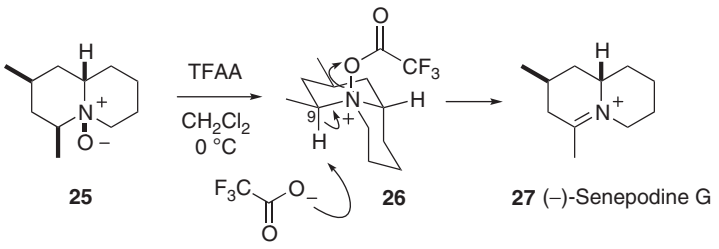
Addition of a base to the reaction mixture can promote deprotonation of the intermediate iminium ion, producing enamines. When strong acylating agents are used in conjunction with the base, the enamine can further react to produce vinylogous amides. Reaction of *N*-oxide **23** with TFAA in the presence of pyridine produced vinylogous amide **24** in 65% yield (equation 4).[13]



(4)

6.17.2.2 Regio- and Stereoselectivity

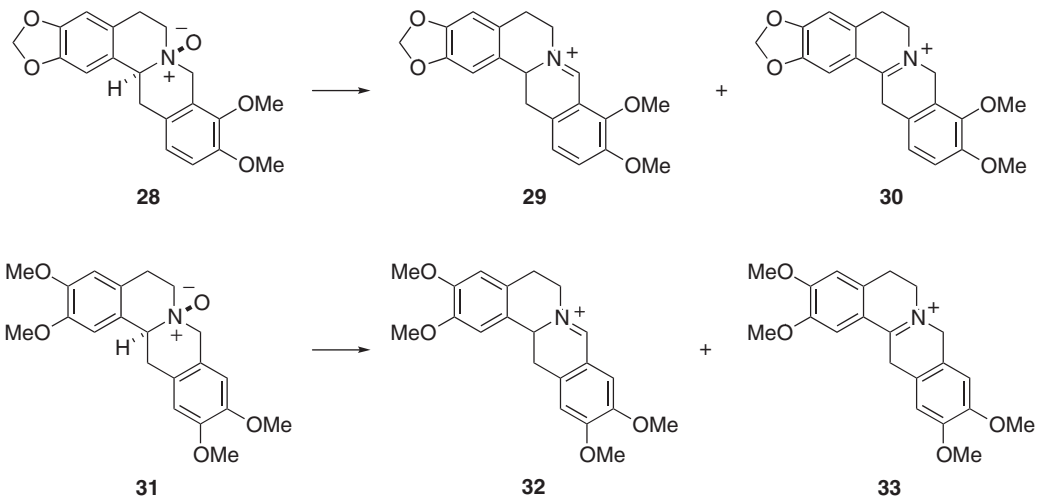
The regio- and stereoselectivity of the Polonovski reaction are highly dependent on reaction conditions and substrate structure. An E2 mechanism for the second step dictates an *anti*-periplaner relationship between the leaving group and the hydrogen being removed, and this preference is typically observed in simple aliphatic systems. In the synthesis of (−)-senepodine G, amine *N*-oxide **25** reacted with TFAA in CH_2Cl_2 at 0 °C to give acyloxyammonium ion **26** (Scheme 4).[14] The structural rigidity of the *trans*-decalin system allows only the C9 hydrogen to be *anti*-periplanar to the acyloxy-leaving group. Accordingly, removal of the C9 hydrogen with concomitant loss of trifluoroacetate gave (−)-senepodine G, **27**, in quantitative yield. No regioisomeric iminium ions were generated, suggesting an antielimination.



Scheme 4

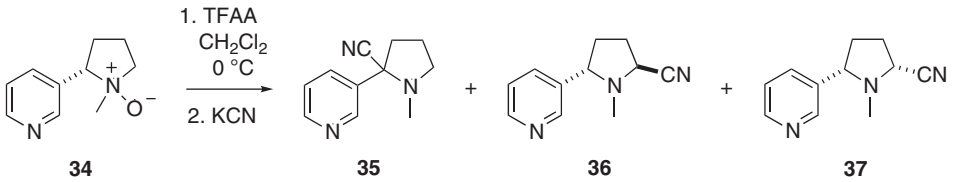
The regiochemistry typically depends on the anhydride used; TFAA produces both a strong nucleofuge, facilitating N–O bond cleavage, and a weak base, inhibiting the C–H bond breaking; this leads to more of an E1-like transition state that favors formation of the more thermodynamically stabile iminium ion. Even under these conditions, an *anti*-stereochemistry still appears to be preferred, as supported by the isolation of **27**. In comparison, acetic anhydride produces a poorer leaving group and a better base, enhancing the relative degree of C–H bond cleavage and promoting a more $E1_{cb}$-like transition state. As the strength of the base that abstracts the proton increases, the kinetic acidity of the proton being removed becomes more important.[15] When *N*-oxide **28** was allowed to react with TFAA in $CHCl_3$, a 37:63 mixture of iminium ions **29** and **30** was observed by nuclear magnetic resonance (Scheme 5).[16] The use of acetyl chloride to initiate the Polonovski reaction produced a similar 39:61 mixture of **29**:**30**. Although there are *anti*-oriented protons on all three carbons alpha to the amine, only the benzylic protons participated in the

reaction. The use of mesyl chloride to effect the reaction resulted in a reversal of selectivity, providing a 58:32 mixture of **29**:**30**. In this case, it was suggested that an intramolecular *syn*-elimination pathway may operate to increase the yield of **29**. Alternatively, *N*-oxide **31**, wherein the aromatic substitution pattern is altered, reacted with TFAA to provide a 64:36 mixture of **32**:**33**, a reversal of regiochemistry, and reaction with acetyl chloride produced a 50:50 mixture.



Scheme 5

As mentioned above, the use of TFAA to promote the Polonovski reaction gives a product distribution that suggests that the weakly basic trifluoroacetate ion promotes formation of the more stable iminium ion, further complicating the mechanistic picture. For example, exposure of a diastereomeric mixture of nicotine *N*-oxides **34** to TFAA in CH_2Cl_2 at 0 °C followed by the addition of KCN produced **35** in 58% yield, **36** in 8% yield, and **37** in 4% yield (Scheme 6).[17] Although the stereochemistry of the *N*-oxide is not well characterized, it would appear that a strict antirelationship between the leaving group and the α-hydrogen is not required under these conditions. In contrast, reaction of **34** with Ac_2O provided the *N*-demethylated acetamide.[18] The different regiochemical outcomes while using different acylating agents highlight the interplay of kinetic acidity, which favors the least substituted carbon in this case and iminium ion stability.

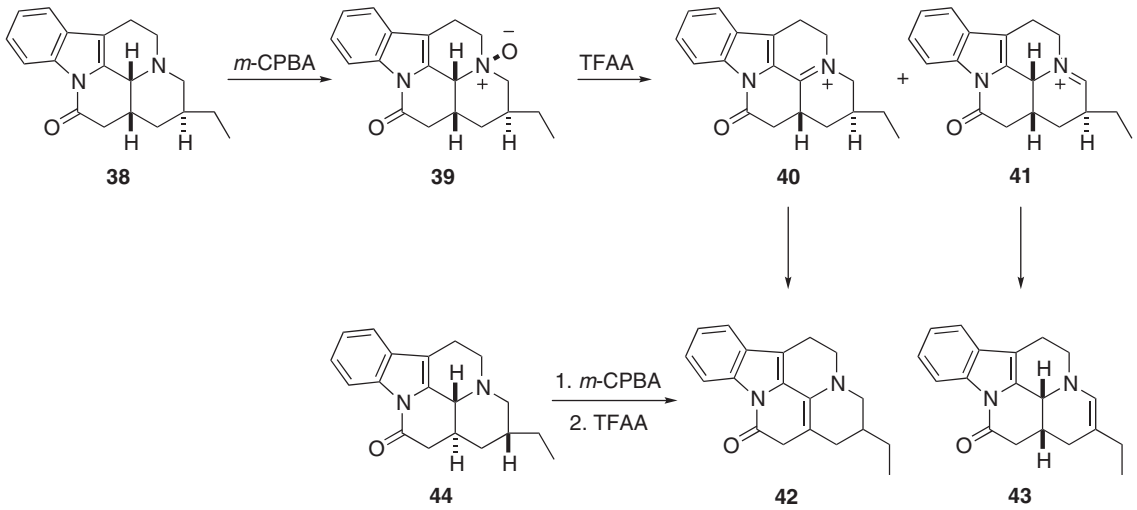


Scheme 6

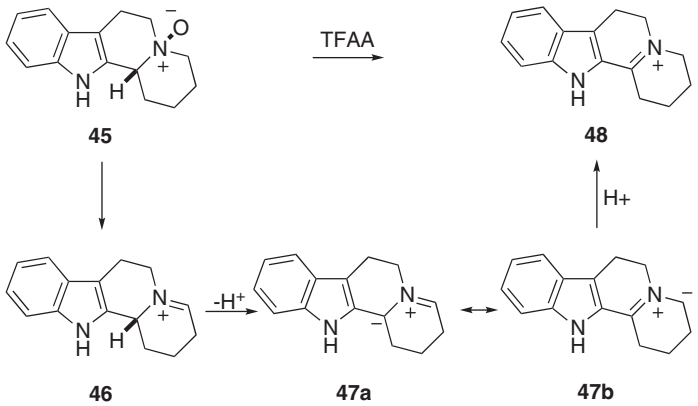
Another example that seems to contradict the strict stereochemical requirements of an E2 mechanism involves the reaction of quinoline and indoloquinoline systems. Reaction of **38** with *m*-CPBA furnished *N*-oxide **39** as a single diastereomer (Scheme 7).[19–21] Although the stereochemistry of the amine *N*-oxide **39** was not proven, the geometry of the molecule suggests the stereochemistry shown. Exposure of the crude oxide to the action of TFAA in CH_2Cl_2 at room temperature produced a 1:3 mixture of iminium ions **40** and **41**, and enamine **43** was isolated in 52% yield. Subjection of amine **44** to the same conditions produced enamine **42** as the only isolable product in 70% yield.

The generation of iminium ion **40** from amine **38** suggests that the antielimination requirement is somewhat relaxed for benzylic hydrogens. Even in more clearly defined systems, such as **45** (Scheme 8), the product distribution of the Polonovski reaction is complex,[22] indicating that the *anti*-periplanar relationship between the leaving trifluoroacetate and the hydrogen is not an absolute requirement. In this case, iminium ion **48** is observed. Several mechanistic explanations have been suggested to account for the observed products:[2] first, the influence of the adjacent aromatic system guides the reaction through more of an $E1_{cb}$ pathway; second, the increased acidity of the benzylic hydrogen allows for epimerization before elimination; and third, initial antielimination produces an iminium ion that is subsequently isomerized to the more thermodynamically stable iminium ion. The latter mechanism invokes the loss of a proton from the initially produced iminium ion **46**, affording 1,3-dipole **47**. Reprotonation provides the more stable iminium ion **48**.

The importance of the iminium ion stability in the Polonovski–Potier reaction is further demonstrated by the different regiochemical courses observed in the reaction of vincadifformine-derived **49** and tabersonine-derived **51** (Scheme 9).[23] Exposure



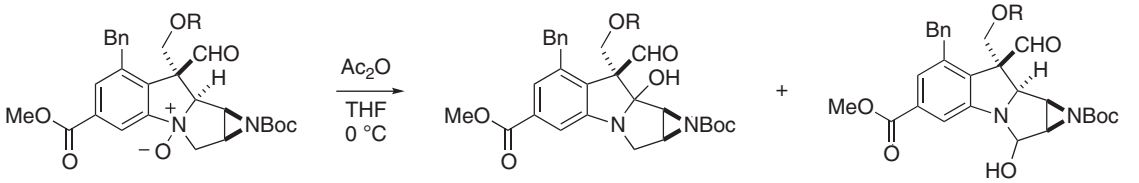
Scheme 7



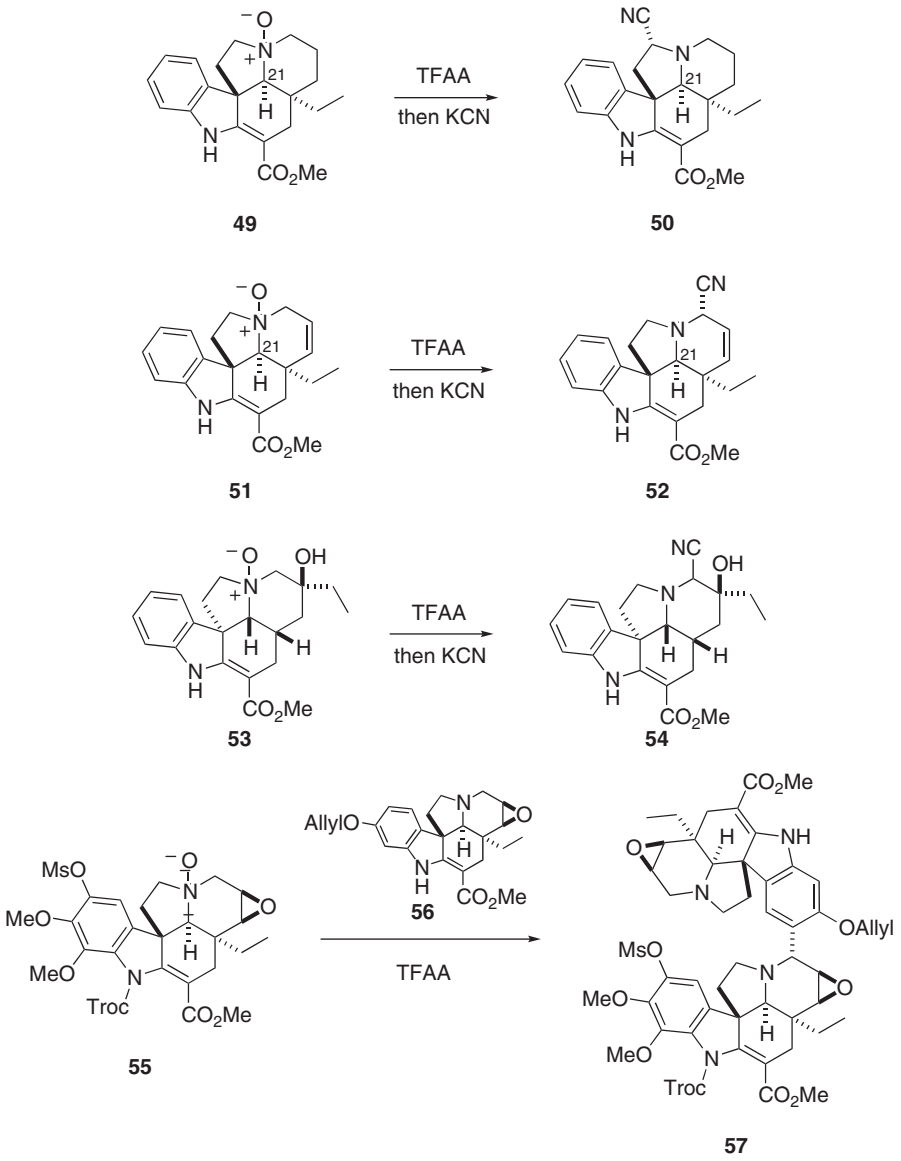
Scheme 8

of **49** to the action of TFAA followed by an aqueous solution of KCN produced **50** in 50% yield. In contrast, subjection of **51** to the same sequence of reactions afforded **52** in 60% yield. In neither case was a C21 elimination product observed, although its presence could not be definitively excluded. Similar to the reaction path observed for **51**, the presence of the hydroxyl group in **53** also affects the regiochemical outcome, providing **54** under the same conditions, although only in 30% yield. The reaction of epoxide **55** with TFAA in the presence of **56** produced the dimerization product **57** in 50% yield.[24]

Intramolecular interactions can also influence the regioselectivity of the reaction. For example, reaction of *tert*-butyldimethylsilyl (TBS)-protected **58a** with Ac_2O in tetrahydrofuran (THF) at 0 °C produced a 1:1.6 mixture of **59a** and **60a** in 64% combined yield (equation 5).[25] Initially, the regiochemical outcome was interpreted to arise from a steric interaction in which the large silyl group slowed down the expected removal of the bridgehead proton. Reaction of **58b**, with a smaller acetate-protecting group, reversed the selectivity and produced a 7.4:1 mixture of **59b** and **60b** in 67% combined yield. Subjecting **58c**, bearing a benzyl carbonate-protecting group, to the same Polonovski conditions furnished a 13:1 mixture of **59c** and **60c** in 68% combined yield. This result suggests that the deprotonation is not simply controlled by steric effects, but rather that the carbonyl of the protecting group, being on the same face of the molecule as the bridgehead proton, acts as an internal base, albeit through a seven-membered ring transition state.

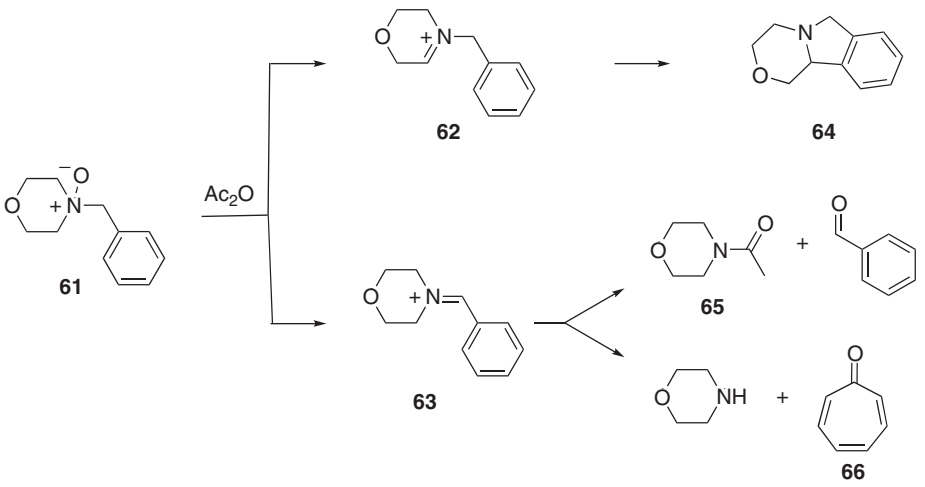


(5)



Scheme 9

Temperature can also have a profound impact on product distribution. *N*-benzyl morpholine *N*-oxide, **61**, reacted with Ac_2O in CH_2Cl_2 at 0 °C to give only 30% yield of the expected acetamide **65** and benzaldehyde (Scheme 10).[26] Isoindole **64** was isolated in approximately 20% yield, and an equimolar mixture of morpholine and **66** constituted the remaining 50% of material. The isoindole product arises from an endocyclic fragmentation that produces iminium ion **62**, and this iminium ion further reacts through a Pictet–Spengler mechanism to give **64**. The other products come from an exocyclic fragmentation that forms iminium ion **63**, which continues to give the expected Polonovski products **65** and benzaldehyde. Alternatively, benzylic iminium ion **63** can rearrange to the more stable tropylium ion that is subsequently hydrolyzed to provide morpholine and **66**. As the temperature of the reaction was raised, the amount of isoindole **64** was increased, making up 50% of the reaction mixture at 55 °C, whereas the ratio of **65** to **66** remained constant (2:3). These results indicate that the regiochemical outcome of the iminium ion formation depends on the reaction temperature, whereas the fate of each iminium ion is less sensitive to temperature. Use of TFAA completely suppressed the formation of **65** and benzaldehyde in favor of **66** and morpholine, reflecting the lower nucleophilicity of trifluoroacetate anion, although the ratio of **64**:**66** reflects the same temperature dependence as for the formation of **62** and **63**. This temperature-dependent shift in iminium ion distribution was explained in terms of conformational dynamics that are enhanced at elevated temperatures.

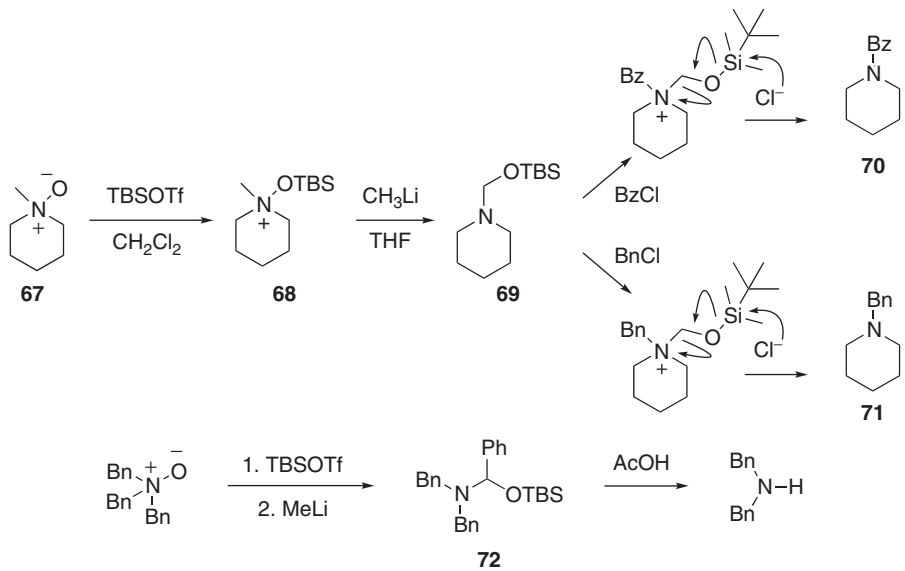


Scheme 10

6.17.2.3 Nonclassical Conditions

6.17.2.3.1 Silicon- and selenium-promoted reactions

Although amine *N*-oxides react with silylating agents, the resulting siloxyammonium ions are comparatively stable. The reaction of **67** with TBSOTf in CH_2Cl_2 at 0 °C produced intermediate ammonium ion **68** (Scheme 11).[27] Although **68** failed to react with a variety of the amine bases used to promote the Polonovski rearrangement (iPr_2NEt, DBU, etc.), MeLi promoted the formation of *α*-silyloxyamine **69**. Reaction of **69** with benzoyl chloride afforded benzamide **70** in 76% yield from **67**. With respect to the formation of silyloxyammonium intermediates, TBSOTf was more effective than either trimethylsilyl triflate (TMSOTf) or trimethylsilyl chloride. Other alkyllithium bases effectively promoted the rearrangement of **68**, whereas amide and alkoxide bases were less effective. Decomposition of the *α*-silyloxyamine could also be accomplished by reaction with an alkyl halide, producing 'transalkylated' tertiary amines, or protic acids, giving secondary amines. If **69** were reacted with benzyl chloride rather than benzoyl chloride, *N*-benzylpiperidine, **71**, was isolated in 58% yield. Alternatively, sequentiual exposure of tribenzylamine oxide to TBSOTf, MeLi, and then to acetic acid gave dibenzylamine in 67% yield.

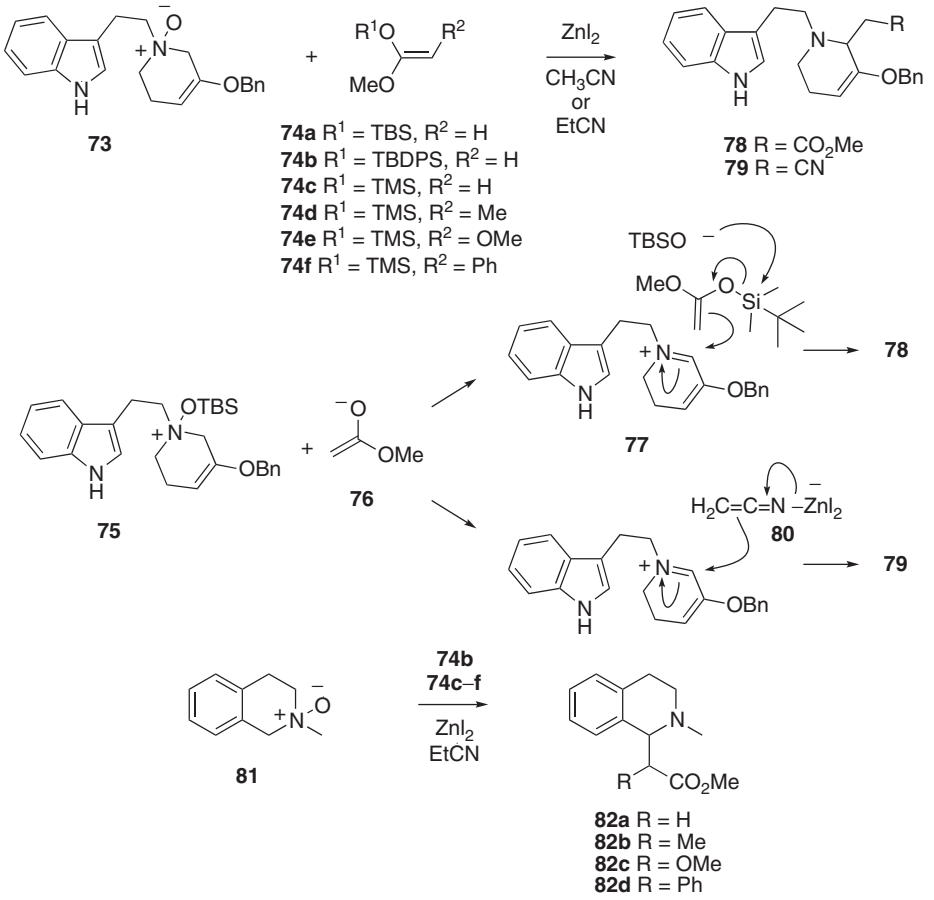


Scheme 11

The selenium Polonovski reaction follows a similar course but under milder base conditions. The sequential reaction of **67** with PhSeOTf, Et_3N, and benzoyl chloride produced **70** in 61% yield.[28] Using DBU to promote the rearrangement was also effective.

Catalytic amounts of ZnI_2 mediate the Polonovski-like reaction between silylketene acetals and amine oxides.[29] In this case, the silyl moiety of the acetal has a dramatic effect on the course of the reaction. For example, reaction of **73** with excess **74a** in the

presence of ZnI_2 and CH_3CN produced *O*-siloxyammonium ion **75** (Scheme 12). Enolate **76**, produced during the silyl transfer, abstracts a proton to give iminium ion **77**. A second equivalent of **74a**, activated by silyloxide, adds to this imimium ion, affording **78** in 66% yield and a small amount of **79** (7%), which arises from the ZnI_2 activation of solvent. Accordingly, silyloxide removes a proton from CH_3CN to give **80**, which adds to the iminium ion. Supporting this mechanism, silyl ketene acetal **74b** reacts with **73** under similar conditions to provide only **79** in 54% yield. In this case, the silane is too sterically hindered to allow activation by the silyloxide. Ketene acetal **74c** failed to initiate the Polonovski-like reaction, and the formation of **79** was suppressed in propionitrile. That **74b** only reacts to activate the amine oxide provides the opportunity to react a variety of nucleophiles with the intermediate iminium ion. The reaction of **81** with **74b** as an initiator and nucleophiles **74c–f** in the presence of ZnI_2 and EtCN provided **82a–d** in 66–72% yield.

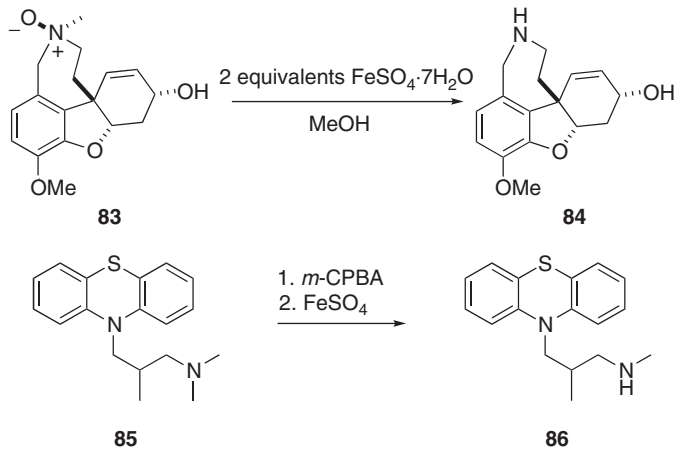


Scheme 12

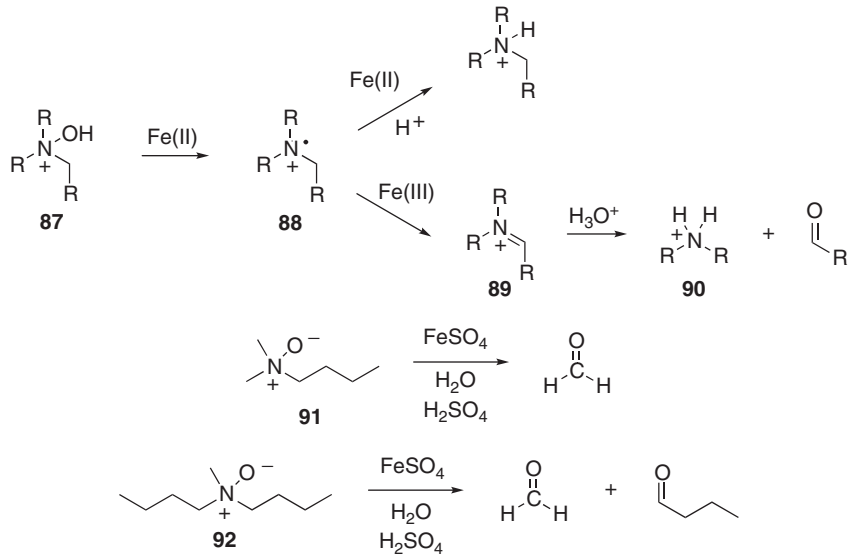
6.17.2.3.2 Iron-mediated reactions

Iron(II) salts undergo redox chemistry in the presence of amine oxides, giving iminium ion intermediates. As opposed to classical Polonovski conditions, iron-promoted reactions tend to be particularly sensitive to the kinetic acidity of the protons adjacent to the nitrogen, making the iron-mediated Polonovski selective for oxidation of methyl carbons in *N*-methyl amine oxides. For example, the reaction of galanthamine *N*-oxide (**83**) with 2 equivalents $FeSO_4 \cdot 7H_2O$ in MeOH at room temperature provided norgalanthamine (**84**) in 76% yield (Scheme 13).[30] Significantly, no benzylic C–N bond cleavage was observed, a common pathway for electron-rich *N*-benzyl amines. Similarly, subjecting the *N*-oxide of the acyclic tertiary amine in cyamemazine (**85**) to similar conditions effected a demethylation, giving **86** in 70% yield.[31]

Under acidic conditions, the mechanism of this iron-mediated Polonovski is thought to involve the reaction of a protonated *N*-oxide, such as **87**, with $FeSO_4$ to give an Fe(III) salt and aminium ion **88** (Scheme 14).[32] Further reaction of **88** with excess Fe (II) salt results in the tertiary ammonium salt, a reduction of the *N*-oxide. Alternatively, reaction of **88** with Fe(III) produces an iminium ion **89**, which hydrolyzes to give secondary ammonium ion **90**. The regioselectivity in the iminium ion formation is correlated with the kinetic acidity of the proton adjacent to the nitrogen. When different protons of similar acidity are present, the statistical probability of α-proton removal also contributes to the observed product distribution. Butyldimethylamine oxide, **91**, produced formaldehyde as the carbonyl component; whereas dibutylmethylamine oxide, **92**, produced a 2:1 mixture of



Scheme 13



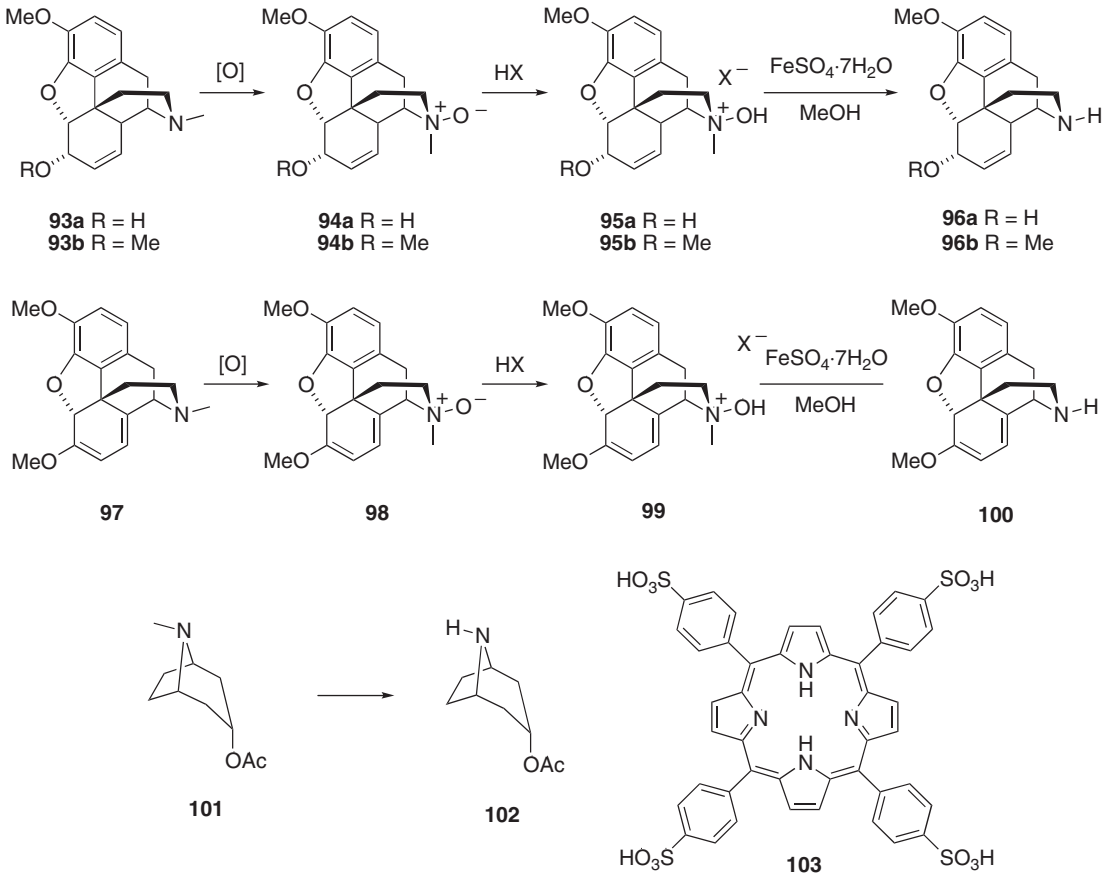
Scheme 14

formaldehyde and butyraldehyde. The product distribution also depends on the pH of the reaction media, with lower pH resulting in more formaldehyde formation.

In opiate alkaloid systems, the iron-mediated Polonovski has proven to be a reliable means of selectively removing *N*-methyl groups. Codeine (**93a**) and its methyl ether **93b**, for example, were converted into their corresponding *N*-oxides **94a,b** in quantitative yield, which were then reacted directly with a variety of Fe(II) salts to give the nor-opioid derivatives (Scheme 15).[33] Using $FeSO_4$ gave the best yields, returning 63% yield of **96a** and 80% yield of **96b**, with the remainder of the *N*-oxide being reduced to **93**. Subjection of thebaine (**97**) to the same conditions provided **100** in 38% yield.

Further investigation revealed that the reaction of the protonated *N*-oxides provided higher yields of nor-opioids, an observation that is consistent with the pH dependence found in other studies (vide supra). Reaction of **95b** (X=Cl), for example, with $FeSO_4$ produced **96b** in 87% yield, and **99** (X=Cl) provided **100** in 74% yield. The ratio of tertiary amine to secondary amine was also sensitive to the counterion of the *N*-oxide salts, with chloride and phthalate providing the best results, each giving a 4.6:1 mixture of **96b**:**93b**, whereas sulfate anion afforded 0.7:1 mixtures in which the tertiary amine predominated.[34]

One drawback to the iron-mediated demethylation reactions involves the removal of iron salts from the reaction mixture. Solutions of EDTA at pH=10 proved effective, although products with base-sensitive functional groups that coordinate strongly with iron could only be isolated in poor yield. Tropane-derived **101**, for example, reacted with 2 equivalents of $FeSO_4$ in MeOH followed by an aqueous EDTA workup to give **102** in only 10% yield. The use of porphorin **103** as an iron chelator in the workup, however, significantly improved the isolated yields. With this workup, **102** was isolated in 56% yield and **96a** was isolated in 78% yield. These results led to the development of the iron porphorin derived from **103**[35] and the use of catalytic amounts of

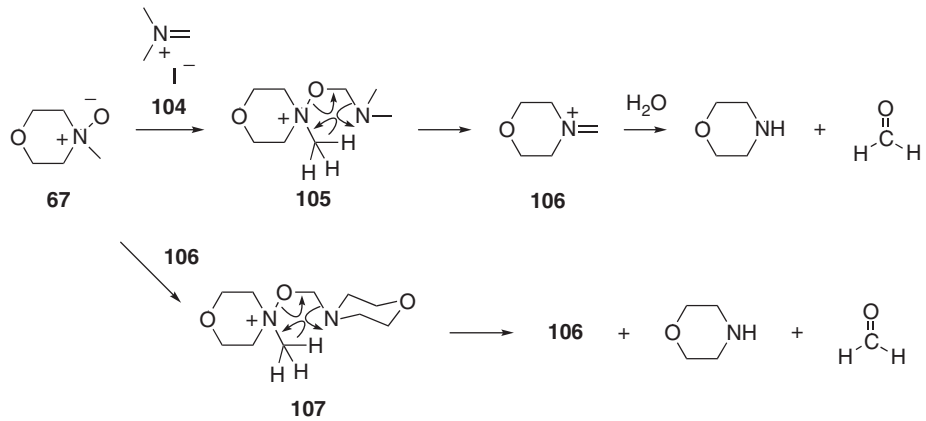


Scheme 15

ferrocene[36] in the iron-mediated demethylation reaction. Exposure of **95b** (X=Cl) to 0.25 equivalent of ferrocene in $CHCl_3$ at 50 °C afforded **96b** and **93b** in 92% and 8% yields, respectively. Iron powder and stainless steel also proved effective as catalysts.[37]

6.17.2.3.3 Iminium ion-induced reactions

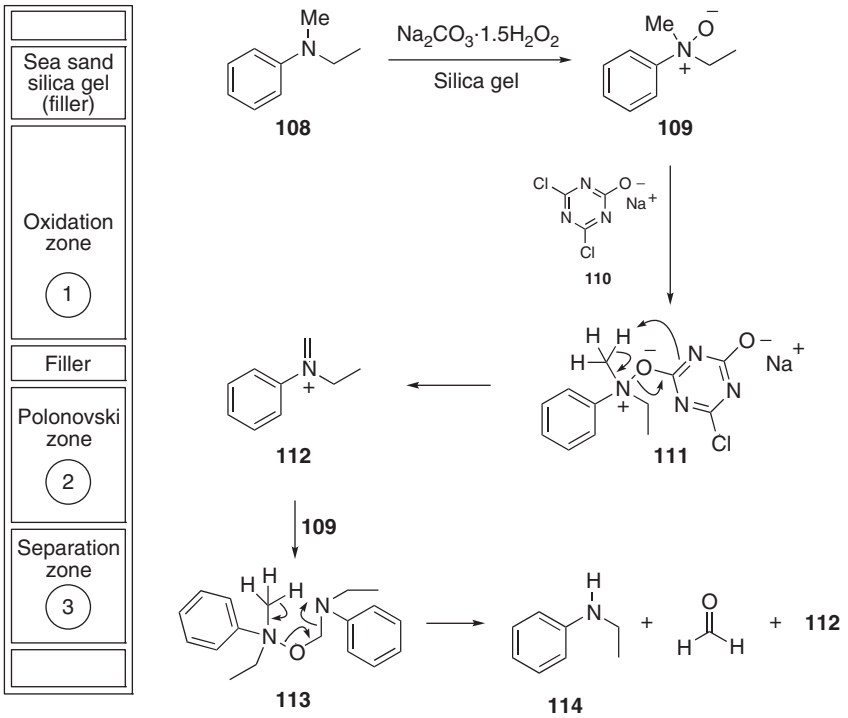
Another method for the selective demethylation of tertiary amines was discovered during an investigation of *N*-methylmorpholine *N*-oxide (NMO)(**67**) decomposition (Scheme 16).[38] The reaction of **67** with 1 mol% each of Eschenmoser's salt (**104**) and H_2O in CH_2Cl_2 afforded morpholine and formaldehyde. The mechanism presumably involves the reaction of the *N*-oxide with the iminium ion, producing salt **105**. Fragmentation then affords iminium salt **106**, which subsequently hydrolyzes to provide dimethylamine and formaldehyde. Increasing the amount of water inhibited the decomposition, as did the addition of acid.



Scheme 16

Addition of small amounts of base, however, increased the decomposition rate. All of these observations shaped the proposal of a second mechanism: It is also possible for iminium ion **106** to promote the further decomposition of **67**. This makes **104** an initiator in an autocatalytic process.

The elucidation of the autocatalytic degradation of **67** led to a solid-phase method for the selective demethylation of a wide variety of tertiary amines.[39] In this process (Scheme 17), amines are introduced to the head of a column containing three reaction zones. In the first zone, sodium percarbonate oxidizes an amine, such as **108**, to the corresponding *N*-oxide **109**. The second zone, containing 1.5 mol% triazine **110**, initiates the Polonovski reaction of **109**, with the bulk of the reaction following the autocatalytic mechanism to provide secondary amine **114**. Finally, the third zone exposes the reaction mixture to a 1:1 mixture of neutral and basic alumina to absorb formaldehyde and purify **114**. A variety of amines gave demethylated products in 89–98% yields, with only the desmethyl products being isolated. Primary and secondary amines were unreactive, so were alcohols.



Scheme 17

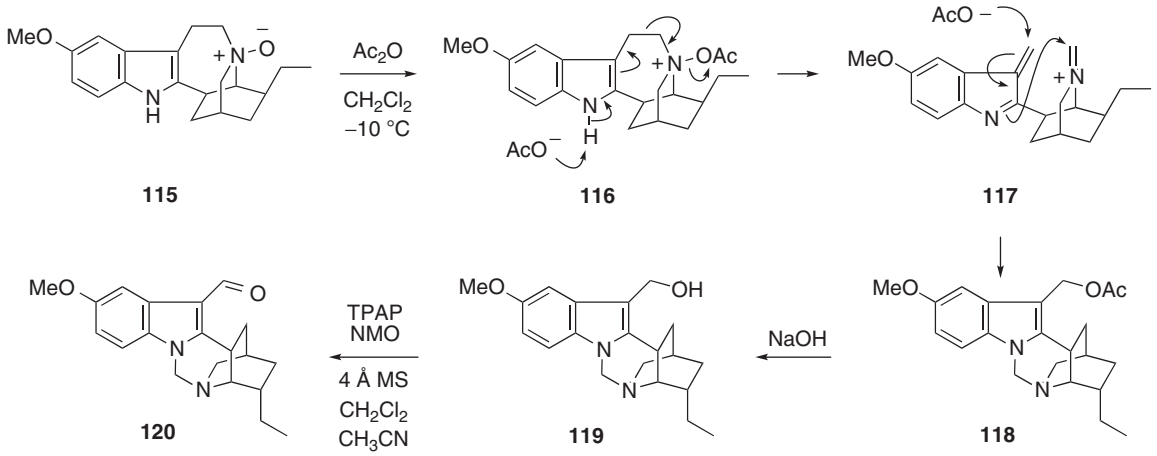
6.17.2.4 Other Reactions

6.17.2.4.1 Fragmentation reactions

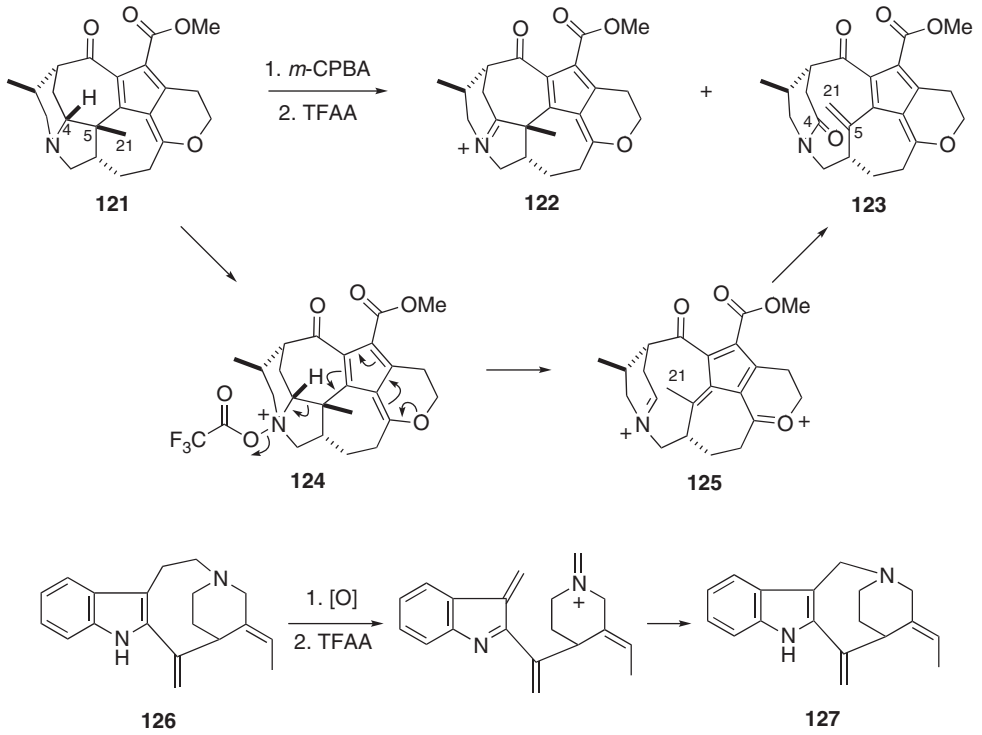
If a bond is *anti*-periplanar to the N–O bond and is also activated by an electron-donating group, a Grob-type fragmentation can occur under Polonovski conditions. These kinds of fragmentations have been leveraged in the biomimetic transformations of a variety of alkaloids. In a synthesis of lirofoline A (**120**), for example, ibogaine *N*-oxide (**115**) reacted with Ac_2O to give intermediate **116** (Scheme 18).[40] Nitrogen-assisted fragmentation of ammonium **116** produced iminium ion **117**. Acetate-initiated addition of the indole nitrogen to the iminium ion gave **118**, which was hydrolyzed to afford **119** in 70% yield from **115**. Oxidation of the alcohol under tetrapropylammonium perrhuthinate (TPAP)/NMO conditions gave lirofoline A.

In many cases, the Polonovski reaction serves to demonstrate a plausable biogenic pathway for the conversion of one natural product into another, rather than establishing an efficient synthetic route to a given alkaloid. For example, daphnicyclidin D (**121**) produced **122** in 37% yield and daphnicyclidin J (**123**) in 18% yield (Scheme 19).[41] In this case, the fragmentation giving **123** is facilitated by the somewhat remote oxygen, as shown in **124**, giving **125**, which loses a proton from the C21 methyl group. Presumably, air oxidation then gives **123**. Similarly, the *N*-oxide of pericine (**126**) was subjected to Polonovski–Potier conditions to give apparicine (**127**) in 26% yield through a fragmentation/*N*-demethylenation/recombination sequence similar to transformation of **116** into **118**.[42]

Although the *anti*-periplanar relationship between the fragmenting C–C bond and the N–O bond is considered a requirement for these fragmentations, it appears that a *syn*-periplanar relationship is also allowed. Sequential exposure of serratinine (**128**) to *m*-CPBA, TFAA, and $NaBH_3CN$ in CH_2Cl_2 at −20 °C produced serratezomine A (**129**) in 48% yield, along with the butanolide **130** in 27% yield (Scheme 20).[43] Higher temperatures favored the formation of **130**, and **129** could be converted into **130** by the action of *p*-TsOH. The fragmentation mechanism likely involves acid-catalyzed hemiketal formation within **131** to give **132**.



