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Reaction Mechanisms

# Lewis Base Catalysis in Organic Synthesis

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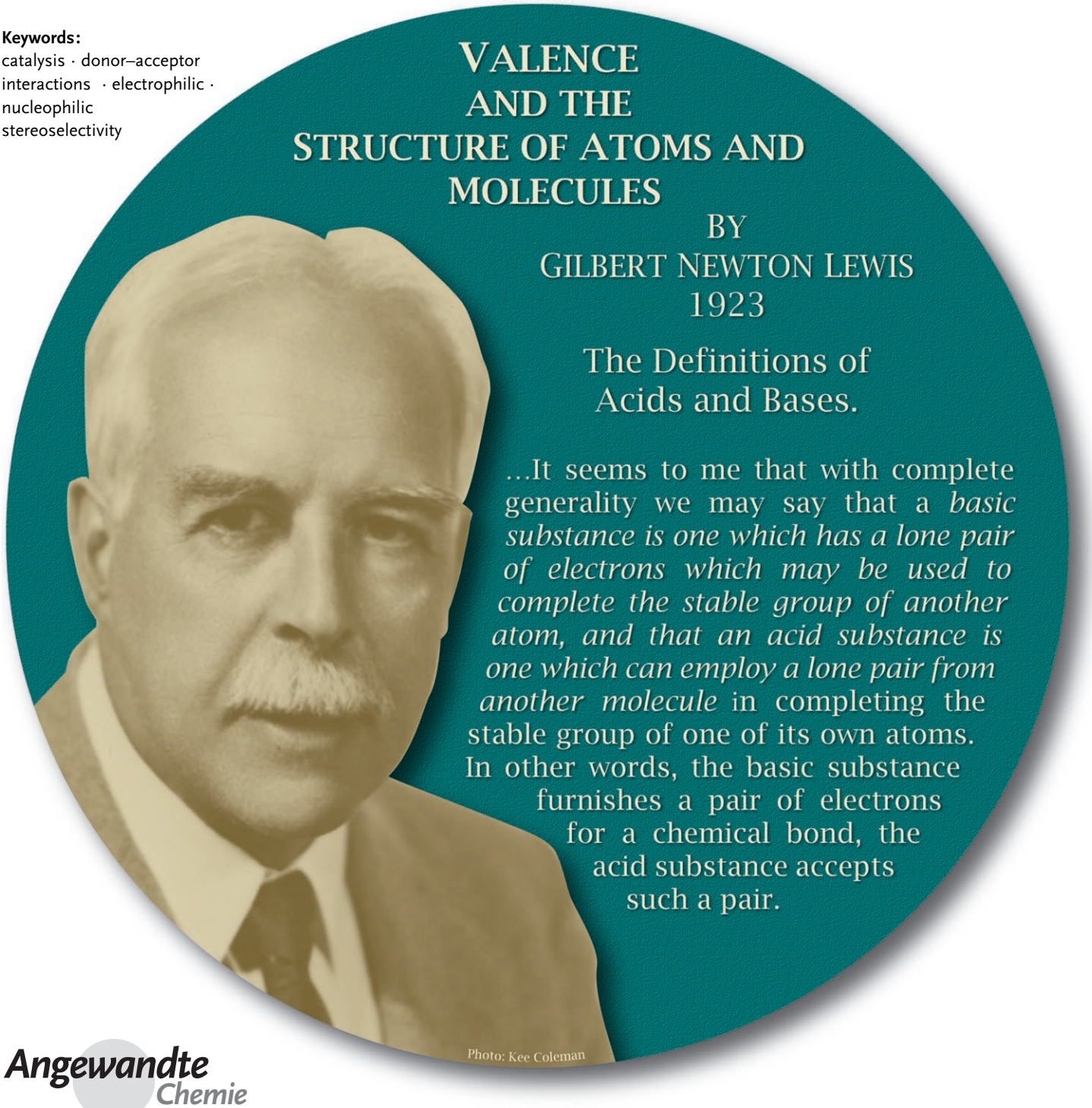
catalysis · donor–acceptor interactions · electrophilic · nucleophilic stereoselectivity



*The legacy of Gilbert Newton Lewis (1875–1946) pervades the lexicon of chemical bonding and reactivity. The power of his concept of donor–acceptor bonding is evident in the eponymous foundations of electron-pair acceptors (Lewis acids) and donors (Lewis bases). Lewis recognized that acids are not restricted to those substances that contain hydrogen (Brønsted acids), and helped overthrow the "modern cult of the proton". His discovery ushered in the use of Lewis acids as reagents and catalysts for organic reactions. However, in recent years, the recognition that Lewis bases can also serve in this capacity has grown enormously. Most importantly, it has become increasingly apparent that the behavior of Lewis bases as agents for promoting chemical reactions is not merely as an electronic complement of the cognate Lewis acids: in fact Lewis bases are capable of enhancing both the electrophilic and nucleophilic character of molecules to which they are bound. This diversity of behavior leads to a remarkable versatility for the catalysis of reactions by Lewis bases.*

**From the Contents**

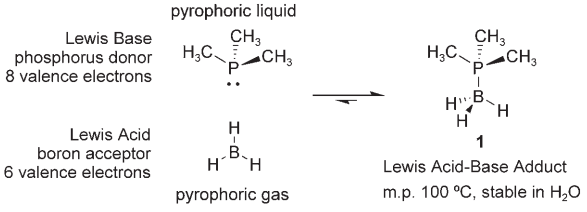


## 1. Introduction

The modern theory of acid–base interactions, pioneered by G. N. Lewis at the beginning of the 20th century, has become one of the most widely accepted, unifying theories of chemical structure and reactivity.[1] In the place of earlier definitions based on complex ideas about the properties of specific species, such as the proton, electrolytes, and solvent interactions, the Lewis definitions provide a simpler, yet all encompassing, picture founded on the sharing of electrons.[2] Lewis envisioned all bonding phenomena as interactions between electron-rich and electron-poor species. Simply put, a Lewis acid is an electron-pair acceptor and a Lewis base is an electron-pair donor.[3]

Inherent to Lewis's definition of the acid–base interaction is the need to satisfy the octet rule and the underlying assumption that this interaction is stabilizing, because in its most stable state an atom should have eight valence electrons. The clear predictive powers of this simple statement, often one of the first concepts taught to students of chemistry, has an impact not only on our understanding of structure, but also of reactivity.[4]

To a first approximation, if the formation of an acid–base adduct is favorable, that is, the donor and acceptor atoms have completed their octets through formation of a dative bond that leads to greater thermodynamic stability, there is an implication of a decreased reactivity of the acid and the base (that is, neutralization). For example, the trimethylphosphane–borane complex (**1**) possesses little of the characteristic chemical reactivity of either of the parent components (Scheme 1).[5]




***Scheme 1.*** The octet rule and the Lewis acid–base adduct $BH_3{\cdot}PMe_3$ (**1**).

However, just as notable exceptions to Lewis' assumptions about the octet rule exist, so do exceptions about this concept of acid–base interactions as stabilizing phenomena that lead to reduced reactivity.[6] A brief survey of the literature reveals numerous examples where stable, acid–base adducts show enhanced reactivity. For example, strongly Lewis basic solvents and additives have found important applications as promoters of a variety of diverse chemical processes.[7] In the chemistry of alkyllithium reagents and lithiated amide bases, additives such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and hexamethylphosphoric triamide (HMPA) exert a strong influence on the reactivity and selectivity [Eq. (1) in Scheme 2].[8] In the case of strong reducing agents such as samarium diiodide, the addition of either HMPA or *N*,*N*-dimethylpropylene urea (DMPU)[7a] leads to a higher oxidation potential and enhanced reactivity [Eq. (2) in Scheme 2].[9] In transition-metal catalysis, the use

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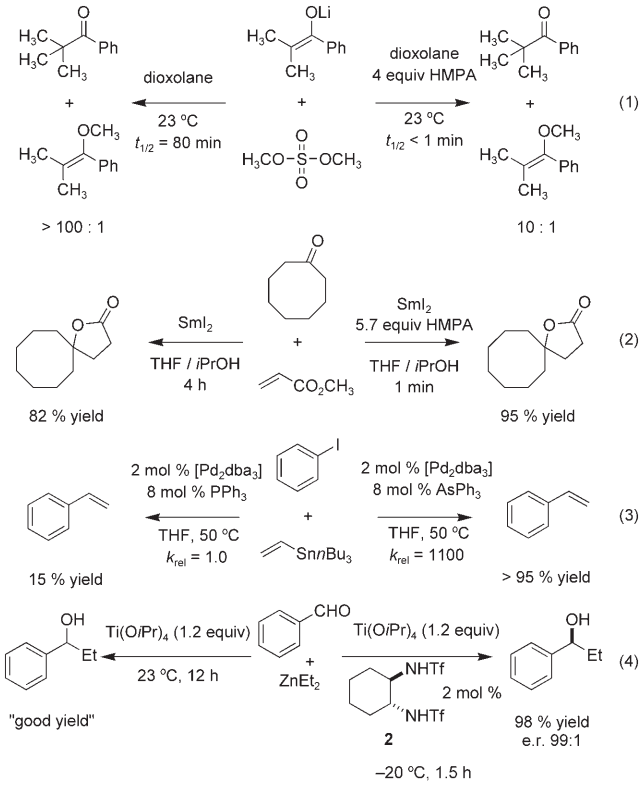



***Scheme 2.*** Influence of Lewis bases on reactivity patterns. Tf = trifluoromethanesulfonyl, dba = *trans,trans*-dibenzylideneacetone.

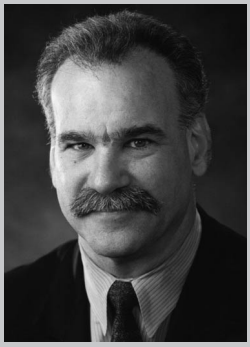
of Lewis basic phosphanes[10] and other ligands[11] provides a method for tuning the reactivity and stereoselectivity in, for example, cross-coupling reactions [Eq. (3) in Scheme 2],[12] and countless other transformations.[13] Finally, the addition of dialkylzinc reagents to aldehydes is greatly accelerated by the addition of a coordinating bis(sulfonamide) ligand derived from cyclohexane-1,2-diamine **2** [Eq. (4) in Scheme 2].[14]

As illustrated in the preceding examples, activation by a Lewis base can enhance the chemical reactivity in a number of ways—from increasing nucleophilicity or electrophilicity to modulation of electrochemical properties. When compared to the influence of Lewis acids,[15] Lewis bases are seen to effect a much more diverse array of reactivity patterns. This may seem surprising at first glance, since both modes of activation rely on the formation of Lewis acid–base adducts. The difference becomes clear by recognizing that Lewis acid activation only leads to net transfer of electron density away from the substrate, whereas Lewis base activation leads to net transfer of electron density toward the substrate. This most fundamental difference between the modes of activation has important consequences in the way in which electron density is distributed in the adducts (see Sections 3.1.1 and 3.1.2).

Although Lewis base activation is quite common (although at times, however, unrecognized as such), it is less widely employed, especially when compared to Lewis acids in organic synthesis.[16] Beyond the extensive use of Lewis basic co-catalysts as ligands in transition-metal catalysis, the use of nonmetallic, Lewis base catalysis remains a less thoroughly explored phenomenon. Reasons for this imbalance include the lack of target Lewis acidic sites in common organic molecules and the limited number of opportunities for valence expansion at carbon centers. However, opportunities to apply this intriguing concept do exist, and a number of novel and distinct catalytic processes have been developed.

One of the main goals of this Review is to provide a conceptual framework that allows a clear formulation of what "Lewis base catalysis" exactly constitutes. As it differs significantly from Lewis acid catalysis, a firm grounding in the fundamental concepts of structure and bonding and the nature of the dative interactions is needed. These, in turn, will explain the origins of the electronic perturbations that lead to the disparate manifestations of Lewis base catalysis.

The Review is organized as follows. We begin by providing a concise definition of the concept and origins of Lewis base catalysis (in the light of current theories on acid–base interactions) and an organizational framework which will aid in the development and identification of new examples. A discussion of the properties of Lewis bases themselves as well as a fundamental mechanism of activation for this class of catalysts will then be presented. We also intend to provide a thorough review of the current literature to highlight established Lewis base catalyzed processes as well as to draw attention to less well-known or even, unrecognized examples. It is hoped that this Review will not only aid in the understanding of this concept but also inspire discussions about new and unprecedented opportunities for catalysis.