Scheme 18

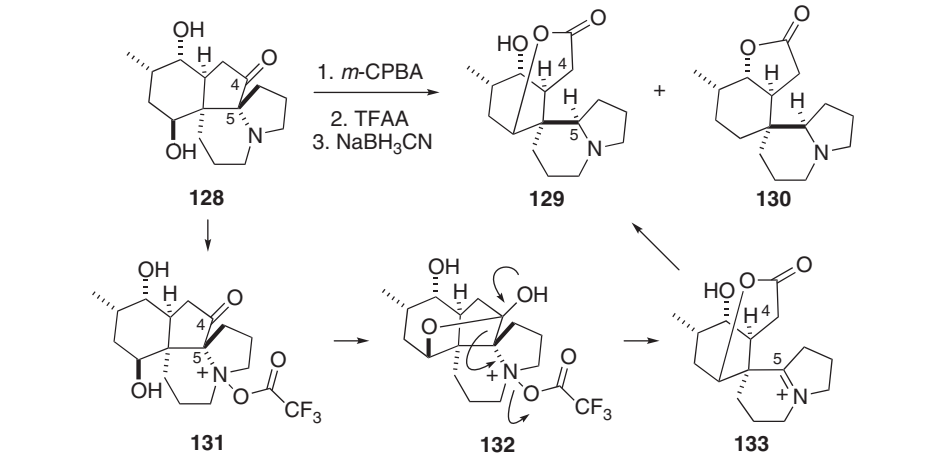


Scheme 19

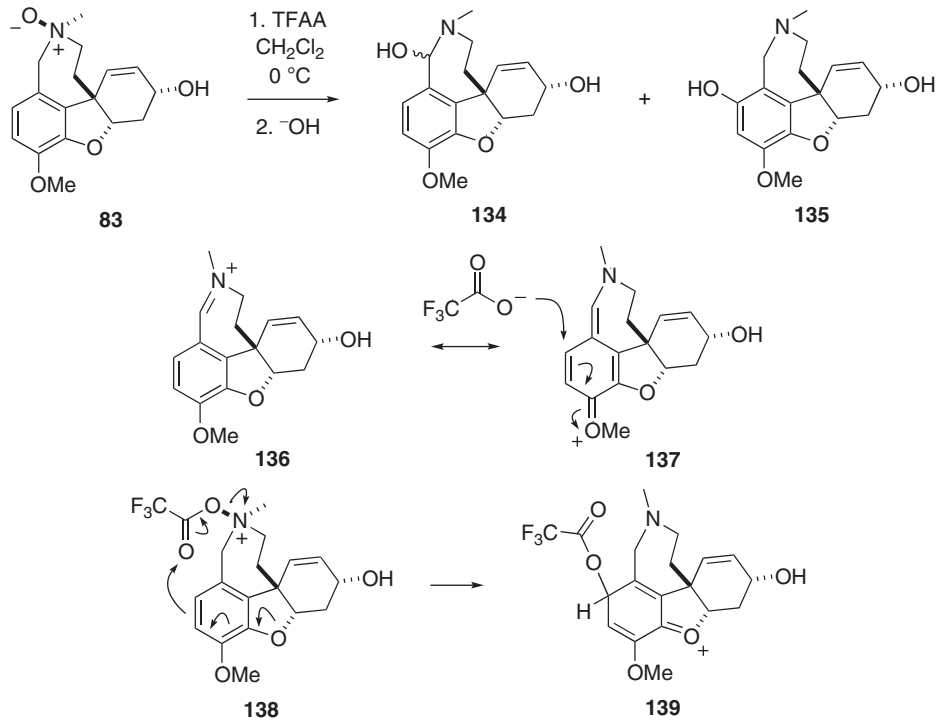
Oxygen-assisted rupture of the C–C bond in **132** gives iminium ion **133** that is reduced to furnish **129**. X-ray crystallographic data of **128** suggest that the *N*-oxide should form with the N–O bond *syn* to the C4–C5 bond, and the fragmentation would have to occur through a *syn*-periplanar geometry.

6.17.2.4.2 Remote functionalization

Although the Polonovski reaction typically serves to transfer the oxidation state from the nitrogen to the α-carbon, more remote centers can react under Polonovski conditions. For example, the reaction of galanthamine *N*-oxide, **83**, with TFAA followed by an aqueous base workup gave *N*-*O*-acetal **134** in 60% yield along with phenol **135** in 30% yield (Scheme 21).[44] Although **135** could arise from the trifluoroacetate ion adding to **137**, the quinonic resonance form of the intermediate iminium ion **136**, subjecting **134** to Polonovski–Potier conditions did not produce **135**. A mechanism wherein the carbonyl oxygen of the trifluoroacetate moiety of **138** participates in an electrophilic aromatic substitution to give **139** was proposed. Proton transfer to reestablish aromaticity and hydrolysis of the trifluoroacetate would then furnish **135**.



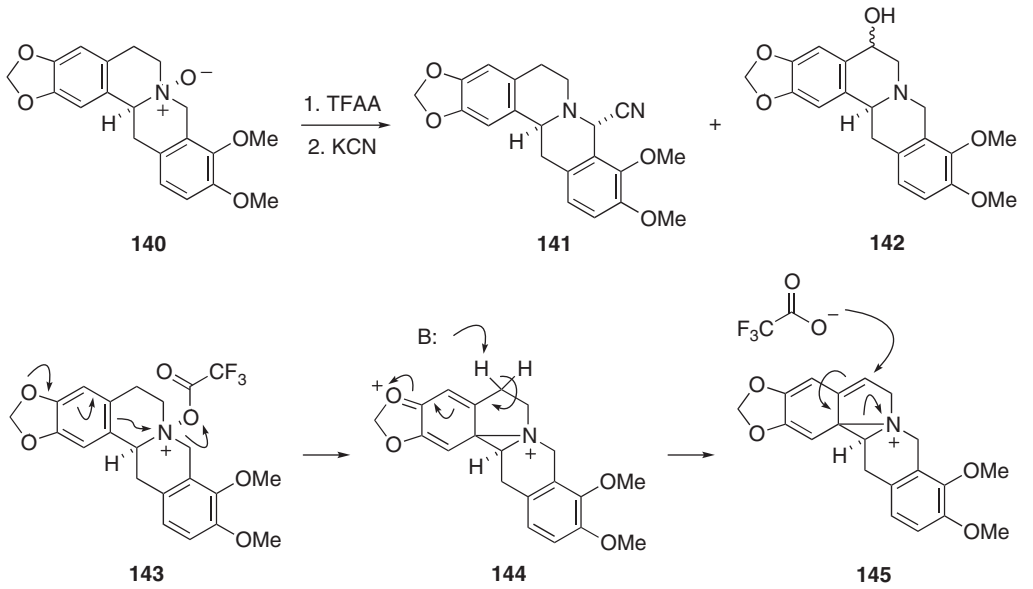
Scheme 20



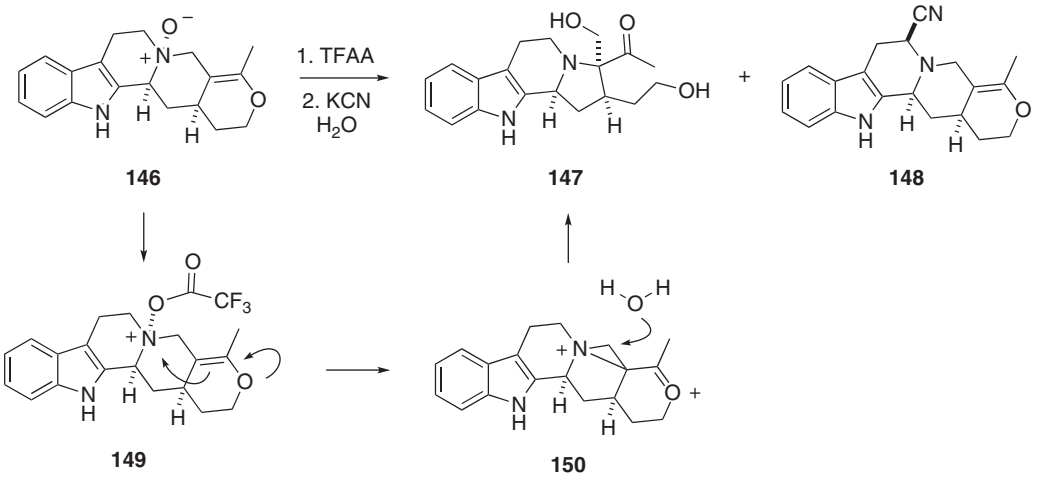
Scheme 21

Unlike *trans N*-oxide **28** (Scheme 5), the reaction of *cis N*-oxide **140** under Polonovski–Potier conditions was somewhat more complicated, producing **141** and **142** in 15% and 20% yields, respectively, after the addition of KCN and an aqueous base workup (Scheme 22).[16] In this case, anchimeric assistance by an oxygen lone pair facilitates the loss of trifluoroacetate from ammonium **143** to give aziridine **144**, and proton abstraction provides **145**. Addition of trifluoroacetate followed by hydrolysis under workup conditions furnishes **142**.

Similarly, amine *N*-oxide **146** reacted under conditions similar as those for **140** to give **147** in 25% yield, along with **148** in 22% yield (Scheme 23).[45] The regioselective formation of **148** can be explained by the rigid stereochemistry that puts only the thermodynamically least favored hydrogen *anti*-periplanar to the N–O bond. It should be noted that the *N*-Boc-protecting group on the indole nitrogen was selected to prevent the Grob-type fragmentation that is often seen in tryptamine derivatives (*cf* Schemes 18 and 19). The formation of **147** is explained by *O*-acyl ammonium **149** forming aziridinium ion **150** and water both opening the aziridinium and hydrolyzing the oxonium moiety to give **147**.



Scheme 22



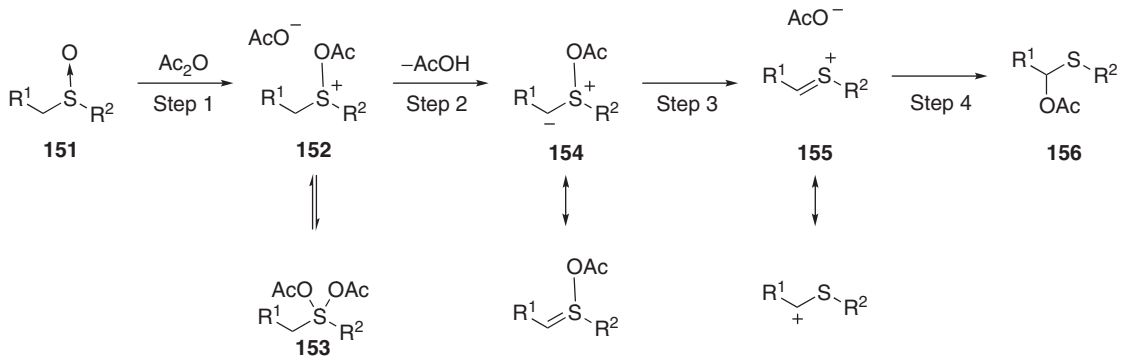
Scheme 23

6.17.3 The Pummerer Reaction

6.17.3.1 Mechanism, Regio- and Stereochemistry

The mechanism of the classic Pummerer reaction can involve four elementary steps as depicted in Scheme 24. In the first step, the oxygen of a sulfoxide, such as **151**, reacts with an electrophilic agent, such as acetic anhydride, to produce sulfonium salt **152**. Under classic conditions, the sulfonium salt **152** is in equilibrium with achiral sulfurane **153**. Loss of a proton from the α-carbon in **152** generates a sulphonium ylide **154**. Cleavage of the S–O bond in **154** produces a sulfur-stabilized carbocation **155**, a thionium ion, which can react with nucleophiles, such as the acetate counterion, producing **156**. This constitutes a formal oxidation of the α-carbon.[1,46–51] A considerable number of variants are known, and the application of Pummerer and related reactions has received considerable attention.[52–55]

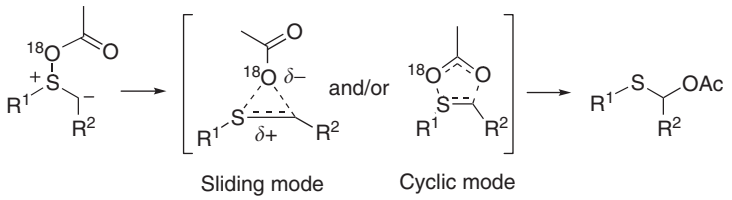
A variety of electrophiles are known to initiate the Pummerer reaction (*vide infra*). The exact mechanism depends on the structure of both the sulfoxide and the electrophile, and the rate-determining step can be any of the steps 1–3. Proton removal and cleavage of the S–O bond can be through either an asynchronous concerted E2 mechanism or a stepwise $E1_{cb}$ mechanism. The $E1_{cb}$ mechanism is observed when an electron-withdrawing group facilitates deprotonation. Although the scheme shows a stepwise mechanism to transform **154** into **156**, several mechanisms may be invoked: a tight ion pair;[56] a concerted 1,2-shift,



Scheme 24

either of which is necessary for asymmetric induction from chiral sulfoxides; or a solvent-separated ion pair. In reactions of aryl, alkyl, dialkyl, and cyclic sulfoxides with acetic anhydride, for example, deprotonation is rate determining, and the regioselectivity of the deprotonation is strongly influenced by the kinetic acidities of the α-protons. Steric interactions can also influence the regiochemical course of the reaction.[56]

Early attempts to effect asymmetric Pummerer reactions by activating optically active sulfoxides with acetic anhydride resulted in α-acyloxy sulfides with little transfer of chirality (<30% *ee*).[57] Two factors may contribute to the low enantioselectivity: First, significant reaction of the acetate counterion with the sulfonium ion **152** to generate achiral **153** may occur. Second, acetic acid generated during the reaction may facilitate the formation of a solvent-separated ion pair (i.e., **155**). Based on the results of ^{18}O-tracer studies, the mechanism of the 1,2-acetoxy migration can be intramolecular, involving a 'sliding' mode and/or a 'cyclic' mode of migration (Scheme 25). The addition of dicyclohexylcarbodiimide to the reaction mixture effectively trapped acetic acid, resulting in α-acyl sulfides with up to 70% *ee*, although in poor chemical yields.[58,59]



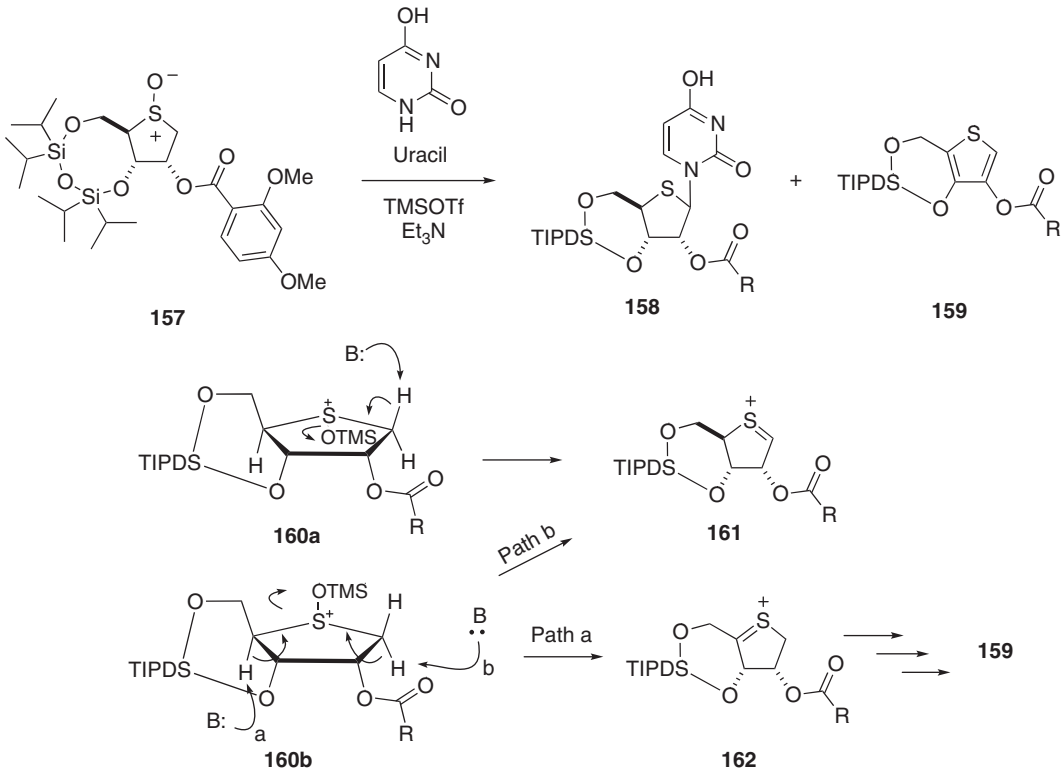
Scheme 25

6.17.3.2 Reaction of Thionium Ions with Nucleophiles

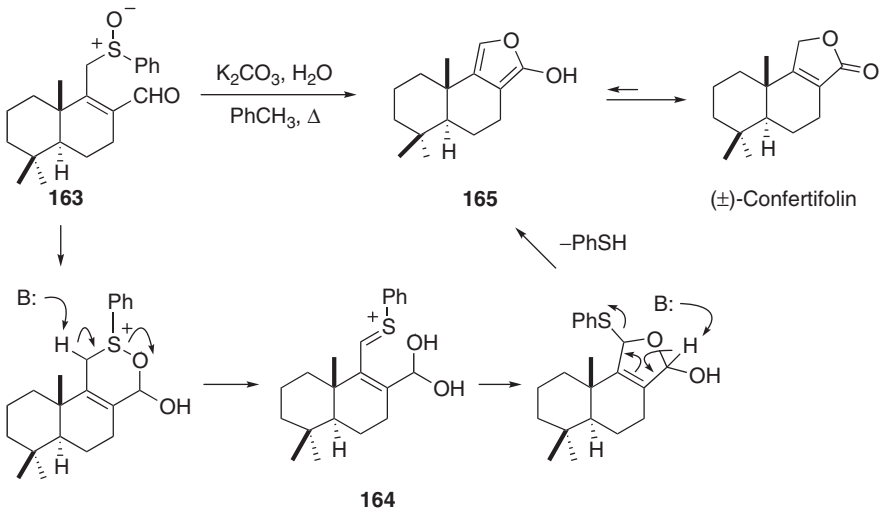
A variety of nucleophiles can react with the thionium ion (e.g., **155**), and Lewis or protic acids can make step 4 reversible, regenerating the reactive thionium ion from the α-acyloxy sulfide (e.g., **156**). Nucleobases, for example, add to thionium ions derived from furanose derivatives to form thionucleosides. Exposing sulfoxide **157**, having an *R*-configuration around the sulfur, to excess TMSOTf in the presence of uracil and excess Et_3N produced **158** in 87% yield (Scheme 26).[60] The diastereomer with an *S*-configuration, however, gave **158** in only 22% yield along with 22% of thiophene **159**. These differing results can be explained by a preference for E2 elimination in the S–O bond-breaking step. The *R*-sulfonium ion **160a** has only one proton *anti*-periplaner to the S–O bond, leading to thionium ion **161**. In contrast, the *S*-sulfonium **160b** can form either the desired thionium ion **161** or thionium ion **162**. The lower reactivity of **162** with the uracil nucleophile provides time for deprotonation/oxidation or decomposition.

Strategically positioned oxygens react with thionium ions to form furan derivatives[61] as demonstrated by the synthesis of (±)-confertifolin (Scheme 27).[62] In this particular instance, heating a toluene solution of allylic sulfoxide **163** with aqueous base initiated a Pummerer reaction, wherein the sulfoxide was activated by the proximal aldehyde to form the thionium ion **164**. The hydroxyl group of the resultant hydrated aldehyde then attacked the electrophilic carbon. Loss of thiophenol under the reaction conditions afforded 2-hydroxy furan **165**, which tautomerized to give (±)-confertifolin in good yield.

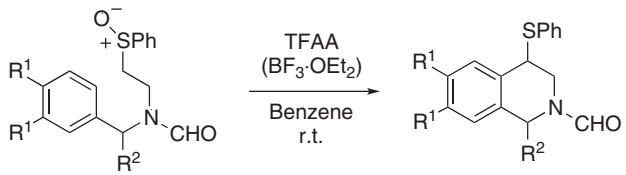
Variously substituted aromatic rings undergo electrophilic aromatic substitution reactions under Pummerer conditions. Subjecting **166a** to the action of TFAA in benzene at 25 °C furnished **167a** in quantitative yield (equation 6).[63] The addition of $BF_3{\cdot}OEt_2$ was necessary to effect the cyclization of substrates without activating groups on the aromatic rings. Accordingly, $BF_3{\cdot}OEt_2$ was added to the reaction mixture after **166b,c** and TFAA were heated in benzene for 1 h, affording **167b,c** in 94–97% yields. The choice of solvent was crucial: reaction of **166a** with TFAA in CH_2Cl_2 produced intractable mixtures, and the same reaction conducted in Et_2O or THF gave lower yields of **167a** (49% and 42%, respectively). The formamide functional group was also critical for the success of these reactions.



Scheme 26



Scheme 27

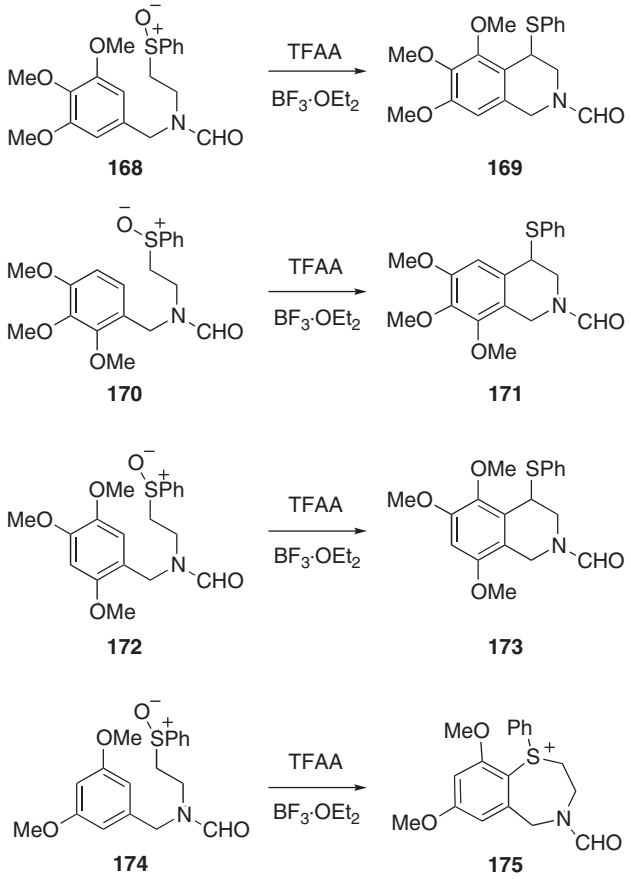


166a R^1 = OMe
166b R^1 = H
166c R^1 = Me

167a R^1 = OMe
167b R^1 = H
167c R^1 = Me

(6)

Electronic effects influence the course of the reaction. When a mixture of compound **168** and TFAA was exposed to $BF_3{\cdot}OEt_2$, tetrahydroisoquinoline **169** was produced in 76% yield (Scheme 28).[64] Similarly, when **170** was subjected to the same conditions, **171** was formed in 99% yield. These reactions do proceed without $BF_3{\cdot}OEt_2$, although the addition of this Lewis acid greatly enhanced the rate of the cyclization. In contrast, treatment of **172** with TFAA and $BF_3{\cdot}OEt_2$ produced **173** in low yields. Alternatively, when the dimethoxy-substituted aromatic **174** was treated with the TFAA/$BF_3{\cdot}OEt_2$ mixture, compound **175**, arising from an interrupted Pummerer reaction (*vide infra*), was isolated as the major product.



Scheme 28

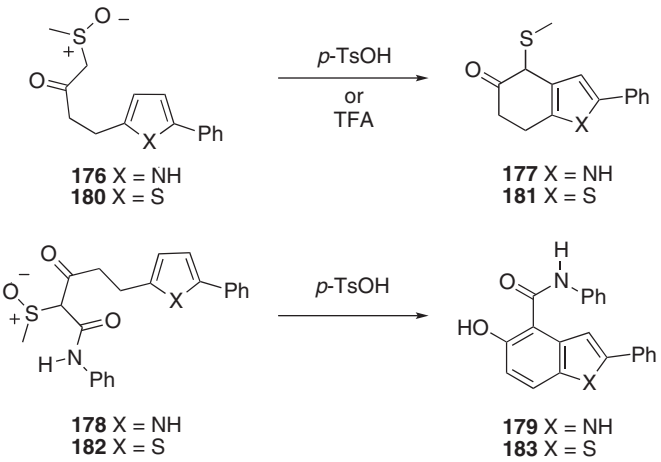
Heteroaromatic nucleophiles, such as pyrroles and thiophenes, also react with thionium ion intermediates. The reaction of sulfoxide **176** with catalytic amounts of *p*-TsOH produced the bicyclic derivative **177** in 63% yield (Scheme 29).[65] Sulfoxide **178** was similarly converted into indole **179** in 91% yield. Benzothiophene derivatives were also obtained under acid-promoted Pummerer conditions. Heating a benzene solution of *β*-ketosulfoxide **180** and TFA at reflux, for example, resulted in isolation of the annulated thiophene **181** in 54% yield. When *p*-TsOH was used to promote the Pummerer reaction, cyclization occurred onto the *α*-acyl thionium ion generated from sulfoxide **182**, and this was followed by elimination of methanethiol to provide benzothiophene **183** in good yield. It should be noted that selection of acid and solvent is important to the successful cyclization of these substrates.

6.17.3.3 Preparation of Reactive Thionium Ions

In the past few decades, the development of new Pummerer reaction methods have occurred primarily, although not exclusively, in the context of the heterocycle and natural product synthesis. The synthetic importance of the Pummerer reaction centers on the reactive sulfonium (e.g., **152**) and thionium ion (e.g., **155**) intermediates (*cf* Scheme 24). Accordingly, a variety of methods focus on ways to generate these intermediates effectively. Reaction of sulfoxides with carboxylic acid anhydrides, sulfonic acid anhydrides, various protic acids, and silylating agents have all been reported to generate thionium ions.

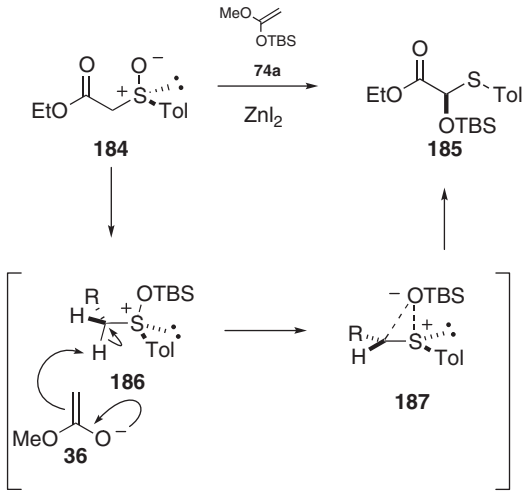
6.17.3.3.1 Silyl ketene acetals

The Lewis acid-mediated silyl transfer from silyl ketene acetals to sulfoxides has proven to be a particularly effective way to promote asymmetric Pummerer reactions.[66,67] Sulfoxide **184** reacted with silyl ketene acetal **74a** (*cf* Scheme 12) in the presence of



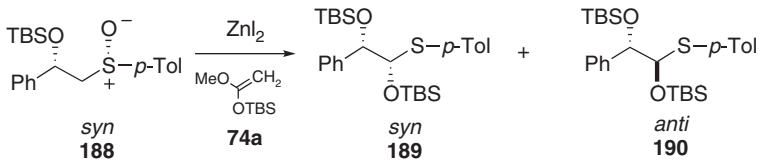
Scheme 29

catalytic amounts of ZnI_2 to produce **185** in 69–72% yield with 86–88% *ee* (Scheme 30). As in the silyl ketene acetal-promoted Polonovski reaction, acetal **74a** acts as a silyl transfer reagent, generating sulphonium ion **186** and enolate **36**. Deprotonation of **186** by the enolate gives **187**. The siloxy group could migrate to the α-position by one of the three mechanisms: (1) an intimate ion-pair mechanism, (2) a radical dissociation–recombination mechanism, or (3) a concerted 1,2-shift. In this case, a concerted 1,2-shift of the silyloxy group in the thermodynamically more stable geometry shown for **18** was proposed to account for the stereoselectivity of the reaction.



Scheme 30

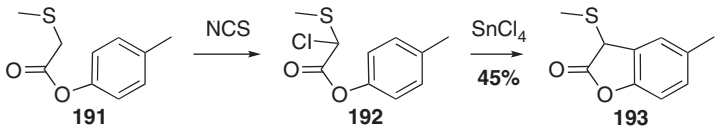
Similarly, catalytic amounts of ZnI_2 in CH_3CN promoted the reaction of nonracemic sulfoxide **188** (>99% *ee*) with **74a** to provide an 88:12 mixture of the *syn* and *anti* α-silyloxy sulfides **189** and **190** in 75% yield (equation 7).[66] Alternatively, *anti*-**188** provided an 82% yield of a 4:96 mixture, this time predominating in **190**, under the same conditions. Various *syn* and *anti*-β-substituted sulfoxides were treated with the *O*-silylated ketene acetal under these reaction conditions to give high yields of the corresponding α-silyloxy sulfides with good diastereoselectivity.



(7)

6.17.3.3.2 N-Chlorosuccinimide

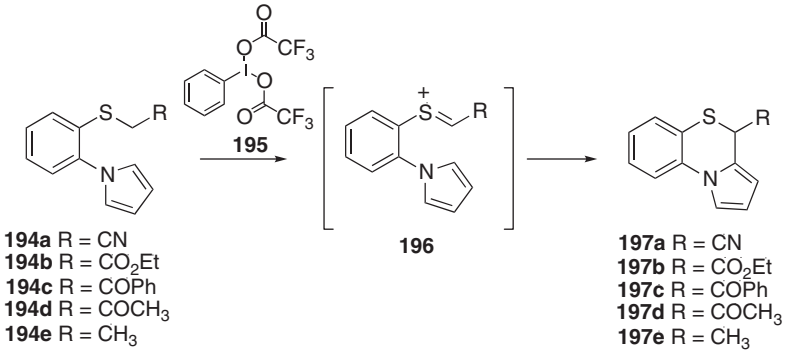
The reaction of sulfides with various oxidizing agents provides an alternative to accessing thionium ions from sulfoxide-starting materials. For example, exposure of the α-methylthio ester **191** to the action of *N*-chlorosuccinimide (NCS) afforded α-chlorosulfide **192** through a process very similar to the Pummerer rearrangement. Catalytic amounts of $SnCl_4$ reacted with **192** to generate a thionium ion that cyclized to produce **193** in 45% yield (Scheme 31).[68] Subjection of the sulfoxide derived from **191** to TFAA-mediated reaction conditions failed to produce **193**.



Scheme 31

6.17.3.3.3 Hypervalent iodine

The reaction of hypervalent iodine reagents with sulfides also initiates Pummerer reactions.[69] Phenyl iodine(III) *bis*-(trifluoroacetate) (PIFA, **195**) was found to be a particularly good initiator for the Pummerer reaction of sulfides **194a–d** to give **197a–d** (Scheme 32).[70,71] Sulfoxides possessing a simple alkyl group, such as **194e**, rather than an electron-withdrawing group, failed to produce heterocycles, such as **197e**, under these conditions. Presumably, the trifluoroacetate anion is too weak to generate **196** from the sulfonium ion produced by the hypervalent iodine. The desired cyclization could, however, be promoted by treating the sulfoxide corresponding to **194e** with a mixture of TFAA and TFA.



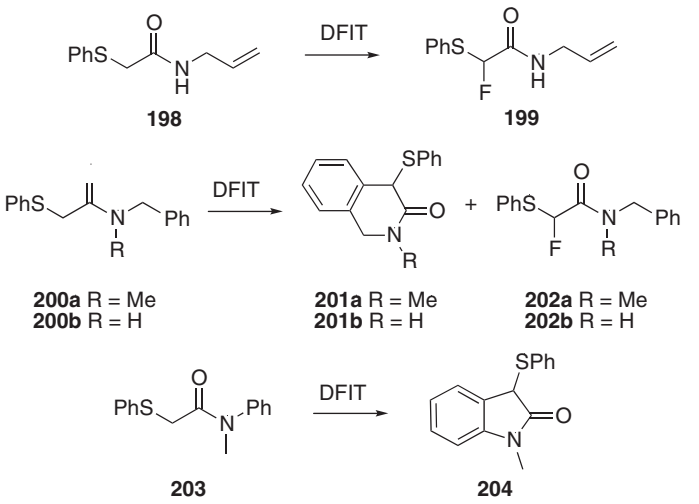
Scheme 32

Another hypervalent iodine reagent, difluoroiodotoluene (DFIT), has been particularly successful for the α-fluorination of α-phenylsulfanyl acetate derivatives via a Pummerer-type process. Heating a CH_2Cl_2 solution of **198** and DFIF at reflux temperature gave **199** in 71% yield (Scheme 33).[72] When an internal nucleophile is present, the rate of fluorine addition to the intermediate thionium ion apparently depends on the population of rotational isomers about the amide bond. For example, subjection of tertiary amide **200a** to the same conditions that produced **199** resulted in cyclization to give **201a** in 47% yield together with a smaller amount of the expected fluorinated product **202a** (25%). When the secondary amide **200b** was treated with DFIT, the product distribution shifted, producing some cyclized material **201b** (11%) as well as the fluorinated product **202b**, which now predominated in 35% yield. Treatment of **203** with DFIT produced the oxindole derivative **204** as the sole product in 59% yield.

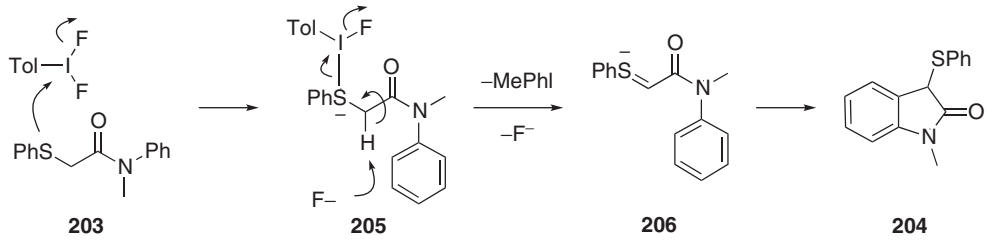
The mechanism of these reactions involves nucleophilic displacement of a fluorine atom in the hypervalent iodine reagent by the sulfur atom, generating sulfonium salt **205** (Scheme 34). The displaced fluoride then abstracts a proton, eliminating iodotoluene and a second fluoride ion from **205**, thereby affording an intermediate thionium ion **206**. In case of **206**, the rate of cyclization is significantly faster than capture of fluoride.

6.17.3.3.4 Dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)

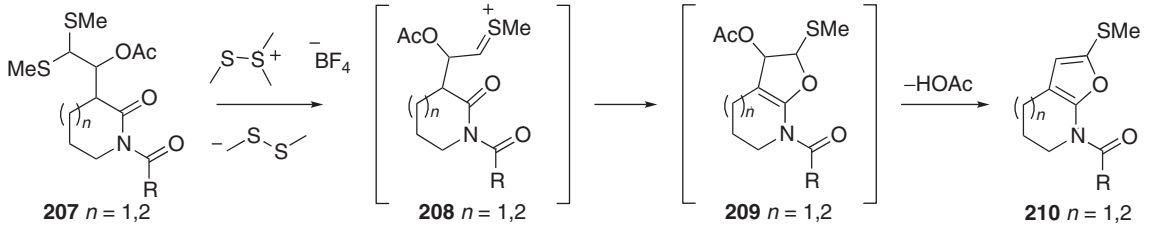
Thionium ions have also been generated from gem-dithianes. Reaction of **207** with commercially available DMTSF, for example, initiated a Pummerer cascade by first transferring a methylsulfanyl group to a sulfur in **207**.[73–75] Subsequent elimination of methyldisulfide produced the reactive thionium ion intermediate **208**. In this particular case, the thionium was intercepted by the nearby carbonyl group to produce **209**, and loss of acetic acid furnished furans **210** in 70–80% isolated yields (Scheme 35).



Scheme 33



Scheme 34



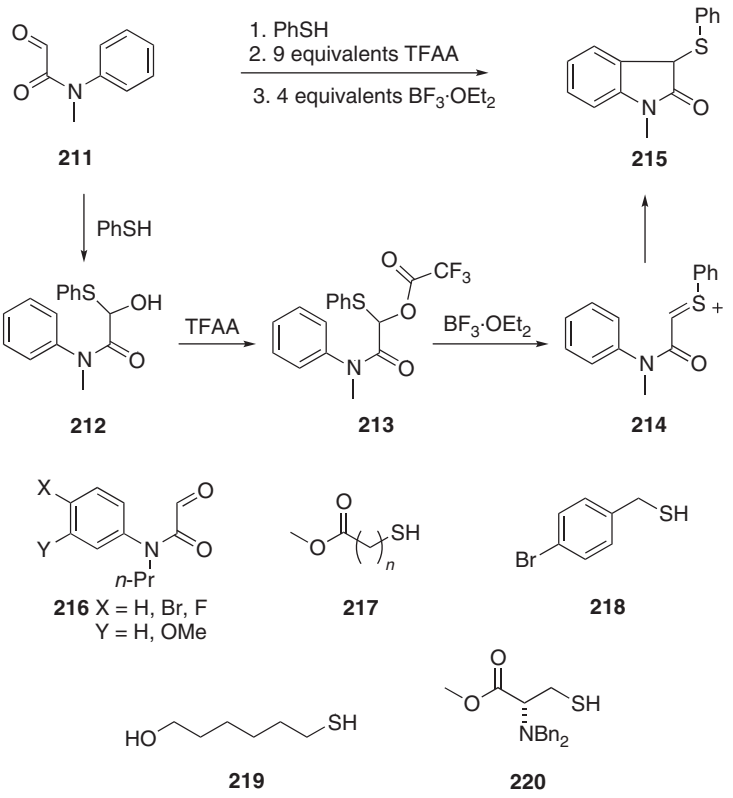
Scheme 35

6.17.3.3.5 Hemithioacetals

Aldehydes can be converted into α-acyloxy sulfides, and the subsequent reaction with a Lewis acid generates a reactive thionium ion (Scheme 36). Stirring a mixture of glyoxamide **211** and benzene thiol followed by sequential exposure to TFAA and $BF_3{\cdot}OEt_2$ provided oxindole **215** in 63% yield.[76] Further experimentation revealed a stepwise sequence of reactions that involves the initial production of hemithioacetal **212**, acylation of **212** by the action of 4 equivalents of TFAA to give acyloxy sulfide **213**, and generation of the thionium ion **214** mediated by at least two equivalents of $BF_3{\cdot}OEt_2$. $Sc(OTf)_3$ provided similar results to $BF_3{\cdot}OEt_2$, whereas $Yb(OTf)_3$ effected the cyclization in lower yields. Glyoxamides with various electron-donating and -withdrawing groups (e.g., **216**) participated in the reaction, as did several alkyl and aryl thiols (e.g., **217–22**), with yields ranging 52–83%.

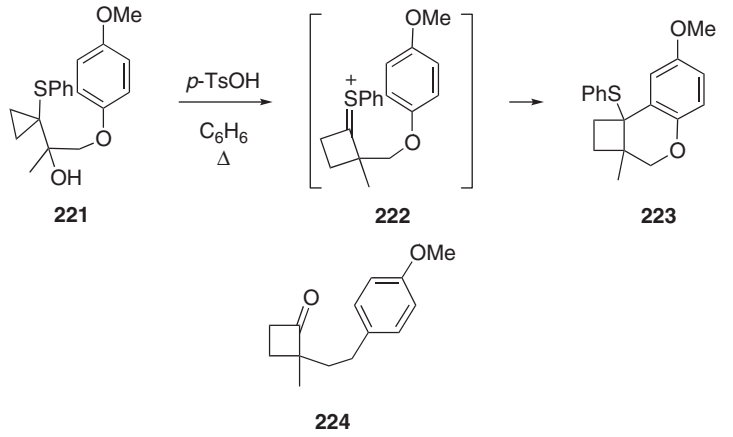
6.17.3.3.6 Rearrangements

Cationic rearrangements can also initiate Pummerer cyclization cascades by generating thionium ions that subsequently cyclize. For example, when cyclopropane **221** was heated with *p*-TsOH in benzene at reflux, a Wagner–Meerwein-type rearrangement occurs on ionization of the hydroxyl group to give the ring-expanded thionium ion **222** (Scheme 37).[77] Subsequent capture of the thionium ion by the pendant aryl group furnished **223** in 77% yield. Aryl groups containing a *p*-Me and *p*-Cl substituents as well as



211 215 212 213 214 216 217 218 219 220

Scheme 36



221 222 223 224

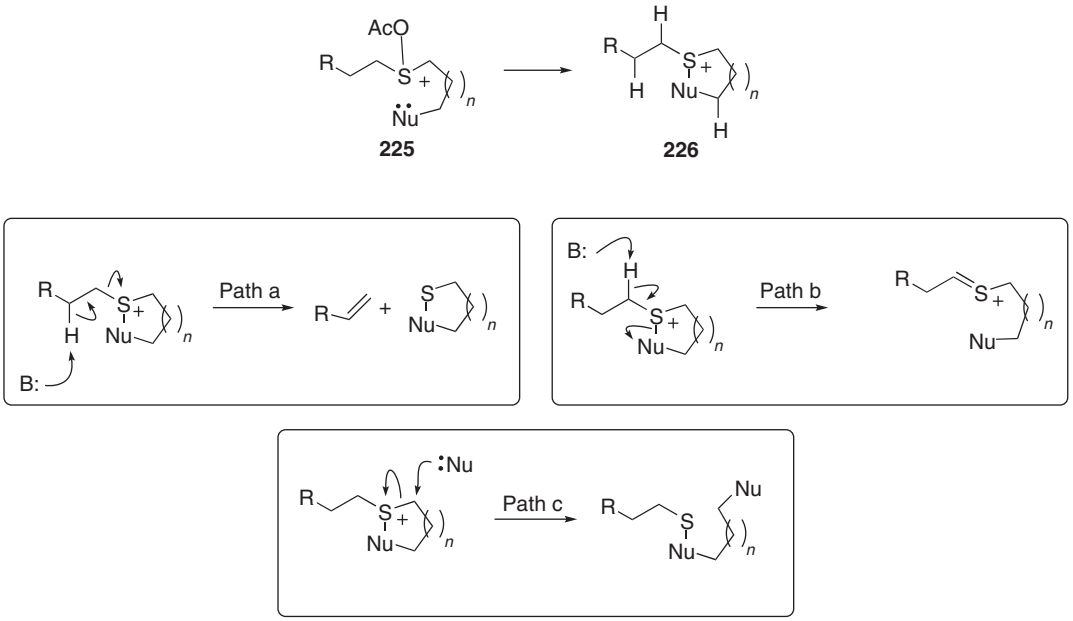
Scheme 37

the unsubstituted substrate also provided tricyclic analogs of **223** (67–80% yield). As in other cases (*vide supra*), the electronics of the ring have a significant impact on the course of the reaction; when the ether linkage in the tether was removed, the cyclization failed and cyclobutanone **224** was isolated in 80% yield.

6.17.3.4 Variants of the Pummerer Reaction

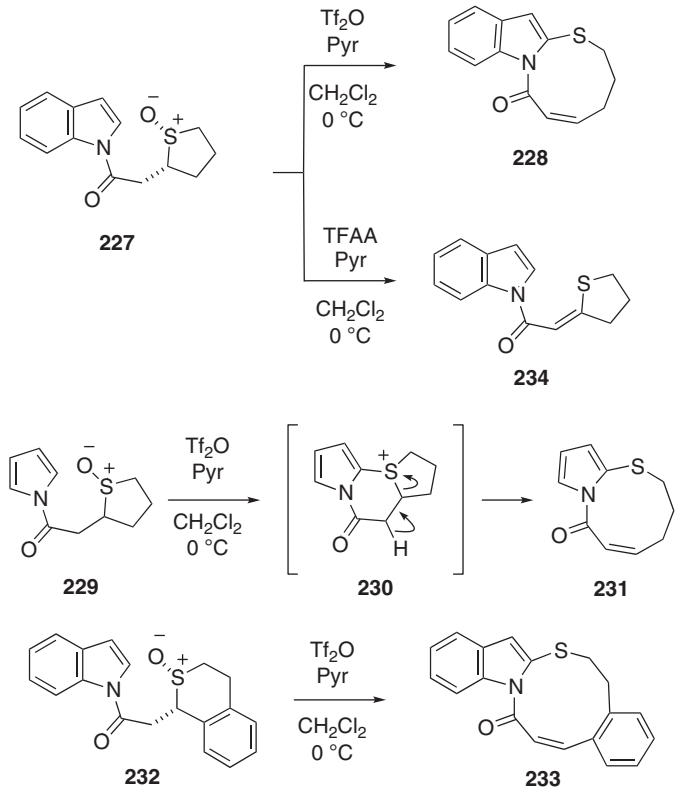
6.17.3.4.1 Interrupted Pummerer reactions

An interrupted Pummerer reaction occurs when a nucleophile can displace the acyloxy (or similar)-leaving group of a sulfonium ion **225**, generating a second positively charged sulfur intermediate **226** (Scheme 38). Further reaction can occur through several distinct mechanisms: elimination of a β-proton, producing an alkene (path a); removal of an α-proton to give a thionium ion (path b); or displacement of the sulfur by a second nucleophile (path c).



Scheme 38

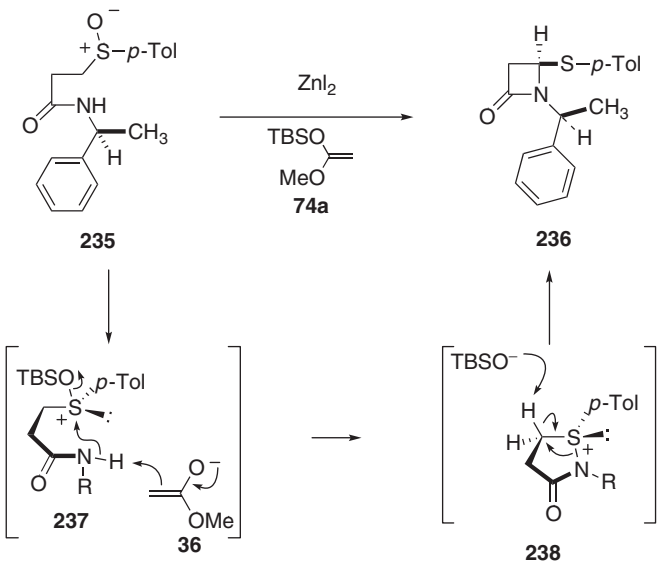
A cascade that forms large-ring *N,S*-heterocycles from sulfoxides tethered to electron-rich aromatic compounds is illustrative of path a, sometimes referred to as a 'sulfoxide electrophilic sulfenylation (SES) process.[78–80] Exposure of the indole-containing sulfoxide **227** to the action of Tf_2O and pyridine in CH_2Cl_2 at 0 °C furnished the heterocycle **228** in 65% yield (Scheme 39).[81] Pyrrole-containing sulfoxide **229** produced the related pyrrole **231** in 60% yield under similar conditions. The mechanism of this reaction presumably involves nucleophilic attack on the sulfonium ion by the adjacent aromatic ring with concurrent displacement of triflate so as to produce a new sulfonium salt **230**. A Grob-type fragmentation, initiated by deprotonation at the carbon



Scheme 39

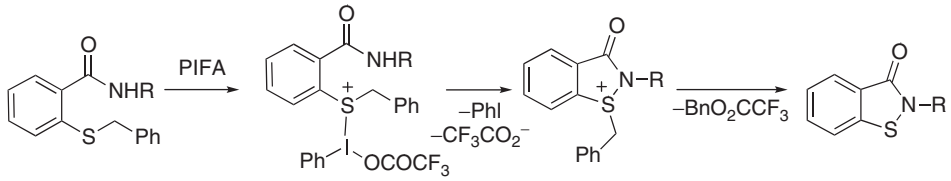
beta to the sulfonium ion, delivered a ring-expanded product **231**. Starting with sulfoxides that are tethered to six-membered rings furnished larger macrocycles. Thus, the 10-membered ring **233** (42% yield) resulted from the reaction of sulfoxide **232** with Tf_2O. The reaction appears to prefer a *syn* relationship between the sulfoxide oxygen and the tether; complex mixtures arose when the *trans*-diastereomer of **227** was subjected to similar reaction conditions and no compound **228** was observed. This reaction relies on the strong leaving group ability of triflate; less reactive acylating reagents gave products derived from deprotonation of an intermediate thionium ion. Accordingly, treatment of **227** with TFAA and pyridine cleanly provided the elimination product **234**.

An asymmetric Pummerer provided enantiomerically enriched β-lactams **236** starting from the chiral, nonracemic β-amido sulfoxides **235** (Scheme 40).[67,82,83] Treatment of the (*S*)-sulfoxide **235** with ZnI_2 and **74a** in CH_3CN gave the (*R*)-β-lactam **236** in 75% yield and with 60% *ee*. Using $ZnCl_2$ in CH_2Cl_2 improved the *ee*, and a variety on *N*-substituted β-lactams was produced in 54–96% yield and with 80–85% *ee*. Further investigation suggested that the first step of the mechanism for β-lactam formation involves silylation of the sulfoxide to give intermediate **237**. The second step is an interrupted Pummerer, wherein the silyloxysulfonium ion is attacked by the amide nitrogen atom to produce chiral isothiazolone **238**. This intermediate was proposed to undergo a preferential 1,2-rearrangement from the α-face (slide mode) to provide β-lactam **236**,[83] although a tight ion pair is possible. This is formally representative of path b (Scheme 38).



Scheme 40

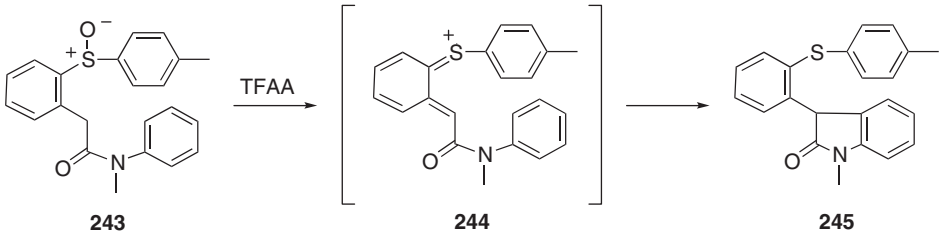
As an example of path c, exposure of **239a** to PIFA and TFA in CH_2Cl_2 gave rise to compound **242a** in 80% yield (Scheme 41).[84] Presumably, this reaction commences with the sulfur atom displacing a trifluoroacetate group from the iodine atom, giving rise to the intermediate sulfonium ion **240**. As seen previously (*cf* Scheme 32), trifluoroacetate is not a strong enough base to effect the elimination of the iodo group and generate a thionium ion without the presence of an electron-withdrawing group at the carbon atom adjacent to the sulfonium salt. Instead, the proximal nitrogen nucleophile displaces the iodo group, resulting in the formation of sulfonium salt **241**. Finally, a nucleophilic displacement of the benzyl group gives rise to **242a** and benzyl trifluoroacetate. Electron-releasing substituents on the nitrogen atom facilitate this reaction. In contrast, **239b**, which contains a strongly electron-withdrawing group on the nitrogen, failed to furnish **242b** under similar conditions.