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## 2. Defining Lewis Base Catalysis

In view of the diverse uses of Lewis basic compounds in a wide variety of reactions, it is important to have a clear definition of Lewis base catalysis, so as not to confuse it with the use of Lewis bases as stoichiometric reagents. When constructing this definition, it is necessary to begin with a clear picture of the nature of the reagents and the effects of their presence (or absence) on a particular reaction. As Lewis bases can influence reactivity in a variety of ways, characterizing these interactions on the basis of their mechanisms at this point would be restrictive and prove problematic in formulating a broad and useful definition.

The concept of "Lewis base catalysis" can be formulated from firmly established chemical definitions. In the most general terms:

*Lewis base catalysis is the process by which an electron-pair donor increases the rate of a given chemical reaction by interacting with an acceptor atom in one of the reagents or substrates. The binding event may enhance either the electrophilic or nucleophilic character of the bound species. Furthermore, the Lewis base should not be consumed or altered during the course of the reaction—a hallmark of any catalytic process.*[17]

This broad definition, while accommodating the divergent reactivity patterns induced by Lewis base catalysts, does provide some constraints and excludes some phenomena that could be, and often are, attributed to it. First, this definition of Lewis base catalysis excludes reactions in which strongly Lewis basic reagents are employed as solvents[18] or as ligands for preformed Lewis acid complexes. The distinction between Lewis base catalysis and the use of Lewis basic catalysts in conjunction with Lewis acids is an important one that will be discussed in Section 8. The use of ligands in transition-metal catalysis—one of the most thoroughly developed areas for the application of Lewis base catalysis—is outside the scope of this Review, although it must be made clear that these systems do fit within the proposed definition. The use of Lewis basic ligands in substoichiometric amounts is a powerful method for tuning reactivity or inducing stereoselectivity in transition-metal systems, and has been extensively reviewed elsewhere.[13] However, the way in which these ligands promote kinetically significant changes in the reactivity of the metal complex occurs through fundamentally different mechanisms from those that will be discussed here.

Although this broad, inclusive definition for Lewis base catalysis is useful, it lacks any mechanistic insights. Therefore, before proceeding further with a discussion of examples of Lewis base catalyzed reactions, it is important to summarize the mechanisms by which a Lewis base can interact with an acceptor and clarify the electronic perturbations that are responsible for the enhanced chemical reactivity.

## 3. Lewis Acid–Base Interactions

### 3.1. Jensen's Orbital Analysis of Molecular Adducts: Identity of the Lewis Acid

A Lewis base catalyzed reaction is defined as one that is accelerated by the action of an electron-pair donor (as the catalyst) on an electron-pair acceptor (as the substrate or a reagent). The binding of the Lewis base to a Lewis acid will lead to a transfer of electron density to the acceptor fragment of a newly formed adduct. In terms of reactivity, this increase in electron density normally translates to enhanced nucleophilicity of the acceptor subunit. The idea of Lewis base catalysis simply as nucleophilic catalysis is valid, but represents only one possible effect of the binding of a Lewis base. A much less appreciated and indeed, even counterintuitive, consequence of the binding of a Lewis base is the ability to enhance the electrophilic character of the acceptor. This phenomenon seems to contradict commonly held views about the effects of acid–base interactions on the properties of the adduct.

In reality, Lewis base catalysis is effective in promoting the reactions of nucleophilic, electrophilic, and ambiphilic reagents. To understand this, more careful consideration must be given to the structural and electronic changes induced by ligation in each mode of activation. Regardless of the nature of the Lewis base or acid, the acceptor fragment within the adduct possesses increased electron density relative to the parent Lewis acid. However, it is the distribution of this electron density among the constituent atoms that must be considered to rationalize the effects of adduct formation on reactivity. To visualize this concept clearly, it is helpful to examine the nature of the newly formed dative bond.

Jensen proposed that all Lewis acid–base interactions could be classified in terms of the identities of the interacting orbitals.[2,19] In his analysis, nine types of bonding phenomena are possible through the combination of three kinds of acceptor orbitals with three kinds of donor orbitals (Table 1).

***Table 1:*** Jensen's orbital analysis of molecular interactions.

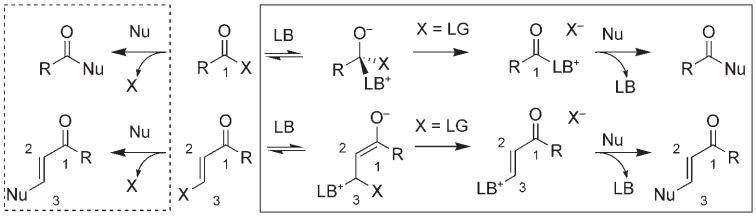
| Donor | Acceptor | | |
|---|---|---|---|
| | n* | σ* | π* |
| n | n–n* | n–σ* | n–π* |
| σ | σ–n* | σ–σ* | σ–π* |
| π | π–n* | π–σ* | π–π* |

Although each of these combinations could represent a productive interaction, in practice, only three of these interactions are significant in terms of catalysis. These are: 1) interactions between nonbonding electron pairs and antibonding orbitals with π character (n–π* interactions), 2) interactions between nonbonding electron pairs and antibonding orbitals with σ character (n–σ* interactions), and 3) interactions between nonbonding electron pairs and vacant nonbonding orbitals (n–n* interactions). This analysis does not exclude the existence of catalytically significant interactions corresponding to the other classes of interactions.[20]

#### 3.1.1. Catalysis by Nucleophilic Addition: n–π* Interactions

The distinction between these classes of interactions is an important one, not only for providing further definition to specific examples of Lewis base catalyzed reactions, but also for understanding the effects of the binding of the Lewis basic

donor on the reactivity of the Lewis acidic acceptor. The family of n–π* interactions represents the largest and most commonly recognized form of Lewis base catalysis, and generally—although incorrectly—termed "nucleophilic catalysis" (Scheme 3).[21,22] Here, the nonbonding electron pair of



***Scheme 3.*** Parallels between the catalyzed (right) and uncatalyzed reactions (left) of unsaturated functional groups.

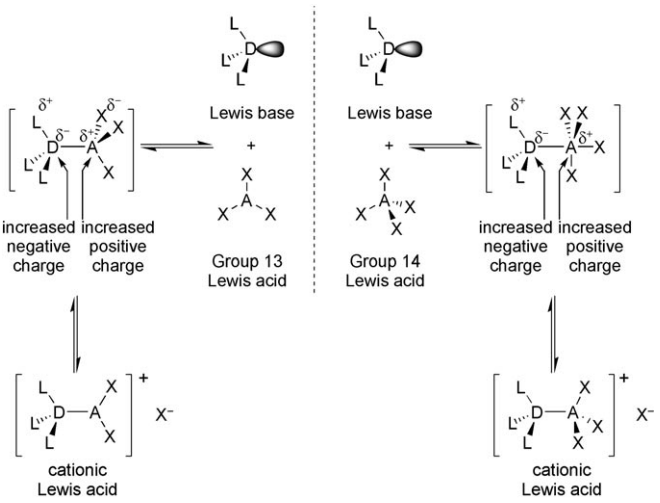
a Lewis base interacts with a π* acceptor orbital, such as those contained in alkynes, alkenes, carbonyls, azomethines, or other common unsaturated functional groups. These reactivity patterns closely parallel those observed in the nucleophilic 1,2-additions to carbonyl groups (that generate alkoxides) and nucleophilic 1,4-additions to α,β-unsaturated compounds (that generate α-stabilized anions). These parallels with well-known reactions resulted in these processes being the first clearly identified examples of Lewis base catalysis. In the case of simple carbonyl groups as acceptors, the attack of the Lewis base leads to the formation of a zwitterionic, tetrahedral intermediate with enhanced nucleophilic character at the oxygen atom. If the carbonyl compound in question possesses a leaving group, such as in an acid chloride and other active carboxylic acid equivalents, this intermediate can collapse to a new ionic species that now possesses enhanced electrophilic character at C1. A similar pattern of reactivity is observed in α,β-unsaturated compounds. In the case of simple unsaturated carbonyl compounds, conjugate addition of the Lewis base leads to formation of a zwitterionic enolate with enhanced nucleophilic character at C2. However, if a suitable group is present at C3, as would be the case in a γ-alkoxy-α,β-unsaturated carbonyl compound, this zwitterion can collapse, thereby generating a species with enhanced electrophilic character at C3. In both cases, proton transfer can lead to additional, unprecedented modes of reactivity. The fact that Lewis base activation can provide both electrophilic and nucleophilic activation is a unique aspect of these methods, and it will be featured prominently in subsequent discussions.

### 3.1.2. Catalysis by Polarization: n–σ* and n–π* Interactions

The other two types of interactions, the n–σ* and n–π* interactions, are less-well known, but equally versatile pathways for catalysis. The use of "σ*" to describe the acceptor orbital on the Lewis acidic species is a general term, because species that participate in these interactions include several organometallic reagents consisting of main-group elements. The "n*" term is representative of a specific group of Lewis acid acceptors such as boranes and other Group 13 elements. An important requirement for these types of interactions is that the Lewis acidic acceptor be able to expand its coordination sphere and attain a "hypervalent" state.[23] The changes in bond order induced by adduct formation allow for the simultaneous enhancement of nucleophilic and electrophilic character, again dependent on bond polarizability as applied in the n–π* analysis. The behavior of hypervalent species and why this often leads to novel forms of reactivity is best understood through Gutmann's empirical analysis of acid–base interactions.[24]

#### 3.1.2.1. Gutmann Analysis

Gutmann recognized that formation of an acid–base adduct leads to an overall increase in the electron density in the acceptor fragment of the adduct, but that the distribution of this electron density is not equal among the constituent atoms (Scheme 4). This redistribution of electron density has noticeable consequences on the bond lengths. These observations serve as the basis of Gutmann's four rules of molecular adduct




***Scheme 4.*** Electronic redistribution resulting from Lewis acid–base complexation.

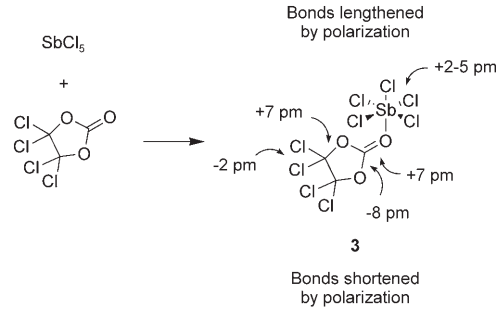
formation:[25] 1) the smaller the intramolecular distance between the donor (D) and the acceptor (A), the greater the induced lengthening of the peripheral bonds (A–X), 2) the longer the bond between D and A, the greater the degree of polarization of electron density across that bond, 3) as the coordination number of an atom increases, so do the lengths of all the bonds originating from that coordination center, and 4) the bonds adjacent to D and A will either contract or elongate to compensate for the changes in electron density at D and A. A corollary to Gutmann's fourth rule deals with charge density variations, and states that:

"*although a donor–acceptor interaction will result in a net transfer of electron density from the donor species to the*

*acceptor species, it will, in the case of polyatomic species, actually lead to a net increase or "pileup" of electron density at the donor atom of the donor species and to a net decrease or "spillover" of electron density at the acceptor atom of the acceptor species. This results from the accompanying changes in the intramolecular charge distribution induced by the primary donor–acceptor interaction. These disperse the net change in electron density among all the atoms and in so doing, overcompensate for the initial changes induced at the donor and acceptor atoms. This result is important as it contradicts the usual assumption of the organic chemist that the net changes in formal charges remain localized on the donor and acceptor atoms."*[25a]

These empirical rules regarding the structural and polarization consequences of adduct formation between a Lewis acid and a Lewis base each represent subtle differences, but can be illustrated by examining specific examples. The effects of the binding of a Lewis base to the Lewis acidic species antimony pentachloride ($SbCl_5$) have been carefully examined by X-ray crystallography (Scheme 5).[24] Binding of tetrachloroethylene carbonate to $SbCl_5$ induces noticeable changes in the bond lengths throughout the complex **3**: while some bonds are lengthened, others contract. In the $(RO)_2C$=O-Sb-Cl subunit, the C=O bond is lengthened, which polarizes it towards the antimony atom, thus leading to a "pileup" of electron density at the carbonyl oxygen atom and a loss of electron density at the carbonyl carbon atom. These changes in bond lengths are a clear manifestation of both the first and fourth rules. The polarization of the C=O bond is compensated for by increased electron donation from the carbonate oxygen atoms, which leads to contractions of the bonds between the distal oxygen and the carbonyl carbon atoms. This observation is also consistent with the predictions of the fourth rule.




***Scheme 5.*** Differences in the bond lengths in $SbCl_5$ and its complex **3**.

The more interesting, and catalytically relevant, effect occurs on the side of the Lewis acid. In response to the binding of the Lewis base, the coordination number of the antimony atom increases by one and the bonds around the antimony center are lengthened, as predicted by the third and fourth rules. This situation corresponds to the "spill-over" effect, where the augmented electron density around the antimony atom is distributed to the more electronegative, peripheral atoms. A crucial consequence of the spill-over effect is that the Lewis acidic center is often rendered more electrophilic than the parent Lewis acid while its ligands are rendered more nucleophilic.

Whereas the structural manifestations of Gutmann's rules can be readily confirmed by X-ray crystallographic analysis of Lewis acid–base complexes, the electronic consequences, that is, the actual fractional charges residing on an atom, cannot be easily discerned without computational analysis. Fortunately, a number of such calculations are available for adducts of various elements.[26]

Without doubt, the most extensive collection of experimental and computational studies on donor–acceptor complexes is found in the Group 13 elements. The "unexpected" trend in Lewis acidity for the various boron halides ($BF_3 < BCl_3 < BBr_3$) has stimulated a great deal of debate and computational analysis.[27] As part of these studies, the Lewis base adducts of the Lewis acids are also examined and the partial atomic charges are often calculated. For example, at the MP2/6-311G(3df,2pd) level of theory, the NBO atomic charges on the boron atom in $BF_3$ and $H_3N{\cdot}BF_3$ are $+1.590$ and $+1.452$, respectively, while the NBO charges on the bpron atom in $BCl_3$ and $H_3N{\cdot}BCl_3$ are $+0.554$ and $+0.518$, respectively.[28,29] As part of a comprehensive computational analysis of Lewis acid–base interactions, Frenking and coworkers calculated the NBO atomic charges on boron in various complexes at the MP2/6-31G(g) level of theory. All of the complexes with nitrogen, oxygen, and carbon donors in various hybridization states were similarly positively charged ($+1.38$ to $+1.49$) as the boron atom in $BF_3$ ($+1.49$).[28c] In addition, two independent calculations on the structure of Lewis base adducts of $GaCl_3$ found similar trends. By density functional theory analysis (B3LYP) using the RHF/LANL2DZ method, the atomic charges on $GaCl_3$, $H_3N{\cdot}GaCl_3$, and $py{\cdot}GaCl_3$ are $+0.71$, $+0.70$, and $+0.71$, respectively.[30] At the RHF//6-311++G** level of theory, the Mulliken charges for $GaF_3$, $H_3N{\cdot}GaF_3$, $GaCl_3$, and $H_3N{\cdot}GaCl_3$ are $+1.514$, $+1.531$, $+0.492$, and $+0.636$, respectively, which clearly illustrates the increase in partial positive charge at the gallium atom upon complexation.

The trends are even more dramatic for the Group 14 elements as these Lewis acids can expand their valences twice. For example, the series $SiF_4$, $SiF_5^-$, and $SiF_6^{2-}$ has Mulliken charges at the silicon atom of $+1.19$, $+1.14$, and $+2.12$[31] whereas the series $SiCl_4$, $SiCl_5^-$, and $SiCl_6^{2-}$ has Mulliken charges at the silicon atom of $+0.178$, $+0.279$, and $+0.539$,[31b] respectively. These trends are truly striking as the binding Lewis base in these cases is charged ($F^-$ and $Cl^-$), thus rendering the adducts formally negatively charged (and erroneously viewed as negative at the silicon atom), yet the acceptor silicon atom increases in its positive character![32]

#### 3.1.2.2. *Hypervalent Bonding Analysis*

An alternative picture of the electronic perturbations that result from n–σ* interactions is provided by the molecular orbital analysis of hypervalent bonding and the formation of three-center, four-electron hybrids. The ability of main-group elements to form compounds which appear to break the Langmuir–Lewis octet rule was originally explained by invoking an availability of d orbitals (such as 3d for silicon)

by using an analogy to transition-metal complexation.[33] However, silicon is not a transition metal, and it is now generally accepted that the 3d orbitals on silicon are too diffuse to engage in meaningful bonding.[34] The ability of silicon to expand its coordination sphere (to engage in hypervalent bonding) is due to the ability of the silicon 3p orbitals to engage in electron-rich three-center four-electron bonding.[23] This analysis will be illustrated for complexes of silicon.[35]

Silicon normally engages in bonding with only four other atoms, which completes the electronic requirement for an outer-shell octet. In $SiL_4$ compounds, the molecules have a tetrahedral geometry, and therefore the central silicon atom displays $sp^3$ hybridization (Figure 1). From the perspective of valence bond theory, expansion to a pentacoordinate silicon complex ($SiL_5$) requires a p orbital to engage in hypervalent three-center four-electron (3c-4e) bonding. The trigonal bipyramidal structure of these complexes employs $sp^2$ hybridization of the central silicon atom. Further expansion of the coordination sphere to an octahedral, hexacoordinate complex ($SiL_6$), requires a second p orbital to engage in hypervalent bonding, and the silicon atom to be formally sp hybridized (Figure 1). The formation of hypervalent p-symmetry orbitals effectively lowers the energy of the hybrid orbitals involved in covalent bonding by increasing the proportion of "s character" in these orbitals.

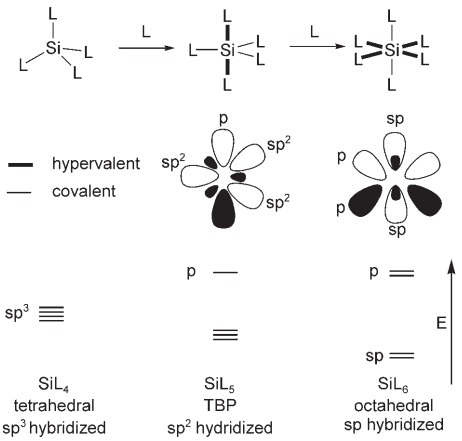



***Figure 1.*** Hybridization scheme and orbital picture of silicon complexes.

The hypervalent bonds are inherently electron rich at the surrounding ligands and electron deficient at the central atom; the combination of three atomic orbitals (AOs) creates three molecular orbitals (MOs)—a bonding, a nonbonding, and an antibonding orbital (Figure 2). Mixing of the filled σ orbital of the acceptor with the filled n orbital of the donor generates a pair of hybrid orbitals. The HOMO of this hybrid orbital ($\Psi^2$) contains a node at the central atom and localizes the electron density at the peripheral atoms. Therefore, it is clear how both enhanced electrophilic and nucleophilic character can be generated at different atoms in this adduct. As the strength of the donor increases, the polarization and the energy gap between the $\Psi^1$ and $\Psi^2$ orbitals increases. In the extreme, this leads to ionization and generation of a cationic species (Scheme 4). Thus, the changes in bond order and the polarization of electron density that occur in the formation of 3c-4e hybrids corresponds to Gutmann's four rules. The formal bond order of the 3c-4e hybrid in $SiF_5^-$ is 0.75 and, indeed, X-ray crystallographic data indicates a significant difference in the bond length between the axial and equatorial fluorine atoms in $SiF_5^-$ ($F_{ax}$ 1.646 Å, $F_{eq}$ 1.579 Å, $F_{eq'}$ 1.602 Å).[36] Moreover, the polarization of electron density from the central atom to the ligands in 3c-4e hybrids corresponds to the predictions of Gutmann's fourth rule and explains the apical positioning of electronegative substituents.[37]

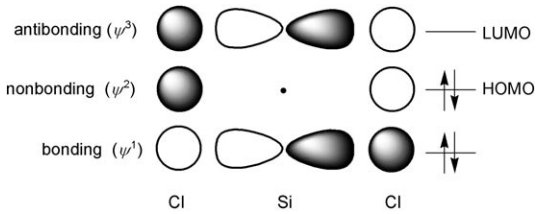



***Figure 2.*** Molecular orbital diagram of three-center-four-electron hybrids.

In a general sense, the n–σ* interaction exists as a continuum between a hypervalent state and an ionized one (Scheme 4). Just as cases of n–π* interactions find analogy with well-known synthetic processes, it is clear how this type of interaction relates to reactions involving the formation of a covalent bond, such as the $S_N2$ displacement. The same kind of 3c-4e bonding present in $S_N2$ transition structures is observed in the highly polarized, hypervalent intermediates formed upon the binding of a Lewis base to a Lewis acid.[38] Taken together with Gutmann's proposal, the molecular orbital analysis of these intermediates further accentuates the intimate relationship between hypervalent or ionized intermediates in cases with n–σ* interactions.

The broad, inclusive definition of Lewis base catalysis proposed above can now be subdivided into three categories to demarcate three significant mechanistic regimes. Each type of interaction, n–π*, n–σ*, and n–n*, clearly separates the regimes on the basis of the nature of the Lewis acid acceptor. These modes of interaction have a similar potential to generate nucleophilic and electrophilic character in the adduct, albeit in different ways. It is the ability of the bonds in the acceptor to become polarized in response to Lewis base binding that is the hallmark of all Lewis base catalysis.

### *3.2. Definitions Revisited*

#### *3.2.1. Why "Lewis Base Catalysis" and Not "Nucleophilic Catalysis"?*

One of the most important consequences of the plurality of interactions, described above, by which Lewis bases can enhance chemical reactivity is the realization that other definitions of catalysis with Lewis bases are at best inadequate

or at worst misleading. The definition of Lewis base catalysis as presented in Section 2 is unambiguous, because it is based on the structure of the species that is added to a reaction, which causes a rate enhancement, and is recovered unchanged at the end. There is no implication nor requirement to know the effect that the catalyst exerts in increasing the reaction rate. The terms nucleophilic and electrophilic should be used to describe those *characteristics of the reactive species* that are enhanced by the catalyst (and thus, tied to the mechanism). The terms Lewis basic and Lewis acidic should be reserved for the *characteristics of the catalysts themselves*, that is, electron-pair donors and electron-pair acceptors, respectively. The unique feature of Lewis base catalysis is that it can operate by enhancing either the nucleophilic or the electrophilic character of a reactive species. The commonly used term "nucleophilic catalysis" is ambiguous as evidenced by comparing the mode of activation in the reactions of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in acylation (enhanced electrophilicity) or ketene reactions (enhanced nucleophilicity). For these reasons, the use of this term should be discouraged.

#### 3.2.2. "Lewis Base Catalysis" or "Ligand-Accelerated Catalysis"?

At first glance, the definition of Lewis base catalysis presented earlier sounds very similar and may be confused with the term "ligand-accelerated catalysis" as defined by Sharpless and co-workers:

"*In ligand-accelerated catalysis the addition of a ligand increases the reaction rate of an already existing catalytic transformation. Both the ligand-accelerated and the basic catalytic process operate simultaneously and in competition with each other.*"[6]

In Lewis base catalysis, the transformation being accelerated is not already a catalytic process. The simultaneous process in competition is the stoichiometric reaction of all of the components. The Lewis base accelerates the reaction by binding to one of those components, thereby enhancing its nucleophilic or electrophilic character toward one of the other reactants. The Lewis base is subsequently released from the product to reenter the catalytic cycle. In this regard, ligand-accelerated catalysis is seen as a special case of Lewis base catalysis when the species being bound and activated is a catalytic rather than stoichiometric component of the reaction. This form of Lewis base catalysis is vast and has already been discussed in detail elsewhere. It will not be covered in this Review because it would obfuscate the important, unifying features of the more general process as it applies to reactions of other primarily main-group elements.

### 3.3. Toward a Scale of Lewis Basicity: Identity of the Lewis Base

To better understand the way in which Lewis acid–Lewis base interactions affect reactivity, Jensen's classification system (based on the identity of the interacting orbitals, Table 1) provides a finer level of distinction, at least with regard to the Lewis acidic fragment. However, this analysis classifies all Lewis bases by the nondescript term: n-type donors. Considering the diversity of Lewis basic entities, this is a gross over-simplification. Although it is true that the Lewis bases discussed in this Review are all nonbonding electron-pair electron donors, they possess significant structural and electronic differences. These differences are especially clear when considering the identity of the donor atom and the kinetic and thermodynamic characteristics of their binding to acceptors.

The issue of the identity of the donor atom is fairly straightforward. The majority of n-type Lewis bases contain donor atoms from Groups 15 and 16 such as nitrogen, oxygen, phosphorus, and sulfur. Notable exceptions are nucleophilic, transition-metal species involving cobalt and iron[39] as well as N-heterocyclic carbenes.[40] The question of the energetics of the donor interactions is more difficult to resolve. Just as the development of a thermodynamic scale of Lewis acidity has been a controversial and difficult task, so too has the development of a scale of Lewis basicity. Although such a scale would be a valuable tool for the development of Lewis base catalyzed reactions, the validity of these measurements are complicated by several major factors, including: 1) the strength of the interactions must be referenced to a specific acceptor, 2) the normalization of contributions from steric effects, 3) the involvement of secondary solvent interactions, and 4) the occurrence of chemical reactions between the donor and chosen acceptor.