Scheme 41

6.17.3.4.2 Vinylogous Pummerer reactions

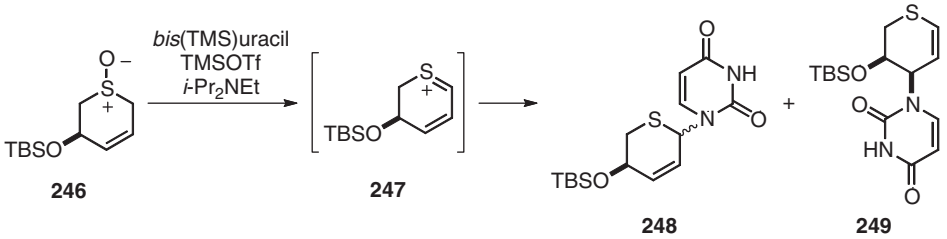
In the vinylogous Pummerer process, a vinyl sulfoxide is activated to generate a β,γ-unsaturated thionium ion. Subsequent trapping at the γ-position by a nucleophile in the reaction medium furnishes the observed products. For example, treatment of amido sulfoxide **243** with TFAA in CH_2Cl_2 at 25 °C generated the transient vinyl thionium ion **244** (Scheme 42).[85] Subsequent cyclization onto the aryl ring produced oxindole **245** in 91% yield.



243 **244** **245**

Scheme 42

Although the example in Scheme 42 requires reaction at the γ-carbon of the vinyl thionium ion so as to regenerate the aromatic ring, other examples suggest that addition to the α-carbon is the kinetically favored mode of addition and that addition to the γ-carbon is the thermodynamically favored mode. For example, **246** reacted with TMSOTf, bis(TMS)uracil, and *i*-Pr_2NEt in toluene and CH_2Cl_2 for 40 min at −40 °C to give a 6:1 mixture of **248** (1:1 *cis*:*trans*), which arises from α-addition to the vinyl thionium **247** and **249**, corresponding to γ-addition, in 65% combined yield (Scheme 43).[86] Extending the reaction time produced **249** as the sole product, as did subjecting **248** to the original reaction conditions.

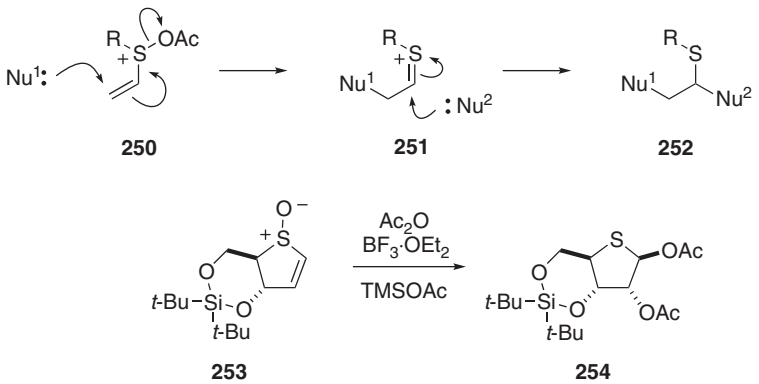


246 **247** **248** **249**

Scheme 43

6.17.3.4.3 Additive Pummerer reactions

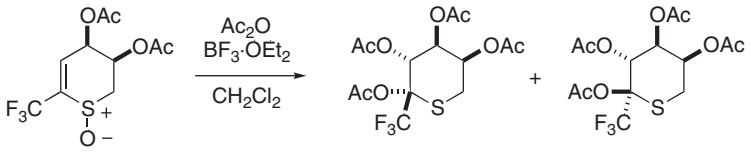
Like the vinylogous Pummerer, the additive Pummerer reaction involves the activation of a vinyl sulfoxide such as **250** (Scheme 44). In this case, however, a nucleophile adds through an S_N2' mechanism, generating a thionium ion such as **251** that can react with a second nucleophile to give products like **252**. For example, reaction of **253** with 7.0 equivalents each of Ac_2O, $BF_3{\cdot}OEt_2$, and TMSOAc at room temperature produced a mixture (13:1) of anomers predominating in **254** in 61% combined yield.[87]



250 **251** **252** **253** **254**

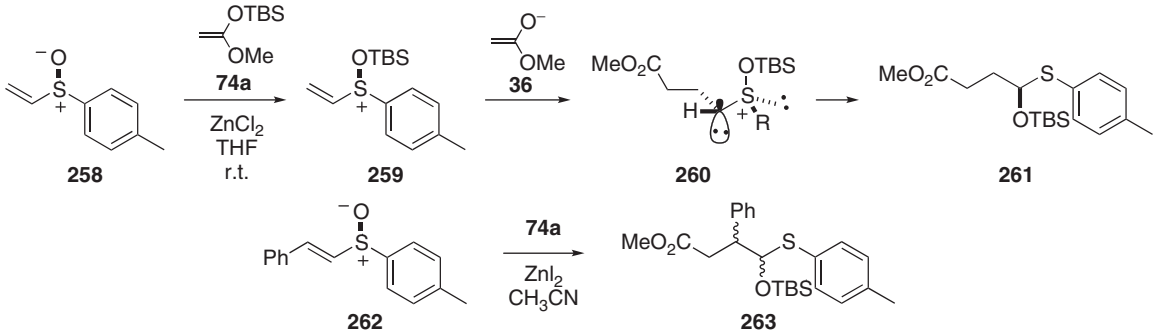
Scheme 44

This proved to be a particularly effective strategy for the synthesis of trifluoromethyl-substituted thiopyrans. The double bond in vinyl sulfoxide **255**, for example, proved resistant to various dihydroxylation or hydroxybromination conditions (equation 8).[88] Alternatively, exposure of **255** to a mixture of acetic anhydride and $BF_3{\cdot}OEt_2$ in chloroform at room temperature produced a mixture (1.5:1) of anomers **256** and **257** in 91% yield.



255 **256** **257** (8)

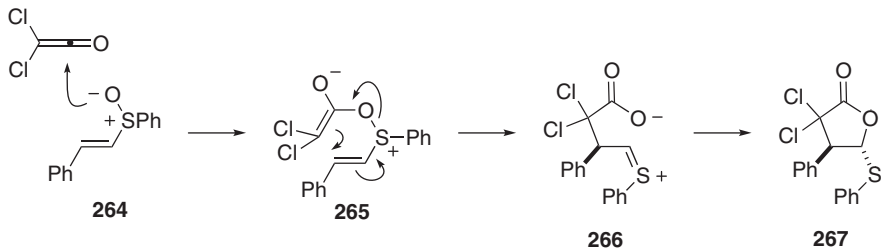
The additive Pummerer reaction can also involve the formation C–C bonds when carbon nucleophiles are present. Catalytic amounts of $ZnCl_2$ promoted the reaction of chiral, nonracemic vinyl sulfoxide **258** with **74a** in THF to give **261** in 78% yield and with 80% *ee* (**Scheme 45**).[89] Conjugate addition of enolate **36** to the siloxysulfonium ion **259** resulted in ylide **260**, wherein the anion is *anti*-periplanar to the silyloxy group. Suprafacial migration of the silyloxy group (*vide supra*) then furnishes the *α*-silyloxy sulfide **261**. *β*-Substituted derivative **262** failed to react under these conditions. Using ZnI_2 to promote the reaction, however, gave **263**, although only in 21% yield and only with 40% *de*.



258 **259** **260** **261** **262** **263**

Scheme 45

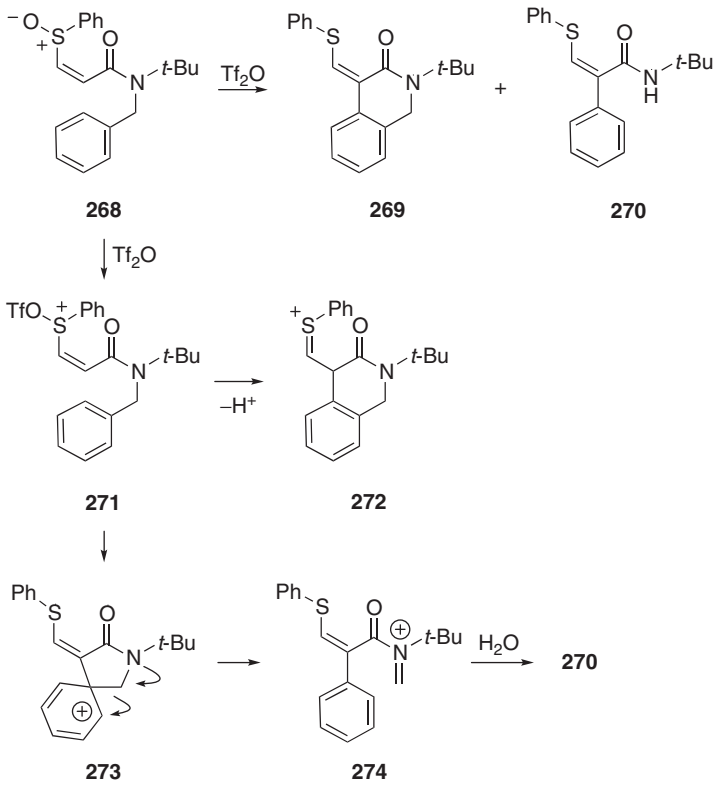
An additive Pummerer reaction was developed that produces *γ*-butyrolactones by the reaction of dichloroketene with vinyl sulfoxides.[90] Vinyl sulfoxide **264**, for example, reacts with dichloroketene to produce the internal salt **265** (**Scheme 46**). The resulting enolate moiety in **265** then undergoes a 3,3-sigmatropic rearrangement to provide thionium ion intermediate **266**. Finally, the resulting carboxylate adds to the neighboring thionium ion to furnish butyrolactone **267**, which reflects the geometry of the starting olefin, in 65% yield. The use of chiral sulfoxides leads to the enantiospecific formation of butyrolactones.[91–94]



264 **265** **266** **267**

Scheme 46

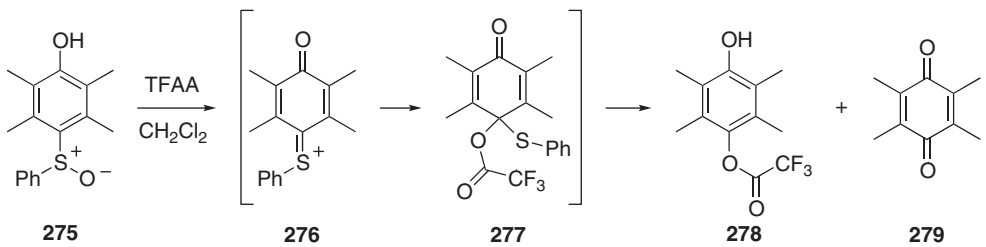
π-Bonds also participate in the additive Pummerer reaction. When sulfoxide **268** was treated with Tf_2O, a mixture of **269** (32%) and the rearranged product **270** (45%) was produced (**Scheme 47**).[85] Bicycle **269** arises from a pathway in which sulfonium salt **271** undergoes cyclization so as to produce **272** after the loss of a proton. A second deprotonation of the resultant thionium ion then delivers vinyl sulfide **269**. The mechanism that is responsible for the formation of **270** probably involves nucleophilic attack of the sulfonium ion by the *ipso* carbon of the pendant aryl group, giving rise to spirocyclic intermediate **273**. Subsequent fragmentation of **273** provides iminium ion **274** that is subsequently hydrolyzed to give **270**.



Scheme 47

6.17.3.5 Aryl Sulfides

The application of Pummerer reaction conditions to *p*-sulfinylphenols produces *p*-quinones. For example, sulfoxide **275** reacted with TFAA at 0 °C to give hydroquinone **278** together with quinone **279** (Scheme 48).[95] Exposing the crude reaction mixture to $NaHCO_3$ produced **279** in 84% yield. In cases with carbonyl-based electron-withdrawing substituents, adding MnO_2 rather than bicarbonate to the crude reaction mixture was necessary to complete the reaction.

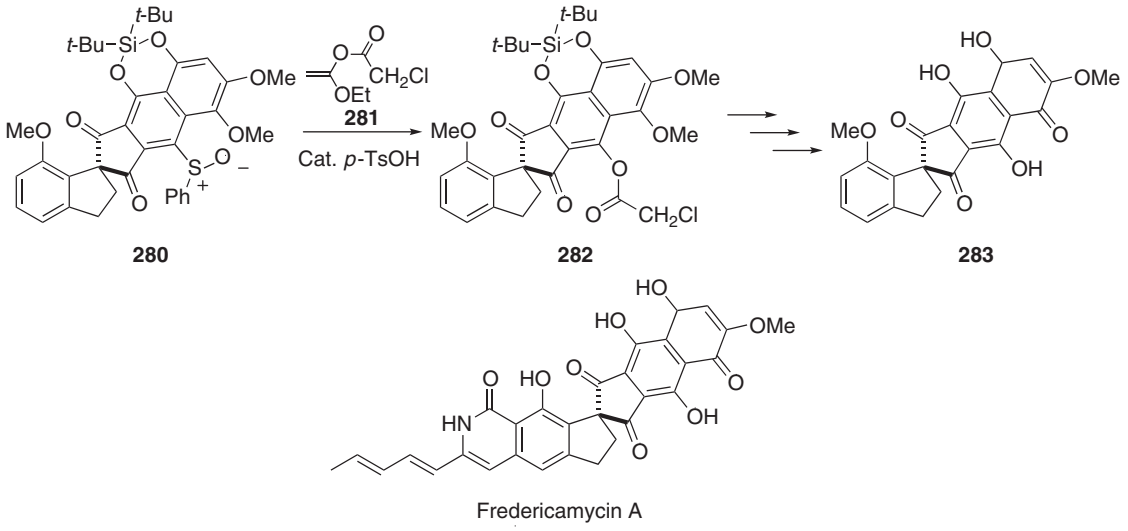


Scheme 48

Using aryl ethers, rather than phenols allows for isolation of the hydroquinone. Sulfoxide **280**, for example, was reacted with ketene acetal **281** in the presence of catalytic amounts of *p*-TsOH in toluene at reflux temperatures to give **282** (Scheme 49).[96] Hydrolysis and deprotection afforded **283**, an analog of fredericamycin, in 40% yield from **280**.

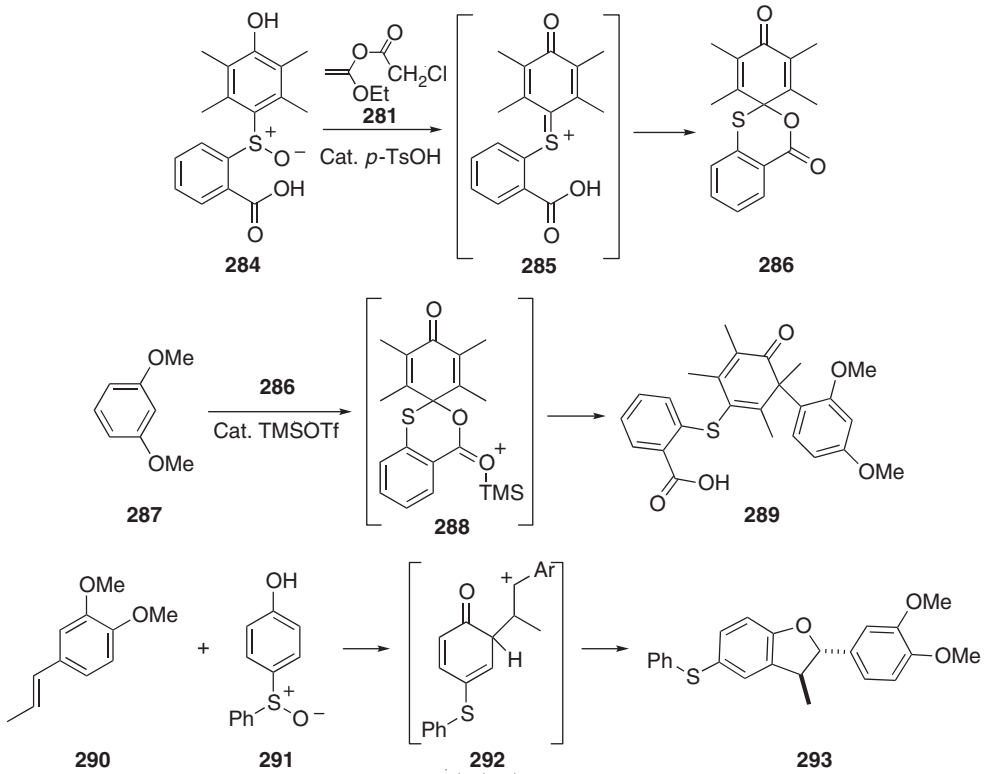
The sulfur in intermediate **277** is cleaved by a nucleophile in the reaction medium. In principle, this can occur either by direct attack at the sulfur or through an S_N2' mechanism. Additionally, either the phenylsulfanyl group or the trifluoroacetate can be cleaved. Reaction of sulfoxide **284** with ketene acetal **281** and catalytic amounts of *p*-TsOH effected a Pummerer reaction to give **286** in 99% yield via thionium ion **285** (Scheme 50).[97] The reaction of electron-rich aromatics, such as **287**, with **286** mediated by catalytic amounts of TMSOTf produced **289** in 89% yield, presumably through activation of the ester by silation (i.e., **288**). Styrene derivatives also add to the quinone thionium intermediate. Electron-rich **290** reacted with **291** in the presence of TFAA to give **293** in 81% yield.[98]

Heteroaromatic systems also undergo Pummerer reactions. Furan **294a** reacted with acetylacetone in CH_3CN to give **295a** in 75% yield (Scheme 51).[99] Reaction with allyl tributylstannane under the same conditions provided **296a** in 62% yield. Similar



280 282 283

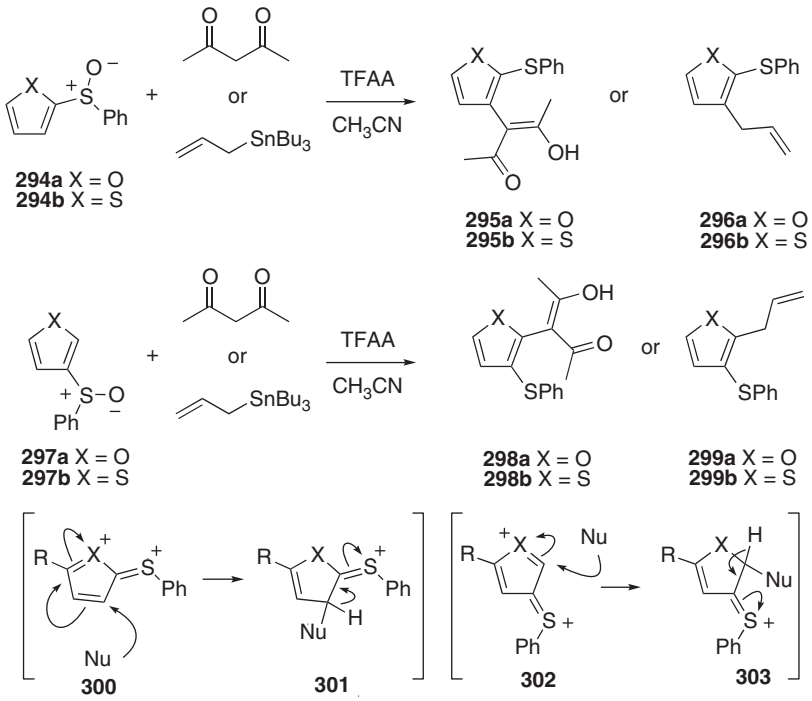
Scheme 49



284 285 286 287 288 289 290 291 292 293

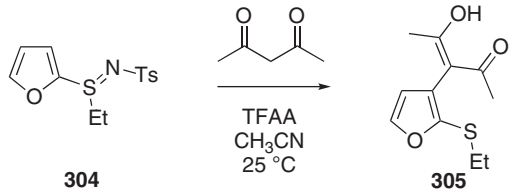
Scheme 50

reactions with thiophene **294b** furnished **295b** and **296b** in 78% and 86% yield, respectively. In each case, the 3-substituted regioisomers were formed exclusively, although chemical yields were poor in solvents other than CH_3CN. Furan **297a** and thiophene **297b** reacted under similar conditions to give furan **298a** in 80% yield, furan **299a** in 73% yield, thiophene **298b** in 80% yield, and thiophene **299b** in 96% yield. Although an additive Pummerer mechanism could be invoked, electron-donating groups on C5 accelerate the loss of the acyloxy group from the initially formed acyloxy sulfonium to give **300** or **302**, suggesting the participation of the 6π-electrons of the heteroaromatic ring. Addition of the nucleophile to either **300** or **302** produces **301** or **303**. Loss of a proton from **301** or **303** reestablishes aromaticity.



Scheme 51

Sulfur-nitrogen ylides (sulfilimines) undergo aromatic Pummerer reactions similar to those in Scheme 51. The TFAA-mediated reaction of sulfilimine **304** with a nucleophile, such as acetylacetone, in CH_3CN at 25 °C provided 3-substituted furan **305** in 69% yield (equation 9).[100]



(9)

Indole derivatives undergo a similar reaction under Pummerer conditions, and this chemistry provides a particularly effective approach to regiochemical control. For example, exposure of **306** to Tf_2O and 2,6-lutidine in CH_2Cl_2 afforded **307** in 76% yield (Scheme 52).[101,102] Similarly, **308** provided **309** in 80% yield on subjection to the same conditions. The sulfoxide derived from **310** failed to provide **311** under either TFAA or Tf_2O conditions, but the Pummerer cyclization could be effected by exposing **310** to PhI(CN)OTf and 2,6-lutidine, providing **311** in 40% yield as a single stereoisomer.

This method also provides highly selective access to 5-substituted indoles. On TFAA activation, for example, indole **312** undergoes a fragmentation reaction, giving rise to intermediate thionium ion **313** (Scheme 53).[103] Addition of nucleophiles, such as acetylacetone, gave indole **314** in 68% yield. A variety of nucleophiles reacted under these conditions, giving 5-substituted indoles, such as **315** (from vinyl phenyl sulfide), **316**, and **317** in 29%, 90%, and 48% yield, respectively.

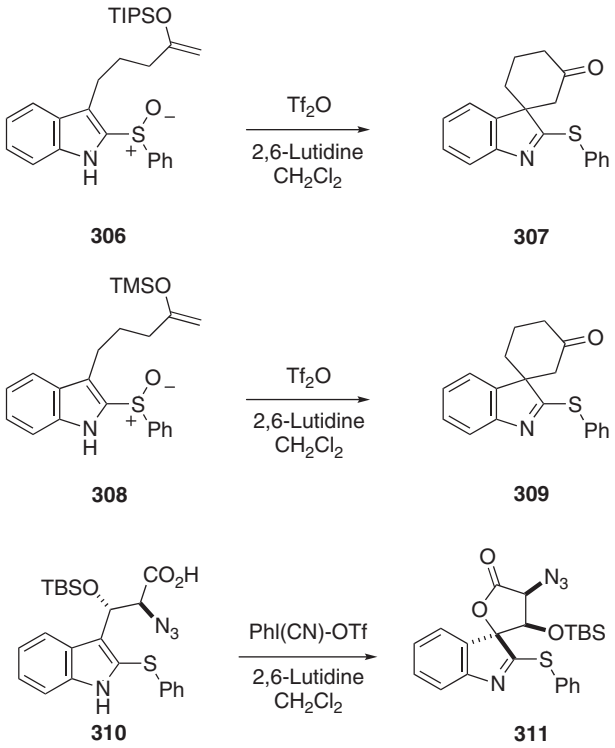
6.17.3.6 Other Processes

6.17.3.6.1 Cycloadditions

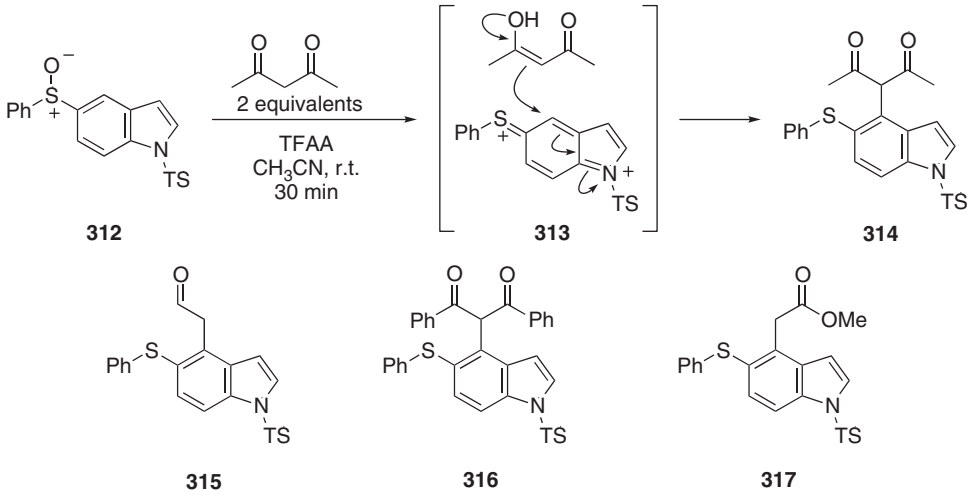
In addition to the additive and vinylogous Pummerer reactions, vinyl thionium ions are also known to participate in intramolecular [4+3]-cycloadditions. For example, TFAA acts on sulfoxide **318** in the presence of 2,6-lutidine to produce cycloadduct **319** in 50% yield and with high diastereoselectivity (>95% *de*).[104,105] Tricycle **319** is an advanced intermediate in the synthesis of pseudolaric acid A (**320**) (Scheme 54).

6.17.3.6.2 Electrocyclizations

A Nazarov-like electrocyclization reaction has been effected under Pummerer conditions. Thionium ion **322** was generated on heating a benzene solution of enamide **321** at reflux with *p*-TsOH. Subsequent electrocyclic-ring closure of **322** gave rise to



Scheme 52

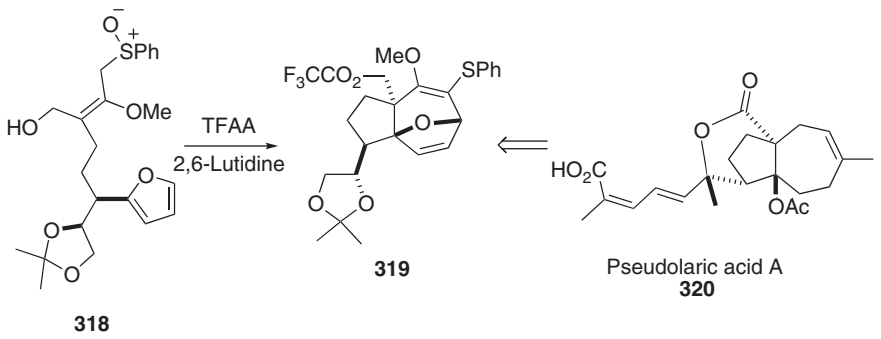


Scheme 53

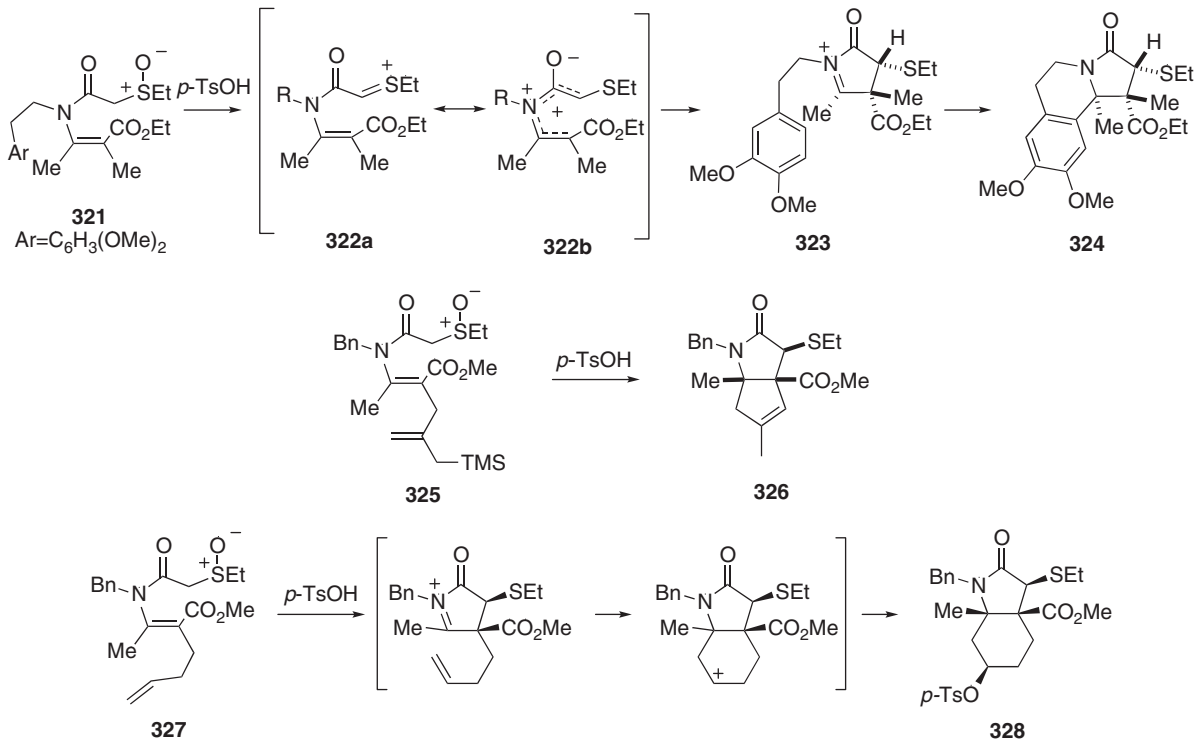
iminium ion **323**, which subsequently reacted with the tethered aromatic ring to furnish **324** as a single diastereomer in 78% yield (Scheme 55).[106] The stereochemistry of **324**, established by X-ray crystallographic analysis, is consistent with a conrotatory ring closure. Several types of π-bonds were found to efficiently terminate the cascade. Allylsilane **325**, for example, provided bicycle **326** in 61% yield under these conditions. Cyclization of terminal alkene **327** furnished **328** in 80% yield, wherein a sulfonate anion added to the secondary carbocation formed on electrophilic cyclization. That only one diastereomer was isolated in each of these cases suggests a concerted 4π-electrocyclization reaction occurs after formation of the intermediate thionium ion.

6.17.3.6.3 Morin rearrangement

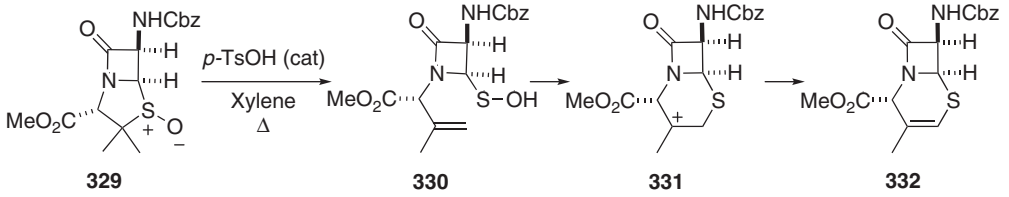
Another process that has occasionally been observed to occur under Pummerer reaction conditions is the Morin rearrangement.[107,108] This rearrangement commences on activation of a sulfoxide, such as **329** (Scheme 56). The initially formed sulfonium salt, however, fragments to produce the ring-opened sulfinic acid **330**. Subsequent protonation of the sulfenic acid followed by



Scheme 54



Scheme 55

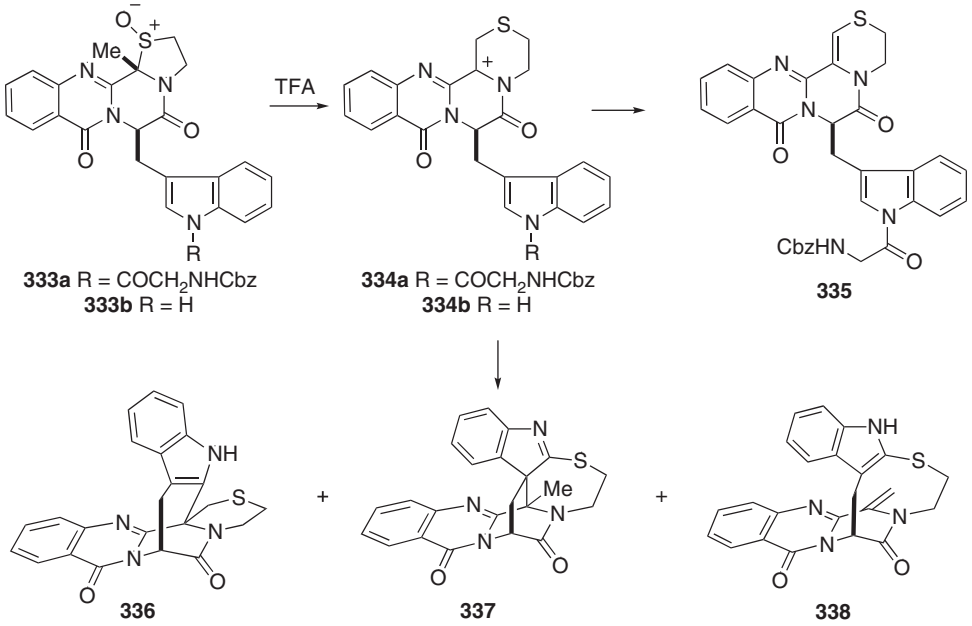


Scheme 56

nucleophilic displacement of water by the proximal π-bond leads to carbocation **331**, and the loss of a proton affords the observed rearrangement product **332**.

A Morin rearrangement was observed when **333a** was heated with TFA in $CHCl_3$, affording **335** in 80% yield.[109,110] Alternatively, the reaction of sulfoxide **333b** with TFA gave **336** (35%), in which the 2-position of the indole had formally intercepted the cation, spirocycle **337** (25%), and alkene **338** (21%). Removing the acyl group on the indole nitrogen increases the

nucleophilicity of the indole ring. Consequently, the indole is better able to capture intermediate **334b**, and this accounts for the formation of **336**. The formation of **337** and **338** was rationalized in terms of the sulfenic acid moiety adding to the indole ring (Scheme 57).

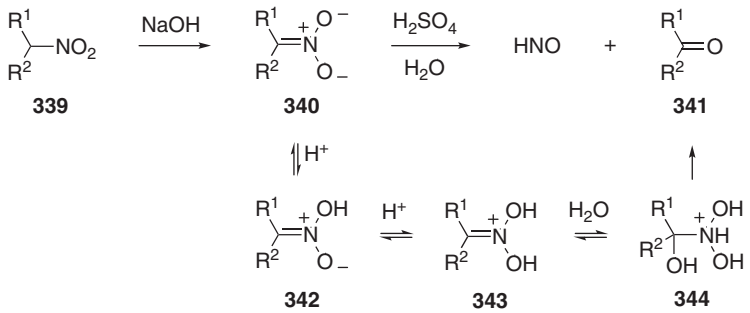


Scheme 57

6.17.4 The Nef Reaction

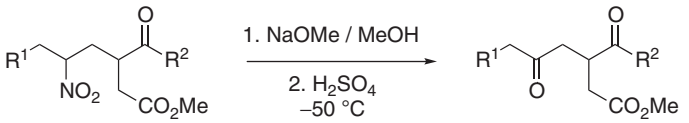
6.17.4.1 Mechanism

The classic Nef reaction involves the hydrolysis of nitroalkanes **339**, giving rise to carbonyl compounds **341** through the intermediacy of the nitronate salt **340** (Scheme 58).[1,3,111] Hydrolysis is thought to occur by protonation of the *aci* form of the nitro group, nitronic acid **342**, to give **343**. Addition of water to the iminium ion delivers **344**, which decomposes to ketone **341** and nitroxyl that ultimately leaves the system as nitrous oxide. The product distribution depends on the pH of the reaction media, with pH > 1 resulting in significant amounts of oxime. In practice, this requires that the nitronate is added to a solution of acid, as addition of acid to the nitronate tends to regenerate the nitro group.



Scheme 58

As an example of the classic reaction, methanolic NaOMe acts on nitroketones **345** producing the corresponding nitronates (equation 10).[112] Pouring the nitronates into concentrated H_2SO_4 at −50 °C afforded the 1,4-diketones **346** in modest yields, typically approximately 65%.

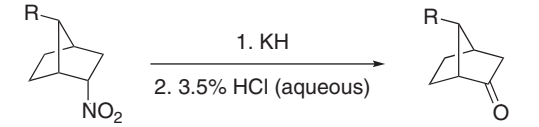


345a R^1 = H, R^2 = Me
345b R^1 = H, R^2 = Ph
345c R^1 = Me, R^2 = Me
345d R^1 = Me, R^2 = Ph

346a R^1 = H, R^2 = Me
346b R^1 = H, R^2 = Ph
346c R^1 = Me, R^2 = Me
346d R^1 = Me, R^2 = Ph

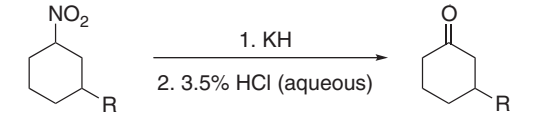
(10)

Some substrates are particularly resistant to the classical Nef reaction. For example, formation of the potassium nitronate derived from bicycle **347a** and subsequent reaction with aqueous HCl gave **348a** in only 16% yield (Scheme 59).[113] Under the same conditions, nitrocyclohexane (**349a**) gave cyclohexanone (**350a**) in only 8% yield. A γ-silyl group, however, assists the hydrolysis. Compound **347b** reacted with KH whereupon it was added to aqueous HCl, producing **348b** in 91% yield, and **349b** afforded **350b** in 87% yield.



347a R = H
347b R = TMS

348a R = H
348b R = TMS



349a R = H
349b R = TMS

350a R = H
350b R = TMS

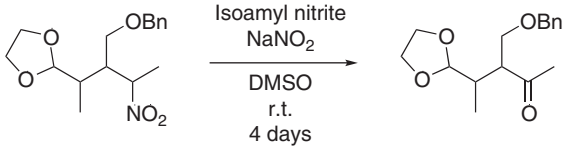
Scheme 59

The use of strongly acidic conditions in the second step somewhat limits the scope of the reaction, so a considerable amount of research has been focused on modifications that promote the hydrolysis under milder conditions. These methods tend to either oxidize the nitronate under mild conditions or reduce the nitronate to a more easily hydrolyzed oxime or imine.

6.17.4.2 Oxidative Methods

6.17.4.2.1 $NaNO_2$

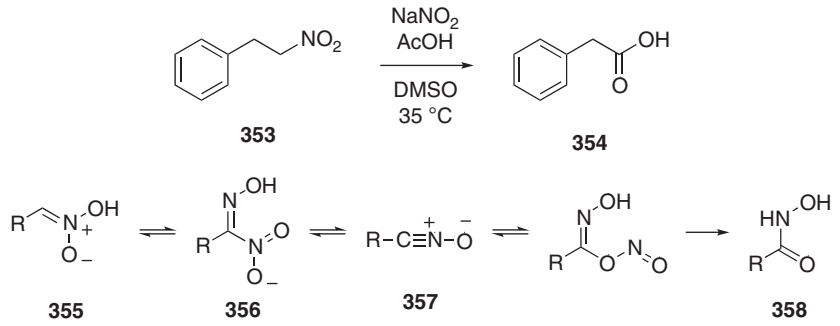
The reaction of nitroalkanes with nitrite esters and $NaNO_2$ produces the corresponding carbonyl compounds in modest yield without exposure to harsh acid.[114,115] Secondary nitroalkanes provided ketones, whereas primary substrates yielded carboxylic acids. For example, exposure of **351** to a mixture of isoamyl nitrite and $NaNO_2$ provided **352** in 73% yield (equation 11).[116]



351 **352**

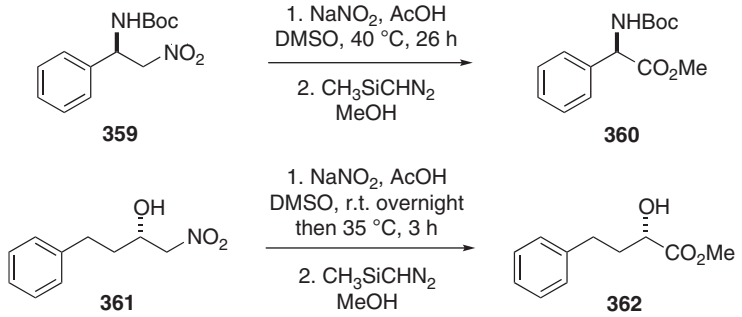
(11)

Both the modest yields and the extended reaction times required for this type of reaction spurred further mechanistic study that led to a modification of conditions. Nitroderivative **353** was converted into **354** in 95% yield by the action of $NaNO_2$ and acetic acid in DMSO at 35 °C (Scheme 60).[117] A variety of primary nitroalkanes reacted under these conditions to provide carboxylic acids in high yields (72–98%). The mechanism involves tautomerization to the *aci* form **355**, followed by addition of NO_2 to give nitrolic acid **356**. Decomposition of **356**, through reactive nitrile oxide-derivative **357**, produces hydroxamic acid **358**, which is readily hydrolyzed to **354**. In support of this mechanism, nitrolic acid **356** could be isolated at lower reaction temperatures, and it could even be subjected to column chromatographic purification.



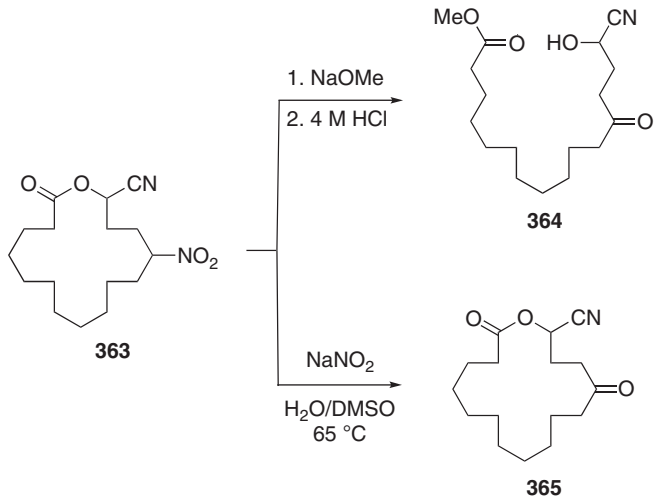
Scheme 60

As this modification does not use a strong base to generate the reactive nitronate, it has found use in the production of carboxylic acid derivatives with adjacent asymmetric centers. Exposure of **359** (97% *ee*) to $NaNO_2$ and acetic acid, followed by methyl ester formation, afforded α-amino ester **360** in 80% yield without loss of enantiomeric purity (Scheme 61).[118] Similarly, alcohol **361** (84% *ee*) afforded **362** in 69% yield without epimerization.[119]



Scheme 61

Under more standard Nef conditions, nitrolactone **363** reacted with NaOMe to effect a transesterification while forming the nitronate salt, and further reaction with 4 mol l^{-1} HCl provided keto ester **364** in 81% yield (Scheme 62).[120] Alternatively, reaction of **363** with $NaNO_2$ in aqueous DMSO at 65 °C furnished **365** in 86% yield.

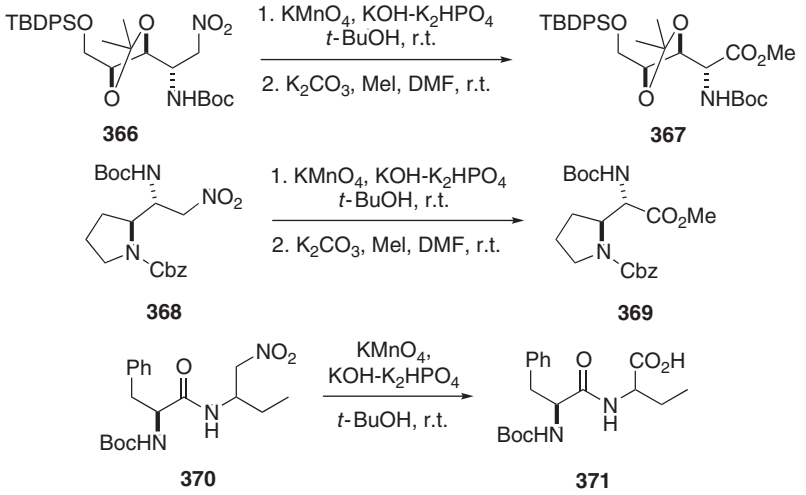


Scheme 62

6.17.4.2.2 $KMnO_4$

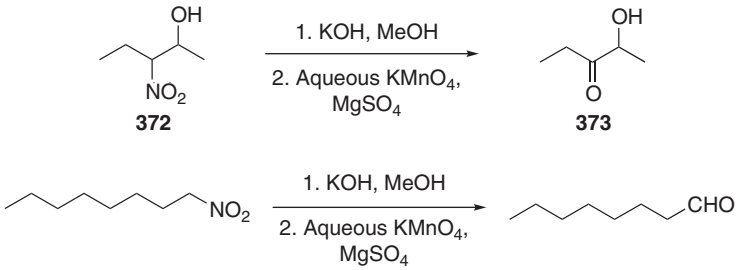
The reaction of nitronates with solutions of $KMnO_4$ also facilitates the hydrolysis to Nef products.[121] Under buffered conditions (pH 11), a variety of functional groups are tolerated, including esters, ketals, and alcohols.[122] Boc-protected amine **366** reacted

with $KMnO_4$ in KOH-K_2HPO_4 in *t*-BuOH to give the corresponding α-amino acid, which was esterified to give **367** in 90% yield over two steps. Likewise, proline derivative **368** produced **369** in 72% yield (Scheme 63).[123] Similarly, **370** afforded **371** under the same conditions.[124]



Scheme 63

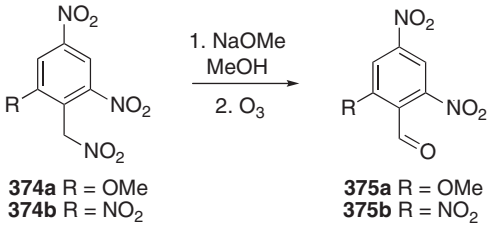
The addition of $MgSO_4$ also helps control the chemoselectivity. For example, reaction of alcohol **372** with methanolic KOH followed by an aqueous solution of $MgSO_4$ and $KMnO_4$ produced hydroxyl ketone **373** in 73% yield, and 1-nitrooctane furnished octanal in 83% yield (Scheme 64).[125] Care must be taken in the reaction of primary nitroalkanes to prevent overoxidation.



Scheme 64

6.17.4.2.3 Ozone

Exposure of nitronate salts to the action of ozone also produces aldehydes and ketones.[126] This method appears to effect the hydrolysis reaction in sterically demanding substrates where $KMnO_4$ caused extensive decomposition. Thus, the reaction of **374a** with methanolic NaOMe followed by exposure of the crude nitronate solution to ozone provided aldehyde **375a** in 86% yield, and the trinitro derivative **374b** was converted into **375b** in 70% yield (equation 12).

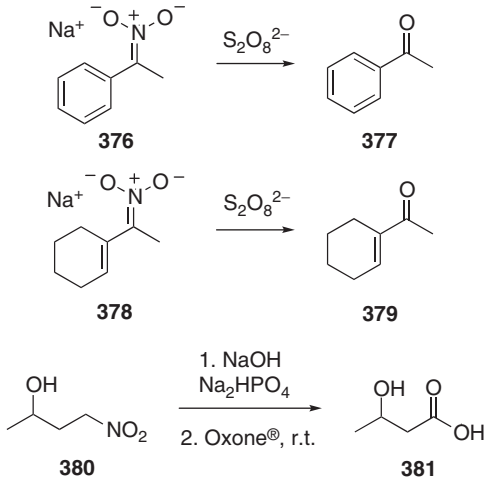


(12)

6.17.4.2.4 Persulfate reagents

Persulfate reagents also oxidize nitronate salts (Scheme 65). In cases of secondary alkyl nitronates having a conjugated aryl (e.g., **376**) or carbon–carbon double bond (e.g., **378**), the reaction with $S_2O_8^{2-}$ at pH 9.5–7 produced the corresponding ketones

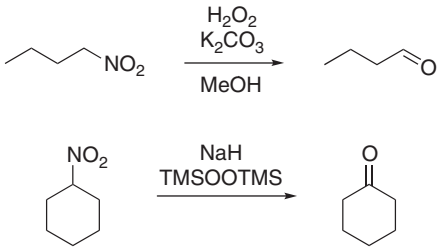
(e.g., **377** and **379**) in modest yields (61–72%).[127] Aliphatic and primary nitronates give primarily vicinal dinitro compounds via an oxidative dimerization. Oxone® has proved to be more selective in oxidizing aliphatic nitronates, tolerating a variety of functional groups such as silyl ethers and acetals. A solution of alcohol **380** in a NaOH-Na_2HPO_4 buffer reacted with Oxone® to give carboxylic acid **381** in 70% yield.[128] Although the range of substrates is higher for Oxone® than for persulfate, primary substrates, such as **380**, commonly overoxidize to give carboxylic acids rather than aldehydes.