Several scales of Lewis basicity have been proposed, although each has inherent assumptions regarding the choice of the acceptor and the existence of secondary interactions that could limit the general applicability of the scale. Despite their inability to provide a unified and consistent quantitative ordering, these scales do present a fairly consistent, qualitative ordering of Lewis bases and provide rough guidelines for catalyst choice and optimization.

As most common Lewis bases are also common organic solvents, physical parameters used to classify solvents are sometimes useful to gauge the relative donor strength of certain compounds. Properties ranging from the Trouton constant, a value that estimates the degree of association between molecules, to the internal pressure ($\pi$), or the dielectric constant ($\varepsilon$) have all been used as reference points.[41] Although these scales are attractive because they avoid problems associated with the choice of the reference acid, this is also their major shortcoming. Moreover, as demonstrated in the previous section, a consideration of the acceptor fragment of any adduct is the major defining factor in identifying these catalytically significant interactions.

One of the most widely used methods for judging the relative strength of Lewis bases is, ironically, the p$K_a$ value.[42] Although this scale is referenced against the proton, which creates an apparent inconsistency between concepts of Brønsted and Lewis acidity,[43] it still represents the largest body of such data. There are several major shortcomings for this scale of Lewis basicity, the most notable being that it is devoid of any complicating steric interactions. Hence, it is not a good model for synthetically useful Lewis acids such as boron trifluoride ($BF_3$) and tin tetrachloride ($SnCl_4$).

A more commonly used scale involving synthetically relevant Lewis acids is the donicity number (DN) scale

developed by Gutmann et al.[24,44] This scale is based on two experimental techniques, depending on the identity of the Lewis acid: the measured enthalpy of adduct formation between $SbCl_5$ and a Lewis base in a dilute solution of 1,2-dichloroethane, and the chemical shift of the $^{23}Na$ NMR signal of the adduct formed between a Lewis base and $NaClO_4$. Although this scale has been widely used because of its reference to synthetically relevant Lewis acids, it has been widely criticized for several reasons. Most notable among the problems are: 1) concerns regarding interactions between $SbCl_5$ and the solvent, 2) variations in the steric demands of the Lewis base on the enthalpy of formation, and 3) the observation of side reactions between certain Lewis bases and $SbCl_5$. Still, these criticisms seem directed only at individual values, especially for measurements of interactions between extremely weak or strong Lewis bases, rather than the method in general.

A second calorimetric evaluation of Lewis basicity that has been constructed uses a similar experimental technique as employed in the DN number scale. Maria and Gal have developed a scale from enthalpies of complexes formed by the interaction of a donor moiety and $BF_3$ in a dilute solution of dichloromethane.[45] This scale directly addresses the concerns raised about the DN scale by comparing the values in two very different solvents ($CH_2Cl_2$ and nitrobenzene) as well as by performing control experiments to allay concerns about erroneous contributions from undesired side reactions. The issue of variable steric contributions to the enthalpy of formation remains, but as the authors note, it should be small because of the size of this reference Lewis acid, and should not significantly effect qualitative conclusions. Furthermore, it should be noted that this scale still comes to the same qualitative conclusions as the DN scale developed by Gutmann.

Whereas the use of $pK_a$ values and specific calorimetric data is always tied to one reference Lewis acid, the E/C scale developed by Drago is a more general, predictive tool that allows for a truly quantitative determination of the strength of an acid–base interaction.[46] The E/C scale assigns two parameters to both the donor and the acceptor. The E term represents the ability of the species to participate in an electrostatic bond, whereas the C term represents the ability of that species to participate in a covalent bond. A large number of these values have been determined experimentally by measuring the enthalpy of formation of a variety of acid–base adducts. By combining these parameters in the equation $\Delta H_{AB} = E_A E_B + C_A C_B$, the enthalpy of adduct formation for a specific acid–base adduct can be determined. This method also avoids the criticisms of other calorimetric methods because it is not tied to a single Lewis acid acceptor but is still subject to concerns regarding its application to ionic systems.[47] Although the E/C method is a powerful tool, it has not been widely used in synthetic organic chemistry.

Several other Lewis acid specific scales have been developed by using such techniques as calorimetry,[44–46] NMR spectroscopy,[48] and ion cyclotron resonance (ICR) spectroscopy.[49] Although most of these scales are limited, they are still in rough agreement with the scales discussed above. In fact, some agreement is found among the values obtained from the different methods, thus demonstrating the general applicability of these scales for most qualitative purposes (Table 2).[50]

***Table 2:*** Comparison of scales of Lewis basicity.

| Entry | Base | $\varepsilon$[a] | $pK_{BH^+}$[b] | DN[c] | DN[d] | $E_B$[e] | $C_B$[e] | $k_{rel}$[f] |
|---|---|---|---|---|---|---|---|---|
| 1 | $NEt_3$ | 2.42 | 10.8 | 61.0 | 135.87 | 0.991 | 11.09 | – |
| 2 | $Et_2O$ | 4.20 | −3.8 | 19.2 | 77.87 | 0.963 | 3.25 | – |
| 3 | EtOAc | 6.02 | ≈−4 | 17.1 | 75.55 | 0.987 | 2.33 | |
| 4 | $CH_2Cl_2$ | 8.93 | – | 0 | – | – | – | – |
| 5 | pyridine | 12.91 | 5.21 | 33.1 | 128.08 | 1.17 | 6.40 | 0.10 |
| 6 | acetone | 20.56 | −2.9 | 17.0 | 76.03 | 0.987 | 2.33 | – |
| 7 | HMPA | 29.6 | | 38.8 | 117.53 | 1.52 | 3.55 | 9900 |
| 8 | acetonitrile | 35.94 | −10 | 14.1 | 60.39 | 0.886 | 1.34 | – |
| 9 | DMF | 36.71 | −1.2 | 26.6 | 110.49 | 1.32 | 2.58 | 0.81 |
| 10 | DMSO | 46.45 | −1.8 | 29.8 | 105.34 | 1.34 | 2.85 | – |
| 11 | PNO | – | 0.79 | – | – | 1.34 | 4.52 | 66 |

[a] Relative permissivity (dielectric constant, 23 °C).[41] [b] $pK_a$ value in water.[42] [c] $\Delta H_{form}$ with $SbCl_5$ in 1,2-dichloroethane.[44] [d] $\Delta H_{form}$ with $BF_3$ in dichloromethane.[45] [e] Ref. [48]. [f] Reaction rate with $Me_3SiOTf$.[48]

The strength of the Lewis base directly relates to the facility by which an active adduct can be formed, be it through an n–π*, n–σ*, or n–n* interaction. As the formation of the adduct represents an equilibrium process, the greater the enthalpic advantage for the formation of the adduct, the greater its equilibrium concentration and, hence, the greater the effect on the observed rate of the reaction catalyzed by the Lewis base. In the subsequent discussion, the strength of the Lewis base will be invoked to explain many of the observations of enhanced reactivity obtained after modification of the catalysts.

## 4. Scope of the Review

Although the definition of what constitutes Lewis base catalysis has been presented in detail above, it would nonetheless be helpful to clarify what will be covered in the sections that follow. We have adopted the most fundamental definition of a Lewis base as "a species that employs a doubly occupied orbital in initiating a reaction."[4] In all of the examples below, the Lewis base initiates a reaction by combining with one of the stoichiometric reactants, facilitates and accelerates bonding changes, and is then released to reenter the catalytic cycle. The most important family of Lewis base catalyzed reactions that cannot be covered are those that fall under the heading of ligand-accelerated catalysis for the reasons described above. Thus, no catalytic transition-metal reactions that are carried out with basic ligands or stoichiometric reactions of organometallic compounds in the presence of coordinating ligands will be discussed. In many of the examples below, the reason for including certain classes of reactions (or not) will be further explained.

## 5. Examples of Lewis Base Catalysis: The n–π* Interaction

Early examples of Lewis base catalyzed reactions are closely related to well-established methods for the addition of strongly basic, anionic reagents to unsaturated organic functional groups. The addition of polar organometallic reagents to carbonyl compounds or to α,β-unsaturated systems directly generates anionic intermediates which are typically protonated or trapped by other electrophiles. The addition of strong, neutral Lewis bases to these same substrates generate highly reactive zwitterionic intermediates. These species exhibit additional reactivity that can be harnessed for the development of new bond-forming processes.

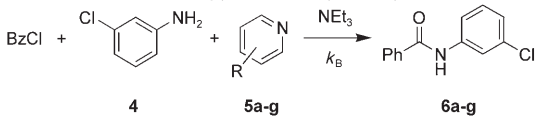
### 5.1. Electrophilic Activation through n–π* Interactions

#### 5.1.1. Lewis Base Catalyzed Acylations

The acylation of alcohols and amines is a common transformation that can be promoted by a wide variety of catalysts, including enzymes, Brønsted bases, Brønsted acids, and Lewis acids. One classic method for the acylation of alcohols employs pyridine, which was originally believed to act as a general base catalyst, and an acid chloride or anhydride.[51] Although these conditions are mild, the reaction rates are slow, especially with hindered secondary and tertiary alcohols.

Beginning in the mid-1960s, studies focused on the development of more active catalysts for this transformation. Litvinenko and Kirichenko and later Steglich and co-workers found that donor-substituted pyridines showed greatly enhanced rates for acylation (Table 3).[52] Hammett studies on the effect of pyridine substituents in the acylation of anilines showed that substituents in the *meta* and *para* positions strongly accelerated the rate of the reaction ($\rho = -3.74$, $R^2 = 0.985$). These investigations eventually led to the identification of DMAP (**5g**) as a highly effective and practical catalyst for these reactions.[53] Most subsequent developments in this area, whether on more active achiral or chiral catalysts, have held fast to this initial design and generally feature a 4-aminopyridine moiety.[54]

***Table 3:*** Rate studies on the pyridine-catalyzed acylation of anilines.




**4** **5a-g** **6a-g**

| Entry | R | $k_B$ [$L^2 mol^{-2} s^{-1}$] | $pK_a$ ($H_2O$) | σ |
|---|---|---|---|---|
| 1 | 3-$NO_2$ (**5a**) | 0.0231 | 0.81 | 0.710 |
| 2 | 3-Cl (**5b**) | 0.0893 | 2.84 | 0.373 |
| 3 | H (**5c**) | 1.80 | 5.17 | 0 |
| 4 | 2-Me (**5d**) | 0.0987 | 5.97 | −0.170 |
| 5 | 3-Me (**5e**) | 3.80 | 5.68 | −0.069 |
| 6 | 4-Me (**5f**) | 3.80 | 6.02 | −0.170 |
| 7 | 4-$NMe_2$ (**5g**) | 10.0 | 9.58 | −0.830 |

As these new catalysts appeared, so did new insights into the mechanism of the acylation reaction. Linear relationships were found between reaction rate, Hammett σ values, and $pK_a$ values. However, both relationships broke down in the case of 2-substituted pyridines. The reaction rate with 2-methylpyridine is almost 100-times slower than that with 3- or 4-methylpyridine, despite a small change in the σ and $pK_a$ values. The dramatic change in the reaction rate between 4- and 2-methylpyridine is inconsistent with simple Brønsted acid catalysis. Therefore, a new "consensus" mechanism that involved Lewis base catalysis was formulated, which has garnered support from numerous mechanistic studies over the last 30 years (Figure 3).[55]

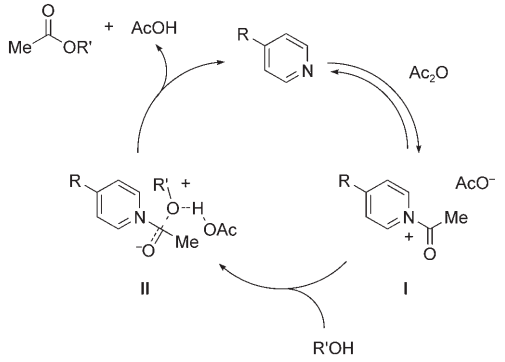



***Figure 3.*** Consensus mechanism for pyridine-catalyzed acylations.

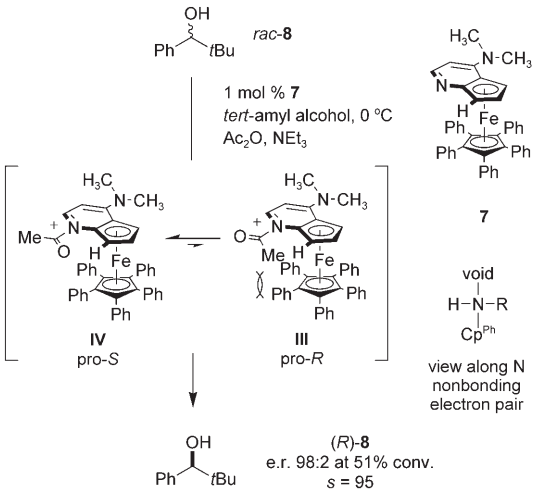
The reaction is initiated by attack of the pyridine nitrogen atom on an acyl donor, such as acetic anhydride. This leads to the formation of a highly electrophilic *N*-acylpyridinium ion **I**. Support for the intermediacy of this activated species has been found by IR and UV spectroscopic as well as crystallographic studies. The planar nature of this ion suggests an explanation for the surprisingly low reactivity of 2-substituted pyridine catalysts. To maximize the conjugation between the donor substituent and the acyl group, a fully planar conformation must be attained. The presence of a flanking 2-substituent creates unfavorable steric interactions and twists the acyl group out of the plane of the molecule, thereby destabilizing it. The importance of the stability of the *N*-acylpyridinium ion **I** and therefore the position of this initial equilibrium has been shown in a recent computational study to directly affect the overall reaction rate.[55b]

Once formed, this highly electrophilic intermediate is subject to attack from the substrate, leading to the formation of species **II**. Although **II** is generally formulated as a classical intermediate in acyl transfer, recent calculations suggest that this is the rate-determining transition structure.[55b] Collapse of **II** by deprotonation completes the catalytic cycle by releasing the acylated product and the catalyst. The addition of a stoichiometric amount of an auxiliary base, such as triethylamine, is generally required to guard against protonation of the Lewis basic catalyst by the acid formed in the rate-determining proton-transfer step.