Scheme 65

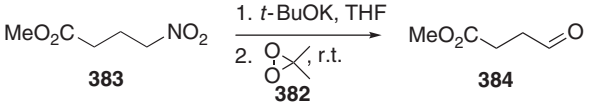
6.17.4.2.5 Peroxide reagents

Another oxidative modification of the Nef reaction involves the exposure of primary and secondary nitro compounds to a combination of H_2O_2 and K_2CO_3 in methanol. Under these conditions, 1-nitro-butane produced butanal in 76% yield, and nitrocyclohexane gave cyclohexanone in 88% yield (Scheme 66).[129] Sodium percarbonate and silica gel in aqueous DMF produced similar results.[130] The use of ionic liquids as a reaction medium with basic H_2O_2 also provided good to excellent yields of the corresponding ketones and aldehydes from simple nitroalkanes.[131] Bis(trimethylsilyl)peroxide reacts with the nitronate salts derived from a variety of secondary benzylic and aliphatic nitro compounds to afford ketones in modest to good yields (60–84%).[132] Nitrocyclohexane, for example, reacted with NaH and then bis(trimethylsily)peroxide to give cyclohexanone in 70% yield, although the only primary nitro compounds to successfully undergo the Nef reaction under these conditions were benzylic.



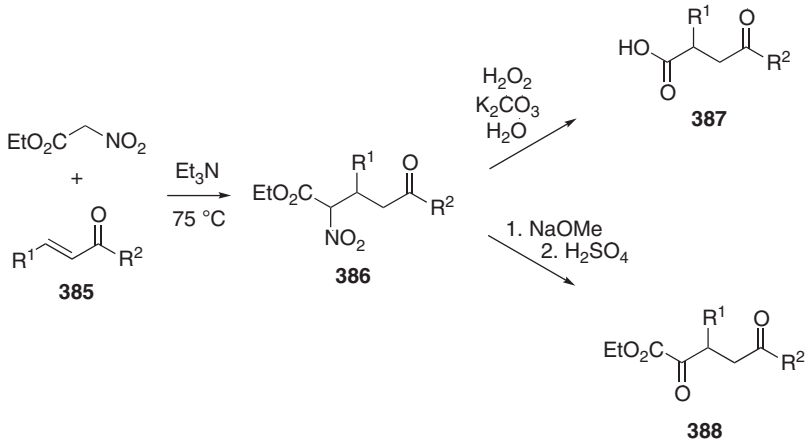
Scheme 66

Oxone® tends to overoxidize nitronate salts derived from primary nitroalkanes, whereas dimethyl dioxirane (**382**, prepared from the reaction of Oxone® with acetone) reacted with the nitronate derived from **383** to furnish aldehyde **384** in 73% yield (equation 13).[133]



(13)

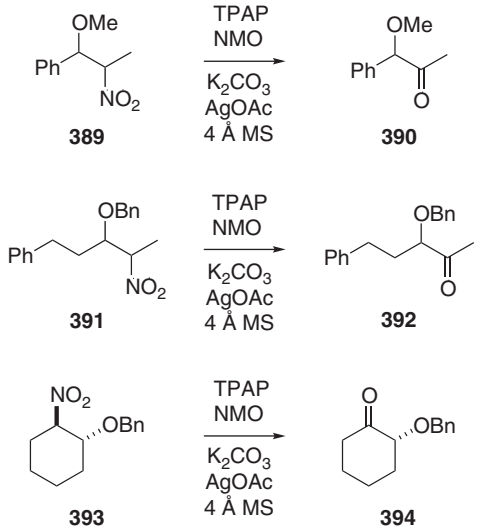
In a tandem Michael–Nef sequence, ethyl nitroacetate was reacted with α,β-unsaturated ketones **385** to give nitro compounds **386** that were further reacted with H_2O_2 and K_2CO_3 to furnish decarboxylated products **387**, in 41–87% yields (Scheme 67). In this case, traditional Nef conditions (NaOMe and then H_2SO_4) gave α-keto esters **388**.[134]



Scheme 67

6.17.4.2.6 TPAP–NMO

Secondary nitro compounds react with catalytic amounts of tetrapropylammonium perruthenate (TPAP) and a mixture of NMO, AgOAc, and K_2CO_3 in the presence of 4 Å molecular sieves to give the corresponding ketones. Under these conditions, for example, compound **389** delivered α-methoxy ketone **390** in 52% yield (Scheme 68).[135] Similarly, subjection of **391** and **393** to the TPAP–NMO conditions furnished **392** and **394** in 76% and 62% yields, respectively.



Scheme 68

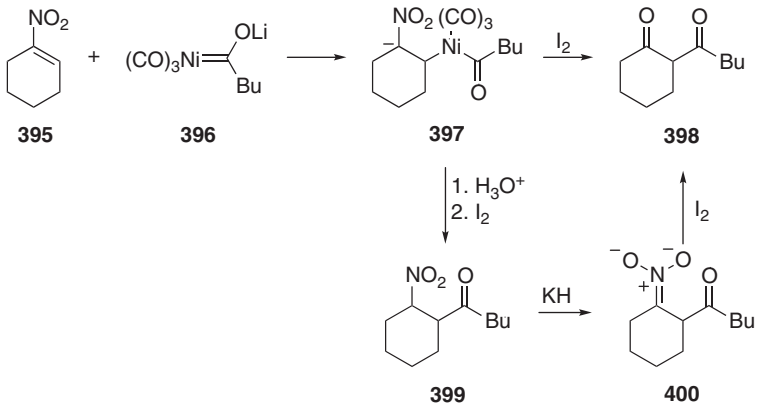
6.17.4.2.7 Molecular iodine

The hydrolysis of nitronate intermediates has also been promoted by molecular I_2. Reaction of nitro alkene **395** with nickel acylate complex **396** produces reactive intermediate **397** (Scheme 69).[136] On exposure to I_2, the Michael adduct **397** was converted into ketone **398** in 47% yield. Alternatively, exposure of **397** to aqueous acid first, and then I_2 produced **399** in 59% yield. That the nitronate was the intermediate that reacted with I_2 was established by the reaction of nitronate **400**, generated by the action of KH on **399**, with I_2 to give **398**.

6.17.4.3 Reductive Methods

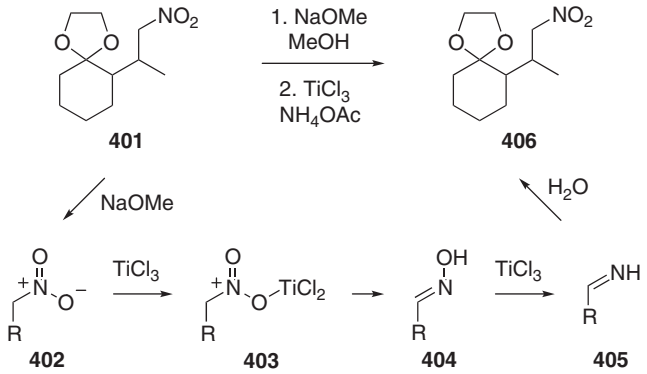
6.17.4.3.1 $TiCl_3$

Several reductive methods have been developed to promote the Nef reaction. The most widely used reductive method appears to be a reaction of nitronate salt with $TiCl_3$, buffered to pH 6.[137,138] Under these conditions, a variety of acid-sensitive functional



Scheme 69

groups, such as ketals, survive whereas the nitro group is converted into the corresponding carbonyl compound. The reaction of ketal **401** with methanolic NaOMe, for example, gave rise to intermediate nitronate **402** (Scheme 70). Addition of this intermediate to an aqueous solution of $TiCl_3$ and NH_4OAc generated titanium nitronate **403**, which was reduced to oxime **404**. Further reduction of **404** gave imine **405** that was hydrolyzed to **406** in 90% yield.



Scheme 70

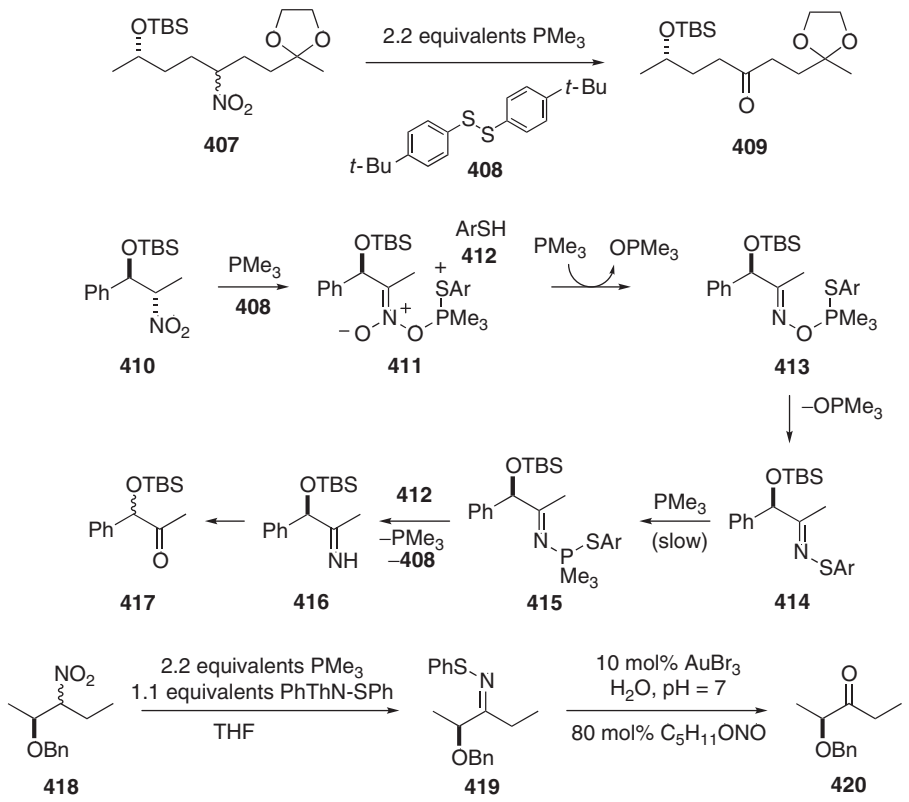
6.17.4.3.2 Trimethylphosphine

Trimethylphosphine and sulfanyl- or selenyl-transfer reagents work together to reduce secondary nitro alkanes to imines, which are hydrolyzed to the corresponding ketone. The reaction of nitroalkane **407** with 2.2 equivalents of PMe_3 and 1 equivalent of disulfide **408** in THF at room temperature for 30 min produced ketone **409** in 94% yield (Scheme 71).[139] Although the mechanism of this transformation is catalytic in disulfide, a full equivalent was used to enhance the reaction rate. Under these conditions, substrate **410** was transformed into **417** in 70% yield. The phosphine and disulfide were proposed to react with the nitro compound to give **411** and thiol **412**. A second equivalent of phosphine acts to reduce the nitronate complex, producing oxime **413** that subsequently decomposes to give rise to thio oxime **414** and trimethylphosphine oxide. A third molecule of phosphine reacts to give **415**, and further reaction with the initially generated thiol **412** returns disulfide **408**, trimethylphosphine, and the imine **416**. Finally, hydrolysis furnishes **417**.

Although the yield of **417** was good, the α-chiral center was epimerized through an imine–enamine tautomerization. Further investigation led to a modification wherein the thiooxime (e.g., **414**) is hydrolyzed by the catalytic action of $AuBr_3$ in the presence of isopentylnitrite (to prevent the sulfur materials from poisoning the catalyst).[140] Under these new conditions, **410** produced **417** in 65% yield with >98% *ee*, and **418** was transformed into **420**, through the intermediacy of thiooxime **419**, in 85% yield and with >98% *ee*.

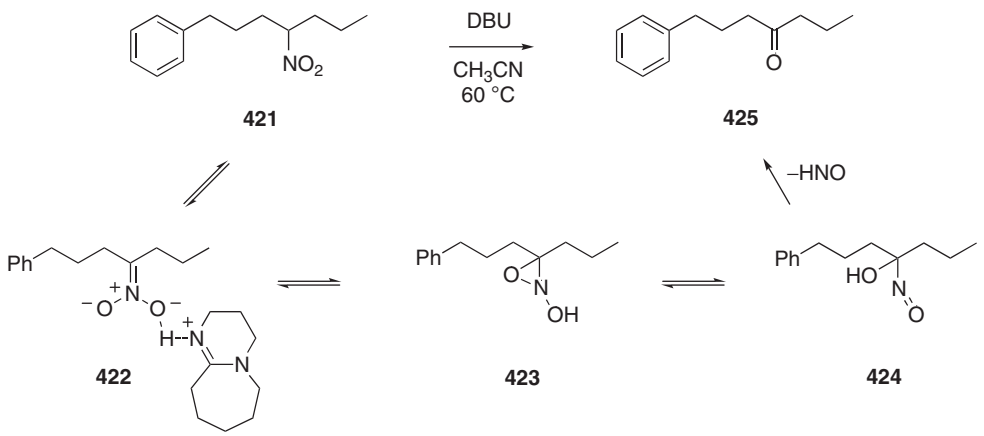
6.17.4.4 Other Conditions

The Nef reaction on secondary nitroalkanes is also promoted by DBU in CH_3CN. The deprotonation of nitroalkane **421**, for example, gives DBU complex **422**, which is in equilibrium with oxaziridine **423** and hydroxynitroso compound **424**



Scheme 71

(Scheme 72).[141] Loss of nitroxyl drives the formation of **425** in 60% yield. In competition experiments, secondary substrates were completely converted into the corresponding ketone, whereas primary nitroalkanes were unreactive. Other bases, such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), also effected the transformation but in lower yields.

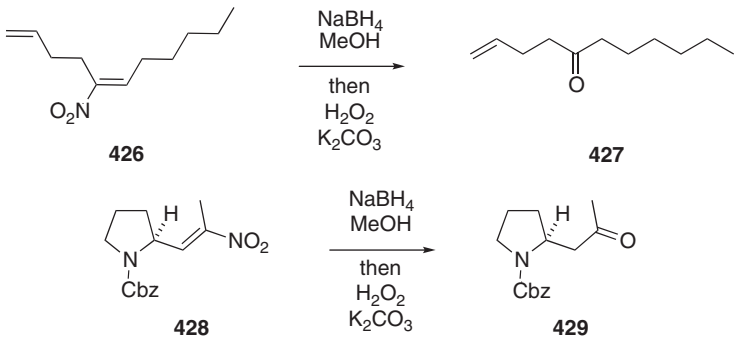


Scheme 72

6.17.4.5 Conjugated Nitroalkanes

6.17.4.5.1 Conjugate reduction

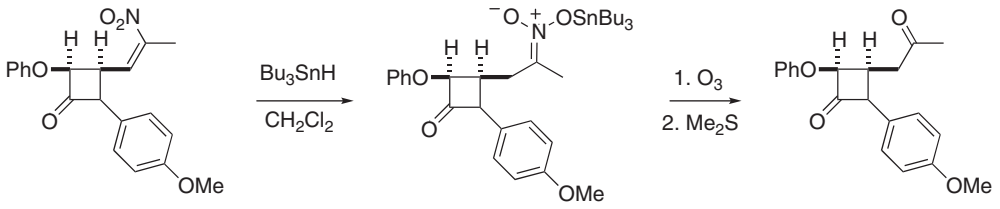
Conjugated nitroalkenes act as Michael acceptors, producing nitronate intermediates that can be subjected to a variety of hydrolysis conditions. Conjugate reduction of nitroalkene **426** by the action of $NaBH_4$ at 0 °C followed by the addition of H_2O_2 and K_2CO_3 delivered ketone **427** in 58% yield (Scheme 73).[142] A variety of nitroalkenes were converted into the corresponding ketones in 48–80% yields under these conditions. In another example, proline-derived **428** produced **429** in 65% yield.[143]



426 427 428 429

Scheme 73

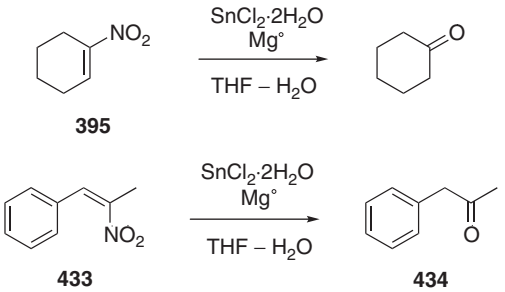
These borohydride/peroxide conditions are considerably basic, and other easily reducible groups are often affected. The use of *n*-Bu_3SnH as the reducing agent offers milder conditions. Accordingly, a solution of *β*-lactam **430** was stirred with *n*-Bu_3SnH so as to effect a conjugate addition, generating the stannyl nitronate **431** (Scheme 74).[144] Subjecting the crude reaction mixture containing **431** to ozonolysis conditions produced **432** in 70% yield.



430 431 432

Scheme 74

A mixture of $SnCl_2{\cdot}2H_2O$ – Mg° in aqueous THF also effected a conjugate reduction, and subsequent hydrolysis of the intermediate nitronate delivered ketones in good yield. Under these conditions, nitroalkene **395** produced cyclohexanone in 80% yield and nitrostyrene **433** afforded **434** in 82% yield (Scheme 75).[145]



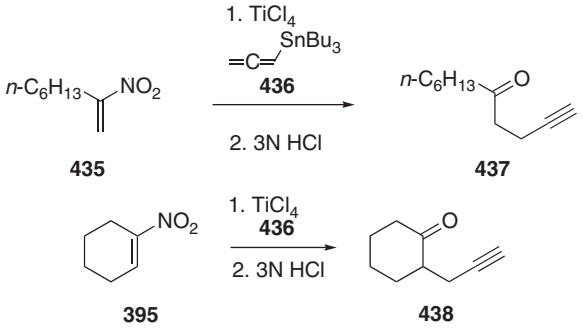
395 433 434

Scheme 75

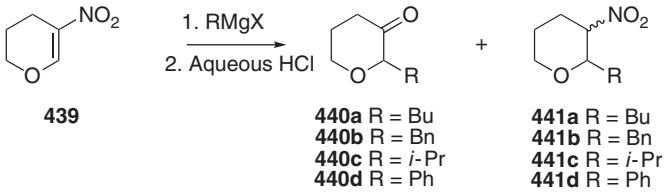
6.17.4.5.2 Organometallics

Nitroalkenes react with a variety of organometallic reagents to give intermediate nitronates (*cf* Scheme 69). The $TiCl_4$-mediated reaction of 2-nitrooct-1-ene (**435**) with stannylallene **436** produced acetylenic ketone **437** in 85% yield, after acid hydrolysis (Scheme 76).[146] Under similar conditions, 1-nitrocyclohexene (**395**) afforded **438** in 73% yield.

Exposure of pyran **439** to Grignard reagents followed by acid-promoted hydrolysis of the intermediate magnesium nitronates afforded mixtures of ketones **440** and nitro compounds **441** (equation 14).[147] The use of primary aliphatic (e.g., butyl) and benzylic Grignards produced primarily ketones such as **440a** in 76% and **440b** in 95% isolated yields with little or no formation of **441a,b**. Secondary and aryl Grignards, however, produced primarily nitro compounds, such as **441c** in 70% yield and **441d** in 63% yield, under the same conditions.

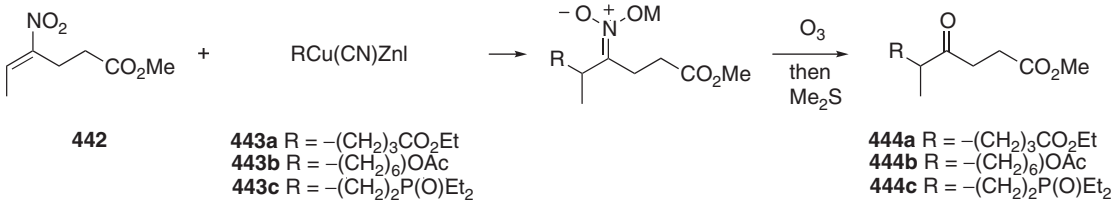


Scheme 76



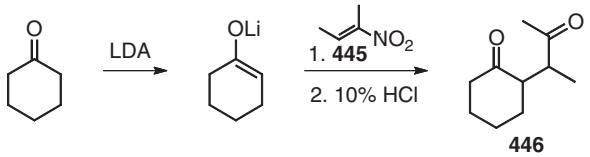
(14)

Copper–zinc reagents also add to α,β-unsaturated nitro compounds, and the resulting nitronates can be reacted with ozone to give tandem conjugate addition/Nef products. The variety of functional groups that are tolerated by the formation of copper–zinc reagents makes this method particularly useful. For example, nitroalkene **442** reacted with organometallic **443a**, and the crude reaction mixture was exposed to ozone, delivering **444a** in 87% yield (Scheme 77).[148] Similarly, **444b** was isolated in 75% yield from the reaction of **442** with **443b**, and **443c** reacted to give **444c** in 78% yield under these conditions.



Scheme 77

Enolates can also act as nucleophiles in these Michael additions. The lithium enolate of cyclohexanone, for example, added to **445**, and further reaction with 10% HCl produced **446** in 78% yield (Scheme 78).[149] Access to 1,4-dicarbonyls in this manner is an example of umpolung reactivity.



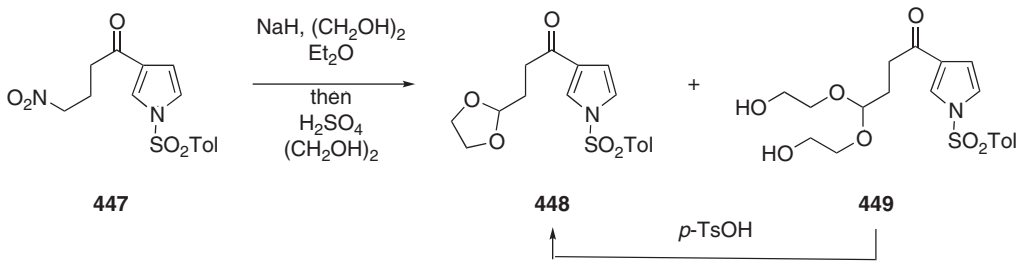
Scheme 78

6.17.4.6 Other Reactions

6.17.4.6.1 Ketal formation

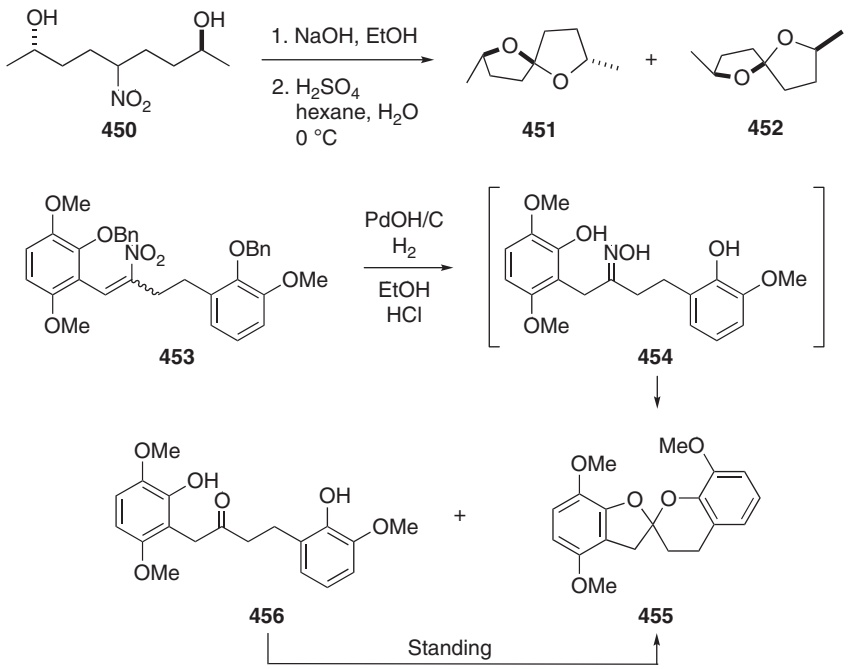
Although the Nef reaction is primarily employed to generate ketones and aldehydes, other reactions also can occur under the same conditions. When the hydrolysis step is conducted in alcohol solvents, ketals are isolated from the reaction mixture. Primary nitro compound **447**, for example, reacted with NaH and then H_2SO_4 in ethylene glycol to give ketal **448** and a small amount of **449** (Scheme 79).[150] Reaction of the crude reaction mixture with *p*-TsOH ensures that **449** is completely converted into **448** in 82% yield.

Spirocyclic ketals, found in a significant number of natural products, can also be formed under Nef conditions.[151] For example, chiral diol **450** sequentially reacted with NaOH and H_2SO_4 to give a 3:1 mixture of **451** and **452** in 41% yield (Scheme 80).



447 448 449

Scheme 79



450 451 452 453 454 455 456

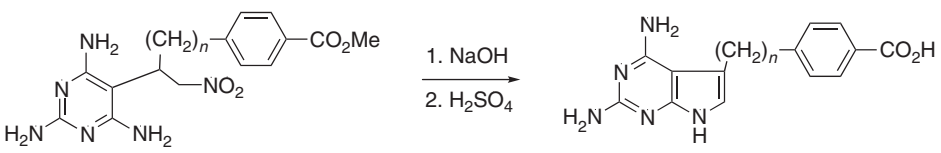
Scheme 80

Nonclassical Nef conditions have also been used. The reaction of nitroalkene **453** with H_2, mediated by Pearlman's catalyst under acidic conditions, triggered a cascade wherein the benzyl-protecting groups were removed and the nitroalkene moiety was reduced to oxime **454**. Subsequent reaction of the oxime with the free phenolic hydroxyl gave rise to spirocycle **455** in 64% yield, along with ketone **456** in 18% yield.[152,153] On standing, **456** spontaneously cyclized to give **455**.

Several sugar derivatives have been constructed using Nef chemistry. Under Nef conditions, for example, thiosugar **457** was converted into **458** in 85% yield (Scheme 81).[154] Stirring acetate-protected sugar derivative **459** in dilute methanolic acid produced **462**, **463**, and **464** in 29%, 31%, and 19% yields, respectively.[155] The reaction presumably began with the hydrolysis of the acetyl-protecting groups to give **460**. An acid promoted conjugate addition, and then produced a mixture of protonated nitronic acids **461**. Further reaction with alcohol gave the final mixture of products.

6.17.4.6.2 Pyrrole formation

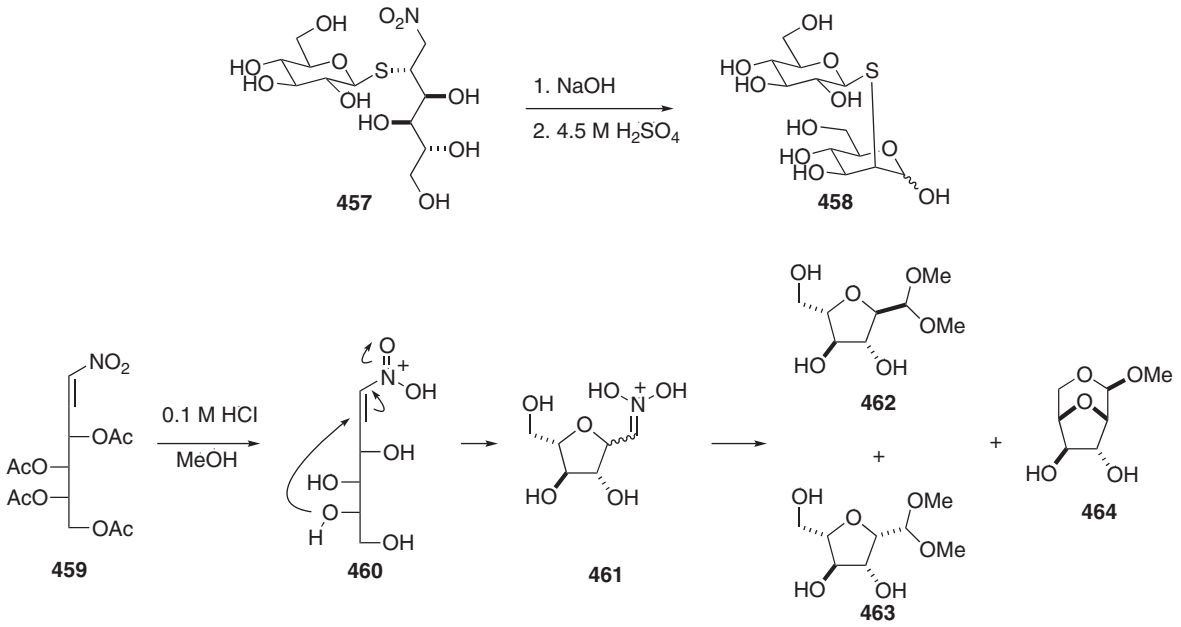
Nitrogen nucleophiles can also intercept either the protonated nitronic acid intermediate or the resulting aldehyde. For example, nitro olefin **465a** reacted with NaOH followed by H_2SO_4 to provide pyrrolo[2,3-*d*]pyrimidine **466a** in 57% yield (equation 15). Similarly, **465b** afforded **466b** in 51% yield.[156–158]



465a $n = 2$
465a $n = 2$

466a $n = 2$
466b $n = 3$

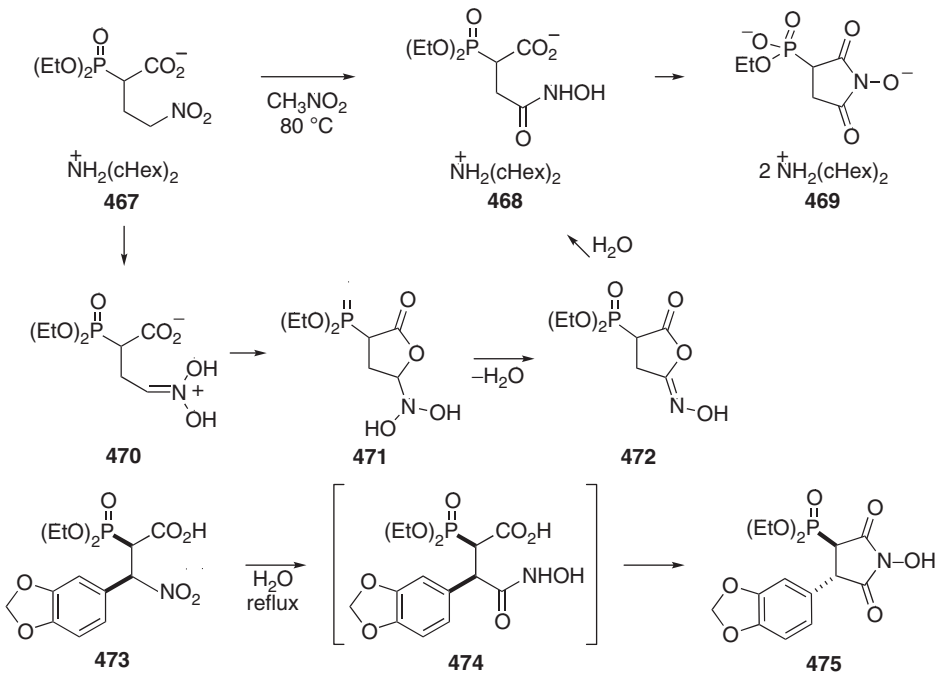
(15)



Scheme 81

6.17.4.6.3 Hydroxamic acid derivatives

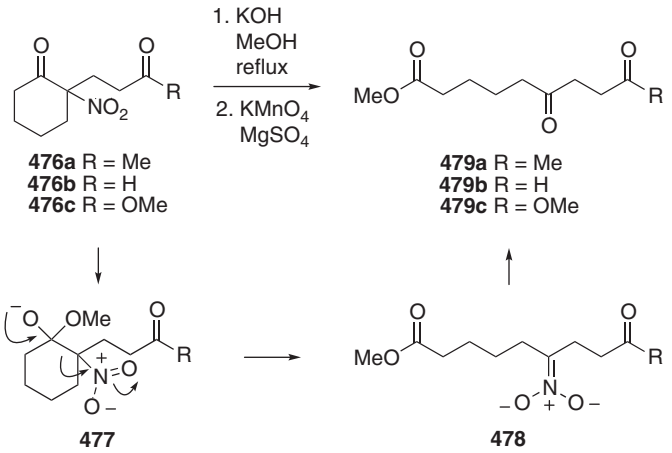
Remote functional groups can trigger the Nef reaction, as demonstrated by the conversion of **467** into **468** in 60% yield simply by heating at 80 °C for 80 min (Scheme 82).[159] Further heating of the reaction mixture produced **469** in 43% yield. The mechanism involves tautomerization of the nitro group in **467** into the *aci* form **470**. Addition of the pendant carboxylic acid gives rise to lactone **471**, and loss of water provides oxime **472**. Hydrolysis of **472** then furnishes hydroxamic acid **468**. Similarly, an aqueous solution of racemic **473** was heated to reflux temperature for 60 min, producing **475** in 79% yield.[160] The stereochemistry indicates a thermodynamic equilibration occurred under the reaction conditions. Similar compounds with secondary nitro groups simply returned the expected ketones.



Scheme 82

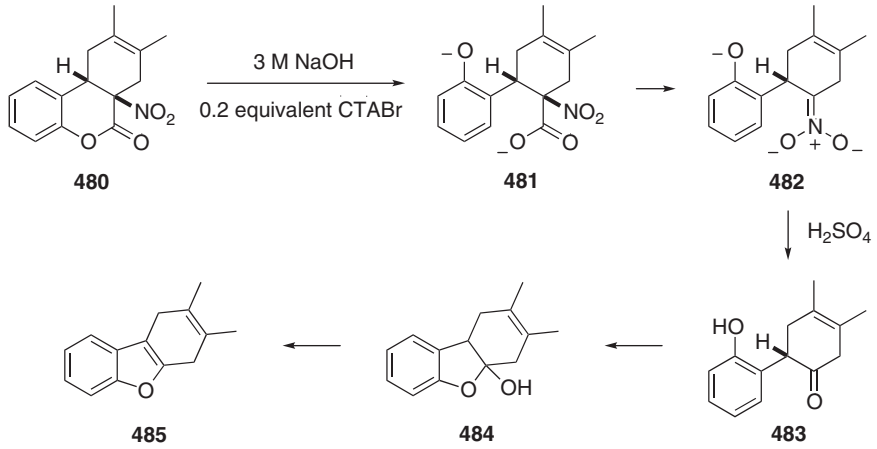
6.17.4.6.4 Fragmentation reactions

The nitronate moiety can act as a nucleofuge, resulting in fragmention reactions under Nef conditions. Nitro ketone **476a** reacted with methanolic KOH at reflux temperatures, followed by the addition of a $KMnO_4/MgSO_4$ mixture to deliver ketone **479a** in 87% yield (Scheme 83).[161] Addition of methoxide to the ketone group in **476** produces alkoxide **477**, which undergoes a ring-opening fragmentation to give intermediate nitronate **478**, which was hydrolyzed to give **479a**. Aldehyde **476b** afforded **479b** in 92% yield, and ester **476c** furnished **479c** in 70% yield under similar conditions.



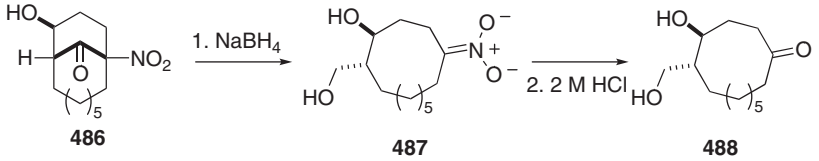
Scheme 83

The reaction of α-nitro lactone **480** with NaOH promoted a rearrangement cascade to produce benzofuran derivative **485** in 48% yield after the addition of H_2SO_4 (Scheme 84).[162] The reaction is initiated by the hydrolysis of the lactone to produce carboxylate **481**, which loses CO_2 to give nitronate **482**. Exposure of **482** to H_2SO_4 gave rise to ketone **483** that was captured by the phenolic oxygen to form hemiketal **484**. Finally, dehydration produced **485**.



Scheme 84

Reductive conditions can also promote fragmentation reactions. Thus, bicyclic ketone **486** reacted with $NaBH_4$ to give intermediate **487**, and further reaction with 2 M HCl delivered ketone **488** in 62% yield (Scheme 85).[163]



Scheme 85

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6.18 Eliminations to Form Alkenes, Allenes, and Alkynes and Related Reactions

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This article is a revision of the previous edition article by Adolf Krebs, Juergen Swienty-Busch, Vol. 6, pp 949–973, © 1991, Elsevier Ltd.

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6.18.1 Introduction

Elimination reactions are oxidative processes that generate π bonds through the removal (elimination) of two atoms, one of which is usually a hydrogen. These reactions differ from other methods of introducing unsaturation in that the reaction 'adds' double or triple bonds to an existing carbon framework. The term elimination is normally reserved for those processes that generate π bonds between carbon atoms.[1,2,3] When the newly formed π bond involves a heteroatom such as nitrogen or oxygen, the process is normally called an oxidation (Figure 1).

 doi:10.1016/B978-0-08-097742-3.00627-3

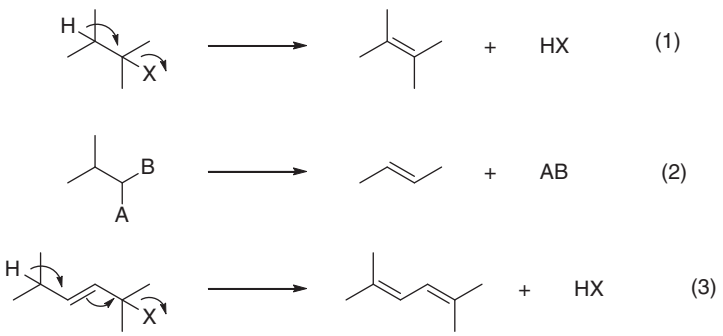


Figure 1 Types of elimination reactions.

The most common eliminations in organic synthesis are those that involve vicinal atoms, and these processes are normally called β-eliminations (equation 1). The elimination may result from the removal of two vicinal heteroatoms, but the majority of β-eliminations involve at least one hydrogen atom that is removed by an external base or solvent. In α-elimination processes, atoms are often removed through reactions that involve carbenes. The carbene intermediates then rearrange to produce carbon–carbon π bonds (equation 2). These reactions are often encountered when A and B are halogens and frequently involve metal halide exchanges. Such methods find utility in alkyne synthesis. Cascading processes that form conjugated systems are also possible (equation 3) but are somewhat less common. These reactions tend to be encountered during the preparation of complex ring systems.

6.18.2 β-Eliminations

These processes typically proceed through the loss of a leaving group and removal of a vicinal hydrogen, although in some cases both of the eliminated atoms may be heteroatoms. There are three general mechanisms for elimination reactions, which differ in the sequence of bond-breaking events.

The first pathway invokes a concerted process of bond formation and cleavage. The hydrogen and leaving group are removed in a single step, forming the double bond, through a process called an E2 (bimolecular) elimination (Figure 2).[4,5]

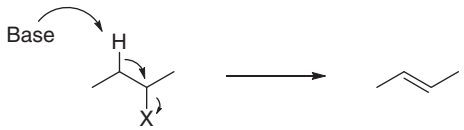


Figure 2 E2 Mechanism.

This mechanism proceeds through a single transition state that implicates the substrate and the base. Depending on the reaction conditions chosen, the bond-forming and -breaking events may not be completely synchronous. From a synthetic point of view, this should be kept in mind, as selectivity and yields can often be influenced by small changes in reagents or conditions. If the transition state is asynchronous, either the carbon–hydrogen bond or the carbon-leaving group bond may be elongated relative to the other. This produces a situation in which the elimination begins to adopt character of other β-elimination pathways (E1 or E1cb). This may have synthetic consequences (regiochemical and stereochemical), and the practitioner should always consider the possibility that a change in selectivity or yield could be due to a drift in mechanism.

E2 reactions may require the use of strong bases and/or elevated temperatures,[6] conditions that may pose difficulties for complex total synthesis. Regiochemistry and stereochemistry are under kinetic control in these processes and can be reliably predicted in many cases.

If the hydrogen is removed before the leaving group, an intermediate carbanion is formed and the mechanism is designated as an E1cb (unimolecular conjugate base) process. Typically, these reactions are favored when the carbanion is stabilized by the presence of electron-withdrawing groups adjacent to the carbanion site.[7,8] This class of elimination is extremely common in synthesis because conditions are mild and the reactions generally afford good regio- and stereocontrol (Figure 3).

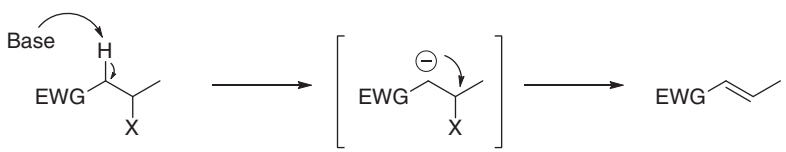


Figure 3 E1cb Mechanism.

E1cb reactions are followed when acidic hydrogens are found on the substrate, when the conjugate base is stabilized by an electron-withdrawing group or resonance. Any group capable of anion stabilization with an appropriately located leaving group can potentially produce an E1cb reaction. These processes are commonly encountered in Knoevenagel and other aldol-based processes.[9,10,11]

Considerable variation is possible in the E1cb process, depending on the acidity of the hydrogen, strength and concentration of the base, and nature of the leaving group.[12] If a large amount of base is used relative to the substrate, and the hydrogen is acidic enough, then the starting substrate will be completely converted into its conjugate base. This collapses the rate expression and the reaction will appear to follow first order kinetics (Figure 4).

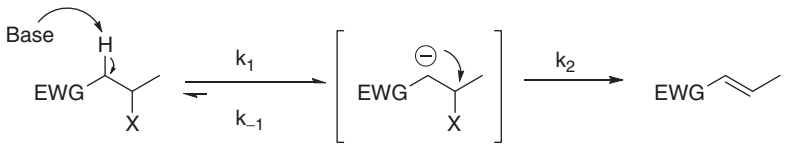


Figure 4 E1cb(anion).

These types of eliminations are very sensitive to the nature of the leaving group and electron-withdrawing function and are often associated with very strong electron-withdrawing groups adjacent to the carbanion. Such a reaction is called an E1cb(anion).

If reprotonation is relatively fast, the concentration of the base will influence the rate, and the reaction displays pseudo second-order kinetics (Figure 5).

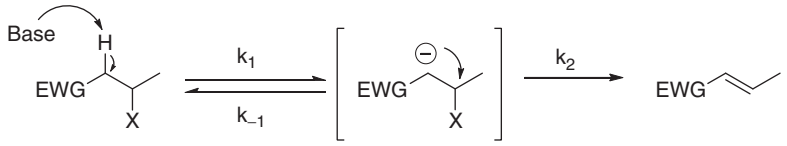


Figure 5 E1cb(reversible).

Such reactions are sensitive to the nature of the base and leaving group and are called E1cb(reversible) eliminations.

In some cases, reprotonation is very slow and therefore anion formation is essentially irreversible. These reactions are relatively insensitive to the nature of the leaving group, but the electron-withdrawing group has a large effect on the behavior of the reaction. Reactions of this type are designated as E1cb(irreversible) (Figure 6).

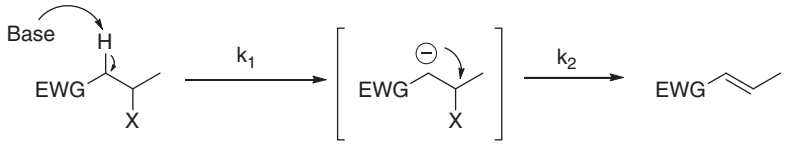


Figure 6 E1cb(irreversible).

From a synthetic point of view, E1cb reactions tend to give complete regioselectivity because the electron-withdrawing group determines the site of anion formation. This factor also promotes lower reaction temperatures and relatively mild reaction conditions. Stereoselectivity is kinetically controlled, but product distribution can often be predicted by the consideration of product stability. Because anion formation produces an intermediate enolate, stereochemical information may be lost, and product distribution is typically established during leaving group removal. Interactions in the transition state of this latter process tend to favor *E*-alkenes in the product. These reactions are very common in aldol processes.[11]

If the groups are removed in opposite order (leaving group first), a carbocation is implicated as an intermediate and the mechanism is designated as an E1 elimination. These types of reactions become dominant when conditions are favorable for the formation of carbocations. If the leaving group is located on a highly substituted carbon or if extensive delocalization of the carbocation is possible, E1 reactions are often encountered (Figure 7).[13]

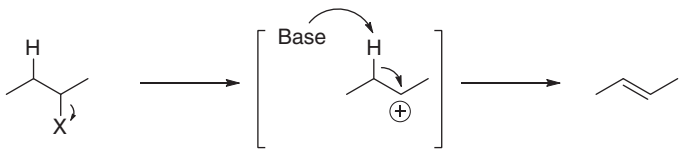


Figure 7 E1 Mechanism.

From a synthetic point of view, E1 reactions are usually avoided because they tend not to afford high levels of control. E1 processes are typically accompanied by significant amounts of substitution products, unless the base and solvent are extremely weak nucleophiles. Because E1 eliminations involve carbocations, rearrangements are also common side reactions. Stereochemical information is typically lost or attenuated in these reactions because of the planar nature of the intermediate carbocations. Some stereochemical memory may be retained if the departure of the leaving group can be impeded relative to the rate of hydrogen abstraction. Structural features that favor carbocations, such as increased substitution, resonance, or anchiomeric assistance, tend to favor E1 eliminations. Higher temperatures generally result in increased amounts of elimination relative to substitution.[3]

Because of the selectivity issues associated with unimolecular eliminations, these reactions are encountered less frequently than bimolecular processes in synthesis; however, E1 eliminations are commonly found in protecting group removal and installation.[14,15] For example, the commonly encountered *tert*-butoxycarbonyl and *tert*-butyl ester groups are both removed by performing E1 eliminations on the departing protecting function.

6.18.2.1 Mechanistic Drift

Because the degree of control and selectivity that is characteristic of each of these modes is highly variable, it is important to consider the mechanistic pathway that will most likely evolve from a chosen reaction when designing a synthesis.[12] Synthetic issues associated with these reactions typically revolve around issues of reliability, competition with substitution, stereoselectivity, and the control of regiochemistry. Many eliminations proceed by processes that are blends of more than one pathway. To describe these situations, More O'Farrall–Jencks plots were developed.[16–18] These plots are contour maps of potential energy surfaces for elimination reactions, plotted with respect to the bond orders of the departing groups (Figure 8).

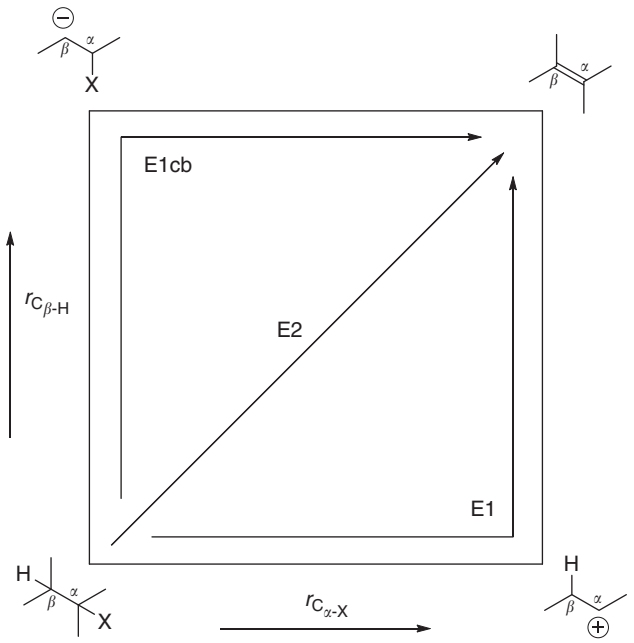


Figure 8 More O'Farrall–Jencks plot.

The vertical axis represents the bond order between the β-carbon and hydrogen, whereas the horizontal axis describes the dissociation of the bond between the α-carbon and leaving group. The plot is a projection of the potential energy surface of the substrate, and this energy is usually read along the third axis of the plot (above the plane and toward the reader), often shown in contour. An 'ideal' E2 reaction (C–H and C–X bonds break simultaneously) proceeds along an energy pathway that follows the diagonal between the starting material (located on the lower left-hand corner) and the products (on the upper right-hand corner) on the diagram (Figure 9).

Mechanistic drift may arise if either of the bond-cleaving events proceeds faster than the other. Reactions in which the C–H bond becomes elongated show deviations in the potential energy curve toward the top of the plot. If this proceeds to an extent that results in fracture of the C–H bond, an E1cb mechanism is followed. The mechanistic pathway for the E1cb, therefore, wraps around the left and top outside axes of the plot through the intermediate carbanion (Figure 10).

Reactions in which the leaving group is initially removed produce deviations toward the bottom of the plot. This is the situation for an E1 mechanism, in which (as in the case of the E1cb) the reaction follows a path toward the outside axes of the plot (Figure 11).

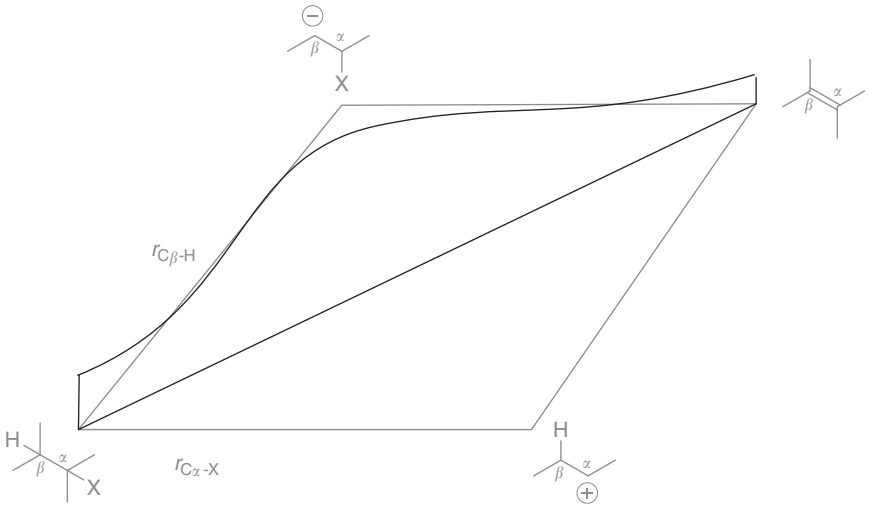


Figure 9 More O'Farrall–Jencks plot of an E2 reaction.

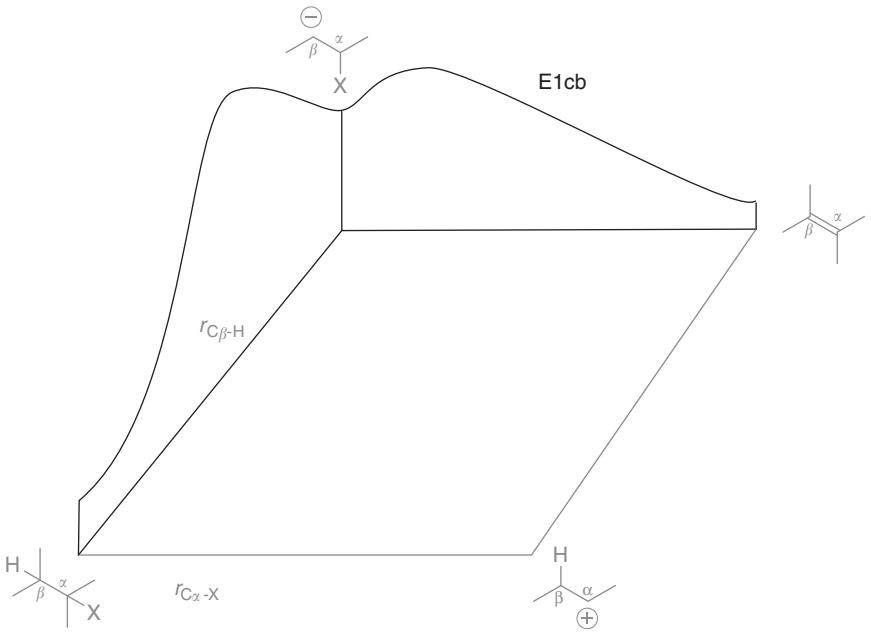


Figure 10 More O'Farrall–Jencks plot of an E1cb reaction.

Many reactions do not follow these ideal limiting situations, but instead occupy reaction coordinate trajectories that are intermediate between two extremes. An elimination reaction may exhibit characteristics of more than one reaction path, and the practitioner will have to take steps to ensure that enough control can be exerted in the reaction to ensure selectivity and conversion.

6.18.2.2 Elimination Versus Substitution

Because of the presence of leaving groups on the substrate, substitutions often compete with β-elimination reactions. The production of these side products is particularly problematic with E1 processes. If a nucleophilic solvent is used on a substrate capable of unimolecular elimination, the S_N1 pathway is usually faster and will dominate over the E1 sequence. This lack of control in E1 reactions makes the process an uncommon choice to produce unsaturation in synthetic sequences. However, E1 reactions are frequently encountered in protecting group chemistry.

Substitution is usually easier to suppress in the E2 and E1cb cases. In the E2 sequence, choosing a nonnucleophilic base can ensure that the elimination dominates and substituted products are minimized. Substitution is also disfavored if the leaving group

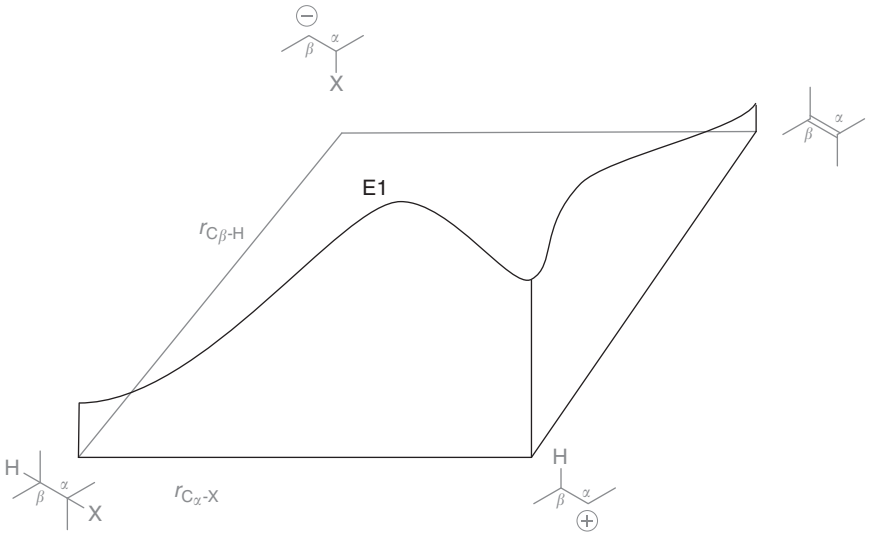


Figure 11 More O'Farrall–Jencks plot of an E1 reaction.

is located on a hindered position. Increasing the concentration of the base or using reverse addition of the substrate to the base is an effective strategy to limit substitution in E2 reactions. Other reaction conditions can generally be tuned to ensure high yields and stereoselectivity. These factors render E2 reactions suitable for synthesis; however, E2 reactions frequently require vigorous reaction conditions.[2–6]

The presence of electron-withdrawing groups on E1cb substrates usually ensures that the substrate behaves in the desired manner and eliminates rather than substituting. Elimination in E1cb-type substrates can also be promoted by increasing the strength and concentration of the base and by the presence of stronger electron-withdrawing groups. The products of E1cb reactions are often conjugated olefins, and these products are susceptible to Michael-type additions of extraneous nucleophiles. This type of product formation may be difficult to suppress.[10,11] However, such indirect substitutions are frequently employed, as the elimination/addition sequence is often more efficient than a standard S_N2 substitution (Figure 12).

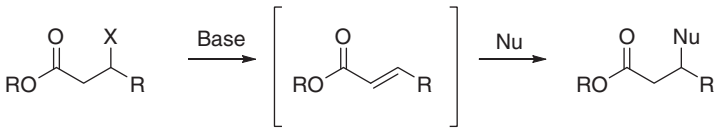


Figure 12 Elimination/addition sequence.

6.18.2.3 Regiochemical Control

The selective formation of regioisomers from elimination processes is frequently a significant concern from a synthetic point of view. If more than one β-hydrogen is available for removal, there arises the possibility that regioisomers may be obtained. Ensuring proper control from an elimination reaction can be complex, as many reaction parameters can influence the final location of the unsaturation. E1cb reactions represent the most straightforward case, because the most acidic hydrogen is the one that is removed. Regioselectivity is, therefore, dictated simply by the location of the electron-withdrawing group.

In other β-elimination processes, the products are usually differentiated by the degree of substitution on the resulting double bond. The product with the most substituents on the double bond is called the Zaitsev product,[19] whereas the compound with fewer groups on the unsaturation is labeled as the Hofmann product.[20,21] Resonance may override substitution and therefore conjugated olefins are usually preferred products when their formation is possible (Figure 13).

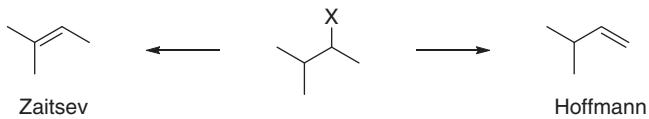


Figure 13 Zaitsev and Hofmann products.

The E1 reaction presents the most difficulties for regioselectivity and affords the least amount of control. Zaitsev's rule predicts that eliminations conducted under basic conditions will predominately produce the more highly substituted alkene.[22] Therefore, product distribution can be predicted by considering product stability. It should be noted that product ratios are often somewhat low in these reactions (less than 4:1 is typical). This selectivity is actually a result of kinetic control when basic conditions are used, proceeding more readily through the transition states leading to the more substituted products.

If acidic conditions are employed, the regiochemistry of an E1 reaction will often revert to thermodynamic control because reprotonation of the alkene may occur to regenerate a carbocation. Substitution generally stabilizes double bonds, and so the Zaitsev product is usually favored in these reactions. Unfortunately, the tendency for reprotonation tends to promote rearrangements. These rearrangement processes are extremely common in E1 reactions and this can further erode selectivity.

Predicting regiochemistry in E2 reactions is more complex. Bimolecular elimination in acyclic systems generally favors the Zaitsev products. This is because the transition states for E2 reactions carry significant double bond character, and factors that stabilize double bonds, therefore, stabilize the transition states leading to them. Product distribution is also affected by statistical factors, which erode selectivity for the Zaitsev products, and so the ratios of products obtained may be somewhat low (Figure 14).[23]

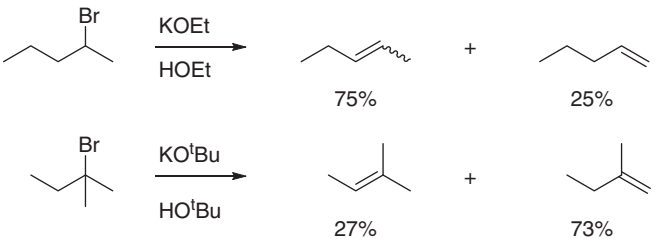


Figure 14 Effect of base sterics on product distribution.

Regioselectivity in E2 eliminations may be reversed to favor production of the less substituted olefin (Hofmann product) when bulky bases are used to remove the proton. The large base becomes encumbered when approaching highly substituted carbons, and so removal of a hydrogen from the less substituted position becomes more favorable, resulting in the production of the Hofmann product. Using stronger bases will also often lead to the selective formation of Hofmann isomers.[24,25] Hofmann products may also be obtained from E2 reactions when positively charged leaving groups, such as tetralkylammonium and sulfonium salts, are employed.[26] These processes may proceed via ylide formation. Experiments suggest that selectivity is primarily due to steric effects wherein gauche interactions are avoided in the transition state leading to the less-substituted alkene, as the use of large leaving groups (charged or neutral) generally leads to the production of Hofmann products (Figure 15).[27,28]

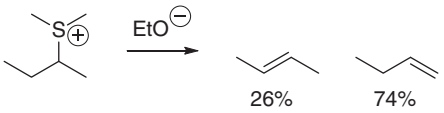


Figure 15 Charged leaving groups produce Hofmann products.

Reactions that proceed through cyclic transition states tend to produce Hofmann products. The Cope elimination provides a way to produce π bonds of less-substituted regiochemistries.[29] The *N*-oxide removes the β-hydrogen through a cyclic transition state that favors substitution. Other leaving groups that can provide cyclic mechanisms also produce Hofmann products.[30] The use of sulfoxide or sulfone-leaving groups may afford the Hofmann product if used to prepare alkenes. Hydrogen removal is achieved by the sulfoxide oxygen (Figure 16).

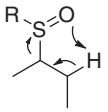


Figure 16 Cope elimination.

Hindered sulfoxides provide an interesting case of regiocontrol by the elimination of diastereomeric leaving groups. Using cholestanes as rigid scaffolds, and adamantyl substituted sulfoxides as leaving groups, complete regiocontrol could be exerted at secondary positions. The selectivity in these reactions was proposed to be a consequence of conformational restrictions dictating the trajectory of base approach in E2 reactions (Figure 17).[31]

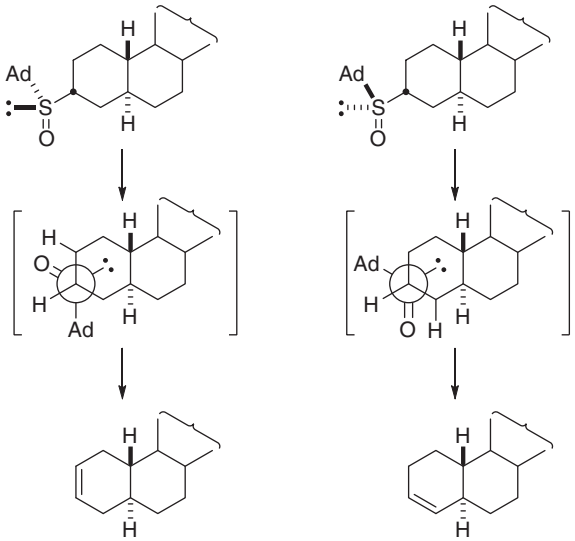


Figure 17 Stereochemical effects in sulfoxide eliminations.

Selenoxide elimination is a popular method for the introduction of unsaturation onto molecules. The phenylselenide group is readily introduced through the use of standard carbanion chemistry and provides a convenient installation tool for double-bond assembly. Selenium is readily oxidized and the eliminations themselves require relatively little thermal persuasion.[32,33] Other functional groups such as esters, xanthates, and sulfoxides have also been used, although these functionalities may require higher temperatures for elimination.

Regioselectivity in cyclic systems is often dependent on orbital alignment. The E2 reaction is stereospecific and usually proceeds from conformations in which the hydrogen and leaving group are antiperiplanar to each other. In such conformations, the carbon–hydrogen σ bond is able to overlap the σ^* orbital of the carbon-leaving group bond achieving a smooth flow of electrons during the course of the reaction (Figure 18).

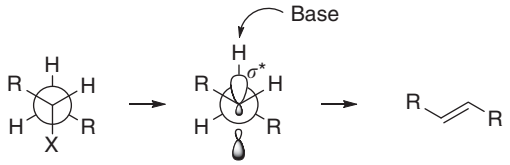


Figure 18 Orbital alignment in E2 eliminations.

Antiperiplanar conformations are normally easy for acyclic molecules to sample, and these materials typically follow a reaction pathway that implicates antiperiplanar conformations. This alignment affords the best overlap between the fracturing carbon–hydrogen σ bond and the accepting σ^* orbital and provides a staggered transition state; therefore, conformers that provide these alignments give eliminations.

In cyclic systems, the requirement for orbital alignment dictates that the hydrogen and leaving group adopt a *trans*-diaxial (or pseudo *trans*-diaxial) alignment. This tends to decelerate those eliminations in which the leaving group is equatorial in the low-energy conformer. In conformationally restricted systems, these reactions may proceed extremely slowly or not at all. Geometrical constraints dictate that regiochemistry in ring systems will depend on the relative configuration between the hydrogen and leaving group. A classic example is that of the E2 elimination of menthyl and neomenthyl chlorides.[34] Menthyl chloride eliminates slowly because the conformer in which the chlorine is antiperiplanar to a hydrogen is relatively unpopulated. Only one hydrogen is available to react in this compound; therefore, the E2 elimination is completely regioselective (Figure 19).

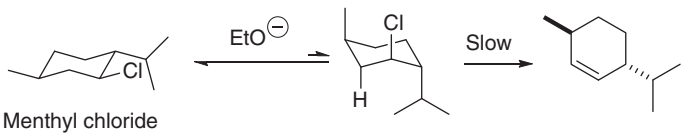


Figure 19 E2 Elimination of menthyl chloride.

The most stable conformer of neomenthyl chloride is also the reactive one, and so neomenthyl chloride reacts much more rapidly than menthyl chloride does. In the reactive conformation, two hydrogens are available for removal, resulting in the production of a mixture. Note that regioselection follows Zaitsev's rule; however, the selectivity is not large (Figure 20).

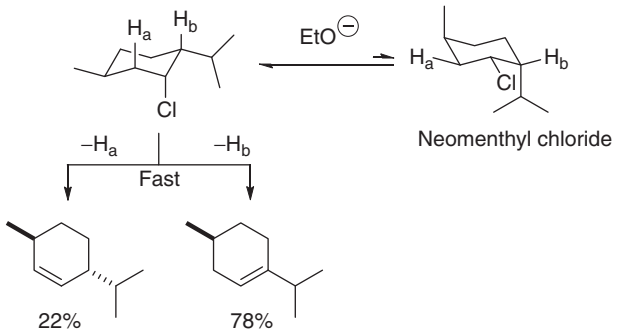


Figure 20 E2 Elimination of neomenthyl chloride.

6.18.2.4 Stereoselectivity

The selective formation of *E*- or *Z*-isomers from elimination processes is a significant concern from a synthetic point of view. Not only does low selectivity impact yields, but also *E*- and *Z*-olefins are often very difficult to separate from each another. This challenge can significantly erode the purity of final products and may produce unwanted effects in subsequent transformations.

Unimolecular eliminations show preference for *E*-isomers.[2–5,13] In the final transition states leading to products, both the E1 and E1cb processes must proceed through conformations that align filled and empty orbitals. In the E1 reaction, the C–H σ bond must align with the empty p orbital of the carbocation to complete the formation of the double bond. This creates steric interactions in the transition state leading to the *Z*-isomer, resulting in a preference for the *E*-product. Ratios of *Z*- to *E*-products are, however, normally low (Figure 21).

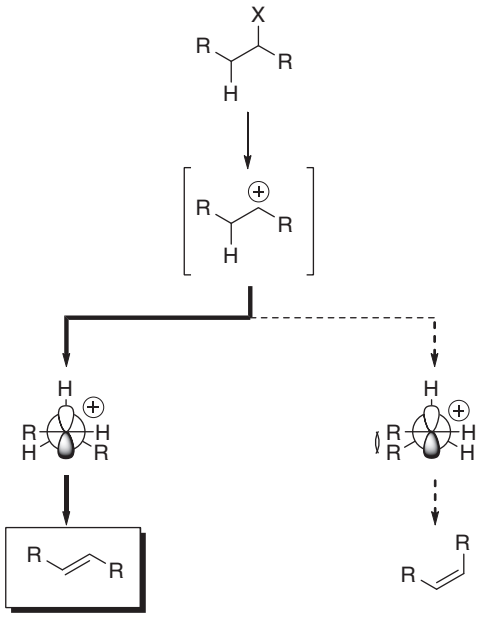


Figure 21 Stereochemical preference in E1 eliminations.

In the E1cb process, a similar situation exists. This reaction requires that the filled π orbital of the enolate become coplanar with the empty σ^* orbital of the leaving group. This alignment produces steric interference in transition states leading to the *Z*-isomers, and so *E*-products are favored (Figure 22).

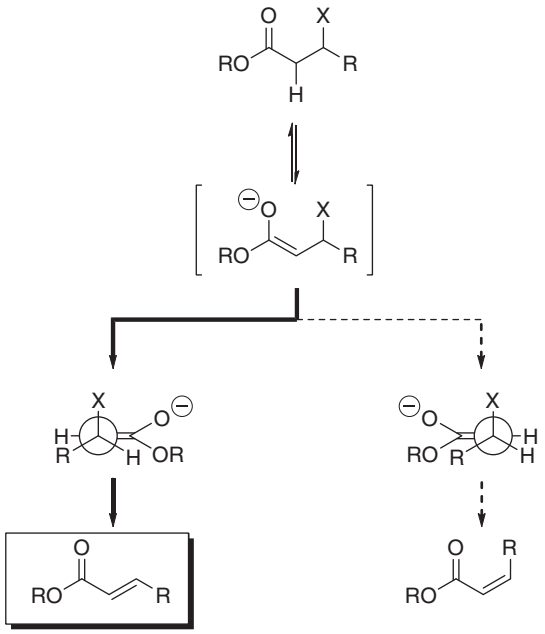


Figure 22 Stereochemical preference in E1cb eliminations.

The prediction of stereochemistry in E2 reactions may require conformational analysis.[5] For acyclic systems, if two hydrogens are available for removal, the base will tend to remove the hydrogen that results in *E*-isomer formation, because of steric interactions that are generated in the *Z*-selective transition states (Figure 23).

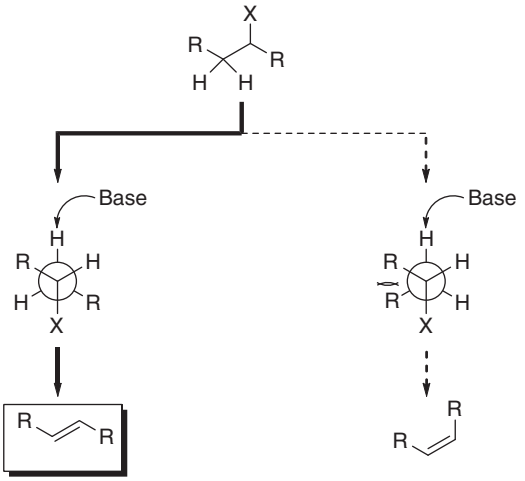


Figure 23 Stereochemical preference in E2 eliminations.

If the removal of only one hydrogen is possible, the stereochemical disposition between the two carbons will determine the stereochemistry of the final product. Examination of a Newman projection can be used to predict the stereochemical outcome of the product.

In some cases, antiperiplanar alignment is difficult, and so a synperiplanar attitude is adopted during elimination. This synperiplanar route is typically disfavored because such conformations are eclipsed, but these pathways can become dominant if the leaving group is capable of undergoing elimination through a cyclic intermediate or transition state. The syn pathway is often encountered in cyclic systems that disfavor antiperiplanar orientations of hydrogen and leaving group.[35,36] This may occur when tetraalkylammonium-leaving groups are employed. In these cases, the positively charged group may interact with the negatively charged base, resulting in removal of the hydrogen in a synperiplanar reaction (Figure 24).

Cope-type eliminations must also follow the synperiplanar pathway.[37] Oxidation of a fully substituted amine to produce the *N*-oxide followed by heating results in synperiplanar hydrogen abstraction through a cyclic transition state.

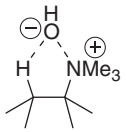


Figure 24 Stereochemical preference with charged leaving groups.

Selenoxide eliminations are commonly used in modern synthesis. The selenide is easily installed and eliminates readily on oxidation. In the example below, the exocyclic double bond is formed preferentially by virtue of the synperiplanar route.[38] Synperiplanar elimination is only possible with a methyl hydrogen. In other cases, the eclipsed nature of the conformers in the transition state may make alignment difficult (Figure 25).[38]

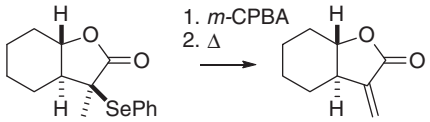


Figure 25 Synperiplanar eliminations of selenoxides.

6.18.3 α-Eliminations

The elimination of two geminal atoms typically involves carbene processes, although some reactions can utilize the β-elimination manifold. Exposing 1,1-vinyl dihalides to organolithiums brings about a Fritsch–Buttenberg–Wiechell rearrangement.[39–41] This process passes through a carbene intermediate that then rearranges to form an alkyne or, in some cases, an allene (Figure 26).



Figure 26 α-Elimination reactions.

These reactions can be carried out with a variety of bases and metals. Lithium is particularly popular, as the initial lithium–halogen exchange is often extremely fast.[42,43] Geminally substituted dibromocyclopropanes can be converted into allenes through a related mechanism. Exposure to magnesium or sodium will trigger the formation of a carbene via metal–halogen exchange.[44] Using other bases, such as methyllithium, will bring about the formation of the same intermediate. Regiochemical and stereochemical issues are not normally problematic in α-eliminations because of the nature of the products.

6.18.4 Stereoselective Methods

6.18.4.1 Eliminations to Form *E*-Alkenes

E-Alkenes are found in a variety of biologically and synthetically valuable compounds. The ability to make *E*-alkenes stereoselectively is significant in synthesis, as the separation from the *Z*-isomers is often not a trivial task. There are a variety of different eliminations that produce doubly substituted *E*-alkenes from nondiastereopure precursors. Stereoselectivity in most of these processes is a consequence of unfavorable interactions in transition states leading to the *Z*-isomers. This influences the selection of the removed hydrogen by favoring productive substrate conformations. In the case of synperiplanar elimination, the *E*-product is also preferentially formed in acyclic systems (Figure 27).

6.18.4.1.1 Doubly substituted alkenes from alkyl halides

Secondary and tertiary alkyl halides can be eliminated to form the corresponding olefins by heating in the presence of an appropriate base.[5] Eliminations of primary halides are usually difficult because competition with substitution processes dominates.[45] Regiocontrol can usually be achieved by careful base selection because bulky or very strong bases tend to produce the less-substituted (Hofmann) materials, whereas smaller bases favor Zaitsev products. In either case, product ratios are normally somewhat low. When stereoisomers are possible, the *E*-isomer is normally produced in excess, although the level of selectivity may not be spectacular. Alkoxide bases are commonly used in the appropriate alcohol solvent to bring about these transformations,

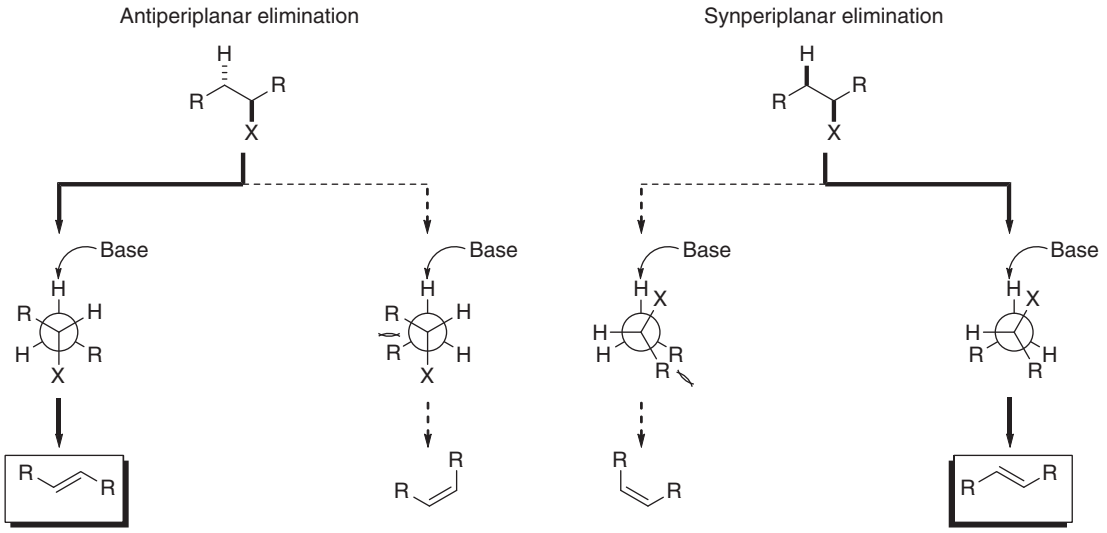


Figure 27 E2 Elimination to form *E*-alkenes.

although tertiary amines are also popular choices.[5] In recent applications, amide bases such as lithium diisopropylamide (LDA) have been increasingly employed.[46,47]

Strong hindered bases, such as 1,5-diazabicyclo(4.3.0)non-5-ene (DBN) or 1,8-diazabicycloundec-7-ene (DBU), have been popular choices in synthesis.[48–50] DBN or DBU are usually required in excess,[51] and their use often results in only moderate yields. To address some of these downfalls, the commercially available nonionic superbase $P(CH_3NCH_2CH_2)_3N$ has been employed to perform dehydrohalogenations on primary and secondary alkyl halides.[52] Both alkyl and aryl alkenes were synthesized by this method. Notably, the use of this base gave exclusive access to the *E*-isomers (Figure 28).

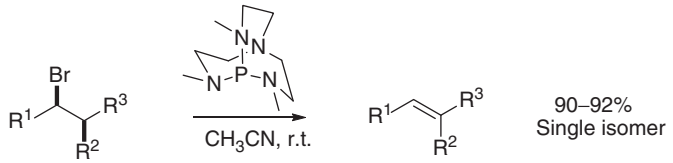


Figure 28 Dehydrohalogenation with nonionic superbase.

An extension of this method used a modified procatalyst[53] that was less expensive and more stable than the original base (Figure 29).

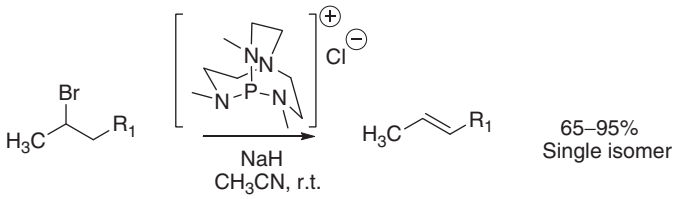


Figure 29 Dehydrohalogenation with nonionic superbase procatalyst system.

6.18.4.1.2 Doubly substituted alkenes from alcohols

The dehydration of alcohols may require strongly acidic conditions that tend to encourage unimolecular (E1) mechanisms.[54,55] This can erode the synthetic utility of the method because rearrangements and substitutions become competitive processes. Regioselectivity can also be a problem in these transformations. Many of these issues can be alleviated through conversion of the alcohol to a sulfonate ester or other efficient leaving group. This expedient provides access to bimolecular pathways for more control and milder reaction conditions.[56,57]

Terminal epoxides can be transformed into *E*-alkenes by the use of a lithium amide base in combination with a variety of organolithiums or Grignard reagents[58,59] to prepare diverse alkenes both stereo- and regioselectively. By adding the hindered base lithium 2,2,6,6-tetramethylpiperidide (LTMP), the researchers were able to selectively deprotonate the epoxide *trans* to the existing

substituent. Addition of an organolithium then opened the epoxide, setting the stage for *syn* elimination of Li_2O and formation of an *E*-olefin (Figure 30).

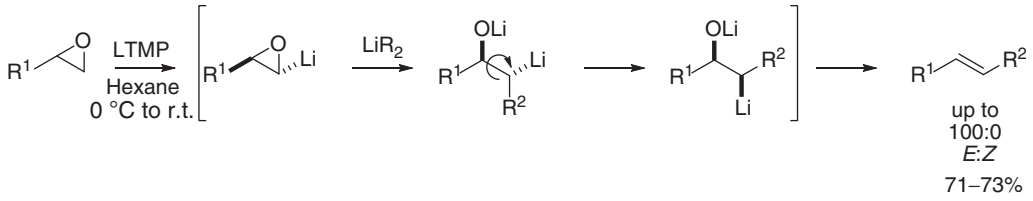


Figure 30 Conversion of terminal epoxides into *E*-alkenes.

The stereochemistry of the α-lithiated epoxide was important for controlling the geometry of the alkene product.[60] This was demonstrated through the use of isotopically labeled epoxides. When a *cis* deuterated epoxide was subjected to the reaction, the product was obtained as a 98:2 mixture of *E*- and *Z*-isomers, both of which had high deuterium content (94% and 96%, respectively). This suggested that the initial lithiation had occurred *trans* to the alkyl group (Figure 31).

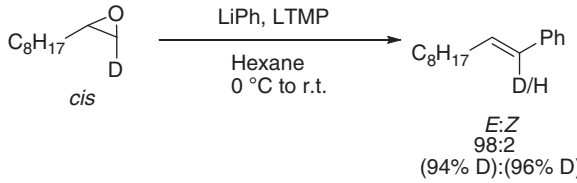


Figure 31 Isotopic labels show site of initial lithiation.

Employing the *trans*-labeled epoxide resulted in much lower *E*/*Z*-selectivity. Significantly, the *E*-isomer contained very little deuterium, consistent with *trans* deprotonation. The *Z*-isomer had very high deuterium content, suggesting that a kinetic isotope effect had resulted in significant *cis* lithiation that was the pathway leading to the *Z*-isomer (Figure 32).

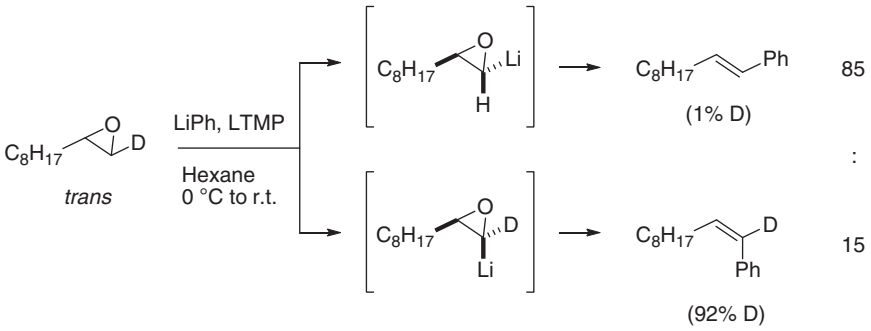


Figure 32 Kinetic isotope effect favors the *Z*-isomer.

The dehydration of alcohols to form *E*-alkenes has been performed with reagents such as anhydrous $CuSO_4$,[61] $POCl_3$,[62] $SOCl_2$,[63] or I_2.[64] As an example, β-methylstyrene was prepared, with a 91:9 *E*:*Z* ratio in 69% yield with only catalytic $CuSO_4$ and the neat alcohol (Figure 33).[61]

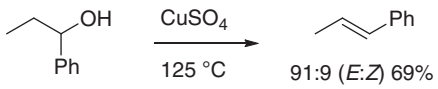


Figure 33 *E*-Alkenes from alcohol dehydration.

A mild, efficient method for the stereoselective production of *E*-aryl alkenes[65] using ethers in neutral ionic liquids and microwave irradiation has been developed. The reactions minimize the formation of unwanted by-products that often arise when

dehydrations are carried out under more harsh conditions.[66] Dimethylsulfoxide (DMSO) has also been used to accomplish the mild dehydration of alcohols by simple heating (Figure 34).[67,68]



Figure 34 Alcohol dehydration in DMSO.

6.18.4.1.3 Doubly substituted alkenes from vicinal dihalides

The dehalogenation of *vic*-dihalides is a common method for the synthesis of alkenes. The reaction may be considered by some to be a deprotection because the vicinal halides are normally prepared from alkenes, and so sometimes serve as protecting groups for double bonds.[69] The sequence of halogenation and then dehalogenation has also been employed for the purpose of olefin inversion.[60] Many organometallic reagents[70,71] and metal catalysts[72–74] have been used for this purpose. A few of the reported methods favor *E*-isomers, but many are nonselective.[6]

An example of an organometallic approach to *vic*-dehalogenation utilizes organodisodium reagents to produce the corresponding alkenes with high yields (more than 90%) and stereoselectivities (up to 100:0 for the *E*-isomer).[75] The reaction was thought to proceed through a single-electron transfer process (Figure 35).

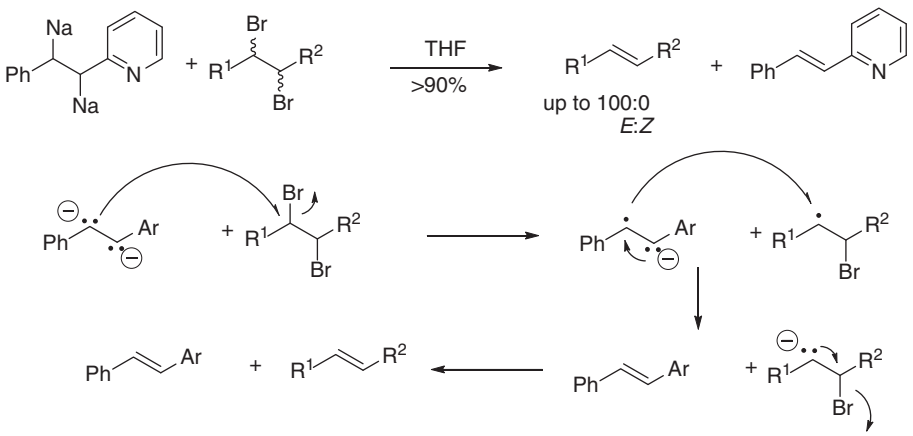


Figure 35 *E*-Alkenes from vicinal dihalides.

6.18.4.1.4 Doubly substituted alkenes using other leaving groups

o-Nitrophenyl sulfoxides have been employed as leaving groups[76] to give rise to both terminal and disubstituted alkenes, as well as α,β-unsaturated esters with high *E*-stereoselectivities. A particular advantage of this method is the facile purification of the alkene through precipitation of the sulfenic acid salt during the course of the reaction (Figure 36).

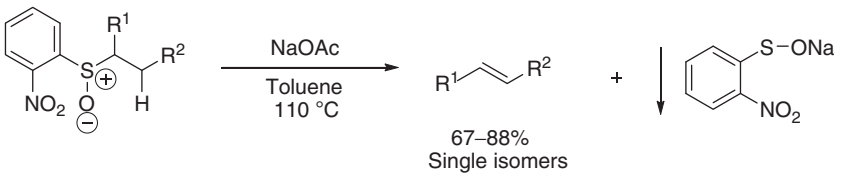


Figure 36 *E*-Alkenes from nitrophenyl sulfoxides.

Sulfone-leaving groups have been used to prepare olefins using the elimination of arenesulfinic acids to produce *E*-alkenes as well as trisubstituted alkenes. Both alkyl–aryl-substituted and alkyl–allyl-substituted alkenes were produced via this arenesulfinic acid elimination reaction (Figure 37).[77]

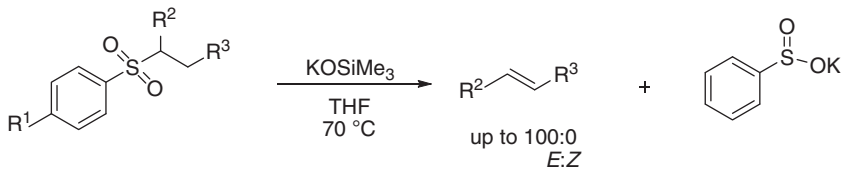


Figure 37 *E*-Alkenes from sulfones.

The use of samarium to promote eliminations which form *E*-nitroalkenes with selectivities higher than 98:2 *E*:*Z* has been described.[78] Eliminations to provide *E*-α,β-unsaturated esters[79] and primary amines[80] stereoselectively were also possible. Additionally, the use of manganese to provide alkenes stereoselectively by elimination has been disclosed.[81,82] The selectivity for the *E*-isomer in this process was thought to be a consequence of a half-chair transition state operating under chelation control, in which the R group was located in a pseudoequatorial position (Figure 38).

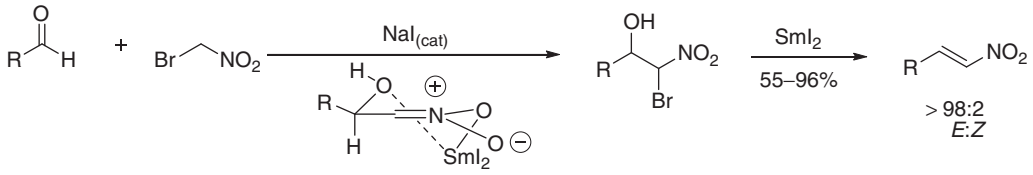


Figure 38 Samarium promoted eliminations to form *E*-Alkenes.

E-Alkenes have been produced from an interesting method involving acetylenes.[83] Various alkyl, aryl, and cyclic alkynes could be converted into their respective alkenes via vicinal borane intermediates. Selectivities ranged from 78:22 in favor of the *E*-isomer to up to complete *E*-selectivity (Figure 39).

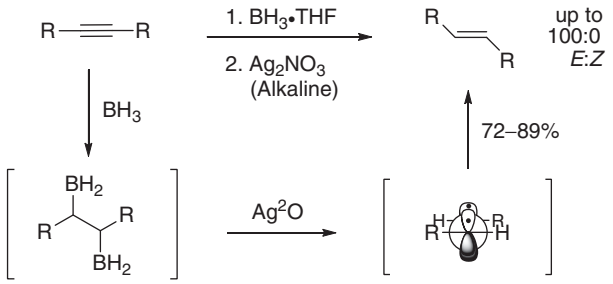


Figure 39 *E*-Alkenes from alkynes.

The removal of nitro groups from nitroalkanes using radical conditions has been employed as a way to prepare *E*-alkenes with some selectivity.[84] The carbon radicals were generated using a Barton ester, and *E*-selectivities of up to 6:1 *E*:*Z* were realized (Figure 40).

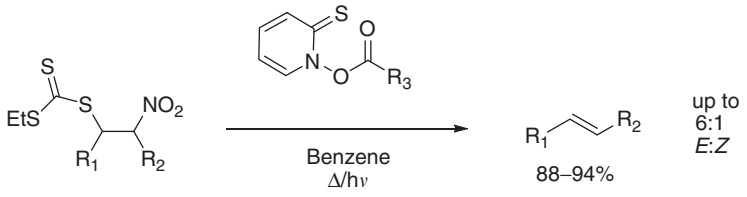


Figure 40 *E*-Alkenes from radical eliminations.

A stereoselective formation of polyenes that consisted of a double elimination involving β-acetoxy sulfones using potassium *tert*-butoxide as base was reported.[85] Polyenes, diynes, and enynes were obtained in good yields, and moderate to excellent selectivities were obtained in the case of the polyenes. This method was used to synthesize dienamides and dienic esters stereoselectively in excellent yields (Figure 41).[86]

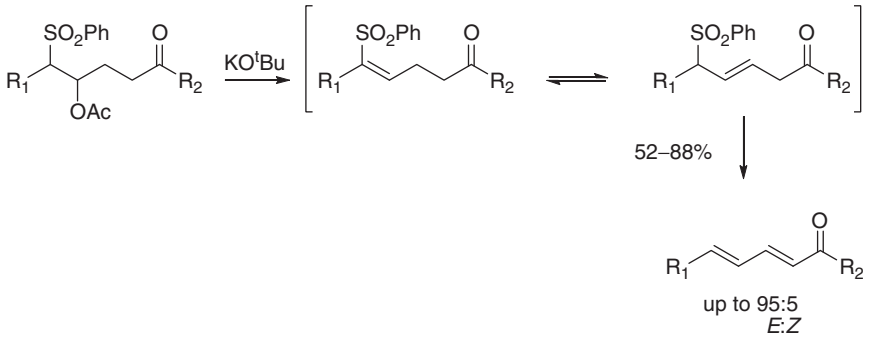


Figure 41 Stereoselective eliminations forming polyenes.

Application of the method to a dienamide-containing natural product resulted in a facile and efficient synthesis of a larvicide, isolated from *Spilanthes mauritiana*, which had previously been used to control the population of *Anopheles* mosquitoes.[87] The key step involved a double elimination reaction to form a key intermediate in the sequence. A similar method has been used in the synthesis of *d*,*l*-muscone as well as methyl retinoate (Figure 42).[87]

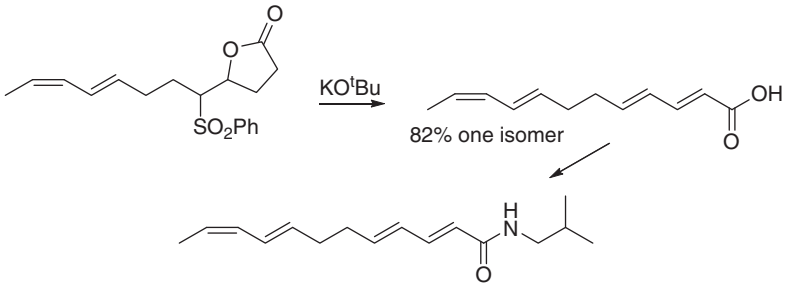


Figure 42 Stereoselective elimination in the synthesis of a natural product.

An *E*-stereoselective synthesis of α,β-unsaturated esters and ketones using sulfides was reported[88] involving the sulfenylation–dehydrosulfenylation of enolates. This method produced α,β-unsaturated esters and ketones in good yields and complete *E*-selectivity (Figure 43).

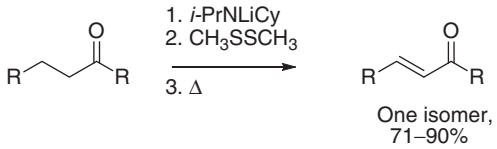


Figure 43 Stereoselective elimination of sulfides.

This thermal elimination of β-ketosulfoxides was employed[89] to make a key α,β-unsaturated ketone intermediate, as a single isomer, that was used in the synthesis of C-ring-modified estrogen derivatives (Figure 44).

Eliminations involving β-acyloxysulfones are generally associated with the Julia–Lythgoe olefination.[90] The elimination step in these olefin-forming reactions is typically initiated reductively by either Na/Hg amalgam[91] or by the use of samarium iodide and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU).[92] Both methods generally give high selectivities for the *E*-isomer. The latter method has been recently applied in the synthesis of haminol A, an alarm pheromone found in cephalospidean molluscs. The stereoselective installation of two of the alkenes in the triene was accomplished by treatment of the benzoyloxysulfone with samarium iodide in THF/DMPU (Figure 45).

The Julia–Lythgoe[93,94] and Kocienski[95] syntheses are popular ways to construct alkenes, involving elimination reactions in the final step. Related methods for olefin production that employ eliminations are named reactions such as the Wittig,[96] Peterson,[97–99] Seyferth–Gilbert,[100] and Horner–Wadsworth–Emmons [101] homologation. Some aldol processes have been employed to prepare alkenes by *in situ* E1cb processes.[102,103]

6.18.4.2 Eliminations to Form *Z*-Alkenes

Elimination methods for the stereoselective preparation of *Z*-alkenes are considerably less common than methods that afford the *E*-isomers. *Z*-alkenes can be found in many biologically important molecules[104,105] and their preparation is commonly achieved

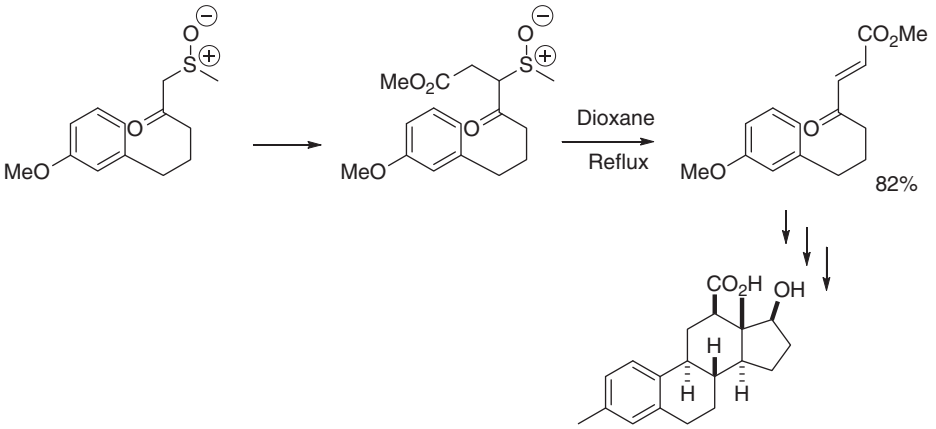


Figure 44 Thermal elimination of β-ketosulfoxides.

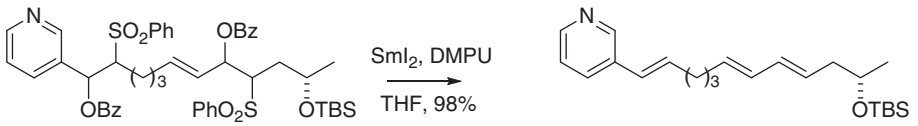


Figure 45 Eliminations involving β-acyloxysulfones.

by methods such as alkyne reduction or Wittig-type processes. Nevertheless, some success has been realized in the development of *Z*-selective eliminations.

6.18.4.2.1 Disubstituted Z-alkenes

The stereoselective synthesis of unfunctionalized *Z*-alkenes was accomplished by utilizing nondiastereopure *O*-acetylchlorohydrins and samarium iodide.[106] Using this method, *Z*-alkenes were obtained in selectivities of up to 98:2 *Z*:*E*, bearing simple alkyl substituents. The use of aryl-substituted *O*-acetylchlorohydrins resulted in a reversal of selectivity to produce the *E*-isomer, with ratios as high as 8:92 *Z*:*E* being observed in these cases. The authors proposed a mechanism for this observation that involved chelation of the Sm^{III} center with the oxygen of the carbonyl in the acetoxy group, giving rise to a six-membered transition state. The high *Z*-selectivity was rationalized by assuming that there was one diastereomer that had a conformation that more readily coordinated to the Sm^{III}, whereas the other diastereomer slowly epimerized into the reactive form (Figure 46).

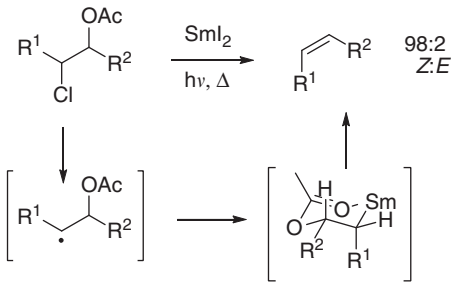


Figure 46 Samarium promoted elimination of acetylchlorohydrins to give *Z*-alkenes.

Samarium iodide has been employed to obtain a variety of functionalized *Z*-alkene products stereoselectively, including *Z*-vinyl halides,[107] *Z*-vinylsilanes,[108] *Z*-allylsilanes,[109] and *Z*-β,γ-unsaturated nitriles.[110] All have been prepared with good yields and selectivities using this technology.

The stereoselective preparation of nonfunctionalized *Z*-alkenes has been carried out by utilizing a zinc homologation–elimination reaction.[111] In this method, α-sulfinyl carbanions were reacted with zinc carbenoids and subsequently eliminated to give *Z*-alkenes with up to 20:1 *Z*:*E* selectivity (Figure 47).

The total synthesis of (+)-crocacin A was carried out by employing an elimination reaction as the final synthetic step in order to provide the product enamide with complete *Z*-selectivity.[104] This key step utilized a Peterson elimination[112–114] process employing tetra-*n*-butylammonium fluoride (TBAF) to afford an oxyanion intermediate that underwent the elimination to afford the *Z*-enamide (Figure 48).