Although the primary contribution to the catalysis of this transformation is derived from the action of a Lewis base, an important secondary contribution from Brønsted base catal-

ysis is present as well. The nonzero Brønsted β values obtained for the reactions of alcohols ($\beta_{MeOH} = 0.20$) and amines ($\beta_{morpholine} = 0.6$) indicate the involvement of proton transfer in the rate-determining step. Recent experimental and computational studies have shed additional light on the role of proton transfer in these reactions. For example, Kattnig and Albert demonstrated that the identity of the *N*-acylpyridinium counterion has a strong effect on the reaction rate.[56a] More basic counterions lead to faster reactions ($k_{rel}$: CN ≫ OAc > Cl), and the auxiliary base also has a significant effect on the acylation rate.

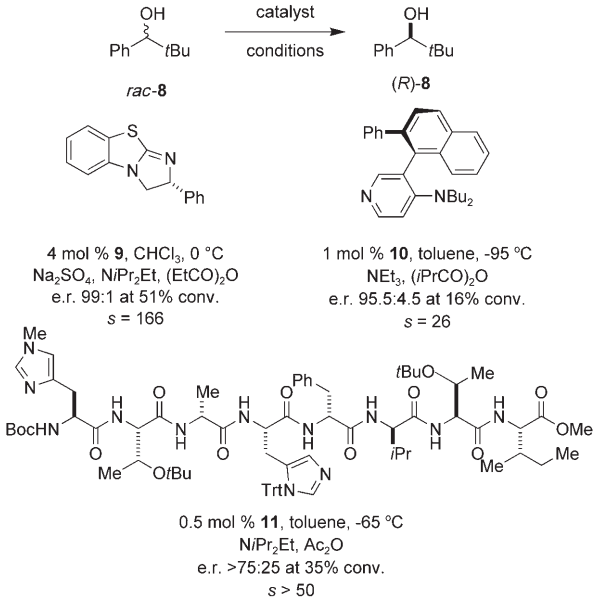
The identification of this acylation as a Lewis base catalyzed reaction provided a strong foundation for the development of a catalytic, enantioselective process. One of the most well-known examples of an asymmetric catalyst for the kinetic resolution of alcohols and amines by acylation is the chiral DMAP derivative **7** developed by Fu and co-workers (Scheme 6).[57] High levels of selectivity can be obtained in the kinetic resolution of aryl alkyl and alkenyl alkyl secondary alcohols in the presence of **7**.




***Scheme 6.*** Kinetic resolutions of alcohols catalyzed by a chiral pyridine derivative.

The design principle behind this class of catalysts can be understood by examining the structure of the acylated catalyst intermediate. From a side-on perspective along the C–N axis of the acyl group, it is clear that a nucleophile should attack from the top face of the catalyst because the lower face is blocked by the bulky cyclopentadienyl ring. However, unless a single conformer of the acylated catalyst is formed, there can be no differentiation between the two diastereotopic faces of the acyl group. In the case of **7**, unfavorable interactions between the substituent on the acyl group and the *ortho* proton on the neighboring ring strongly disfavor the *pro-R* conformer **III**. Therefore, reaction proceeds through the *pro-S* conformer **IV** and high selectivity is observed. The ability of a given complex to exist as a single conformer of this acylated intermediate is directly tied to its success as a chiral catalyst.

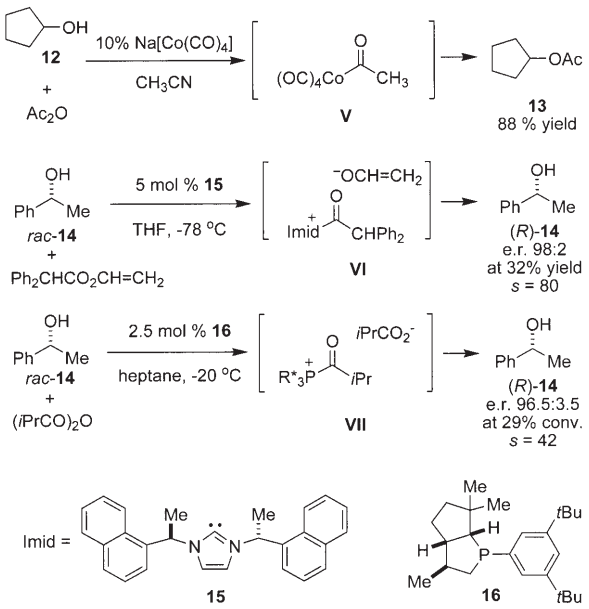
The use of this chiral Lewis base in kinetic resolutions sparked a great deal of interest in other related catalyst structures (Scheme 7). A wide array of pyridine-based catalysts that incorporate elements of "central"[58] and "axial"[59] chirality show comparable levels of selectivity when compared to the original "planar-chiral" DMAP derivatives. Another class of nitrogen-containing heterocycles such as **9** developed by Birman et al. also gives high selectivities.[60] The incorporation of *N*-alkylimidazoles into synthetic peptides (such as **11**) by Miller and co-workers has led to the development of a class of catalysts that can be tuned to obtain high selectivity for a given substrate.[61] In most cases, the structure of the acylating agent has also been optimized to give high selectivity. This dependence has been ascribed both to poor conformational control in the acylated catalyst intermediate[57] and to competitive background reactions when a simple acetyl donor is employed.[55]




***Scheme 7.*** Chiral catalysts for the kinetic resolution of alcohols. Trt = triphenylmethyl.

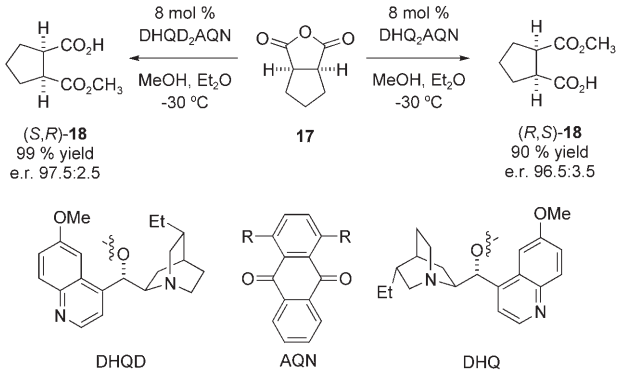
The diversity of nitrogen-centered Lewis bases that catalyze this reaction is reflected in the number of species that promote this reaction through related, acylated catalyst intermediates (Scheme 8). Cobaltate ions,[62] N-heterocyclic carbenes (NHCs),[63] and phosphanes[64] are all effective catalysts for these acylations. Phosphane catalysis of the kinetic resolution of alcohols is particularly noteworthy. In these reactions, no auxiliary base is required to prevent catalyst deactivation through protonation; the divergence between Brønsted and Lewis basicity allows for the development of simpler synthetic procedures. The reactions are still believed to proceed by similar mechanisms, although the *N*-acylpyridinium ion discussed above has been replaced by a different acylated catalyst intermediate. Spectroscopic studies by Vedejs and Diver with tri-*n*-butylphosphane support the conclusion that the active species in phosphane-catalyzed acylations is an acylated phosphonium ion **VII**.[65] Incorporation of the Lewis basic site in a chiral environment, as in the

catalyst **16**, enables comparable levels of selectivity to be obtained in the kinetic resolution of secondary alcohols. Bulky acylating reagents are required to enhance the bias between the two conformers of the acylated catalyst intermediate.




***Scheme 8.*** Diversity of Lewis base catalysts for alcohol acylation.

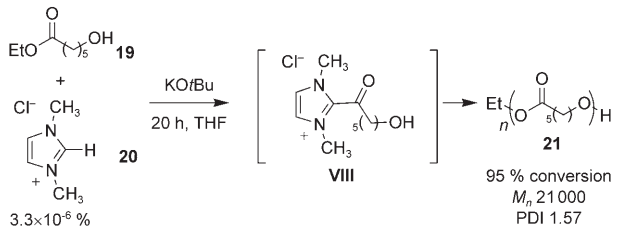
Despite the broad scope of catalysts that can perform this transformation, the line distinguishing a Brønsted from a Lewis base catalyzed process is a fine one, and requires some care when a classification is made. An excellent example of this issue comes from studies on the desymmetrization of *meso*-anhydrides with cinchona alkaloids (Scheme 9). Originally investigated by Oda and others,[66] recent studies by Deng and co-workers have shown this to be a highly selective method for performing desymmetrizations with a wide variety of anhydride structures.[67] On the surface, little difference can be seen between this transformation and the acylative kinetic resolutions described above. However, mechanistic studies by Oda and co-workers have shown that these reactions likely proceed through a general base catalyzed mechanism rather than a Lewis base catalyzed one. The observation of a large $k_H/k_D$ ratio of 2.3:1 when MeOD is used is in line with the $k_H/k_D$ value of 3:1 obtained in known, general base catalyzed ester hydrolyses. The increased steric demand around the quinuclidine nitrogen atom attenuates its Lewis basicity without affecting its Brønsted basicity. This analysis may also bring into question the mechanism of related transformations with chiral tertiary amines, from Oriyama et al., on the kinetic resolution of alcohols.[68] Oriyama et al. speculate that the differentiation of *meso*-diols involves an acylammonium salt from a proline-derived catalyst which, in the absence of supporting spectroscopic evidence, seems unlikely.




***Scheme 9.*** Catalytic desymmetrizations of *meso*-anhydrides.

### 5.1.2. *Extending the Electrophilic Reactivity of Acylated Lewis Base Catalysts*

The breadth of catalysts capable of promoting the acylation of alcohols and amines, all of which involve highly electrophilic acylated catalysts, hinted that this particular intermediate may have applications beyond these simple kinetic resolutions. In recent years, numerous reports have appeared that show the versatility of these intermediates for a variety of new bond-forming processes (Scheme 10). Waymouth and co-workers have shown that transesterification reactions catalyzed by NHCs are a powerful and useful method for the formation of polyesters with controlled molecular weights and low polydispersities.[69]