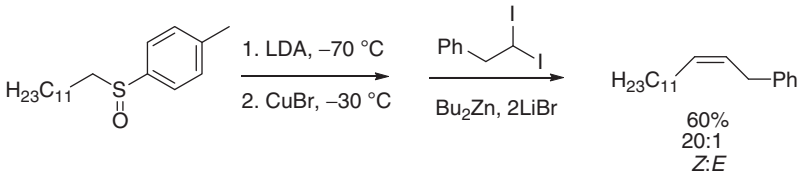


Figure 47 Elimination of sulfinyl groups to give *Z*-alkenes.

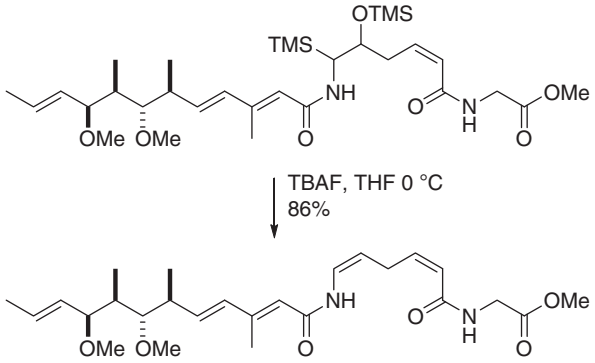


Figure 48 *Z*-Selective elimination in the synthesis of (+)-crocacin A.

6.18.4.3 Trisubstituted Alkenes

The stereocontrolled synthesis of trisubstituted olefins has applications in the preparation of many bioactive molecules. *β*-Elimination reactions are often preferred to alternative methods of stereoselective alkene construction, such as the Wittig reaction for these processes, and are often associated with aldol processes.[11]

The stereoselective conversion of Baylis–Hillman adducts into trisubstituted alkenes has been investigated by a few different research groups in recent years to obtain trisubstituted olefins with complete *E*-stereoselectivity.[115] The observed selectivity could be rationalized by consideration of the transition states leading to the formation of the *E*- and *Z*-products, respectively. In the case of the transition state leading to the *Z*-alkene, $A_{(1,3)}$ strain was operative. When nitriles were employed as electron-withdrawing groups, the selectivity favored the *Z*-alkene product (Figure 49).

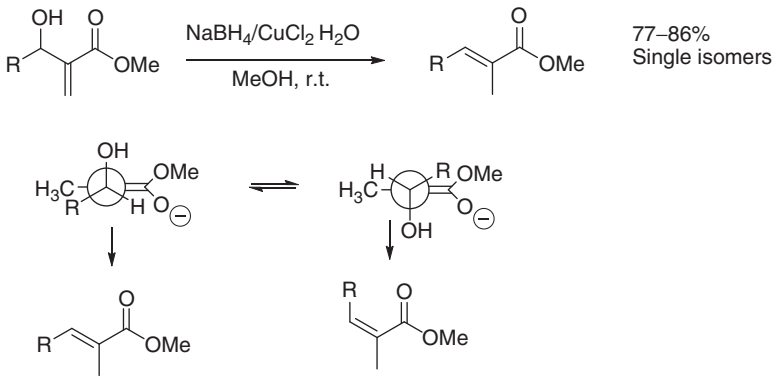


Figure 49 Stereoselective eliminations during the Baylis–Hillman process.

An alternative method of stereoselectively converting Baylis–Hillman adducts into trisubstituted *E*-alkenes was investigated recently.[116,117] In this method, SmI_2 was used with Baylis–Hillman adducts, or the corresponding acetates were treated with Sm powder in the presence of a catalytic amount of I_2, to furnish the desired trisubstituted alkenes with exclusive *E*-selectivity. The high *E*-selectivity was rationalized by a model employing chelation control (Figure 50).

The *E*-stereoselective synthesis of trisubstituted nitroolefins was accomplished using a copper-mediated addition–elimination reaction.[118] The authors found that the addition of cuprates onto 2-nitro-1-phenylthiopropene derivatives gave the corresponding

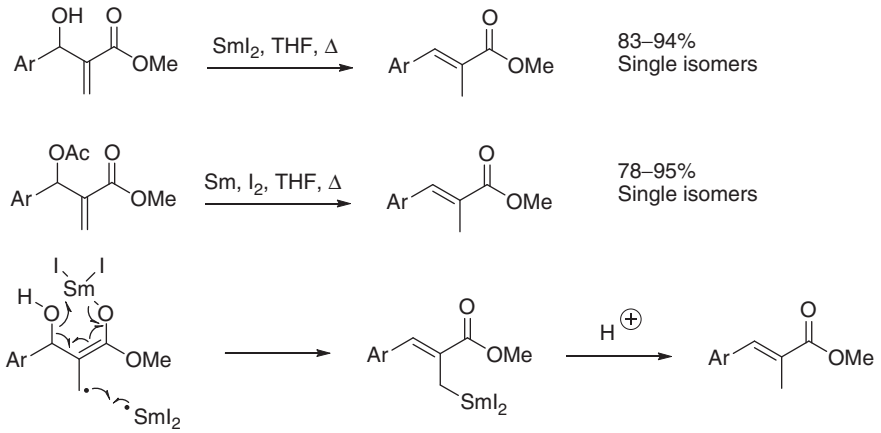


Figure 50 Samarium promoted stereoselective eliminations in Baylis–Hillman reactions.

trisubstituted nitroalkenes. Oxophillic reagents such as Grignards or organolithiums tended to produce only addition, with no detected elimination products.

Nitroalkenes can be useful synthetic intermediates in Michael additions and cycloaddition reactions[119]; therefore, stereoselective methods of preparing these compounds can be very important. The origin of the *E*-stereoselectivity was proposed by the authors to arise from a conformation in which allylic strain was minimal (Figure 51).

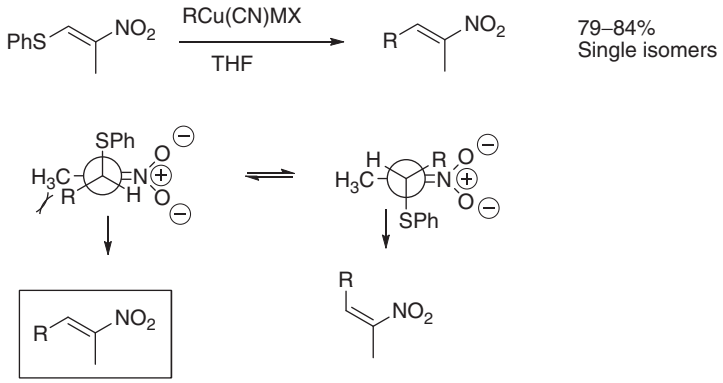


Figure 51 Stereoselective eliminations to *E*-nitroalkenes.

Dihaloalkanes can be used as a protection strategy for syntheses involving vulnerable alkenes,[60] provided that a stereoselective dehalogenation reaction exists for unmasking the alkene. Toward this end, a stereoselective radical debromination utilizing Ru(bpy)$_3$Cl$_2$ as a visible light photoredox catalyst[120] was developed to obtain the *E*-trisubstituted olefins stereoselectively from a series of dibromoalkanes. Stereoselectivity was rationalized by the authors as arising from a radical intermediate which could break down to form the thermodynamically more stable *E*-alkenes (Figure 52).

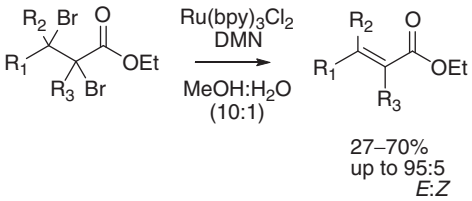


Figure 52 Elimination of vicinal dihalides to trisubstituted alkenes.

Methods to produce trisubstituted fluoroalkenoates have become somewhat popular in recent years, owing to the high importance of fluorinated derivatives in medicinal chemistry,[121] crop protection,[122] and modified pheromones.[123] An early approach to synthesizing *Z*-fluoroalkenoates stereoselectively was demonstrated in 1991.[124] In this method, α-fluorinated arylsulfinyl acetates were alkylated and subsequently heated to promote elimination, giving rise to a variety of *Z*-fluoroalkenoates.

The method was shown to be compatible with functional groups such as esters, acetates, silyl ethers, imides, and amides (Figure 53).

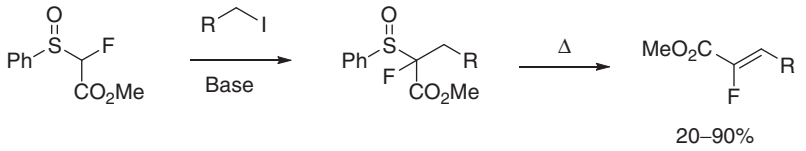


Figure 53 Elimination of α-fluorinated arylsulfinyl acetates.

The selectivity was rationalized by comparison with nonfluorinated *Z*-alkenes that had been prepared using a similar method.[125] The stereoselectivity was said to have risen because of the lack of steric interactions between the substituent group and the ester in the transition states leading to the *Z*-alkene isomers. Ratios of up to >95:5 in favor of the *Z*-isomer were obtained by this method (Figure 54).

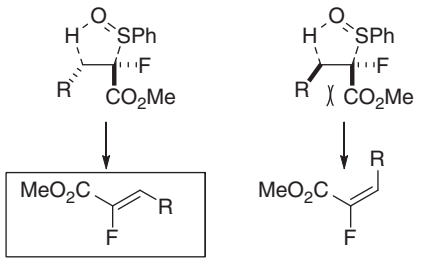


Figure 54 Rationalization of stereoselectivity for *Z*-fluoroalkenoates.

Another method for the stereoselective synthesis of *Z*-fluoroalkenoates involved a three-step process starting from a fluorosulfide.[126] This preparation gave rise to *Z*-fluoroalkenoates with selectivities up to 98:2 *Z*:*E*, in yields ranging from 50% to 60% overall. Both aromatic and aliphatic aldehydes could be used in the reaction, and each class of reactant gave comparable overall yields. The authors suggested a radical or anionic elimination mechanism, due to the high *Z*-selectivity obtained (98:2), even from diastereomeric mixtures (Figure 55).

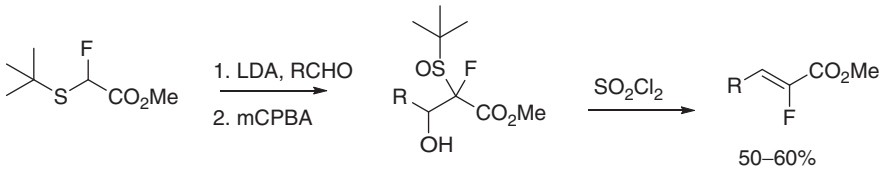


Figure 55 *Z*-Fluoroalkenoates from sulfoxide elimination.

The preparation of both tri- and tetrasubstituted fluoroalkenoates was achieved using diethylzinc to facilitate the addition of ethyldibromofluoroacetate to various aldehydes and ketones,[127] which produced tri- and tetrasubstituted fluoroalkenoates, respectively. High *Z*-selectivities were obtained with both aldehydes and ketones (Figure 56).

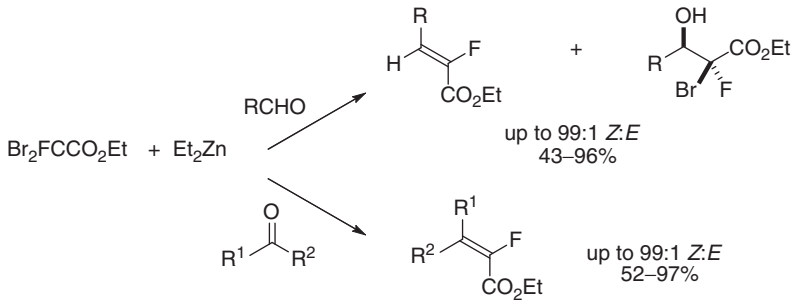


Figure 56 Eliminations in Reformatsky reactions.

An E2 elimination mechanism was proposed for the aldehyde derivatives, in which a chair-like transition state involving a zinc-aldolate intermediate held the bromine atom antiperiplanar to the leaving group. This transition state produced selectivity for the *Z*-isomer. These reactions also gave rise to a *syn*-α-bromo-α-fluoro-β-hydroxyester by-product in varying amounts. This material was thought to arise from the diastereomeric zinc aldolate intermediate, in which the bromine atom and leaving group were not antiperiplanar and so elimination was not possible. On workup, this intermediate was converted into the hydroxyester product. For ketones, an E1cb mechanism was proposed using a similar transition state model (Figure 57).

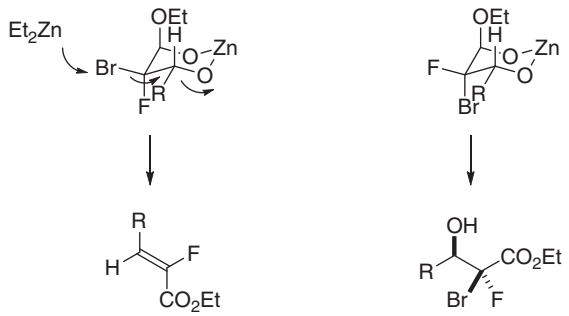


Figure 57 Reformatsky elimination stereoselectivity.

The stereoselective synthesis of unfunctionalized trisubstituted alkenes was carried out by using an iron-promoted elimination of β-thioalkoxy alcohols.[128] This method consisted of ring opening of propargylic dithioacetals with *n*-BuLi and subsequent reaction with aldehydes to obtain homopropargylic alcohols as a mixture of diastereomers. These alcohols were then treated with $Fe(acac)_3$ and MeMgI to afford the corresponding enynes with excellent stereoselectivities. The selection was thought to be a consequence of equilibration between the intermediate iron complexes (Figure 58).

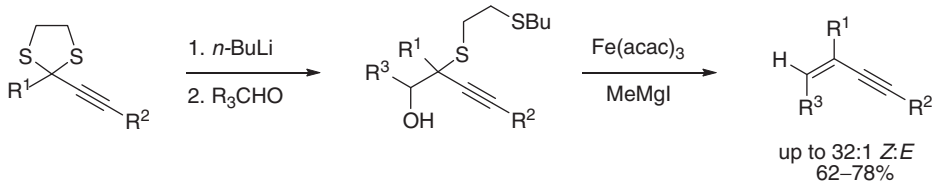


Figure 58 Iron-promoted elimination of β-thioalkoxy alcohols.

Unfunctionalized trisubstituted *Z*-alkenes have also been selectively prepared by utilizing selenophosphates and thiophosphates.[129] In this method, $NaBH_4$ was added to the seleno- or thiophosphate to obtain diastereomeric oxyanions, which underwent phosphoryl migration. This was followed by cyclization to produce episelenides or episulfides, which subsequently underwent spontaneous loss of selenium (or sulfur) to produce alkenes with high stereoselectivity. The selective formation of *Z*-isomers was rationalized by invoking the Felkin–Anh model (assuming that the $(EtO)_2P(O)Se$ group was the largest) in the reduction step (Figure 59).

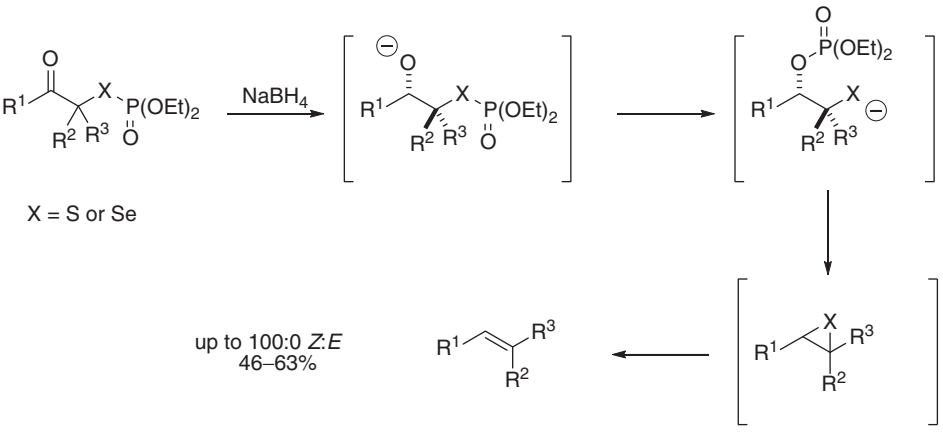


Figure 59 Stereoselective elimination of β-thioalkoxy alcohols.

A variety of disubstituted unfunctionalized olefins were prepared with good stereoselectivities from episulfides.[130] Conjugated dienes were synthesized in near complete stereoselectivity for the *E*-isomers using thio-and selenophosphates.[131] A similar method allowed the preparation of alk-2-enenitriles with excellent stereoselectivity.[132] Tetrasubstituted enynes and conjugated dienynes could also be accessed using this technology, albeit with lower selectivities.[133,134]

The construction of α,β-dehydroamino acids[135–137] was carried out with up to complete *Z*-selectivity in the case of trisubstituted examples.[138] The trisubstituted olefins were synthesized by E2 eliminations of the corresponding carbonate derivatives. The authors proposed that the *Z*-selectivity may arise from equilibrated intermediates that break down to give the thermodynamically more stable *Z*-olefins (Figure 60).

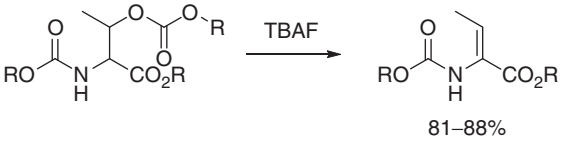


Figure 60 *Z*-Selectivity in eliminations to form α,β-dehydroamino acids.

6.18.4.4 Tetrasubstituted Alkenes

Only a few methods exist that can stereoselectively prepare tetrasubstituted olefins via elimination reactions.[139] Methods involving E2 processes can give rise to selectivity, but the hydrogen and leaving group must have an antiperiplanar arrangement for the reaction to proceed. In the case of tetrasubstituted olefins, the rotation needed to achieve an antiperiplanar arrangement may be difficult due to the fact that vicinal tertiary and quaternary centers are implicated. The resulting steric interactions can promote E1 processes instead, resulting in poor stereoselectivity or rearrangements. Because of this danger, elimination processes that produce tetrasubstituted olefins are uncommon (Figure 61).

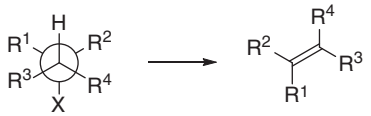


Figure 61 Eliminations to give tetrasubstituted olefins.

One method involved the *E*-stereoselective preparation of tetrasubstituted alkenylboronates.[140] This method enabled the preparation of various alkenylboronates from the addition of 1,1-diboronates to carbonyl compounds (Figure 62).

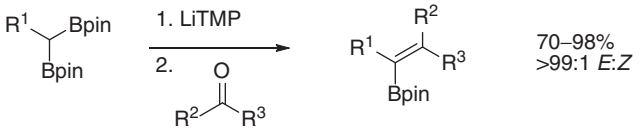


Figure 62 *E*-Selective elimination forming alkenylboronates.

The resulting alkenylboronates could be further elaborated via Suzuki–Miyaura coupling to produce all-carbon tetrasubstituted alkenes. This idea was applied to the synthesis of a tamoxifen derivative, which had previously not been prepared in a stereoselective fashion. The stereoselectivity was rationalized by performing density functional theory calculations on the lithium alkoxide intermediates. The results supported the observed experimental data by suggesting that one boron atom was specifically involved in a *syn*-elimination process, regardless of which boron's pinacol group was chelated to the lithium (Figure 63).

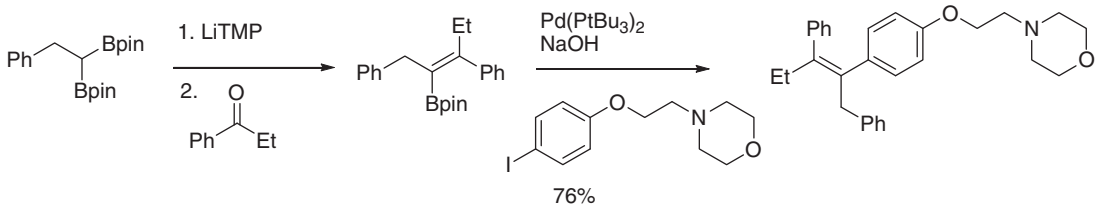


Figure 63 Stereoselective elimination in synthesis of tamoxifen derivative.

In 2004, an example of a stereoselective synthesis of a tetrasubstituted alkene en route to a synthesis of the alkaloid eupolauramine was reported.[141] One of the key steps in the synthesis involved an elimination of a benzotriazolyl unit promoted by anchimeric assistance, followed by the stereoselective formation of the olefin through proton removal. The *Z*-isomer was obtained in a ratio of 80:20 *Z*:*E*, in an 86% yield. The *E*- and *Z*-isomers were separable, and the *Z*-isomer was used for a subsequent oxidative radical cyclization reaction. Final replacement of the pivaloyl group with a methoxy group led to the product eupolauramine (Figure 64).

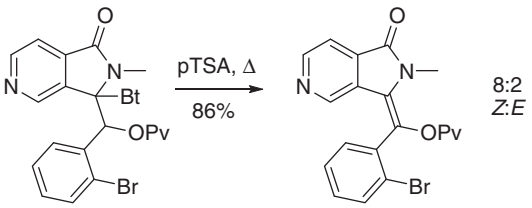


Figure 64 Stereoselective elimination in eupolauramine synthesis.

6.18.5 Stereospecific Methods

There are a variety of stereospecific methods to prepare alkenes through eliminations of stereodefined precursors. The stereochemical information in the starting materials translates in a predictable manner to the alkene products in these protocols, and such stereospecific eliminations can be used to prepare a variety of polysubstituted olefins. There are numerous types of substrates that can be used to prepare olefins in a stereospecific manner. Many methods involve *vic*-dihalides, but there are other interesting methods starting from precursors such as *vic*-diols (and related materials), halohydrin derivatives, *β*-hydroxy selenides, epoxides, episulfides, aziridines, *epi*-phosphonium, and phenylsulfide derivatives. The use of these methods for the preparation of substituted olefins is discussed below.

6.18.5.1 Alkenes from Vicinal Dihalides

Vicinal dihalides can act as protecting groups for alkenes.[60] This attribute makes eliminations that form alkenes from *vic*-dihalides particularly useful, provided that the stereochemistry of the resulting olefin can be controlled. Some stereoselective methods for the elimination of *vic*-dihalides were discussed below, but there are a variety of stereospecific methods for the 'unmasking' of *vic*-dihalides to alkenes.

Many of these methods involve the use of metal reductants to effect the dehalogenations. Several metal–metal salt systems have been developed for this purpose in recent years, including $NiCl_2{\cdot}6H_2O/In$,[142] $FeCl_3{\cdot}6H_2O/In$,[143] $BiCl_3/In$,[144] $CoCl_2{\cdot}6H_2O/In$,[145] Cp_2TiCl_2/Ga,[146] and $BiCl_3/Ga$.[147] These systems constitute inexpensive, mild conditions and generally give high yields of disubstituted *E*-alkenes. *α*,*β*-Unsaturated aldehydes, ketones, carboxylic acids, and esters, as well as a variety of aryl-substituted alkenes were prepared using this strategy as well as terminal and cyclic alkenes. The mechanism of the process is still unclear; however, the authors speculate that it occurs in two stages: the metal salt is reduced by the metal and this reduced species eliminates bromide from the substrate (Figure 65).

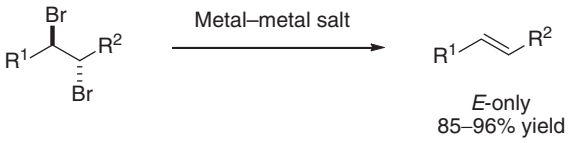


Figure 65 Stereospecific elimination of vicinal dihalides with metal-metal salt systems.

The stereospecific debromination of *vic*-dibromides using only DMSO was investigated in 2007.[148] This method consisted of simply heating the *vic*-dibromides in DMSO. The reaction tolerated a variety of functional groups such as esters, acids, amides, nitro, and keto groups and afforded good yields in most cases. Phenyl, pyridyl, and thiophenyl alkenes were also prepared; however, with certain derivatives, the bromoolefin was obtained as well (mostly in the thiophenyl series). The reaction mechanism was thought to proceed from attack of the DMSO oxygen atom in an S_N2 fashion onto one of the bromide positions, followed by the loss of Br^+ (to form the olefins) or H^+ (to form bromoolefins). The reactions were often completely *E*-selective; however, the carboxylic acid derivatives did show some erosion in stereointegrity. In general, this procedure was a mild, efficient way to obtain olefins from their *vic*-dibromide precursors (Figure 66).

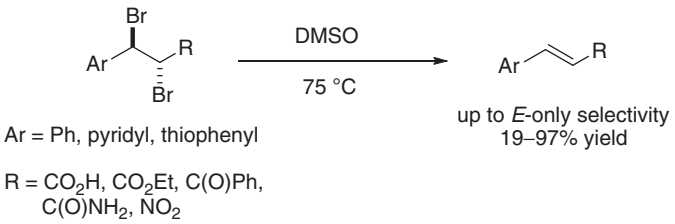


Figure 66 Stereospecific elimination of vicinal dihalides using DMSO.

6.18.5.2 Vicinal Diols or Dialkoxy Derivatives

The synthesis of alkenes from elimination reactions of *vic*-diols, or related derivatives, has been investigated by various research groups over the years. Most methods involve converting the *vic*-diols into leaving groups, such as the thiocarbamate derivatives of the Corey–Winter reaction[149] or xanthate derivatives such as those described by Barton.[150] *vic*-Dimesylates have also been converted to alkenes in a stereospecific manner by a few different research groups as discussed below.

In 1996, a variety of *vic*-dimesylates were eliminated to afford the corresponding alkenes stereospecifically using telluride or selenide dianions.[151] In this method, the dimesylates were treated with either Li_2Te or Li_2Se to afford the corresponding alkenes. The dianions could be made from the direct addition of Et_3BHLi to the metal or by treating the metals with sodium in liquid ammonia. The reaction mechanism was thought to proceed via a three-membered ring intermediate, after 'double attack' of the dianion on the dimesylated compound. The reaction was especially useful for the synthesis of dideoxynucleosides; however, the technology could also be used to prepare acyclic *E*- and *Z*-olefins stereospecifically (Figure 67).

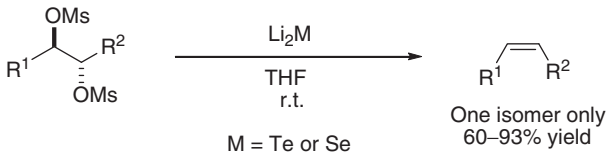


Figure 67 Stereospecific elimination of vicinal dimesylates.

A related process has also been reported from dimesylates using lithium areneselenates, which had a similar substrate scope.[152] A potential drawback to this method, however, was that a stoichiometric amount of the tellurium or selenium reagent was used, which could potentially be problematic on larger scale.[150] In an effort to make this process more amenable to scale up, some reaction parameters were modified to use a perfluorinated diselenide derivative as a catalyst.[153] This method had an excellent substrate scope and stereospecificity and allowed the use of a catalytic amount of the selenide derivative (a stoichiometric amount of $NaBH_4$ was required). Additionally, the catalyst could be recovered by using continuous fluorous extraction (Figure 68).

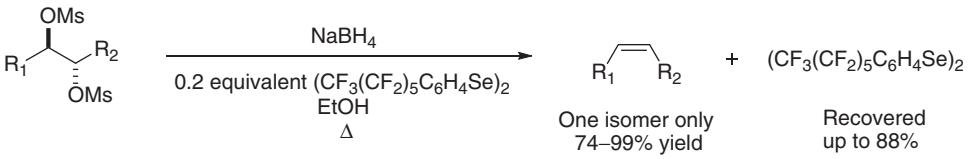


Figure 68 Stereospecific elimination of vicinal dimesylates to *Z*-alkenes.

The use of both dimesylates and ditosylates with sodium hydrogen telluride to form alkenes stereospecifically in excellent yields was reported in 1996.[154] This method was compatible with esters, amides, ketones, and nitriles, but not with halides.

The elimination of *vic*-diols has also been accomplished directly using a rhenium catalyst.[155] In this method, $Re_2(CO)_{10}$ was heated to 170 °C in the presence of *vic*-diols to produce the corresponding olefins. Only *syn vic*-diols were compatible with these conditions, and *E*-stereospecific examples were shown along with cyclic and terminal examples. The reaction mechanism is unknown as of yet; however, the authors suggested the intermediacy of a rhenium diolate species (Figure 69).

6.18.5.3 Halohydrin Derivatives

The conversion of halohydrin derivatives to alkenes has been demonstrated by a few different research groups. Generally, these derivatives provide advantages over using *vic*-dihalides as substrates for the eliminations because the alkene can be formed in a

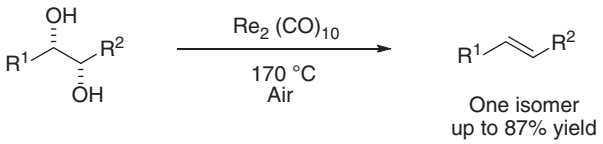


Figure 69 Stereospecific elimination of vicinal diols to *E*-alkenes.

stereospecific manner. This method, however, cannot be used for olefin inversion reactions (*anti*-addition followed by *anti*-elimination leads to the starting alkene).

In 1996, a method of stereospecifically converting *vic*-alkoxyiodoalkanes into the corresponding olefins via a *syn*-elimination process was disclosed,[156] which provided a route for olefin inversion. BuLi was added to *vic*-alkoxyiodoalkanes to obtain alkenes with selectivities of up to 96:4 for either the *E*- or *Z*-isomers, depending on the stereochemistry of the starting substrate. Yields ranged from 64% to 85%, and the method could also be used for the preparation of trisubstituted olefins. The authors proposed an E2 *syn*-periplanar mechanism in which the oxygen of the methoxy group coordinated to BuLi, changing the conformation of the molecule so that a *syn*-elimination of the I atom and the methoxy group takes place (Figure 70).

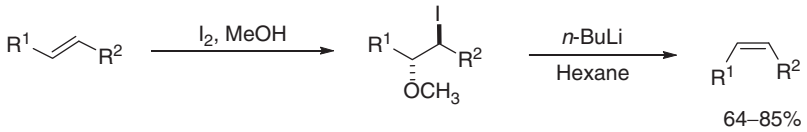


Figure 70 Stereospecific *syn*-elimination of vicinal alkoxyiodoalkanes.

The process could be rendered stereoselective by using a Grignard reagent (BuMgBr in Et_2O) as the base to afford *E*-alkenes exclusively (>99:1 *E*:*Z*), regardless of the configuration of the starting alkoxyiodoalkane. Yields were generally good for this process, ranging from 66% to 97%. The authors proposed that a single electron transfer from the Grignard reagent to the substrate provided a radical intermediate that formed a single anion after accepting a second electron; this anion then eliminated the methoxy group to selectively afford the *E*-alkene.[157]

A stereospecific *anti*-elimination of alkoxyiodoalkanes has also been described, using an allylsilane–titanium tetrachloride system.[158] This method provided alkenes in ratios up to >99:1 in favor of the *E*-isomers or 96:4 in favor of the *Z*-isomer, depending on the relative configuration of the starting substrate. Yields of up to 97% were obtained. The involvement of an intermediate iodonium ion (after coordination of the methoxy oxygen to titanium) was proposed, which was then attacked by the allyltrimethylsilane to obtain the alkene. This method has also been used successfully to convert epoxides stereospecifically into alkenes using Bu_4NI (Figure 71).[159]

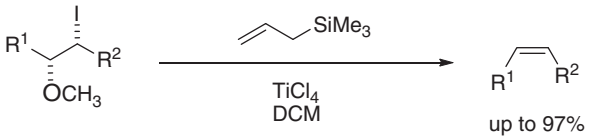


Figure 71 Stereospecific *anti*-elimination of alkoxyiodoalkanes.

6.18.5.4 β-Hydroxy Selenides

In 1976, a method was described which converted β-hydroxy selenides into di-, tri-, and tetrasubstituted olefins.[160,161] The β-hydroxy selenides could be prepared from a variety of different methods.

The epoxides were opened in a *trans* fashion by either phenyl or methyl selenol to provide the corresponding β-hydroxy selenide, which was then transformed to the alkene by a stereospecific elimination, using one of the methods described (Figure 72).

6.18.5.5 Epoxides

The elimination of epoxides to form alkenes has been known for many years, and epoxide formation is a strategy sometimes used for the protection of alkenes.[162] Early methods usually employed a stoichiometric amount of a reducing reagent including phosphines,[163] silanes,[164] iodides,[165] or heavy metal reduction, especially those utilizing tungsten.[166] More recent methods tend to focus on the catalytic deoxygenation of the epoxides to form alkenes.

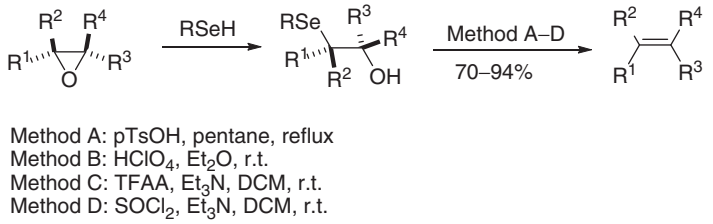


Figure 72 Stereospecific elimination of β-hydroxy selenides.

In the past few years, catalytic processes have been developed for the stereospecific elimination of epoxides to obtain alkenes using either silver[167] or gold nanoparticles as catalysts.[168] These methods employed hydrotalcite ($Mg_6Al_2(OH)_{16}CO_3$)-supported Ag or Au nanoparticles in conjunction with alcohols and used CO/H_2O or H_2 as the reducing agent. Eliminations to form alkenes with stereoselectivities of more than 99% and isolated yields between 69% and 95% were reported. The types of alkenes prepared included diaryl-, alkyl–aryl-, terminal, and α,β-unsaturated esters, ketones, and amides. The mechanism for these reactions was thought to involve the coordination of the metal nanoparticle with the Lewis basic sites of the hydrotalcite, such that the metal hydride species and H^+ (on the basic site) reacted with the epoxide, producing the alkene and water (Figure 73).

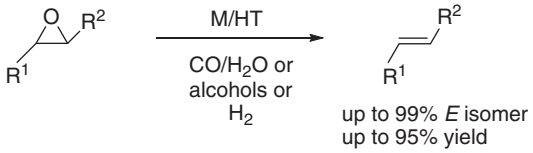


Figure 73 Catalytic elimination of epoxides.

The elimination of epoxides has also been affected stereospecifically using a combination of $ZrCl_4$ and NaI.[169] This method enabled a variety of alkenes to be prepared with alkyl, aryl, ether, carbonyl, ester, and hydroxy functional group tolerance. The technology was mainly employed for terminal alkene synthesis; however, both *trans*- and *cis*-stilbene could be prepared stereospecifically from the corresponding epoxides. A mechanism involving coordination of the $ZrCl_4$ to the epoxide, followed by opening by iodide was proposed. Subsequent iodide-mediated elimination of the leaving group produced the alkene (Figure 74).

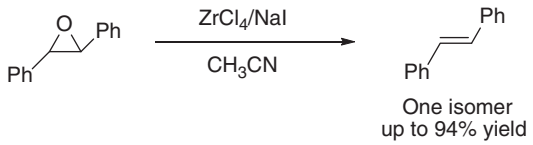


Figure 74 Stereospecific elimination of epoxides.

Despite the recent focus on catalytic methods, older methods are very reliable and are often encountered in synthesis. In 2006, the polyketide macrocycle (–)-kendomycin, which shows a variety of biological activities,[170] was synthesized. During this synthesis, it became necessary to protect an olefin function. This was accomplished by the simple expedient of epoxide formation. Deprotection to reveal the desired olefin was performed using Sharpless' deoxygenation protocol,[165] and the alkene was obtained stereospecifically in 71% yield (Figure 75).

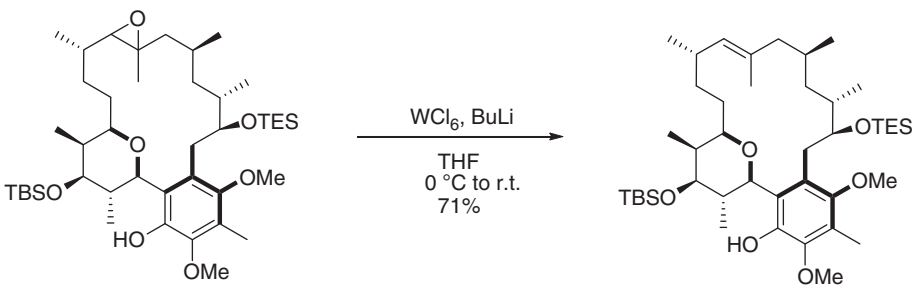


Figure 75 Stereospecific epoxide elimination in kendomycin synthesis.

6.18.5.6 Episulfides

There are relatively few methods to convert episulfides into alkenes stereospecifically. In one report,[171] both *cis*- and *trans*-episulfides were treated with phenyllithium or triethyl phosphite to obtain the corresponding *cis*- and *trans*-alkenes, respectively. Although this process was demonstrated only for *cis*- and *trans*-2-butene, it provided near quantitative yields of the corresponding olefins with almost complete stereospecificity. A similar method of desulfurization to afford the corresponding alkene that uses either an alkyllithium or an iron carbonyl compound as a base has been reported (Figure 76).[172]

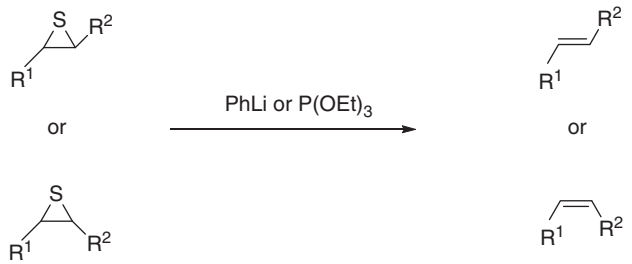


Figure 76 Stereospecific elimination of episulfides.

Another method of converting episulfides into alkenes that involves the treatment of 2-(1-chloroethyl)thiiranes with phenyllithium in order to obtain 1-phenylsulfanylbut-2-enes stereospecifically was demonstrated recently.[173] Terminal alkenes, along with di- and trisubstituted alkenes were obtained by this method, and the disubstituted alkenes were obtained stereospecifically. The authors proposed an *anti*-elimination following the attack of the phenyllithium on sulfur with subsequent ring opening (Figure 77).

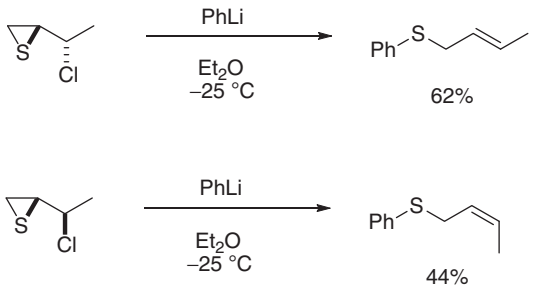


Figure 77 Stereospecific elimination from episulfide opening.

6.18.5.7 Aziridines

There are several different ways to obtain alkenes by the elimination of aziridines. Some of these reactions have been performed using reagents such as *N*-nitroso-3-nitrocarbazole,[174,175] nitrosyl chloride,[174,176] methyl nitrite,[174] and *n*-butyl nitrite.[177]

A more recent method involves the deamination of aziridines by exposing them to N_2O_4 under relatively mild conditions.[178] This reaction could be applied to the synthesis of disubstituted alkenes as well as to a single trisubstituted olefin example. Aryl- and alkylaryl alkenes were also prepared stereospecifically, with yields ranging from 70% to 95%. The authors proposed an *N*-nitroso intermediate, arising from the nitrosating conditions (self-ionization of N_2O_4 to NO^+ and NO_3^- in solution) as being operative in the elimination (Figure 78).

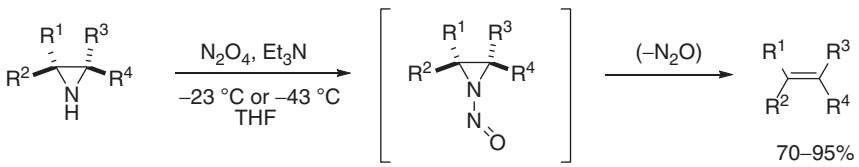


Figure 78 Stereospecific elimination of aziridines.

6.18.5.8 *Epi*-Phosphonium

There are a few examples of the elimination of *epi*-phosphonium species to yield alkenes.[179–181] Recently, a method was introduced that converts the *epi*-phosphonium species stereospecifically into the corresponding alkene.[182] Alkylaryl-disubstituted

alkenes were successfully synthesized using this method with good stereochemical ratios. The elimination method consisted of the treatment of β-hydroxyphosphines with PCl_3 and NEt_3 to convert the hydroxyl function into a good leaving group thereby forming the *epi*-phosphonium species, which then suffered elimination on treatment with NEt_3 (Figure 79).[183]

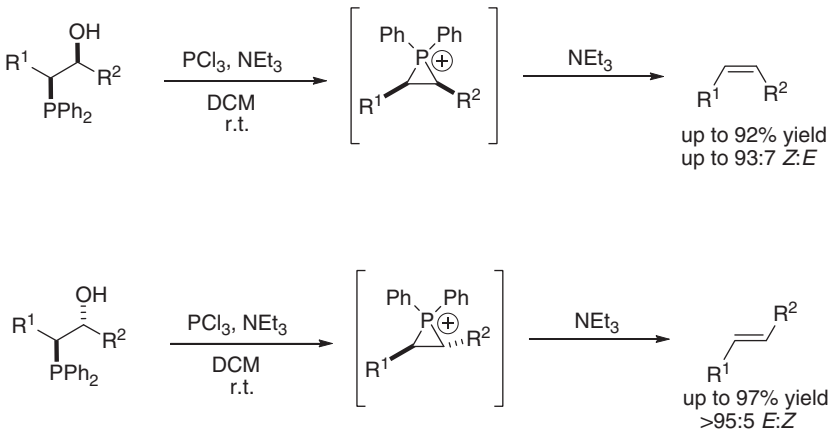


Figure 79 Stereospecific elimination of *epi*-phosphoniums.

6.18.5.9 Phenylsulfides

Phenylsulfides can be useful for the synthesis of alkenes because they are generally tolerant to acidic and basic conditions and can be readily eliminated in a *syn*-fashion once converted into the corresponding sulfoxides.[184] These eliminations, however, must usually be carried out at approximately 100–150 °C. In an effort to eliminate phenylsulfides at lower temperatures, a method that converted the phenylsulfides into their corresponding N–H sulfilimine derivatives was developed in 2006. This transformation then allowed facile *syn*-eliminations to take place at room temperature.[185] The phenyl sulfides were aminated using *O*-mesitylenesulfonylhydroxylamine (MSH) at 0 °C, and subsequent addition of K_2CO_3 at room temperature provided the alkenes stereospecifically. Trisubstituted alkenes were prepared with selectivities more than 99:1 for the *Z*-isomers and 40:1 for the *E*-isomers, depending on the configuration of the starting substrates used. The lower ratios for the *E*-isomers were rationalized by invoking slow isomerization from *E*- to *Z*-products over time (longer reaction times gave lower *E*:*Z* ratios). α,β-Unsaturated carbonyl compounds could be prepared using this method with complete selectivity for the *E*-isomers (Figure 80).

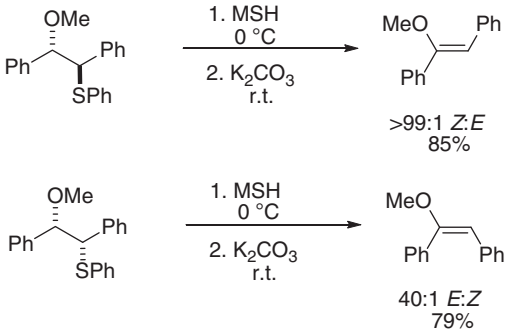


Figure 80 Stereospecific elimination of phenylsulfides.

6.18.6 Eliminations to Form Terminal Alkenes

The preparation of terminal olefins by elimination processes generally presents fewer selectivity issues than other elimination motifs. Regiochemical issues may arise for the production of Hofmann isomers, and many methods incorporate strategies to address this. Some methods favor the production of Hofmann products through steric influences. These include the Cope elimination[186] and related eliminations involving sulfonium and ammonium salts.[187]

6.18.6.1 Preparation from Alkyl Halides

Primary halides do not normally provide a reliable method of elimination to form terminal olefins because of the tendancy of these materials to undergo substitution. To overcome this difficulty, extremely hindered bases must be used.[188] Primary iodides can be eliminated to give the corresponding terminal olefins by the use of nonnucleophilic bases such as TBAF in DMSO,[189] conditions that minimize the formation of S_N2 products.

Vinyl bromides have been prepared through a selective elimination process developed for use on vicinal dihalides.[190] A variety of olefins could be converted into vicinal halides, which were then selectively eliminated to afford terminal vinyl bromides. DBU was used as a base in these transformations; however, selectivity required the presence of additives such as K_2CO_3. Other additives have been employed together with DBU in related transformations (Figure 81).[191]

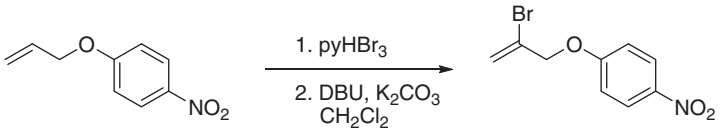


Figure 81 Vinyl bromides from stereospecific eliminations.

6.18.6.2 Preparation from Alcohols

Reliably converting alcohols into terminal alkenes normally requires E2 chemistry, as the use of acidic conditions to remove the hydroxyl group tends to promote the formation of Zaitsev products and encourages rearrangements.

One interesting method to achieve β-elimination was developed specially for tertiary alcohols.[192] Subjecting these materials to conditions normally employed for Swern[193] oxidations resulted in β-elimination (rather than the usual α-elimination) and smoothly converted the tertiary alcohols into terminal olefins (Figure 82).

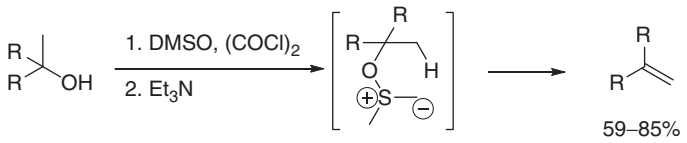


Figure 82 β-Elimination of tertiary alcohols under Swern conditions.

6.18.6.3 Preparation from Epoxides

A variety of methods have been utilized to convert epoxides and vicinal diols into terminal alkenes through elimination processes. Adding alkyl cerium reagents to substituted styrene oxides gave a variety of terminal alkenes under relatively mild conditions.[194] This reaction worked very well for styrene derivatives, but selectivity was somewhat lower when alkyl epoxides were used (Figure 83).

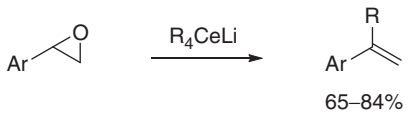


Figure 83 Terminal alkenes from epoxide eliminations.

Epoxides have also been electrochemically eliminated using zinc electrodes to afford the corresponding double bonds in excellent yields.[195] Terminal alkenes have been obtained by the eliminative deoxygenation of epoxides catalyzed by gold nanoparticles (Figure 84).[196]

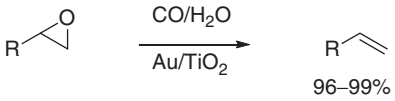


Figure 84 Electrochemical elimination of epoxides.

Vicinal diols can be converted into terminal olefins using a variety of methods. A common theme in this chemistry is the conversion of one of the hydroxy functions into a halogen. This transformation is then followed by metal-promoted elimination.[197] An example of this involved the selective conversion of vicinal diols into iodohydrins.[198] These deriviatives could then easily be converted into terminal olefins by exposure to BuLi at low temperature.[199]

6.18.6.4 Terminal Olefins from Selenium and Sulfur-Based Leaving Groups

Selenoxide chemistry provides a convenient and mild way to carry out eliminations.[200] Selenium groups are easily introduced using standard carbanion chemistry, and the eliminations usually proceed under very mild conditions once the selenium atom has been oxidized. The selenoxide group eliminates via a synperiplanar mechanism, and this should be taken into account in synthesis as this factor can be manipulated to control regiochemistry.

A selenium elimination was employed during the synthesis of xenicane diterpenes to introduce a cyclic double bond. This event was performed during the endgame of the synthesis, and so reliable and mild conditions were required. A phenylselenide was introduced through enolate formation. This group was oxidized using *meta*-chloroperoxybenzoic acid (*m*-CPBA) and readily eliminated at low temperature in the final step of the synthesis (Figure 85).[201]

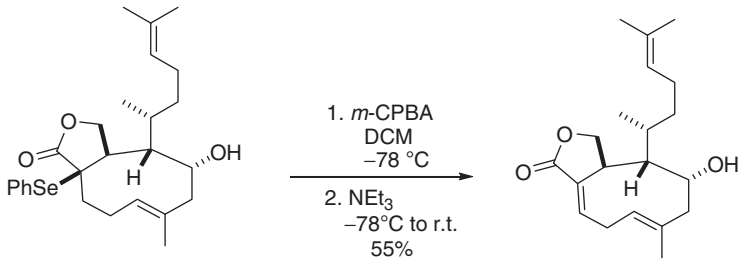


Figure 85 Eliminations during xenicane diterpene synthesis.

A phenylselenide group was introduced by using a regioselective epoxide opening during a recent morphine synthesis.[202] The selenide group was then oxidized using $NaIO_4$ and underwent a highly regioselective elimination (Figure 86).

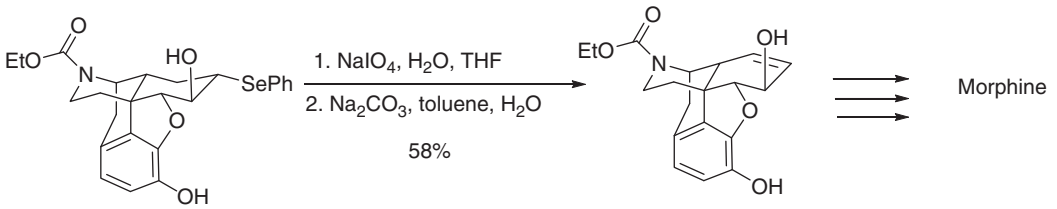


Figure 86 Elimination of phenylselenides in morphine synthesis.

Endocyclic unsaturation was introduced into a five-membered ring intermediate during a recent synthesis of (+)-intricarene (Figure 87).[203]

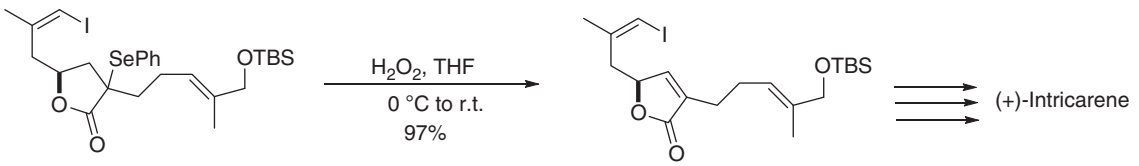


Figure 87 Eliminations during intricarene synthesis.

A phenylselelenide elimination was also employed to achieve the construction of a key cyclopentadiene-containing intermediate during a total synthesis of absinthin (Figure 88).[204]

Methods using sulfur-based leaving groups usually employ the thermolysis of sulfoxides and sulfones. The departure of these groups is not as facile as other functionalities and thus higher temperatures and longer reaction times may be required.[205–207]

The Ramberg–Bäcklund reaction[208] has a well established past in synthesis, installing double bonds by the extrusion of SO_2. This reaction was employed during a recent synthesis of fawcettidine to introduce a double bond with high *Z* selectivity into a macrocyclic ring (Figure 89).[209]

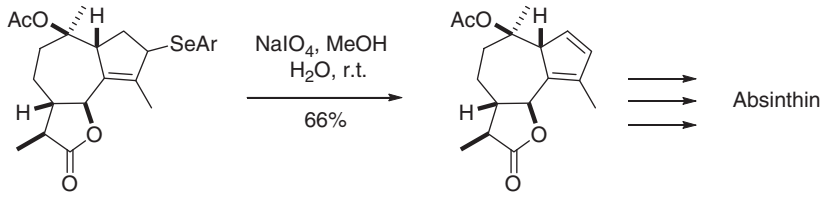


Figure 88 Eliminations during absinthin synthesis.

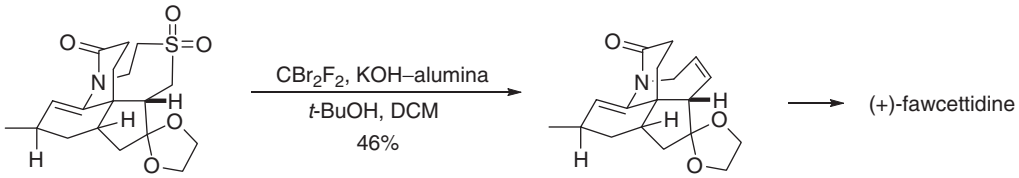


Figure 89 Eliminations during fawcettidine synthesis.

6.18.7 Eliminations to Form Allenes

In recent years, research toward the synthesis of allenes has become very popular. Allenes are highly useful as synthetic intermediates and also occur in natural products and biologically relevant molecules.[210] Allenes can be prepared by a variety of methods including substitution, addition, rearrangement, and elimination. Elimination reactions to form allenes generally employ an alkene precursor or involve an alkene intermediate.

6.18.7.1 Stereocontrolled Methods

There are relatively few methods to synthesize allenes in a stereocontrolled fashion, although the preparation of chiral allenes would be useful for applications in natural product synthesis and in the synthesis of pharmacologically active compounds. The majority of methods that have been developed for the production of chiral allenes involve propargylic alcohol derivatives as starting materials.

In 1992, a method for preparing chiral allenes by the hydrostannation/deoxystannylation of propargylic alcohols was developed.[211] A variety of racemic-disubstituted allenes were prepared using this method, along with a single example of a chiral allene compound. This asymmetric synthesis came about by oxidizing the racemic stannyl allylic alcohol, and then enantioselectively reducing the resulting ketone with the Corey-Bakshi-Shibata catalyst.[212] This provided an enantiopure alcohol, which was acetylated and then treated with Bu_4NF to afford the chiral allene. This process involved the stereospecific elimination of the stanyl and acetoxy groups, initiated by an attack of fluoride on the stanyl group. The allene was obtained with complete stereospecificity in 94% *ee* and 81% yield (Figure 90).

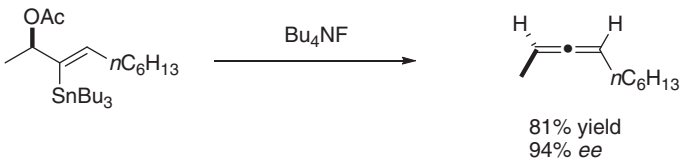


Figure 90 Stereocontrolled elimination to form allenes.

This method was later applied to the synthesis of a series of allenic hydrocarbons that are found in Australian melolonthine scarab beetles (Figure 91).[213]

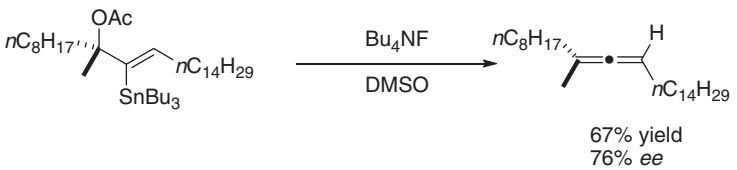


Figure 91 Elimination to form allenes hydrocarbons.

Another method, developed in 1996, employed a Mitsunobu reaction on both enantiopure and racemic propargyl alcohols, using arenesulfonyl hydrazides as nucleophiles. These transformations afforded the corresponding propargyl hydrazides that were subsequently fragmented via a retro-ene reaction in methanol at room temperature to provide the respective allenes.[214] A variety of functional groups displayed tolerance to this method, including tertiary amines, tertiary alcohols, acetals, ketals, silyl ethers, and nitriles. An example demonstrating the synthesis of a trialkylsilyl allene was also reported, along with an allene-ene-yne example. Complete stereospecificity was observed in all examples of this transformation (Figure 92).

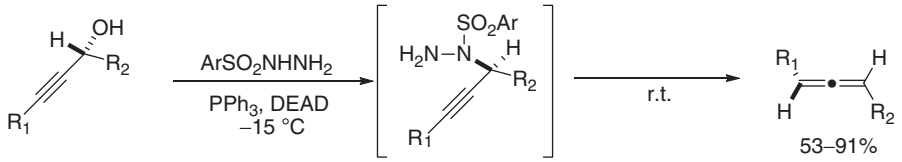


Figure 92 Elimination of arenesulfonyl hydrazides.

The synthesis of chiral allenes utilizing a chromium (III) catalyst in the presence of propargylic alcohol derivatives has been recently reported.[215] This method was developed for the synthesis of stereodefined 1,3-allenes, with good yields and high enantiomeric excesses reported for some examples. The mechanism was thought to involve *syn*-carbometallation followed by a *syn*-elimination to afford the corresponding allenes. Yields up to 83% and *ee*'s of up to 86% were reported (Figure 93).

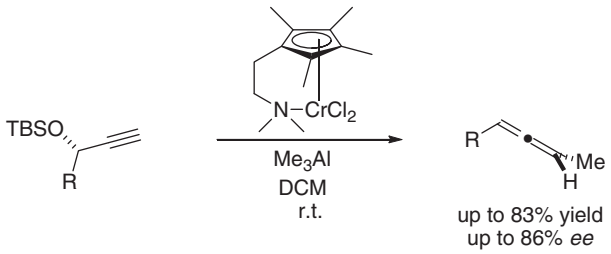


Figure 93 Eliminations to form chiral allenes.

The use of alkynyl sulfoxides and sulfones for the preparation of allenes via a carbocupration-zinc homologation-β-elimination sequence was described in 2000.[216] This method was later applied to the preparation of a single example of a chiral allene.[217] This material was obtained in 65% *ee* and 75% yield, starting from a chiral ethenyl *p*-tolyl sulfoxide. The enantioselectivity was rationalized by invoking the intermediacy of an allylic zinc derivative that underwent epimerization to the more stable intermediate, in which the tolyl and butyl groups were *anti* to one another. A *syn*-β-elimination then took place to afford the corresponding allene (Figure 94).

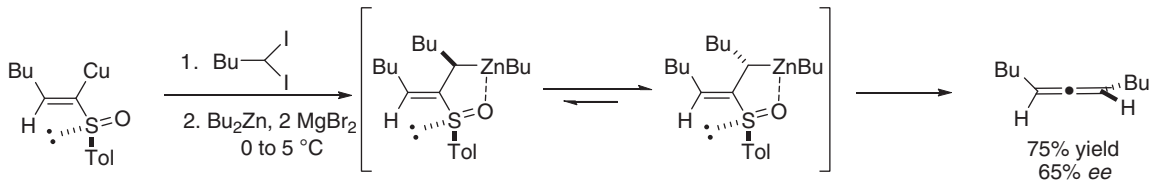


Figure 94 Elimination of alkynyl sulfoxides.

The synthesis of bioactive chiral allenes was undertaken in 2010, using an *i*-PrMgBr mediated elimination of enantioenriched 3-acetoxy-2-iodo-propene derivatives.[218] The enantiomer of a sex-attractant of the male dried bean beetle was synthesized using this technology in 91% *ee*, starting from a propargylic alcohol derivative. The elimination step proceeded in 89% yield (Figure 95).

6.18.7.2 Other Methods

It is very difficult to synthesize chiral allenes stereoselectively, but methods to form allenes by elimination without concern for stereoselectivities are very common.

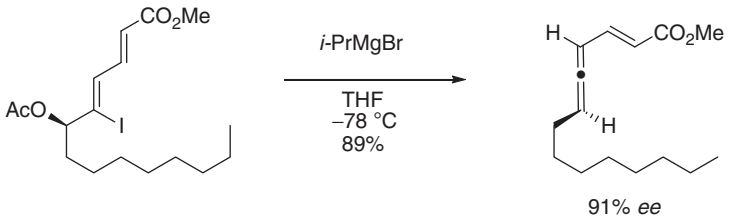


Figure 95 Chiral allene formation by elimination.

6.18.7.3 From Alkene Precursors

The synthesis of allenes by the elimination of alkene precursors constitutes the primary strategy of a large majority of the methods used in the literature. One account described the preparation of 1,1-difluoroallenes from the β-elimination of an acetoxy group after a lithium–halogen exchange reaction.[219] The allenes were produced in good yields, and a variety of aryl and alkyl–aryl 1,1-difluoroallenes were produced (Figure 96).

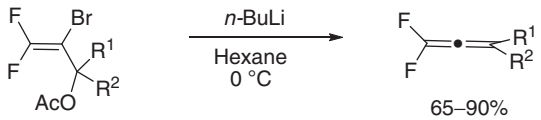


Figure 96 Alkene precursors for elimination to allenes.

Magnesium-sulfoxide exchange was another method of preparing allenes by inducing eliminations from alkene precursors.[220,221] This process involved metal–halogen exchange to induce a 1,1-elimination of the S(O)-tol group. This was followed by an attack of 2-lithio-5-methoxyfuran on the carbenoid intermediate. This gave rise to an alkenyl anion that opened the furan ring by a cascading elimination. This process provided a trienyl intermediate that tautomerized to give the corresponding allene in yields of up to 54% (Figure 97).

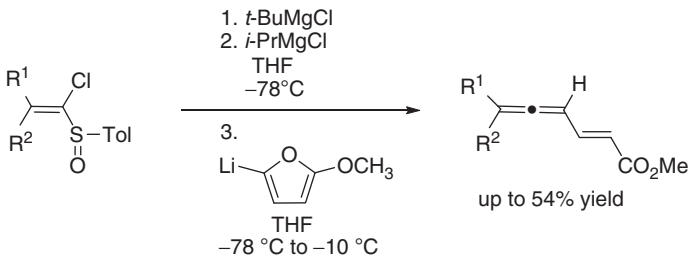


Figure 97 Magnesium-sulfoxide induced eliminations.

The synthesis of allenyl esters was achieved by dehydrating β-ketoesters using lithium bis(trimethylsilyl)amide (LiHMDS) as a base.[222] After initial treatment with LiHMDS, the enolate was trapped with Tf_2O. A second addition of LiHMDS would provide the corresponding ester enolate. Hexamethylphosphoramide (HMPA) was then added, presumably to destabilize the lithium complexes that can form between the enolate anion and HMDS and could result in anion quenching through intracomplex protonation.[223] The role of the $ZnCl_2$ was unclear; however, this additive was shown to be necessary to form allenes in appreciable yields. Both disubstituted and terminal allenes could be prepared with this method (Figure 98).

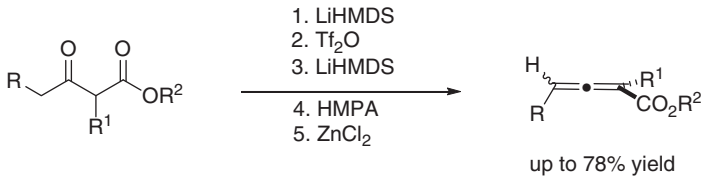


Figure 98 Dehydrations of β-ketoesters.

Another method which employed the intermediacy of enol derivatives for the construction of allenes was that utilizing silyl enol ethers.[224,225] This process involved the treatment of silyl enol ethers with LDA to generate an allylic carbanion, which would produce

the terminal allene by either direct elimination of $-OSiR_3$ or sequential 1,3 O–C silyl migration–Peterson elimination. The allene could then be transformed to the corresponding bislithiated allene by treatment with LDA, and then quenched with electrophiles. This method was mostly used for the preparation of bissilylated allenes; however, some examples of doubly stanylated and bismethylated allenes were shown. Overall yields ranged from 60% to 84% for these reaction sequences (Figure 99).

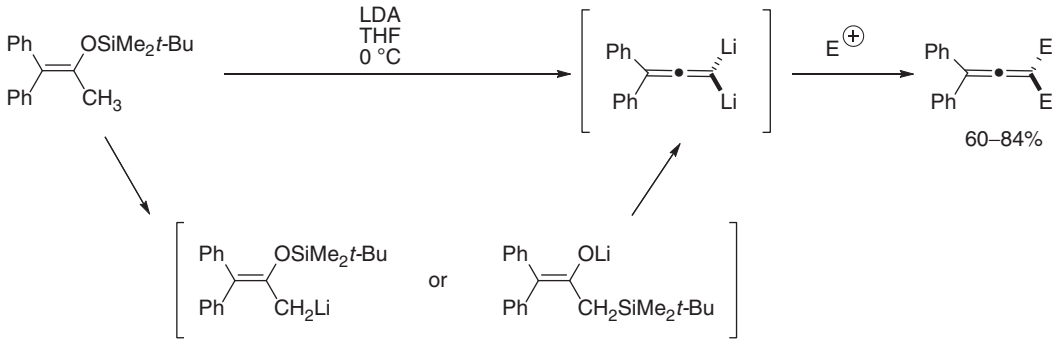


Figure 99 Elimination of silyl enol ethers.

The use of β-chlorovinylsilanes to prepare terminal allenes has also been demonstrated.[226,227] Treatment of β-hydroxyvinylsilanes with either acids or bases surprisingly did not affect elimination. But when the β-hydroxyvinylsilanes were converted into their β-chlorovinylsilanes by exposure to thionyl chloride, elimination to the allene could be induced by treating with fluoride salts. The yields were only moderate for this transformation (Figure 100).

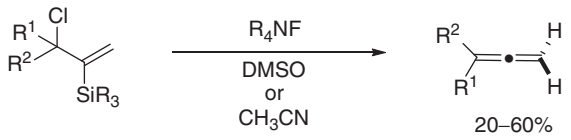


Figure 100 β-Chlorovinylsilane eliminations.

The use of $Pd^{(0)}$ in the presence of $ZnEt_2$ was demonstrated to form both terminal and internal allenes from allylic alcohol derivatives.[228] Terminal allenes bearing a neighboring protected amino group were synthesized along with alkyl- and aryl- substituted allenes. Yields ranged from 47% to 90%. The reaction was proposed to proceed via a π-allyl palladium intermediate, which then eliminated the vinylic bromide to produce the allene and a Pd^{II} species (regenerated to $Pd^{(0)}$ with diethyl zinc). The possibility of Zn/Pd transmetallation of the π-allyl palladium intermediate was not ruled out as a potential reaction mechanism (Figure 101).

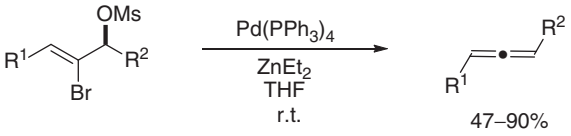


Figure 101 Palladium induced vinyl bromide eliminations.

The radical-based synthesis of allenes using vinylsulfoxides with azobisisobutyronitrile (AIBN) and tris(trimethylsilyl)silane (TTMS) has been described.[229] The vinyl sulfoxides were prepared from the corresponding aldehydes and ketones. This method demonstrated the preparation of terminal, di-, and trisubstituted allenes in modest yields and was tolerant to aryl, ester, silyl, and ether functionalities. Yields ranged from 30% to 80%. The mechanism was thought to proceed through a radical β-elimination of the vinyl sulfoxides (Figure 102).

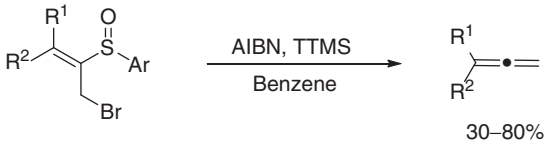


Figure 102 Radical based eliminations to form allenes.

6.18.7.4 From Alkyne Precursors

The synthesis of tetraaryl-substituted allenes starting from aryl substituted propargylic alcohols was disclosed.[230] This method used a Pd-catalyzed addition–elimination sequence to obtain the tetraaryl allenes. The mechanism for the reaction was unclear; however, the authors postulated that a β-hydroxyvinyl palladium intermediate was formed from insertion of Pd onto the alkyne via carbopalladation, which then eliminated the β-hydroxy group to produce the corresponding allenes (Figure 103).

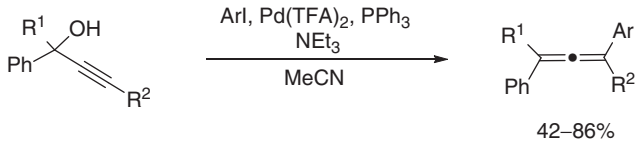


Figure 103 Palladium catalyzed addition-elimination involving alkynes.

The synthesis of α-allenic alcohols was demonstrated by the treatment of mono-O-tetrahydropyran (THP) derivatives of alkynyl diols with $LiAlH_4$.[231] This method provided access to the α-allenic alcohols in high yields. Applications to the synthesis of linear and branched α-allenic alcohols as well as the synthesis of a sex pheromone were demonstrated. The mechanism of the reaction was proposed to involve an intramolecular hydride transfer after attachment of the aluminum hydride to the alcohol. The hydride would attack the alkyne and expel the O-THP group on the other end (Figure 104).

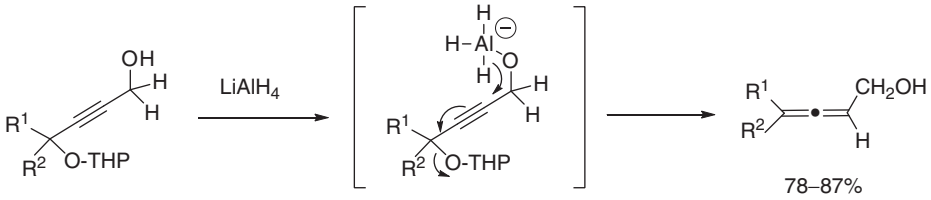


Figure 104 Elimination of alkynyl diols.

The synthesis of α-allenic aldehydes was demonstrated by the conversion of propargyl diol derivatives to give an intermediate triene.[232] 1-Trimethylsilyloxy-4-methoxy-2-alkynes were treated with *t*-BuLi to induce deprotonation, which led to elimination of the methoxy group. Subsequent hydrolysis of the silyl group led to the formation of the α-allenic aldehydes (Figure 105).

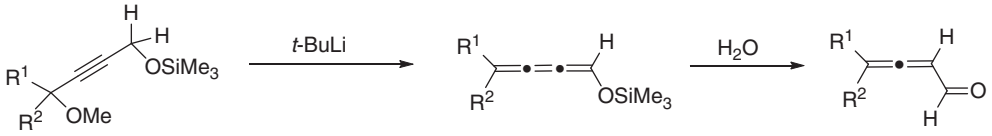


Figure 105 Elimination of propargyl diol derivatives.

6.18.8 Eliminations to Form Alkynes

Elimination reactions are popular methods to prepare triple bonds, and many strategies are available for these transformations.[233] Most strategies employ one or two β-eliminations to achieve the alkyne construction, but α-elimination protocols may also be followed.[234] α-Eliminations have been extensively used in the preparation of polyconjugated systems[235] including those of natural products.

α,α-Dichloroalkenes can be transformed into alkynes by treatment with base. The process can occur by β-elimination followed by halogen exchange or by halogen exchange followed by α-elimination. The latter process generates a carbene that rearranges to afford an alkyne. Two named reactions are associated with the use of α,α-dichloroalkenes, the Corey–Fuchs synthesis[236] and the Fritsch–Buttenberg–Wiechell rearrangement.[40–42]

α,α-Dichloroalkenes were recently employed to generate a key intermediate in the synthesis of tulearin C.[237] In this synthesis, MeLi was used as a base to carry out a Fritsch–Buttenberg–Wiechell rearrangement by lithium–halogen exchange. The methyl chloride that was formed from the initial exchange process then served as the electrophile to cap the alkyne product of the carbene rearrangement with a methyl group (Figure 106).

A series of alkynyl imines was prepared by treating α,α-dichlororketimines with either NaH in DMSO or KO^{t}Bu in THF.[238] Other groups have transformed α,α-dibromoalkenes into terminal alkynes by using Cs_2CO_3 as a base.[239] The authors postulated that the reaction proceeded by a β-elimination, followed by hydrogen exchange involving the base (Figure 107).[240]

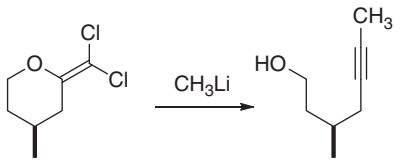


Figure 106 α-Elimination in synthesis.

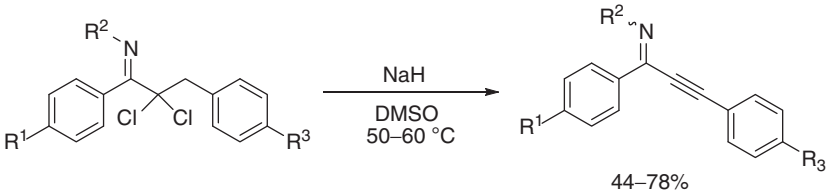


Figure 107 Alkynyl imines from α-elimination.

The elimination of vicinal dihalogen compounds to provide alkynes is a well known transformation in organic chemistry.[3,6] This method can be used to transform double bonds into triple bonds by bromination followed by double elimination with a variety of bases. The first elimination to form a vinyl halide is normally facile, but the second elimination often requires the use of stronger bases such as $NaNH_2$, LDA, or BuLi.[6] Recently, it has been shown that the eliminations can be carried out in warm dimethylformamide (DMF) using DBU[241] or TBAF[242–244] as a base.

A method has been disclosed for preparing alkynes through the TBAF-promoted elimination of β-fluorovinylsilanes.[245] The process was used to unmask protected alkynes during the synthesis of oligoynes. Exposing the materials to TBAF at 0 °C smoothly carried out the transformation (Figure 108).

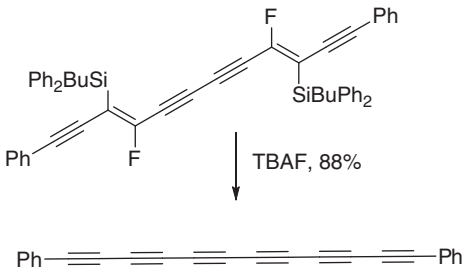


Figure 108 Oligoynes from alkene elimination.

β-Eliminations involving ketones have been explored in the synthesis of *S*-alkynyl sulfoximines. In this chemistry, the treatment of alkyl sulfoximines with Tf_2O in pyridine was sufficient to bring about alkyne formation. These transformations involved enolsulfonate formation followed by elimination (Figure 109).[246]

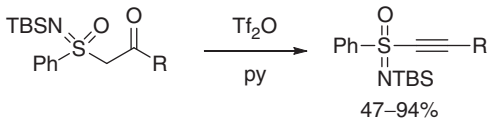


Figure 109 Alkynes from β-elimination.

Aldehydes have been converted into terminal alkynes using similar reaction sequences that could be induced with nonaflate groups.[247] The high leaving group ability of the nonaflate provided for extremely mild conditions, and the method was chemoselective for aldehydes. A specialized base was required for these transformations (Figure 110).[248]

A combination of sulfone- and phosphate-leaving groups was employed in an alkyne assembly strategy. Sulfones were condensed with aldehydes using chlorophosphonates as a quench. *In situ* treatment with base-induced double β-eliminations to produce a series of (1-propynyl)arenes (Figure 111).[249]

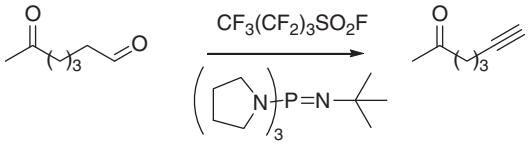


Figure 110 Terminal alkynes from elimination processes.

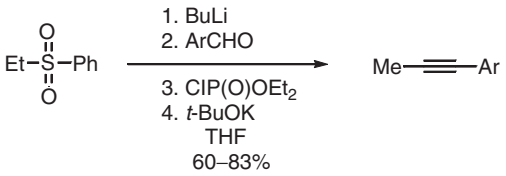


Figure 111 Alkyne assembly by sulfone elimination.

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6.19 Fragmentation Reactions

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Glossary

Electrofuge The site of initial electron density and the originating point for the flow of electrons in a fragmentation reaction.

Fragmentation In organic synthesis, bond-cleavage reactions in which a molecule breaks into three (or more) pieces.

Frangomeric effect The increased rate of concerted fragmentation relative to ionization and/or other (asynchronous) pathways for the specific conformation possessing proper stereoelectronic alignment for fragmentation.

Heterolytic A bond-cleavage event involving an ionic mechanism.

Homolytic A bond-cleavage event involving a radical mechanism.

Nucleofuge The terminating point for the flow of electrons in a fragmentation reaction, similar to the leaving group in substitution and elimination reactions.

6.19.1 Introduction

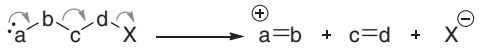
This chapter on fragmentation reactions follows a format similar to the one published in the first edition of *Comprehensive Organic Synthesis* in 1991.[1] The emphasis here is on the literature since 1991, with notable exceptions, and interested readers are referred to the original chapter for additional examples from the earlier literature. Other recent reviews should also be consulted.[2,3]

6.19.1.1 Definition

'Fragmentation' means to break or separate into fragments; by this broad definition, any bond-cleavage event, whether homolytic or heterolytic, can be considered a fragmentation. Perhaps, the most common use of the term is in mass spectrometry, to describe the breakdown of high-energy molecular ions in the gas phase. Reproducible fragmentation patterns of molecular ions are excellent for characterization and comparative analysis, but not for chemical synthesis, because they lack the proper degrees of predictability and control.

More specifically, Grob defined fragmentation reactions in organic synthesis as heterolytic bond-cleavage reactions in which a molecule breaks into three (or more) fragments (equation 1).[4] The fragmentation substrate comprises three key components: an electrofuge (a–b), a middle part (c–d), and a nucleofuge (X). The suffix *fuge* comes from the Latin *fugere*, 'to flee' and typically means, 'that which drives away or out.' Using standard arrow-pushing conventions, electron density from the electrofuge moves toward the middle part and ultimately onto the nucleofuge, resulting in two bond-cleavage events. A new π-bond is formed in the middle part, and the nucleofuge (the 'fleeing nucleus') provides the terminating point for the flow of electrons. Note that the nucleofuge is similar in identity to what is called the 'leaving group' in substitution and elimination reactions. The 'leaving group'

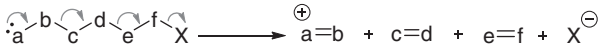
designation is insufficient in this context because fragmentation reactions involve at least two leaving groups: typically the middle part and the nucleofuge, depending on the frame of reference.



(1)

Although Grob explicitly differentiated fragmentation reactions from 1,2-elimination reactions, there are mechanistic similarities between the two. One can think of fragmentation as a specific type of (homologated) elimination, and early examples were sometimes referred to as 1,4-eliminations. Elimination reactions can proceed by E2, E1, and E1cb mechanisms (*see* Chapter 6.18); likewise, there are three mechanistic extremes for fragmentation reactions.[5] A one-step process is depicted in equation 1, in which all three fragments are formed simultaneously. Alternatively, two-step processes can be envisioned in which departure of either a–b or X precedes formation of the other two fragments. Mechanistic aspects of fragmentation reactions are discussed in more detail in Section 6.19.1.3.

The formation of three independent fragments is not a strict requirement for classifying a reaction as fragmentation. For example, ring-opening reactions are recognized as fragmentations if the accepted mechanism involves the five-center (a–b–c–d–X; equation 1) heterolytic cleavage process are outlined above. Many such cases have found application in synthesis. Extended systems that fragment into more than three pieces are also recognized as fragmentations (equation 2). However, related bond-cleavage processes like retroaldol (equation 3), retro-Claisen condensations, and cycloreversions do not fit the strict criteria outlined by Grob. These processes have not historically been described as fragmentation reactions, and they are not included in this chapter. Gas-phase thermolytic (pyrolysis) or ionization-related (MS) processes are also excluded from this chapter. No attempt is made to cover free-radical (homolytic) scission processes, although a few examples are provided. The focus here is on solution-phase heterolytic fragmentations of strategic value in organic synthesis.



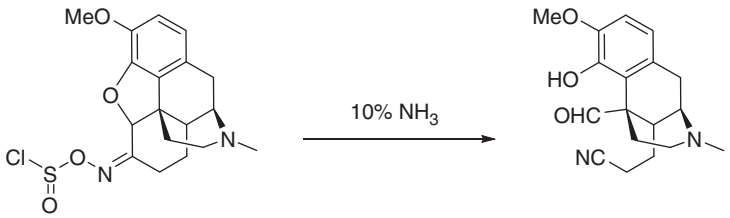
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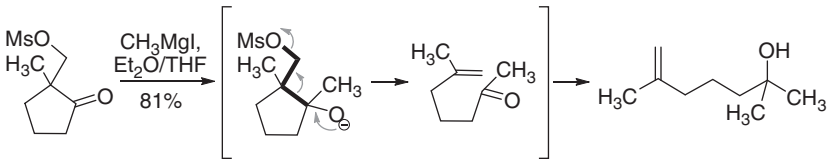
6.19.1.2 History

The first reactions that are now recognized as fitting the modern definition of fragmentations involve the degradation of oximes to produce nitriles: the Beckmann fragmentation.[6] Several examples of this reaction were reported in the early part of the twentieth century, including its application in degradation studies focused on the structure elucidation of morphine (equation 4).[7] These reactions were not well understood at the time, nor were they connected mechanistically to scattered examples of what in retrospect were examples of anionic fragmentation reactions.[2]



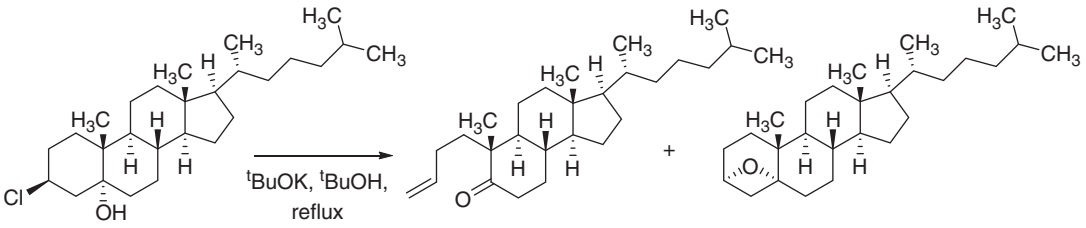
(4)

Eschenmoser reported the first rationally designed fragmentation reactions in 1952.[8] This seminal report includes design parameters aimed at site-selective installation of an alkene under basic conditions, a review of literature antecedents that had not previously been mechanistically connected, and several examples of reactions that would later be defined as fragmentations (equation 5). In 1952, the English also made key advances in the cationic fragmentation of 1,3-diols.[9]

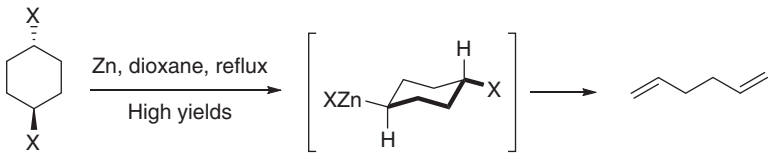


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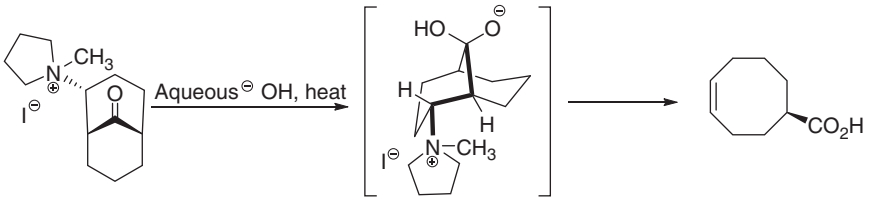
Several important and substantial contributions came in the following years. Henbest was the first to note the importance of antiparallel alignment of the cleaving bonds during steroid degradation studies (equation 6).[10] Grob executed metal-mediated 1,4-elimination of cyclic dihalides (equation 7)[11] and offered important mechanistic insights.[5] Stork reported the first ring expansion by fragmentation for the synthesis of a *cis*-cyclooctene (equation 8),[12] and Wharton began his classic studies in stereospecific ring-expanding fragmentations soon thereafter (equation 9).[13] Marshall conducted a series of elegant studies[14] in which boronates (equation 10) and other alternative electrofuges including dithianes and malonates (not shown) were exploited. Corey demonstrated the synthetic utility of emerging fragmentation technology in his now-classic synthesis of caryophyllene (equation 11).[15]



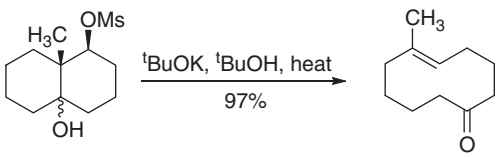
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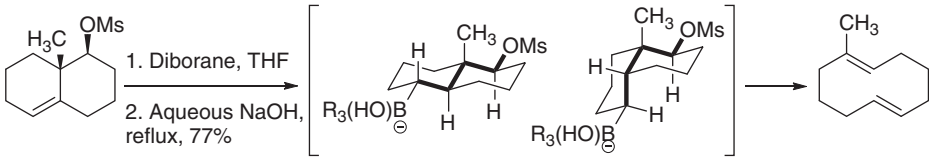
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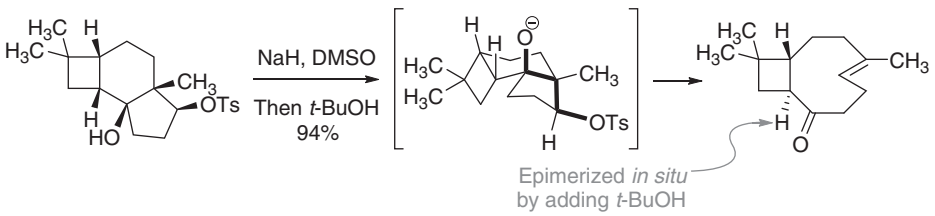
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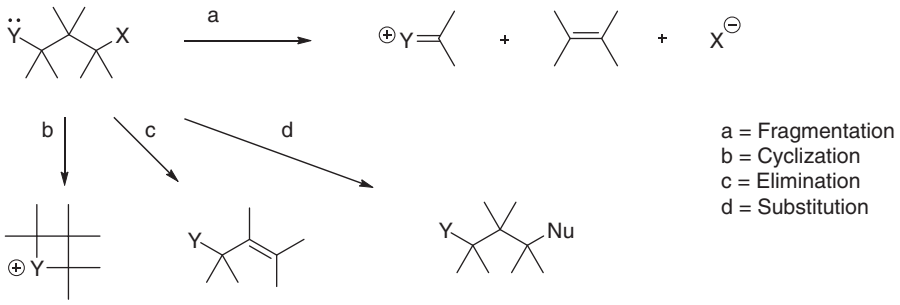


(11)

This list is by no means comprehensive; omitted here are cationic fragmentation in alkaloid degradation studies going back to the nineteenth century, as well as diverse synthetic applications and mechanistic insights from many prominent academic and industrial research teams. A more thorough historical analysis of the development of heterolytic C–C fragmentations is available elsewhere.[2]

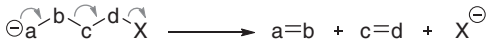
6.19.1.3 Mechanistic Considerations

Proper orbital alignment is prerequisite for fragmentation to occur. In acyclic substrates, the five-center system is typically depicted in an extended 'W' conformation, which satisfies the perceived need for antiparallel orientation of the two cleaving bonds and the electrofugal electron pair. Alternative conformations also meet these criteria. In systems for which these conformations are either inaccessible or disfavored, fragmentation pathways may be shut down or suppressed relative to competing pathways. Competing pathways often include 1,2-elimination, nucleophilic substitution, and ring-closing cyclization (Scheme 1).

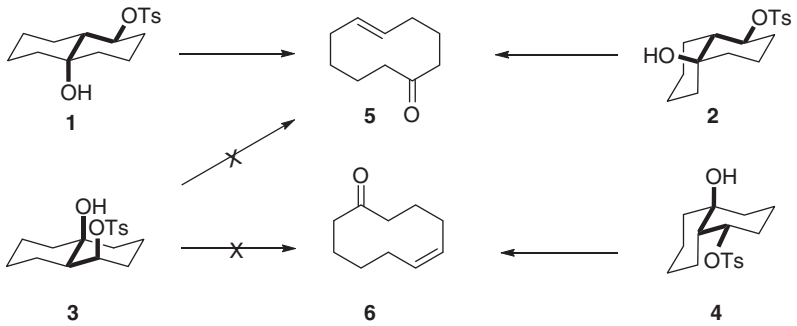


Scheme 1

As mentioned in Section 6.19.1.1, heterolytic fragmentation can occur by concerted (one-step) or stepwise (two-step) processes. Studies on the fragmentation of cyclic systems have been quite informative, as the rigidity of the ring makes it easier to link the fragmentation event to a specific conformation. Anionic fragmentations are probably concerted in most cases, with all five centers participating in a single fragmentation transition state (equation 12). The concerted nature of anionic fragmentations and the importance of antiparallel alignment of the cleaving bonds are perhaps best illustrated by Wharton's studies involving stereoisomeric 1,10-decalindiol monotosylates (Scheme 2).[16] Fragmentation predictably leads to either *cis*- (**4**→**6**) or *trans*- (**1** or **2**→**5**) cyclodecenones in a stereospecific manner as long as the antiparallel alignment of the cleaving bonds can be achieved. Isomer **3**, which cannot adopt this antiparallel orientation, is not a viable fragmentation substrate. The increased rate of concerted fragmentation relative to ionization and/or other (asynchronous) pathways, given proper stereoelectronic alignment, has been dubbed the 'frangomeric effect.'[5]

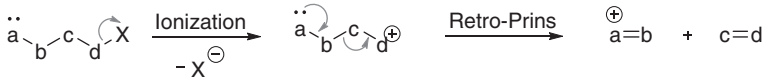


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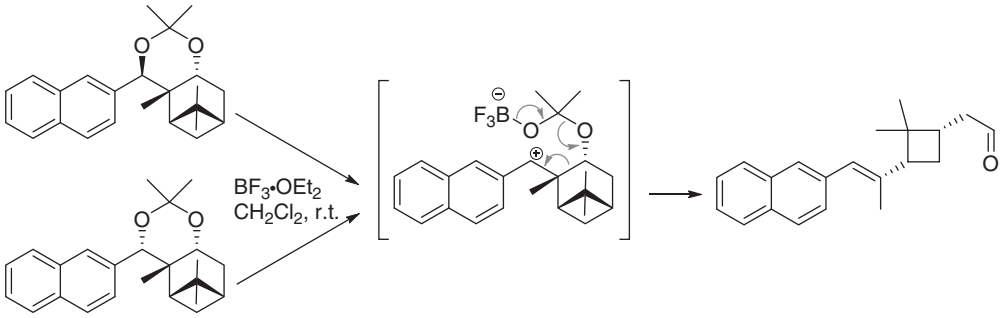


Scheme 2

Cationic processes are more likely to occur in a stepwise manner, with initial departure of the nucleofuge followed by cleavage of the bond between the electrofuge and middle part (equation 13). The first stage, ionization, is governed by the familiar parameters associated with carbocation stability. The second stage is the reverse of a Prins addition and could properly be called a retro-Prins reaction. A two-step process is consistent with the observation that the stereochemistry of the nucleofugal group is not a critical factor in the overall reaction efficiency (Scheme 3). The mechanistic connection between cationic fragmentation and Prins cyclization is highlighted later in this chapter (cf. Scheme 5, below; *see* Chapter 2.03).

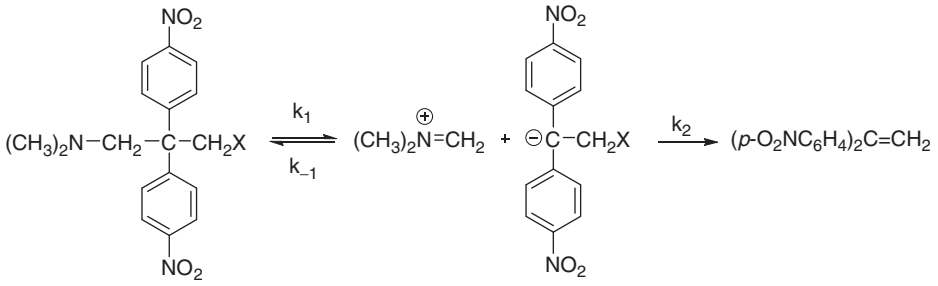


(13)



Scheme 3

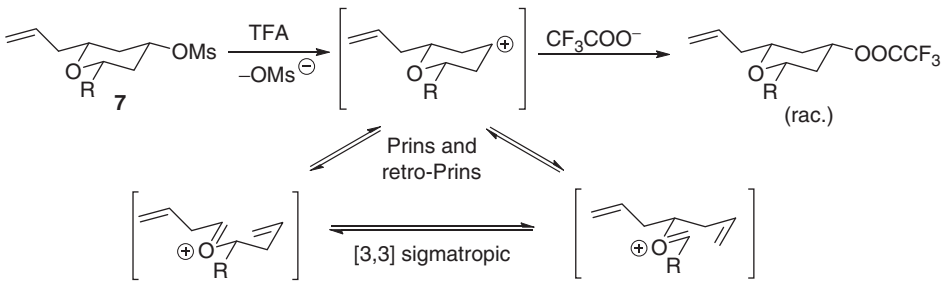
The third mechanistic possibility involves initial release of the electrofuge, which is the mechanistic homolog of the E1cb process. Few examples of such processes have been reported, perhaps because they are difficult to differentiate from concerted (asynchronous) anionic processes. Grob has outlined kinetic parameters and made preliminary kinetic arguments in support of this pathway (Scheme 4).[5]



X = OH, C_6H_5COO, *p*-$CH_3C_6H_4COO$, *p*-$CH_3OC_6H_4COO$, *p*-$O_2NC_6H_4COO$;
All undergo fragmentation at a similar overall rate

Scheme 4 Grob kinetics for two-step ionic mechanism.

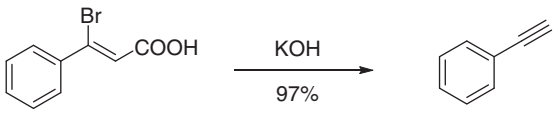
Several mechanistic and stereoelectronic features are embodied in an interesting solvolytic racemization reported by Rychnovsky and Jasti (Scheme 5).[17] Mesylate **7** in trifluoroacetic acid is observed to undergo substitution with retention of relative stereochemistry around the tetrahydropyran ring. However, an enantioenriched starting material gives way to racemic product. To explain the loss of absolute stereochemistry, the researchers postulate a dynamic intervening process comprising fragmentation, sigmatropic rearrangement, and Prins cyclization (the reverse of the fragmentation event), in which at least one of the processes is not stereospecific.



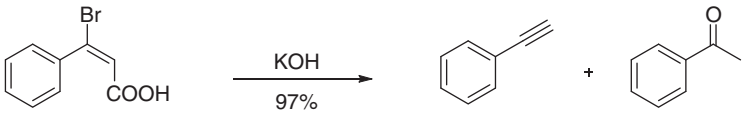
Scheme 5

For concerted fragmentation reactions, the most important consideration seems to be coplanarity of the cleaving bonds. Most concerted fragmentations involve transition states in which the cleaving bonds align in an antiparallel fashion. However, *syn*-fragmentation pathways are also well documented and in some cases offer synthetic advantages (cf. equations 14 and 15).[18] The predominance of *anti*-fragmentation reactions is probably because 1,2-*syn* (eclipsed) conformations are often energy maxima without finite lifetimes, and *gauche* or perpendicular conformations do not provide the requisite orbital overlap. Holton noted the

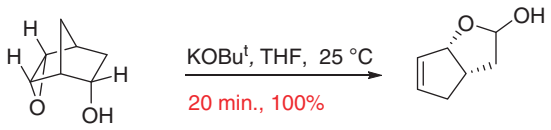
importance of coplanarity while documenting the facility with which *endo*-epoxide undergoes fragmentation (via an apparent *syn*-transition state) compared with the diastereomeric *exo*-epoxide (equations 16 and 17).[19]



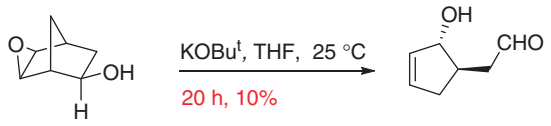
(14)



(15)



(16)



(17)

Additional discussion on the mechanistic and stereoelectronic factors involved in heterolytic fragmentation events can be found elsewhere.[3,5]

6.19.2 Scope and Synthetic Applications

The synthetic applications of fragmentation reactions are presented here in three sections based on what emerges from the 'middle part' of the fragmentation substrate. The first section covers representative examples of fragmentation reactions that generate alkenes. The second section covers the synthesis of alkynes and allenes. Alkenes are typically easier to generate by fragmentation reactions, despite the fact that alkene π-bonds are generally longer and weaker than alkyne π-bonds.[20] This apparent contradiction is reconciled by considering that the sacrificial σ-bonds *en route* to alkenes are also generally longer and weaker.

In practice, the greater facility with which alkenes are generated by fragmentation (compared with alkynes and allenes) has translated into a more broadly developed collection of examples in chemical synthesis, as well as a greater diversity of strategies for triggering fragmentation. However, there have been important advances in 'alkynogenic' and 'allenogenic' fragmentation method in recent years, as noted later in Sections 6.19.2.2 and 6.19.2.3.

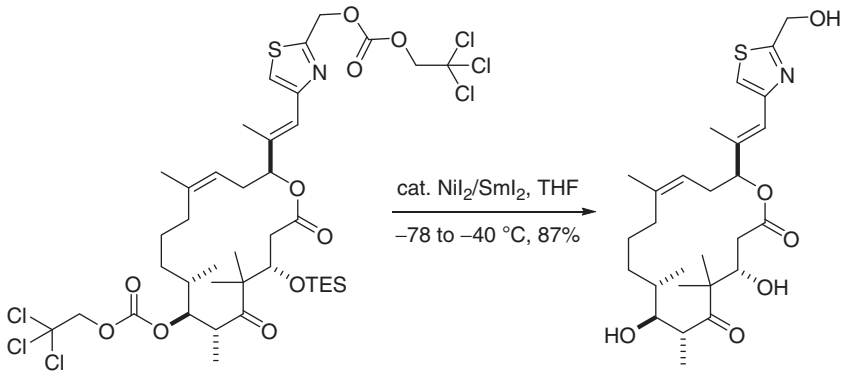
6.19.2.1 Fragmentation Reactions that Generate Alkenes

The foundation and guiding mechanistic principles governing fragmentation reactions were established in the early literature. Useful methodological advances and elegant synthetic applications from recent decades are the focus here. Fragmentation reactions, particularly within cyclic systems, result in topographical changes to the carbon skeleton that can be synthetically advantageous in the appropriate context. The opportunity for strategic deployment of such processes may not be clear at the outset, but synthetic chemists will often make a conscious effort to scan for nonobvious transformations that enable more efficient strategies. Still, synthetic application of fragmentation reactions may be underdeveloped for lack of clearly defined retrons (recognizable structural features associated with a particular reaction), suggesting opportunities for advancement in this area.