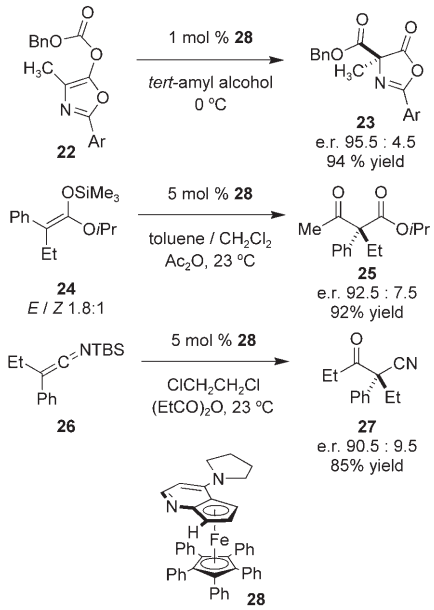



***Scheme 10.*** Lewis base catalyzed polymerizations of hydroxy esters.

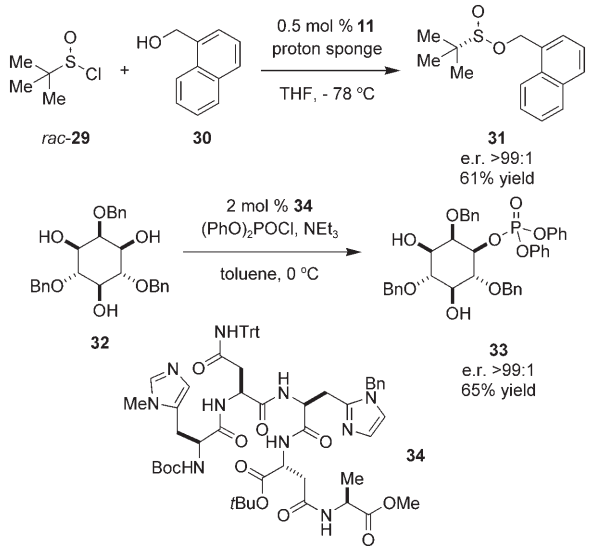
Carbon–carbon bonds can be formed by the attack of a carefully chosen nucleophile on the acylated catalyst intermediate (Scheme 11). Fu and co-workers have shown that the reaction of an O-acylated azlactone **22** with a chiral DMAP analogue **28** leads to the formation of a quaternary stereocenter with high levels of enantiopurity.[70] Recent reports have further expanded this method to furanones, benzofuranones, and oxindoles, thus making it a general method for the generation of quaternary carbon stereocenters.[71] In related work, it was shown that silyl ketene acetals and silyl ketene imines are also capable of intercepting *N*-acylpyridinium ion intermediates, further highlighting the utility of Lewis base catalysis for the generation of quaternary carbon stereocenters.[72]

Novel extensions of this general reaction class are found with variations of the nucleophile structure (Scheme 12). Analogous reaction processes have been found for sulfinyl-



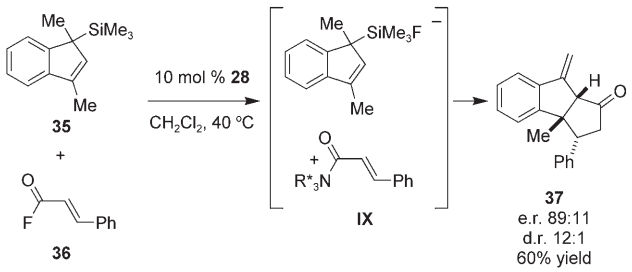

***Scheme 11.*** Lewis base catalyzed acylations of carbon-centered nucleophiles. TBS = *tert*-butyldimethylsilyl




***Scheme 12.*** Lewis base catalyzed sulfinylations and phosphorylations. Bn = benzyl, Boc = *tert*-butyloxycarbonyl.

ations[73] as well as phosphorylations.[74] In both cases, the optimal catalysts for these reactions were already known to be active and selective in simple acylations.

New reactivity patterns have also emerged from continuing investigation of this class of n–π* Lewis base catalyzed reactions (Scheme 13).[75] Studies with α,β-unsaturated acyl fluorides have shown that the enhanced electrophilicity of an *N*-acylpyridinium ion need not be confined to the *ipso* carbon atom. In fact, in the reaction of cinnamyl fluoride (**36**) with the allylic silane **35**, the enhanced electrophilicity is manifested at the β-carbon atom, allowing for conjugate addition of the allylic silane in **IX**. The resulting enolate then collapses




***Scheme 13.*** Lewis base catalyzed allylation/acylation cascade.

to form a ketene, which can be trapped by the pendant olefin to afford the tricyclic product in good yield and stereoselectivity.

### *5.2. Nucleophilic Activation through n–π* Interactions*

#### *5.2.1. Nucleophilic Reactions of Acylated Lewis Base Catalysts*

In the Lewis base catalyzed acylations described above, the intermediate *N*-acylpyridinium salt serves two roles: acyl donor and general base catalyst. The conversion of an anhydride or acid halide into what effectively is a bifunctional reagent is responsible for the high reactivity of this type of catalyst system.

By analogy to this process, the addition of cyanoformates to carbonyl groups presents an interesting, but mechanistically distinct, opportunity for Lewis base catalysis (Figure 4). In this reaction, the attack of an amine-derived Lewis base on the cyanoformate generates a highly reactive adduct **X**

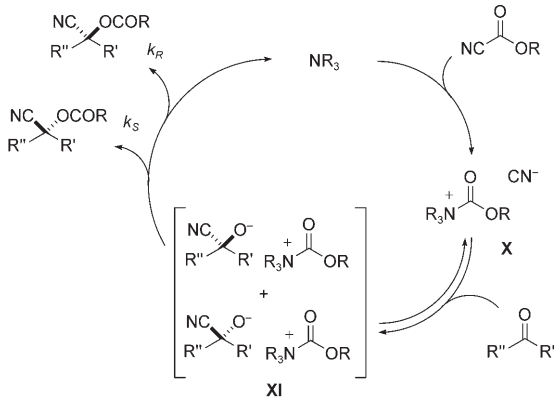


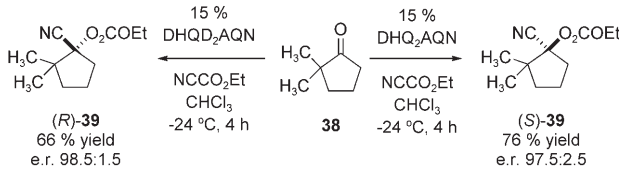

***Figure 4.*** Mechanism of Lewis base catalyzed cyanoformylations.

comprised of an electrophilic *N*-alkoxycarbonylammonium cation and a nucleophilic, rather than basic, cyanide anion. Addition of this nucleophilic anion to a carbon–oxygen double bond followed by trapping of the resulting alkoxide with the *N*-alkoxycarbonylammonium cation leads to the formation of a cyanohydrin derivative and releases the Lewis base catalyst. As shown by Poirier and co-workers, a secondary amine is capable of mediating the addition of a

cyanoformate across the carbon–oxygen double bond of a ketone.[76]

The initial disclosure of this reaction suggested its use as a protecting group, but more recent studies have revealed it to be a method for asymmetric synthesis through the use of cinchona alkaloids. Tian and Deng have investigated this reaction with a wide variety of cyclic and acyclic ketones (Scheme 14).[77] The products are generally obtained in high yields and enantioselectivities. Although a simple mechanism for the reaction can be envisioned, the results suggest a more complex situation because the reaction exhibits time-dependent enantioselectivity. To explain this, it is proposed that the initial cyanide addition is reversible and that carbonate formation is the rate- and stereochemistry-determining step. This hypothesis is intriguing because it assumes that a dynamic kinetic resolution of the intermediate cyanohydrin alkoxides **XI** is being mediated by the electrophilic, chiral *N*-alkoxycarbonylammonium cation.



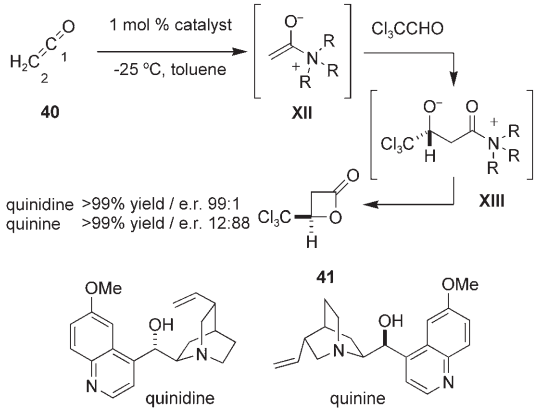

***Scheme 14.*** Lewis base catalyzed cyanoformylation of ketones.

### 5.2.2. *Lewis Base Catalyzed Reactions of Ketenes*

The addition of a strong, neutral Lewis base to a carbonyl group is not unique to the reactions of esters, anhydrides, formates, and acid chlorides, but also plays an important role in the chemistry of ketenes. Ketenes have long held strong interest for organic chemists in view of their high reactivity with nucleophiles and electrophiles as well as olefins in [2+2] cycloadditions.[78] The addition of alcohols and amines across the carbon–carbon double bond of ketenes is a well-known reaction, and asymmetric versions have been developed.[79] However, there has been some debate regarding the mechanism of these reactions, and it appears that Brønsted base catalysis may be operative in some cases.[80] In the case of [2+2] cycloadditions, studies point more conclusively toward a Lewis base catalyzed pathway. The Lewis base is generally proposed to lead to the formation of a zwitterionic enolate intermediate with enhanced electrophilic character at C1 and nucleophilic character at C2.

In a preparative sense, the use of chiral amines to promote the [2+2] cycloadditions of ketenes with activated aldehydes has been the subject of numerous studies over the past 50 years.[81] Attempts to develop an asymmetric, Lewis base catalyzed variant of this formal cycloaddition date back to the pioneering studies of Prelog, Pracejus, Wegler, and Borrmann.[82]

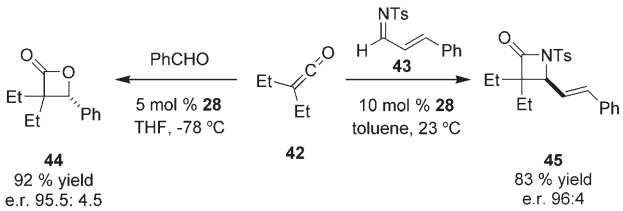
In the early 1980s, Wynberg and Staring began a systematic investigation of the formal cycloaddition between ketenes and aldehydes (Scheme 15).[83] Here, the reaction is believed to proceed through the attack of the amine on the ketene (**40**), which leads to the formation of a highly reactive amidonium enolate **XII**. This enolate then adds to an electrophilic aldehyde to generate an alkoxide that can close onto the acylammonium ion **XIII**, thereby releasing the Lewis base catalyst and forming the β-lactone **41**. In a classic series of studies, it was shown that both enantiomers of the product could be obtained simply through judicious choice of the alkaloid catalyst. Subsequent analysis of the crystal and solution structures of these compounds provides a clear rationale for the factors influencing the stereoselectivity.[84] In the context of the Lewis base catalyzed reactions discussed so far, it is interesting to note that enhanced nucleophilicity at C2 played a role in the formation of the carbon–carbon bond while enhanced electrophilicity at C1 played a role in the final cyclization step.




***Scheme 15.*** Lewis base catalyzed [2+2] cycloadditions of ketenes.

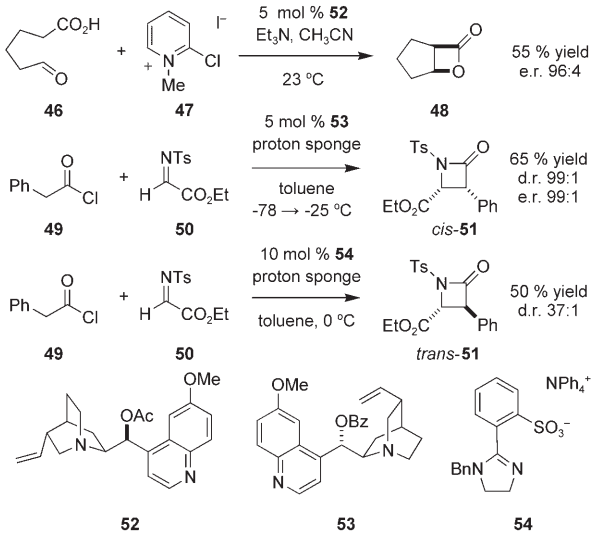
Lewis base catalysis has also been applied to the development of an asymmetric [2+2] cycloaddition of ketenes and imines (Staudinger reaction).[85] Although the analogy to the reactions of ketenes and aldehydes is clear, these studies have led to considerable advances in the technique. Two major strategies for this reaction have been introduced: one involving purely Lewis base catalysis[86] and a second involving a combination of Brønsted/Lewis base catalysis.[87] Exclusive Lewis base catalysis of the reactions of preformed ketenes with chiral DMAP analogues or a modified cinchona alkaloid led to high enantio- and diastereoselectivities (Scheme 16).[86]

The second strategy, which avoids the use of preformed ketenes, involves a chiral base that serves two roles: both as a Brønsted and as a Lewis base catalyst at different points in the




***Scheme 16.*** Lewis base catalyzed [2+2] cycloadditions of aldehydes and imines. Ts = toluenesulfonyl.

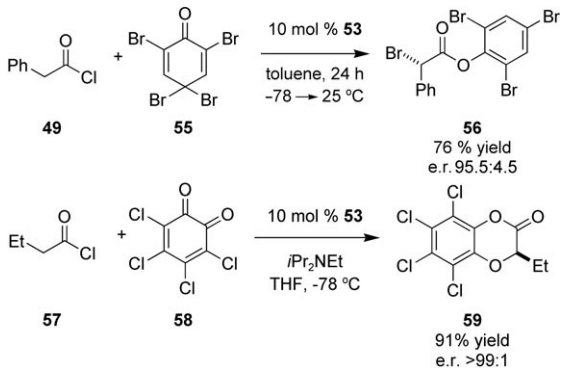
  




46 47 48 49 50 *cis*-51 *trans*-51 52 53 54

***Scheme 17.*** Lewis base catalyzed [2+2] cycloadditions with in situ generated ketenes. Bz = benzoyl.

catalytic cycle (Scheme 17). In these reactions, either a carboxylic acid or an acid chloride can be used as the ketene source. In the case of the carboxylic acid, *N*-methyl-2-chloropyridinium iodide (**47**)[88] is used to generate the ketene. With acid chlorides, deprotonation and formation of an amine hydrochloride leads to liberation of the ketene. This intermediate salt then serves as a "shuttle", transferring the proton to a second Brønsted base (present in stoichiometric quantities), such as diisopropylethylamine. This process frees the Lewis base to reenter the cycle, where it adds to the ketene and leads to the formation of the active amidonium enolate intermediate (similar to **XII**). As in earlier examples, the use of cinchona alkaloids such as **52** or **53** as the basic catalyst provides a well-differentiated chiral environment, and the desired β-lactones or lactams can be formed in high enantio- and diastereoselectivities. Both of these methods involving the in situ generation of the ketene have allowed for the development of highly selective, formal cycloadditions that are complimentary to existing strategies, and allow the use of ketenes that normally prove difficult to isolate. The research groups of Calter and Romo have shown that cinchona alkaloids are effective and highly selective catalysts for the dimerization of ketenes to afford β-lactones.[89]



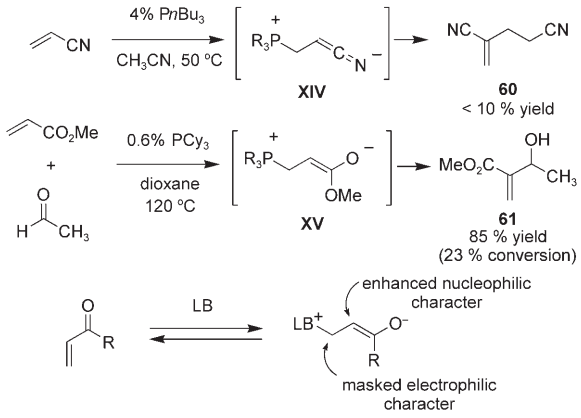

49 55 56 57 58 59

***Scheme 18.*** Lewis base catalyzed α-halogenations.

For example, the use of in situ generated ketenes has allowed for the development of other novel reactions. For example, Lectka and co-workers have investigated in situ generated ketenes and their reactions with halonium ion equivalents for the generation of chiral, nonracemic α-halo esters (Scheme 18).[90] Lewis base catalysis has also made possible the first [4+2] cycloaddition of a ketene with an *o*-quinone **58**, again through the intermediacy of a similar amidonium enolate.[91] Cleavage of **59** affords high yields of enantioenriched α-hydroxycarboxylic acid derivatives.

### 5.2.3. The Morita–Baylis–Hillman Reaction: Lewis Base Catalyzed Reactions of Alkenoates

The reactions of ketenes are not broadly representative of n–π* type activation because the n–π* interaction need not necessarily lead to both enhanced electrophilic and nucleophilic character of the intermediate. One reaction that is driven solely by the enhanced nucleophilic character of a Lewis basic adduct is the reaction of α,β-unsaturated carbonyl compounds with aldehydes and imines, commonly known as the Morita–Baylis–Hillman reaction (Scheme 19).[92] Strong Lewis bases, such as trialkylphosphanes, promote the dimerization of α,β-unsaturated nitriles.[93] The suggestion that the reactions proceed via the intermediacy of a highly reactive carbanion such as **XIV** or **XV** makes clear the analogy between this process and the conjugate addition of polar organometallic reagents, such as organocuprates. Consideration of this analogy presages the use of electrophiles, such as aldehydes, to trap this zwitterionic species, thus allowing for a more selective and productive process.




***Scheme 19.*** Lewis base catalysis in the Morita–Baylis–Hillman reaction.

The Morita–Baylis–Hillman reaction is commonly performed using highly Lewis basic phosphanes or amines, such as 1,4-diazabicyclo[2.2.2]octane (DABCO), as catalysts.[94] Nevertheless, these reactions are notoriously slow, often requiring days to reach useful levels of conversion. Although physical methods, such as high pressure,[95] could address this problem, a chemical solution was lacking. Numerous mechanistic studies have attempted to explain the low catalytic efficiencies observed. However, because of the complexity of

the mechanism and its sensitivity to the reaction conditions, a clear understanding of the Morita–Baylis–Hillman reaction has only recently emerged.

The catalytic cycle is initiated by the conjugate addition of a Lewis basic catalyst, such as DABCO, to an α,β-unsaturated carbonyl compound (Figure 5). This reaction leads to the formation of a zwitterionic enolate **XVI**, which possesses enhanced nucleophilic character at C2 through the action of the Lewis base. This species then attacks the aldehyde, leading to formation of the zwitterionic alkoxide **XVII**. The involvement of both of these species has been supported by the isolation of key reaction intermediates[96] related to **XVI** and **XVII** as well as recent NMR[97] and ESI-MS[98] studies. At this point, the mechanism diverges and two distinct pathways lead to the observed products. In the first pathway, proton transfer in **XVIII** followed by elimination of the Lewis basic catalyst completes the catalytic cycle. The second pathway involves attack of the alkoxide **XVII** on a second molecule of aldehyde which leads to the formation of the zwitterionic hemiacetal **XIX**. This intermediate facilitates proton transfer and subsequent elimination of the Lewis basic catalyst.[99] Support for this second pathway is gained from the observation of dioxanone-containing products in certain Morita–Baylis–Hillman reactions.[99b]

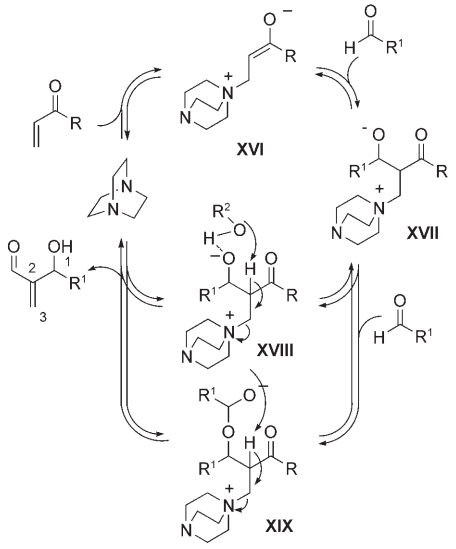



***Figure 5.*** Mechanism of the Morita–Baylis–Hillman reaction.

Examination of these proposed intermediates gives some clues regarding the low reaction rates encountered in these reactions. The stability of the zwitterionic enolate **XVI** is one contributor to the low observed rates. Once formed, two reaction pathways are available to **XVII**: elimination of the catalyst or nucleophilic attack on the aldehyde. In the absence of additional interactions that stabilize this species, elimination of the catalyst is an intramolecular process and it has an inherent kinetic advantage over intermolecular nucleophilic attack. A low, equilibrium concentration of the active zwitterionic enolate will translate to a low reaction rate in the carbon–carbon bond-forming step.

Once formed, the zwitterionic aldolate **XVII** has additional problems that have a further impact on the reaction rate. Much like aldol additions, the absence of a reagent that can trap the alkoxide **XVII** renders the carbon–carbon bond-forming step a reversible process, again leading to a low equilibrium concentration of **XVII** and a low rate for the subsequent product-forming step.

The fact that there are complicating thermodynamic issues throughout the reaction pathway helps to explain why the Morita–Baylis–Hillman reaction has traditionally been difficult to perform. It also helps to explain the results of contradictory kinetic studies that show various reaction orders in the aldehyde, although the reactions are always first order in both the α,β-unsaturated carbonyl compound and the catalyst.[100] Subtle variations in the electronic nature of the aldehyde or the reaction conditions can lead to a shift in the relative rates of the fundamental reaction steps. In fact, recent studies have suggested that the rate-determining step changes over the course of the reaction:[101] At early stages of the reaction, proton transfer in the zwitterionic alkoxide **XVII** is rate-determining. However at later stages in the reaction—as a significant concentration of the product builds up—autocatalysis of the proton transfer occurs and the rate-determining step shifts to the formation of the carbon–carbon bond.

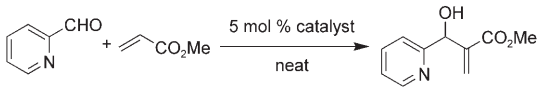
Understanding the vital importance of proton transfer in **XVII** has greatly aided the design of catalytic systems for the Morita–Baylis–Hillman reaction. One strategy for the development of rapid, high-yielding reactions still focuses on the use of simple Lewis basic catalysts in alcoholic solvents. Studies have shown dramatic rate accelerations in alcoholic solvents, even when compared to traditional polar solvents.[102] A second strategy involves Lewis basic catalysts that incorporate Brønsted acidic groups. The discussion of these reactions will be divided between two sections and only examples involving simple Lewis basic catalysts will be discussed here. Methods that employ hydrogen-bonding groups which have been specifically engineered into the catalyst structure will be discussed in Section 8.4.

One way of approaching the rate problems inherent to the Morita–Baylis–Hillman reaction is through the use of more basic catalysts. As the basicity of the catalyst increases, the initial equilibrium between the α,β-unsaturated carbonyl compound and the initially formed zwitterionic enolate will shift to the right. An increase in the equilibrium concentration of this species, other factors aside, should translate to an increased reaction rate. Recent studies by Aggarwal et al. have shown that there is a direct relationship between the $pK_a$ value and the overall reaction rate within a group of structurally related amines (Table 4).[103] The authors were clear to point out that earlier studies that concluded that no relationship existed between the $pK_a$ value and the rate were not applicable to their particular system since they used $pK_a$ values obtained in water.[104] Having obtained $pK_a$ values in DMSO, a common organic solvent used for these transformations, a clear relationship was apparent.

A similar trend often appears in studies of phosphane-catalyzed Morita–Baylis–Hillman reactions.[105] Strongly basic alkyl phosphanes, such as tri-*n*-butylphosphane ($pK_a(H_2O) =$

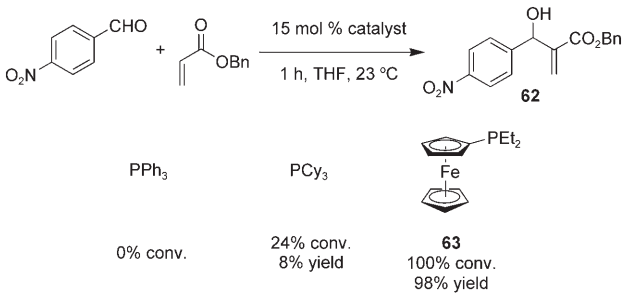
  

***Table 4:*** Relationship between basicity and reaction rate in the Morita–Baylis–Hillman reaction.



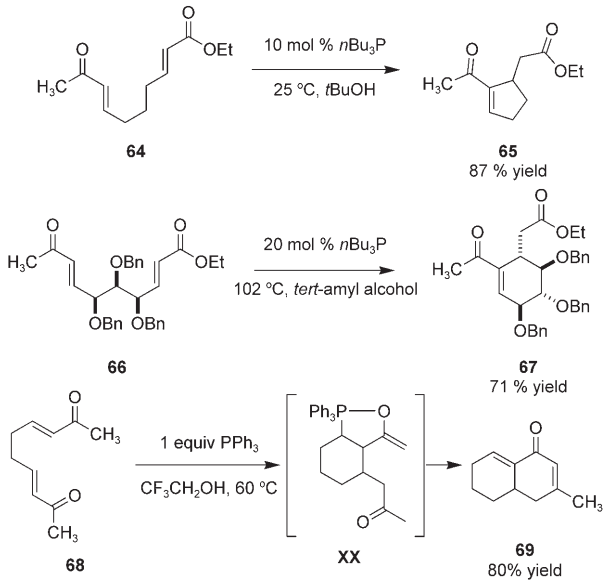

| Catalyst | Rate [% min$^{-1}$] | p$K_a$ ($H_2O$) | $k_{rel}$ |
|---|---|---|---|
| quinuclidine | 1.8 | 11.3 | 9.0 |
| 3-hydroxyquinuclidine | $8.8\times10^{-1}$ | 9.9 | 4.3 |
| 3-acetoxyquinuclidine | $3.1\times10^{-2}$ | 9.3 | 0.15 |
| DABCO | $2.1\times10^{-1}$ | 8.7 | 1 |