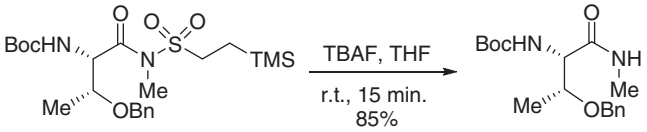
6.19.2.1.1 Fragmentation of acyclic substrates

Fragmentation of acyclic substrates is of limited strategic value in organic synthesis. C–C bond cleavage of acyclic systems necessarily results in degradation of the carbon skeleton, which is not typically desirable. Moreover, the conformational flexibility of acyclic substrates provides access to diverse reaction pathways, which can be associated with reduced selectivity for a specific fragmentation product. Cyclic systems, in contrast, can provide a strong bias for the frangomeric[5] conformation, and the resulting ring-opening event does not necessarily result in skeletal erosion because the fragments remain tethered.

However, many valuable synthetic transformations of acyclic systems either feature or include aspects of C–C bond-cleaving fragmentation. For example, deprotection of Troc carbonates and carbamates can be viewed as a metal-mediated fragmentation (equation 18),[21] as can the fluoride-induced cleavage of trimethylsilylethyl carbonates. Fragmentative cleavage of a trimethylsilylethyl sulfonamide plays a supporting role in amidation methodology based on sulfonyl azide chemistry from the Williams laboratory (equation 19).[22]

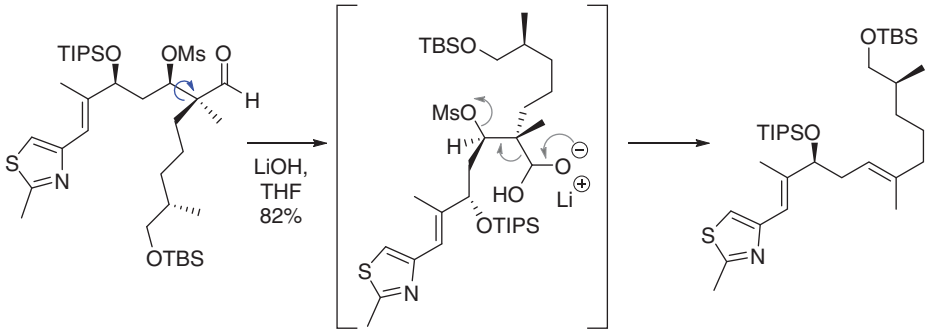


(18)

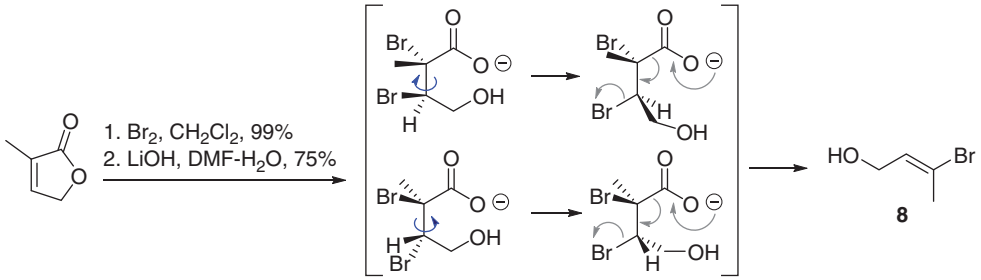


(19)

In principle, concerted decarboxylative fragmentation can be used to generate alkenes stereospecifically from aldol adducts. Fragmentation of *syn*-aldol derivatives via an antiparallel transition state would yield *trans*-alkenes, whereas *anti*-aldol derivatives would provide *cis*-alkenes.[3] An illustrative example of a related decarbonylative fragmentation for the stereocontrolled synthesis of a trisubstituted alkene is provided in equation 20.[23] Likewise, *β*-halo carboxylates are susceptible to stereospecific decarboxylative fragmentation, as the Smith laboratory demonstrated with an efficient synthesis of vinyl bromide **8** (equation 21),[24] a useful building block for terpene synthesis.



(20)

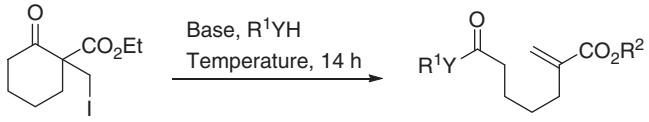


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6.19.2.1.2 Ring-opening fragmentation of cyclic substrates

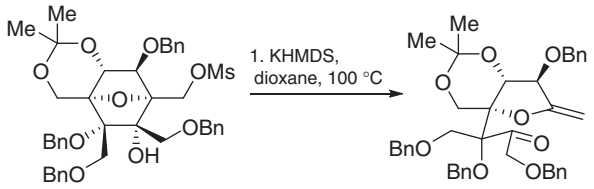
Eschenmoser's seminal fragmentation method (cf. equation 5, above) was limited in scope to five-membered rings because of competition from other pathways (i.e., cyclization). Lupton rationalized that an appropriately positioned electron-withdrawing

group would promote fragmentation by stabilizing developing negative charge in the transition state. It was thus found that cyclic α-iodomethyl-β-keto esters of various ring sizes undergo nucleophile-triggered fragmentation (equation 22).[25] The researchers propose a concerted fragmentation process, as opposed to a stepwise retro-Dieckmann and elimination sequence, based on the combined weight of two kinetic observations: (1) Cyclopentanones fragment faster than cyclohexanones or cycloheptanones, consistent with the ring opening being part of the rate-determining step. (2) Iodide is a better (faster) nucleofuge than bromide or mesylate, suggesting that release of the nucleofuge is *also* involved in the rate-determining step. These observations are instructive for optimizing new fragmentation processes.



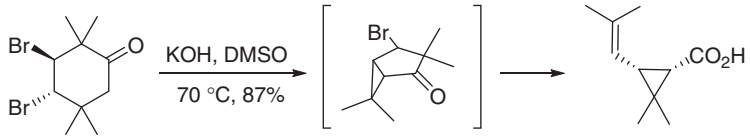
(22)

Part of the challenge in the Eschenmoser system may relate to the conformational flexibility of the nucleofuge. Similar conformational freedom is available in mesylate **9**, which undergoes anionic fragmentation at elevated temperatures (equation 23).[26] Proper orbital alignment is critical for concerted anionic fragmentation, and systems that provide a favorable conformational bias are likely to be good fragmentation substrates. Krief took advantage of such a bias to complete a masterful synthesis of *cis*-chrysanthemic acid.[27] Dibromide **10**, prepared in three steps from dimethyl dimedone, undergoes base-mediated cyclization, followed by hydroxide-triggered fragmentation (equation 24). The *exo*-stereochemistry of intermediate bromide **11** was postulated by analogy to earlier work in their laboratory; the alternative *endo*-isomer does not provide the proper antiparallel alignment for fragmentation. The researchers confirmed the structural assignment by isolating **11** from separate experiments.



9

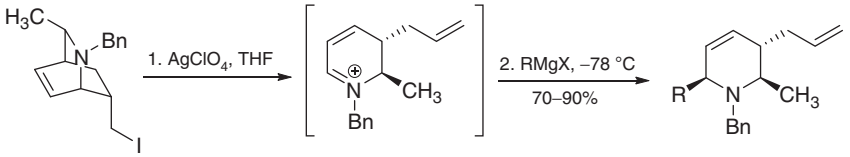
(23)



10 **11**

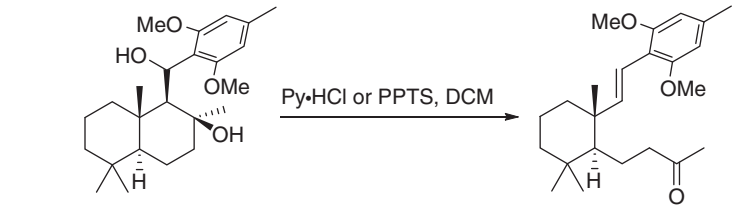
(24)

Charette reported a silver-mediated fragmentation of γ-amino halides (equation 25)[28] that is reminiscent of early alkaloid degradation studies[29] and Grob methodology.[30] Fragmentation presumably occurs by a concerted mechanism to generate an intermediate iminium cation. The resulting iminium cation can be trapped *in situ* with Grignard reagents, resulting in good overall yields of versatile piperidine derivatives. γ-Amino triflates fragment spontaneously (no silver or other additive),[28b] consistent with the general trend that triflate is a better nucleofuge than iodide.

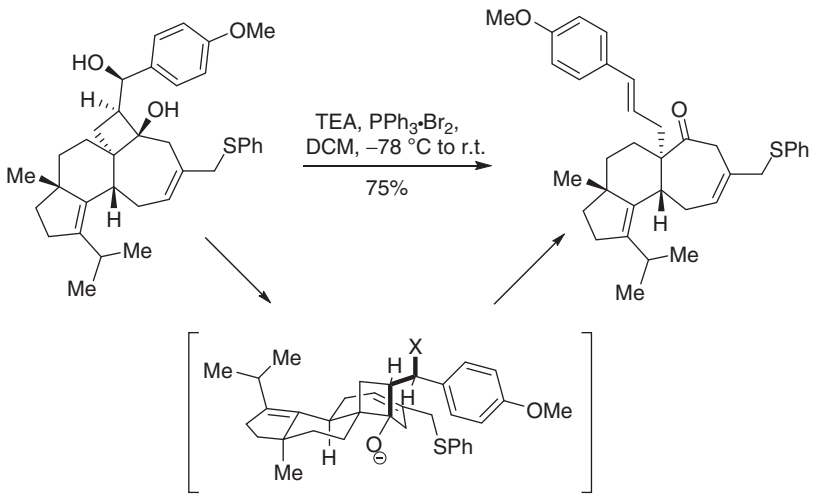


(25)

Cationic ring-opening fragmentation by a two-step process is exemplified by a fast and efficient reaction reported by the Kato laboratory (equation 26).[31] The researchers invoke a stepwise mechanism of rate-limiting ionization of the nucleofuge followed by fragmentation of the electrofuge and middle part, although a concerted asynchronous mechanism cannot be ruled out. The electron-rich aromatic ring plays a key role in accelerating fragmentation. In the absence of electron-donating methoxy groups, fragmentation is less efficient and requires harsher conditions. Cha featured a similar ring-opening fragmentation in the synthesis of cyathane diterpenes (equation 27); in this case, release of ring strain in concert with arene-assisted ionization of the nucleofuge is likely responsible for facile fragmentation.[32]



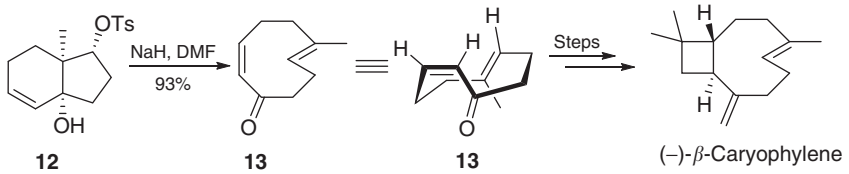
(26)



(27)

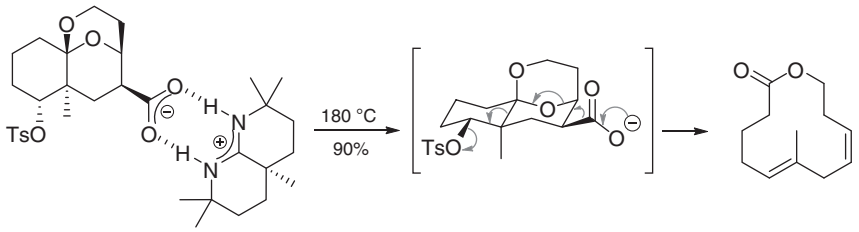
6.19.2.1.3 Ring-expanding fragmentation of polycyclic substrates

Fragmentation reactions are exceptionally valuable in the stereospecific production of medium-sized cycloalkenes, which can be difficult to prepare by other methods. Many powerful examples are available in the literature, beginning with Corey's classic synthesis of β-caryophyllene.[15] Corey recently revisited this challenging sesquiterpene to develop an enantioselective synthesis by means of chiral dienone **13** (Scheme 6).[33] Fragmentation of **12** yields **13** (93%); dienone **13**, like *trans*-cyclooctene, is chiral and configurationally stable due to conformational restrictions. This conformational asymmetry provides stereocontrol over the ensuing annulation of the four-membered ring. This work illustrates the value of fragmentations in the production of chiral cycloalkenes and the perhaps underdeveloped strategic use of cycloalkenes as chiral building blocks for chemical synthesis.



Scheme 6

Eschenmoser reported elegant double ring-expanding fragmentations that ultimately change the connectivity of nine atoms, exemplified in equation 28.[34] Four bond-cleavage events are involved. It is unclear to what degree this process is concerted, but any intermediate would likely be short lived as a consequence of being conformationally predisposed to continue the tandem sequence.

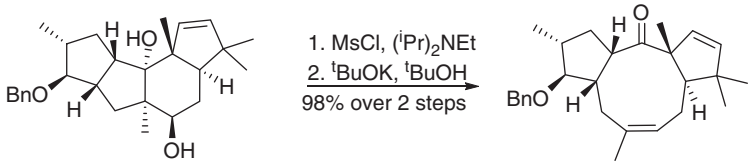


(28)

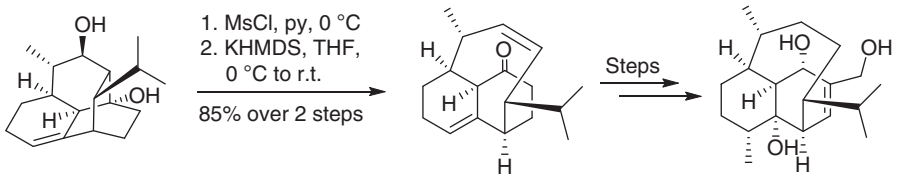
Ring-expanding fragmentation of bicyclic diol monosulfonates (e.g., Scheme 2) is often associated specifically with Wharton, due to his pioneering studies on decalindiol monotosylates.[13] The Wharton fragmentation has particular synthetic utility for

complex natural products with unusual ring structures. It is often easier to assemble fused bicyclic structures comprising five-, six-, and seven-membered rings than it is to prepare larger ring sizes. Ring-expanding fragmentations enable one to leverage accessible bicyclic substructures to generate larger and more daunting ring systems.

Two compelling examples of the utility of Wharton fragmentation in total synthesis are presented here. Paquette and coworkers prepared fused tetracyclic diol **14** (equation 29) *en route* to the antileukemic natural product, jatrophatrione. Conversion to the monomesylate and base-mediated fragmentation opens the core bicyclo[4.3.0]nonane into central cyclononene **15**, thereby revealing the proper carbon skeleton of the target structure.[35] Baran recognized the strategic utility of fragmentation for generating the unusual *ansa*-bridged diterpene vinigrol (equation 30).[36] Tetracyclic diol **16** was constructed with the aid of classic cycloaddition chemistry, and the derived secondary monomesylate cleanly fragmented under basic conditions to generate *ansa*-bridged tricycle **17**. A series of creative maneuvers completed this instant classic synthesis of vinigrol.

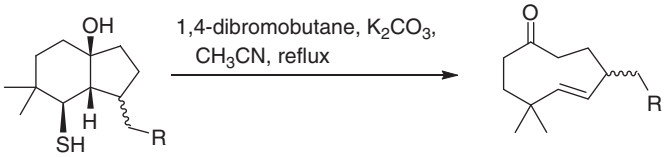


14 **15** (29)

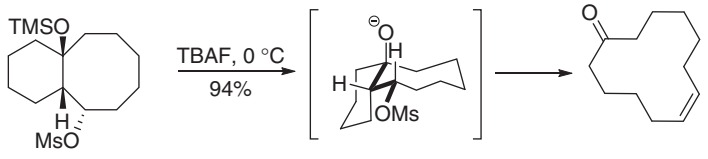


16 **17** Vinigrol (30)

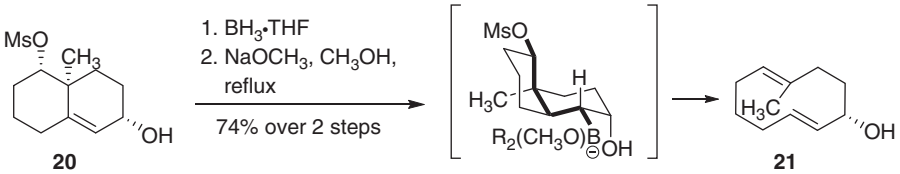
Diol monosulfonates are not unique in their ability to fragment by the pathways blazed by Wharton; alternative tactics have been exploited within the same mechanistic framework. γ-Hydroxy thiols provide effective fragmentation substrates upon double alkylation of the thiol (equation 31).[37] The intermediate sulfonium nucleofuge undergoes fragmentation under the mildly basic reaction conditions. Fluoride-induced fragmentation of bicyclo[6.4.0]dodecane **18** produced cyclododecenone **19** in excellent yields (equation 32),[38] illustrating an alternative to the use of strong base for activating the electrofuge. Ley drew upon Marshall's fragmentation studies using boronate electrofuges in recent synthetic efforts; hydroboration of homoallylic mesylate **20** led to ring-expanding fragmentation to produce cyclodecadiene **21** in a stereocontrolled manner (equation 33).[39]



(31)

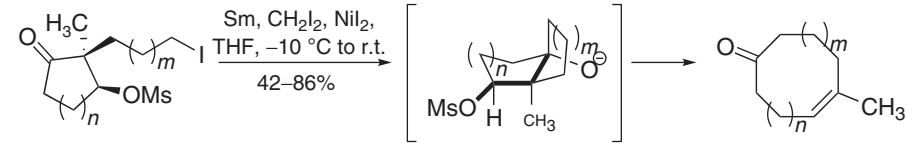


18 **19** (32)



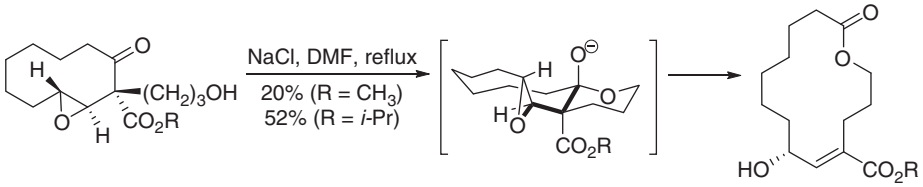
20 **21** (33)

Nucleophilic cyclization can also give rise to viable fragmentation substrates. Molander showed that intramolecular samarium–Barbier reaction of α-iodoalkyl-β-mesyloxy cyclic ketones provides alternative entry into the Wharton fragmentation pathway (equation 34).[40] The tandem cyclization/ring expansion offers convenient access to eight-, nine-, and ten-membered *Z*-cycloalkenones. Molander's cyclizations were predated by Hesse's alkoxy anion-triggered ring expansion for the synthesis of macrolactones (equation 35).[41] Several features of this tandem process warrant further comment. The preexisting ester functional group is likely both an asset and a liability. As Lupton postulated,[25] the ester stabilizes developing negative charge in the fragmentation transition state, resulting in a faster and more efficient bond cleavage. However, the ester presents an alternative and unproductive cyclization pathway, which perhaps explains why the hindered isopropyl ester is advantageous compared with methyl ester. The macrolactone product necessarily features an allylic alcohol as a consequence of the epoxide nucleofuge.



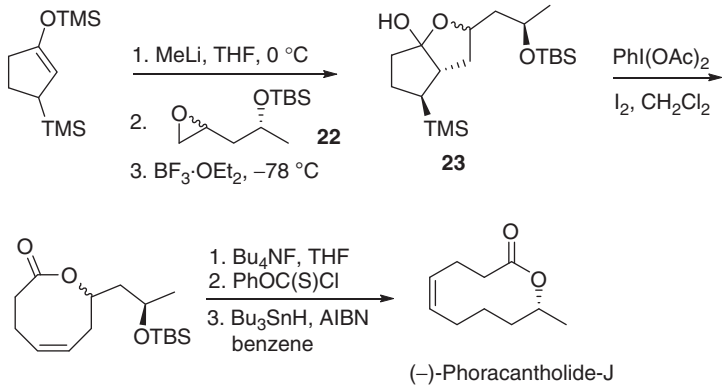
(34)

$n = 1, 2$
$m = 1, 2$



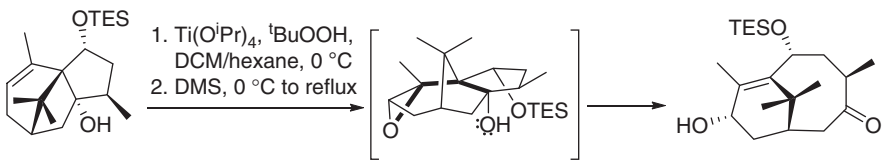
(35)

Posner offered an umpolung twist on the synthesis of macrolactones by ring-expanding fragmentation (**Scheme 7**).[42] Enolate opening of epoxide **22** produces bicyclic hemiacetal **23**, which undergoes fragmentation under oxidative conditions and with cleavage of a carbon–silicon bond. A second ring expansion and deoxygention complete a concise synthesis of (–)-phoracantholide-J.



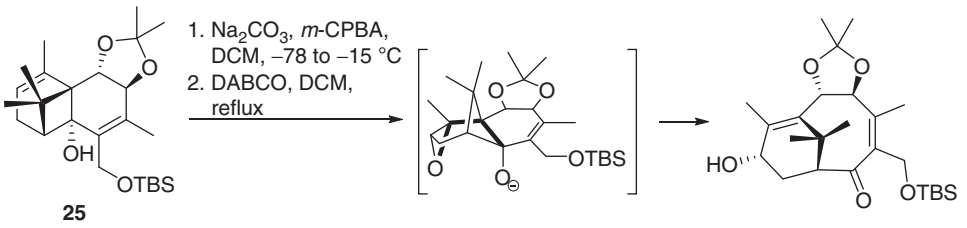
Scheme 7

Epoxide fragmentations played a key role in two of the landmark total syntheses of taxol. Holton's earlier studies on the *syn*-fragmentation of epoxides[19] guided the two-step titanium-mediated epoxidation/fragmentation of homoallylic alcohol **24** shown in equation 36.[43] As noted above, *syn*-epoxy alcohol stereoisomers proved to be better fragmentation substrates than *anti*-isomers in model systems, perhaps due to better periplanar alignment of the cleaving bonds in the *syn*-isomer. In contrast to Holton's Lewis acid-catalyzed epoxide fragmentation, Wender used a base-mediated epoxide fragmentation of the bicyclo[3.1.1.]heptene core of **25** (equation 37).[44] The Wender fragmentation entry into the taxane system involves a cyclobutane ring opening, which provides the added benefit of release of ring strain.



24

(36)



(37)

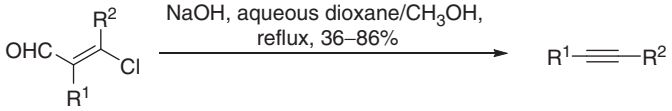
The examples provided here are meant to be representative of the myriad and diverse applications of heterolytic fragmentation reactions in organic synthesis. For additional examples and discussion, please consult other recent reviews.[1,2,3]

6.19.2.2 Fragmentation Reactions that Generate Alkynes

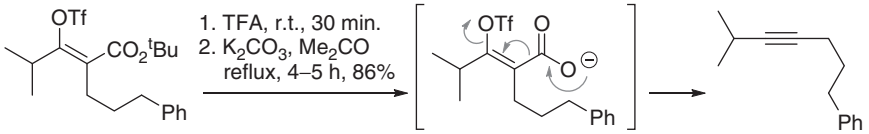
Distinct considerations are involved in the design and execution of 'alkynogenic' fragmentations as opposed to the more typical fragmentation reactions that generate alkenes. One of the major factors in the alkene-generating fragmentations is establishing the proper *anti-* (or *syn-*) coplanar alignment of the cleaving bonds. In contrast, the cleaving bonds in olefinic substrates are virtually locked into near-perfect orbital alignment, so entropic (conformational) barriers are generally lower. However, bonds involving sp^2-hybridized carbons are typically stronger than their sp^3-hybridized counterparts, so enthalpic barriers are generally higher. This enthalpic penalty is partially offset by the formation of the stronger alkyne π-bond.[20] Nonetheless, most synthetic applications of alkynogenic fragmentation involve powerful nucleofuges (e.g., molecular nitrogen or triflate) and/or elevated temperatures.

6.19.2.2.1 Fragmentation of acyclic substrates

Bodendorf reported what are likely the first examples of alkynogenic fragmentation in 1963 (equation 38): reaction of β-chloroacroleins with aqueous hydroxide at an elevated temperature gives rise to formate and acetylenes.[45] The following year, Grob made the interesting observation involving related decarboxylative fragmentation of β-bromocinnamic acids noted in Section 6.19.1.3 (equations 14 and 15):[18] the *Z*-isomer decomposes exclusively to phenylacetylene, whereas acetophenone is observed as a byproduct from the *E*-isomer. Acetophenone likely arises by decarboxylation of an intermediate β-keto acid, which suggests that hydrolysis of the vinyl bromide competes with fragmentation in the *E*-isomer. Fleming reported that the corresponding enol triflates, prepared in many cases as mixtures of *E*/*Z* stereoisomers, give rise to a wide range of alkynes and alkynoic acids (e.g., equation 39).[46]

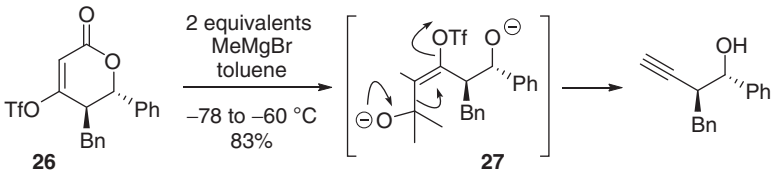


(38)

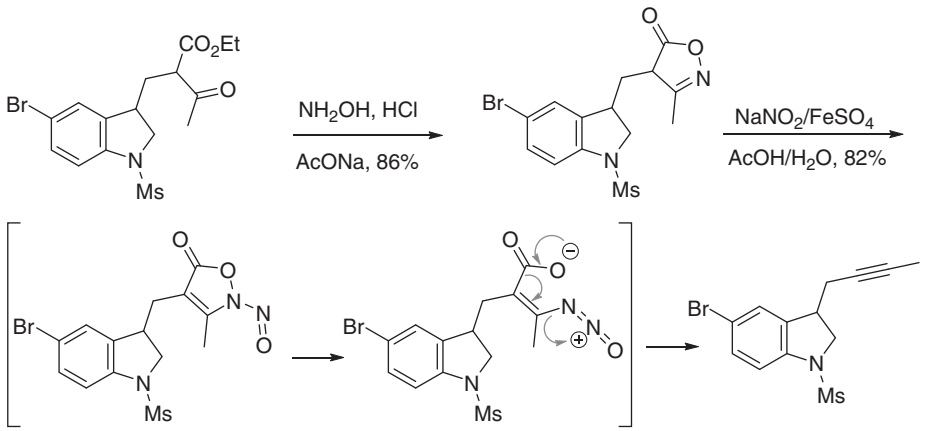


(39)

Fragmentation of acyclic intermediates is the final step in several mechanistically distinct cascade sequences for converting heterocycles into acyclic alkynes. For example, Zard developed a convenient synthesis of internal alkynes from β-keto esters via isoxazolinones.[47] Oxidation of isoxazolinones with sodium nitrite and ferrous sulfate gives rise to an *N*-nitroso intermediate, which undergoes ionization and decarboxylative *syn*-fragmentation to produce internal alkynes (e.g., **Scheme 8**). The mechanistic detective work involved in the discovery of this process was featured in a 2002 review.[48] Dudley reported a synthesis of homopropargyl alcohols from heterocyclic vinylogous acyl triflates (equation 40).[49] Addition of methyl Grignard to dihydropyrone triflate **26** produces intermediate acyclic dianion **27**, which releases the alkyne and acetone, presumably, by *anti*-fragmentation upon warming.

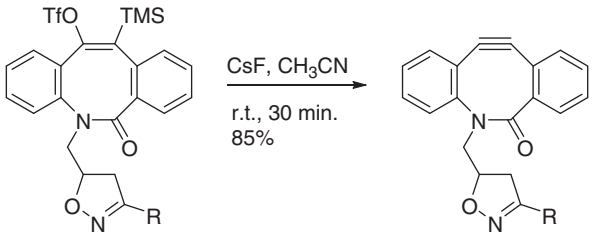


(40)



Scheme 8

Fluoride-triggered *syn*-elimination of trimethylsilyl triflate, though not commonly referenced as a 'fragmentation,' is analogous to the boronate fragmentations originally reported by Marshall (cf. equation 10, Section 6.19.1.2).[14] Benzyne and other highly reactive strained cycloalkynes can be generated using this tactic.[50] For example, Bertozzi used it to prepare BARAC, one of the more reactive strained cyclooctynes being developed for strain-promoted azide–alkyne cycloaddition (SPAAC) reactions (equation 41).[51]

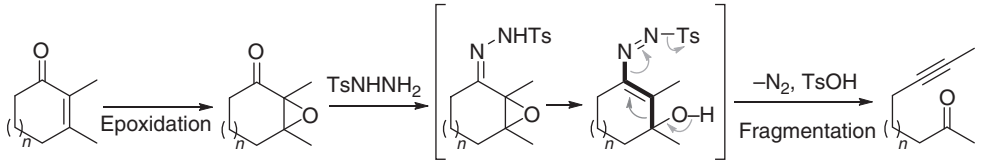


(41)

6.19.2.2.2 Ring-opening fragmentation of cyclic substrates

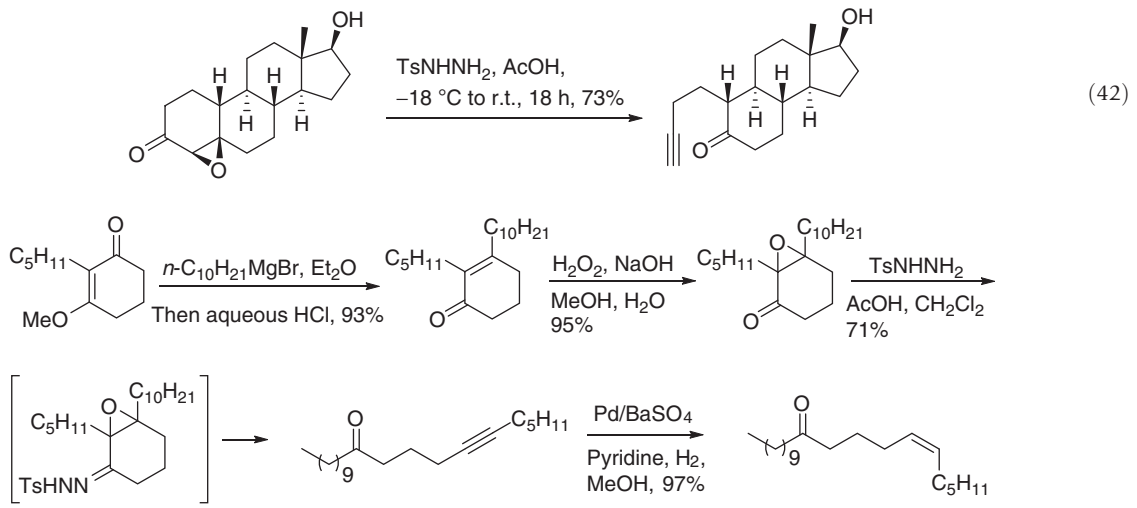
Compared with acyclic substrates, alkynogenic fragmentation of cyclic substrates has received considerably more attention from the synthetic community. The Eschenmoser–Tanabe fragmentation is by far the most prominent reaction of this type. Discovered independently by the two laboratories in the late 1960s,[52] this controlled decomposition of cyclic epoxy sulfonylhydrazones provides convenient access to acyclic alkynyl ketones from readily available cyclic enones. Most examples involve tosylhydrazones, with the 2,4-dinitrobenzenesulfonyl- (nosyl-) hydrazone being one of the popular alternative options for challenging substrates.[53]

The Eschenmoser–Tanabe fragmentation process typically begins with a cyclic enone (Scheme 9). Epoxidation and hydrazone formation can be executed in either order to assemble the requisite epoxy sulfonylhydrazones. Once formed, these intermediates rearrange (generally with the aid of acid or base) to vinyldiazenes that are disposed for a seven-center fragmentation event. The epoxy hydrazone is elegantly engineered to release both strain and molecular nitrogen to drive the rearrangement and fragmentation events leading to tethered alkynyl ketones.



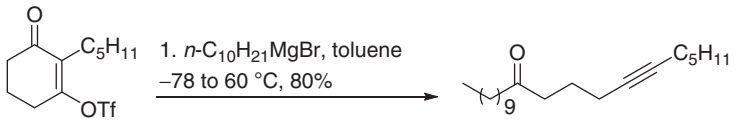
Scheme 9

The Eschenmoser–Tanabe fragmentation is often exploited for strategic cleavage of the steroid A ring (equation 42).[54] Kocienski's synthesis of a moth pheromone illustrates the successive synthesis and fragmentation of cyclic enones derived from vinylogous esters (Scheme 10);[55] Dudley demonstrated the use of vinylogous acyl triflates as a truncated alternative to such sequences (equation 43).[56] Tandem addition and fragmentation reactions using the triflate nucleofuge[57] were foreshadowed by related fragmentations from Coke[58] (halides) and Kuwajima[59] (selenones).



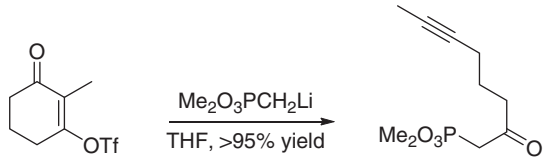
(42)

Scheme 10



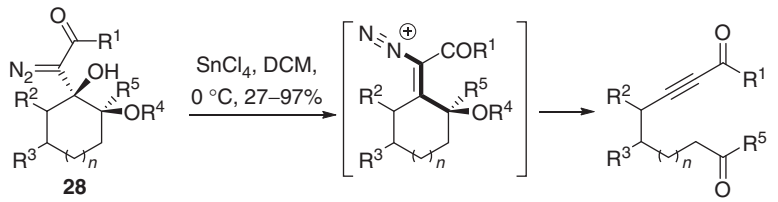
(43)

Dudley's fragmentation method provides access to alkynes tethered to ketones, amides, alcohols, and other functional groups based on the choice of nucleophile for the initial addition step.[56] Synthesis of a β-keto phosphonate was a starting point for a recent synthesis of palmerolide A (equation 44).[60] Vinylogous acyl triflate chemistry was the subject of a recent review.[61]



(44)

Brewer generated vinyldiazene intermediates for fragmentation by a unique and innovative strategy (equation 45): tin tetrachloride-mediated ionization of diazo monoprotected diol **28** initiates a cationic fragmentation to generate alkyne dicarbonyl compounds.[62] Molecular nitrogen is the nucleofuge. One of the attractive features of this method is the facility with which aldehydes ($R^5 = H$) are produced.



28

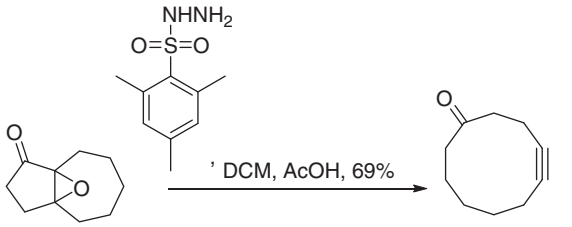
(45)

$n = 0, 1, 2$ R^1 = OEt, aryl, alkyl
R^2, R^3 = H, unsaturated
R^4 = silyl, Bn, Me
R^5 = H, Me, OMe

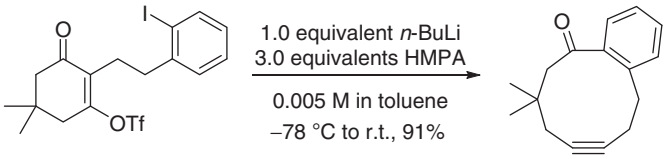
6.19.2.2.3 Ring-expanding fragmentation of polycyclic substrates

The three general strategies for ring-opening alkynogenic fragmentation discussed in Section 6.19.2.2.2 have all been applied to ring-expanding fragmentation reactions for the synthesis of cycloalkynes. Cycloalkynes are especially difficult to prepare by cyclization reactions because of entropic barriers related to the linear geometry of alkynes. Fragmentation is one of the several attractive options for avoiding entropic barriers *en route* to medium-sized cycloalkynes. Eschenmoser and Tanabe each demonstrated the utility of ring-expanding fragmentation of epoxy hydrazones derived from bicyclic enones for the synthesis of cyclic alkynyl ketones.[51]

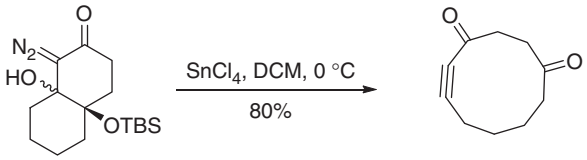
Reese later revisited the Eschenmoser–Tanabe method for the synthesis of medium-ring cycloalkynes (equation 46).[63] Dudley[64] and Brewer[65] have likewise developed ring-expansion analogs of their alkynogenic fragmentation processes (equations 47 and 48, respectively). Kuwajima generated both cyclic alkynes and cyclic allenes by thermal fragmentation of regioisomeric enol triflates **29** and **30** (equations 49 and 50).[66] An interesting feature of the latter reaction was that the cyclic allene was generated (slightly) more efficiently, perhaps because the cleaving C–C bond is weaker and more polarized in the allene precursor by virtue of connecting sp^3-hybridized carbons. Williams recently provided direct evidence that fragmentation can provide allenes selectively over alkynes (**Scheme 11**). Experimental and computational data suggest that the alkyne is thermodynamically preferred, but the kinetic barrier to allene formation (allenogenic fragmentation) is lower.[67]



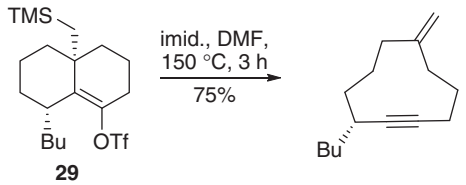
(46)



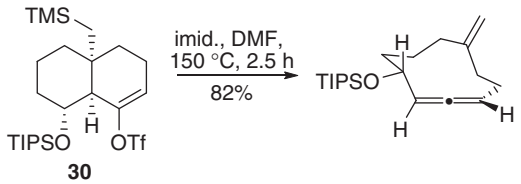
(47)



(48)



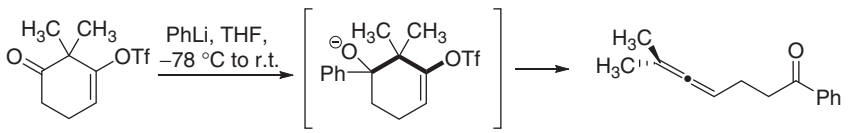
(49)



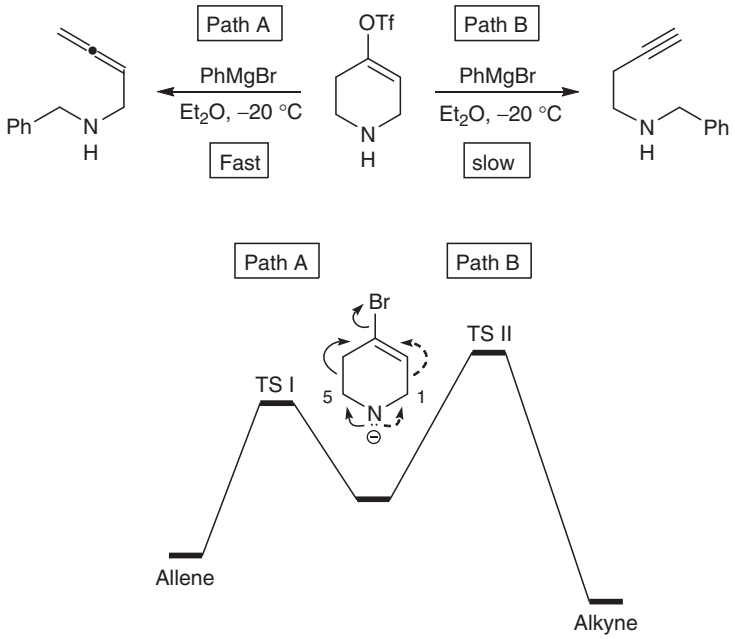
(50)

6.19.2.3 Fragmentation Reactions that Generate Allenes

Allenogenic fragmentation reactions were virtually unknown until recently, although 1,2-elimination reactions to give allenes foreshadowed their feasibility (*see* Chapter 6.18). The first systematic examination of allenogenic fragmentations appeared in 2009, when Williams reported tandem addition and fragmentation of cyclic β-trifloxy-β,γ-enones, the deconjugated analogs of vinylogous acyl triflates discussed in Section 6.19.2.2.2 (equation 51).[66] A range of carbon nucleophiles triggered fragmentation to allenyl ketones and related species.

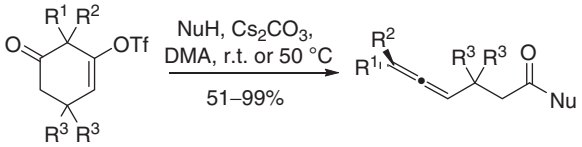


(51)



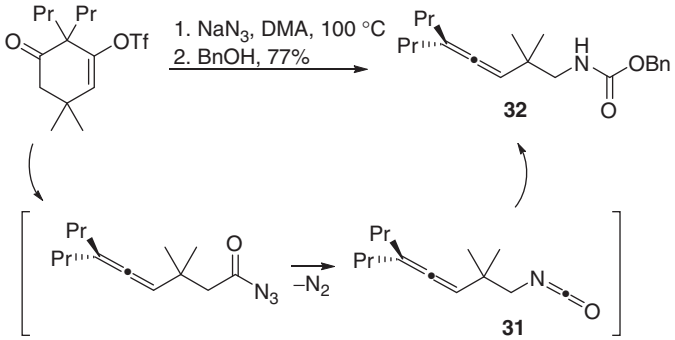
Scheme 11

The scope and synthetic applications of this process was quickly expanded by Cramer to include various heteroatom nucleophiles, giving rise to allenyl carbonyl compounds at the carboxylic acid oxidation level (equation 52).[68] Cramer cleverly capitalized on the broad scope of nucleophiles to design domino processes based on this allenogenic fragmentation. For example, sodium azide as the nucleophile generates an acyl azide, which undergoes Curtius rearrangement *in situ* to isocyanate **31** *en route* to CBz-protected amine **32** (equation 53).



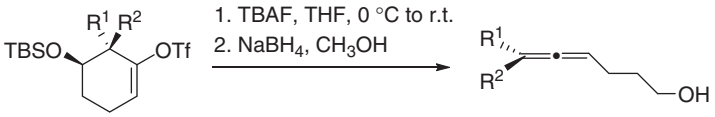
(52)

R^1 = CH_3, *n*Pr, allyl
R^2 = CH_3, *n*Pr, allyl, Bn, Ph
R^3= H, CH_3
NuH = H_2O, BnOH, PhOH, PhSH, NH_3, $BnNH_2$, $PhNH_2$, $TsNH_2$, $BnNHCH_3$, PhNHOH, morpholine, *p*-aminophenol

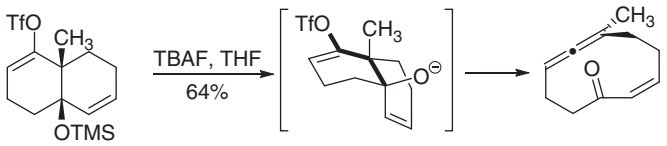


(53)

Williams documented several important features of this new allene synthesis, including the facility with which they occur compared with the analogous alkyne synthesis (cf. Scheme 11). Allenogenic fragmentation is stereospecific (equation 54), and can be exploited for the synthesis of cyclic allenes (equation 55). These two examples also reveal that fluoride can be used to promote fragmentation of silyl ether substrates. Synthesis of allenes by fragmentation was perhaps overdue, in retrospect, and it is not unreasonable to forecast significant progress in this area in the coming years.



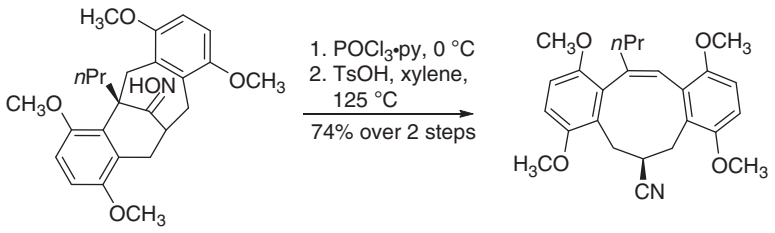
(54)



(55)

6.19.3 Beckmann Fragmentation

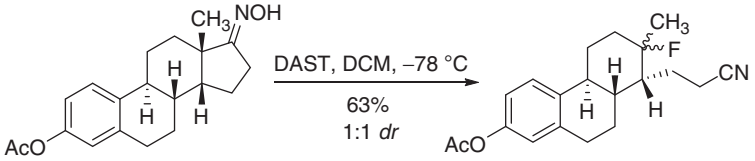
Conversion of oxime derivatives into nitriles is referred to as the Beckmann fragmentation. Its role in early structure determination studies was mentioned in Section 6.19.1.2. Grob was one of the first to study this process in detail and extend it to the ring-opening synthesis of alkene nitriles, which is how it is now most commonly applied in synthesis. The first such synthetic application came in Stork's synthesis of (±)-byssochlamic acid (equation 56).[69] Cyclic ketone oxime **33** was activated with phosphorus oxychloride and then heated under acidic conditions, presumably to promote ionization to the tertiary, benzylic cation with release of the phosphate nucleofuge and nitrile middle part. Loss of a proton from the cationic electrofuge provides the ring-expanded cyclononene **34**.



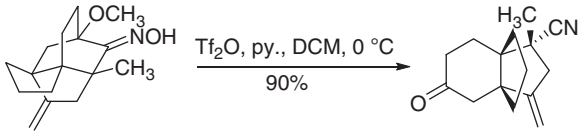
33 **34**

(56)

Recent developments in the use of ring-opening Beckmann fragmentation are highlighted in equations 57–59. Kirihara reported a ring-opening fluoridation of ketoximes;[70] applications included functionalizing the steroid D-ring (equation 57). Subba Rao drew upon early morphine degradation studies[7] with a facile heteroatom-assisted Beckmann fragmentation of tetracyclic oxime **35** to produce [4.3.3]propellane **36** (equation 58).[71] Hu identified an interesting fragmentation of oxime **37** involving selective formation of *exo*-alkene **38** (equation 59), optimally using a bulky, nonnucleophilic base at a reduced temperature.[72]

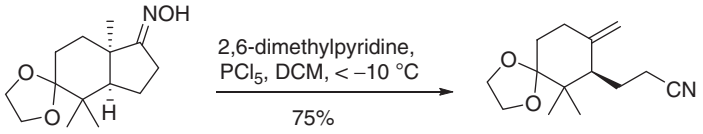


(57)



35 **36**

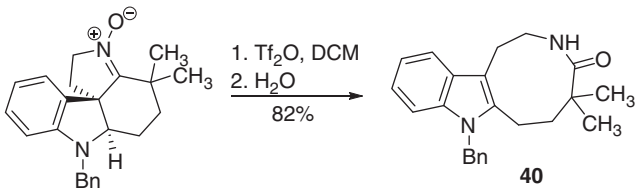
(58)



37 **38**

(59)

Murphy recently expanded the scope from oximes to nitrones (equation 60).[73] Nitrone **39** is activated with triflic anhydride to induce C–C and N–O bond cleavage. Hydration of the resulting cyclic nitrilium ion generates ring-expanded lactam **40**.



(60)

6.19.4 Concluding Remarks/Practical Considerations

Fragmentations are defined as heterolytic bond-cleavage reactions in which a molecule breaks into three (or more) fragments derived from an electrofuge, a middle part, and a nucleofuge. Many fragmentation processes involve concerted cleavage of two or more bonds in a single step through a well-ordered transition state featuring parallel alignment of the cleaving bonds. Non-concerted (stepwise) fragmentation processes usually involve initial release of the nucleofuge followed by further cleavage of a cationic intermediate, although stepwise anionic fragmentation is possible.

The energetic considerations associated with the design of a successful fragmentation event are essentially opposite to those of addition and other bond construction processes. The bond-cleavage events involve sacrificing σ-bonds for the creation of independent π-bond systems. To a first approximation, reactions that break two σ-bonds to form two new π-bonds and two new fragments are endothermic but entropically favorable. Strong nucleofugal groups like halides, sulfonates, and molecular nitrogen provide enthalpic assistance. Overall reaction entropy is generally favorable, but the requirement for a highly ordered transition state can result in unfavorable activation entropy. Substrates that are predisposed to proper alignment are more likely to fragment efficiently, and those that undergo concerted fragmentation can benefit from the synergy of the electron-rich electrofuge and the electron-deficient nucleofuge during the bond-forming and bond-breaking process.

Perhaps the best examples of strategic application of fragmentation reactions in organic synthesis involve ring opening and ring expansion. The seminal ring-opening examples from the Eschenmoser laboratory[8] featured precise control over stereochemistry and regiochemistry in the production of trisubstituted alkenes. Many other examples have since followed in which cyclic systems undergo fragmentation to generate intricate acyclic building blocks. Likewise, ring expansion of bicyclic structures provides medium and large rings, including unusual *ansa* bridges. Fragmentation may be considered an indirect method for constructive synthetic chemistry, but thoughtful execution of such a process to prepare a challenging molecular framework can result in an efficient and perhaps elegant synthetic process.

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