8.43) and diphenylmethylphosphane (p$K_a$($H_2O$) = 6.50), are typically more effective than aryl phosphanes, such as triphenylphosphane (p$K_a$($H_2O$) = 2.73).[106] However, some cases have been documented wherein triphenylphosphane is superior, although the reasons for this may have to do with other changes in the reaction conditions.[107] This insight into the role of catalyst basicity has inspired the design of new catalysts. The use of the ferrocenylphosphane **63**, without the addition of any Brønsted acid co-catalyst, provides high yields in short reaction times for the addition products of acrylates with a wide range of aromatic and aliphatic aldehydes (Scheme 20).[108]




***Scheme 20.*** Phosphane-catalyzed Morita–Baylis–Hillman reactions.

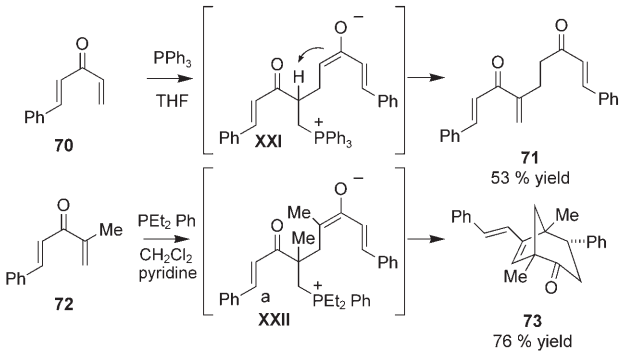
Although major advances in the asymmetric Morita–Baylis–Hillman reaction have come through the use of bifunctional catalysts, some novel synthetic methods have been developed which rely solely upon Lewis base catalysis.[109] The study of intramolecular Morita–Baylis–Hillman reactions, known as Rahut–Currier cyclizations, has received increasing attention in recent years. In the intramolecular system, many of the problems associated with the traditional reaction are avoided and simple Lewis base catalysts prove remarkably effective. In these Rahut–Currier cyclizations, the site selectivity for ring closure can be understood in terms of the relative reactivity of the two α,β-unsaturated systems (Scheme 21).[110] This method allows for ring closures to provide highly functionalized cycloalkenes.[111] A variety of Michael acceptors have been examined, including esters, ketones, and sulfones. In some cases, subsequent enolization and aldol reaction can lead to the formation of bicyclic systems.[112] In the case of diketone **68**, the initially formed zwitterionic enolate is thought to serve as a general base




***Scheme 21.*** Lewis base catalyzed Rahut–Currier cyclizations.

catalyst for the enolization.[113] The selectivity of the enolization is enhanced by the β-phosphonium group through the formation of an oxaphospholidine **XX**.

Another interesting class of substrates for these reactions are divinyl ketones (Scheme 22).[114] When **70** is employed, the simple Morita–Baylis–Hillman product is obtained because intramolecular proton transfer in **XXI** is facile and leads to elimination of the catalyst. A different result is obtained when no acidic proton is present at C2: In the case of **72**, the zwitterionic enolate **XXII** undergoes an intramolecular conjugate addition at position **a** followed by proton transfer and olefination. This sequence eventually leads to the formation of the bicyclo[3.2.1]octenone **73** in good yield.

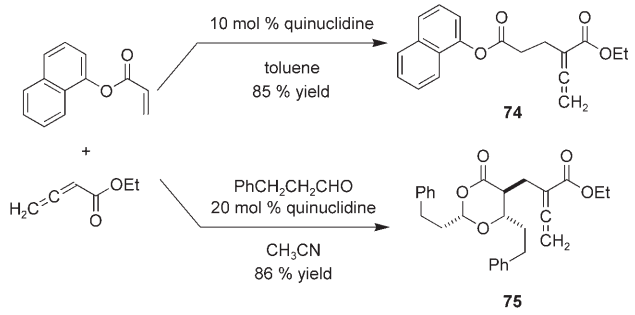



***Scheme 22.*** Lewis base catalyzed reactions of divinyl ketones.

A straightforward extension of the Morita–Baylis–Hillman reaction comes through variation in the structure of the α,β-unsaturated carbonyl compound. The use of an allenoate forms a slightly different enolate intermediate with similar reactivity. Miller and co-workers have shown that these conjugate additions are promoted by amine catalysts such as quinuclidine (Scheme 23).[115] Furthermore, the addition of an

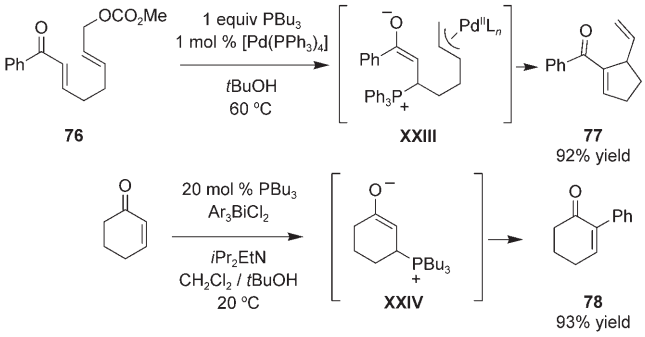
  

aldehyde to this reaction mixture allows for the formation of highly functionalized dioxanone derivatives such as **75**. Shi and co-workers have extended this method to include *ortho*-hydroxy benzaldehydes and imines.[115b,c]




***Scheme 23.*** Lewis base catalyzed reactions of allenoates.

Much as the highly electrophilic *N*-acylpyridinium ions involved in DMAP-catalyzed acylations have found application outside the boundaries of those reactions, so too have the highly nucleophilic, zwitterionic enolates which are key to these Lewis base catalyzed Morita–Baylis–Hillman reactions (Scheme 24). In this context, Krische and co-workers have shown that π-allylpalladium species are effective electrophiles, which lead to the formation of cyclic 1,4-dienes from acyclic precursors.[116] Phosphane catalysis has also allowed for reactions with C($sp^2$) electrophiles, such as aryl bismuth(V) compounds.[117] Clearly, the combination of mild reaction conditions and high reactivity makes these phosphane-catalyzed reactions of α,β-unsaturated carbonyl compounds a versatile synthetic method.




***Scheme 24.*** Lewis base catalyzed reactions of α,β-unsaturated ketones.

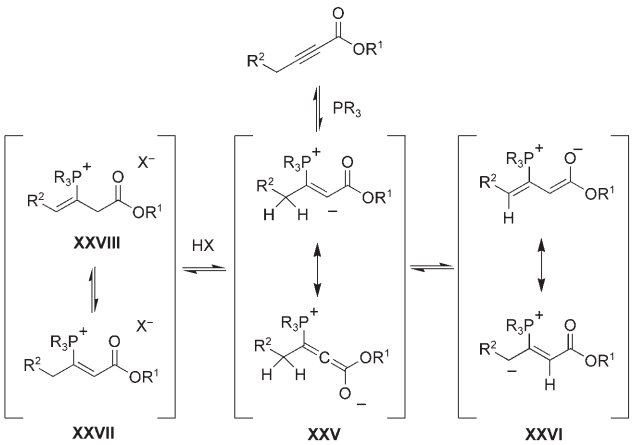
### 5.3. Nucleophilic and Electrophilic Activation through n–π* Interactions

#### 5.3.1. Beyond the Morita–Baylis–Hillman Reaction: Lewis Base Catalyzed Reactions of Alkynoates

In the preceding examples of n–π*-type Lewis base activation of α,β-unsaturated carbonyl compounds, the high nucleophilicity of the zwitterionic enolate intermediates such as **XVI** is harnessed for the formation of a new carbon–carbon bond. In intramolecular reactions, such as the Rahut–Currier cyclization, this desired bond formation process effectively competes with the unproductive collapse of the initially formed zwitterionic enolate and release of the catalyst (Scheme 22). Therefore, good yields and selectivities can be obtained. In the case of intermolecular Morita–Baylis–Hillman reactions, the situation is less favorable and the experimental conditions must be carefully controlled to obtain a synthetically useful carbonyl addition process.

In the absence of a productive reaction pathway, such as that provided by the nucleophilic attack on an aldehyde, highly reactive zwitterions such as **XVI** are prone to seek out alternative pathways for further reaction. This was clearly illustrated above by the uncontrolled formation of oligomers in the attempted dimerization of acrylonitrile catalyzed by phosphanes. With simple substrates such as acrylonitrile, oligomerization occurs through attack of **XIV** on another molecule of acrylonitrile or on the desired product **60** (Scheme 19).

The use of alkynoates rather than alkenoates provides several new productive reaction pathways. Upon conjugate addition of the Lewis base, the initially formed vinyl anion **XXV** can undergo rapid intramolecular proton transfer from C4, thereby leading to the formation of a new zwitterionic species **XXVI** and shifting the site of nucleophilic character away from C2 (Scheme 25). If a pathway for intermolecular proton transfer is available, it can further diversify the number of synthetic intermediates. Protonation transforms the nucleophilic species **XXV** into a vinyl phosphonium salt **XXVII** with enhanced electrophilic character. Rapid equilibration between a number of these zwitterionic species allows for the identification of a low-energy reaction pathway that can lead to a product instead of regeneration of the starting material. This rapid rate of equilibration between the diverse reactive intermediates generated by Lewis base catalysts has led to a number of unprecedented phosphane-catalyzed reactions.[118]

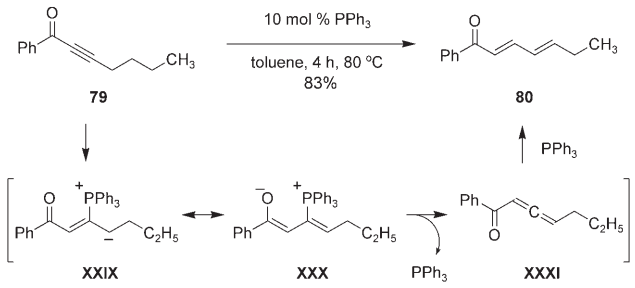



***Scheme 25.*** Proton transfer equilibria in the conjugate additions of Lewis bases.

The possibilities for phosphane-catalyzed reactions can clearly be seen in the simple case of the Lewis base catalyzed isomerization of alkynoates to dienoates. Trost and Kazmaier have observed that in the absence of an electrophile or

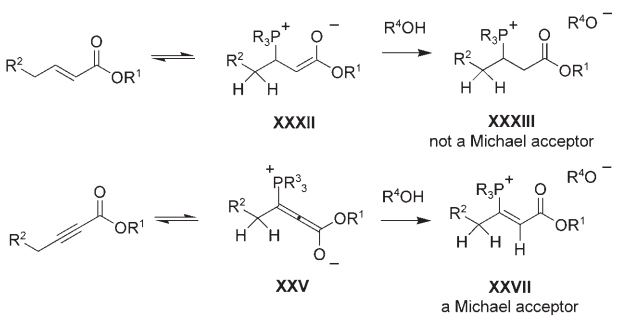
external nucleophile, alkynoates can be isomerized to dienoates in the presence of triphenylphosphane (Scheme 26).[119c] It is proposed that, in the absence of an external proton source that can protonate the zwitterion **XXIX**, intramolecular proton transfer from the γ position becomes kinetically significant. Transposition of the double bond in **XXIX** can then occur to yield the extended dienolate **XXX**. Elimination of the catalyst from **XXX** then generates the allenone **XXXI** that is subject to further isomerization through intramolecular proton transfer to eventually form the observed product **80**. Further investigations of these isomerizations have expanded the scope of this interesting reaction to include more highly functionalized alkynoates as well as the isomerization of enynes to trienes and diynes to tetraenes.[119] Recognition of the diverse structures present in this reaction mixture heralded the numerous possibilities for the use of external reagents and the development of novel bond-forming processes.




***Scheme 26.*** Lewis base catalyzed isomerization of alkynoates.

In this section, triphenylphosphane will play a prominent role as a Lewis base catalyst. Although triphenylphosphane is a weakly basic phosphane ($pK_a(H_2O) = 2.73$), it often proves superior to more basic trialkylphosphanes. In fact, the use of tri-*n*-butylphosphane ($pK_a(H_2O) = 8.43$) is detrimental and leads to the formation of undesired oligomers. The use of strongly basic amines is not effective in these reactions, although it does not exclude the involvement of basic amines in related processes (Section 5.3.2).

If the addition of a phosphane to an alkynoate is performed in the presence of protic pronucleophile, such as an alcohol, amine, or a compound with an acidic carbon atom, a "catalytic" conjugate addition process can be envisioned. Numerous examples of these processes have been reported, although the true role of the phosphane in these reactions is debatable.[120] A careful distinction must be made between the phosphane-catalyzed processes that occur with alkynoates, and the phosphane-initiated processes that occur with alkenoates (Scheme 27). The differences between these two processes becomes clear upon consideration of the intermediates involved. Deprotonation of a protic substrate by the initially formed zwitterion (**XXXII** or **XXV**) leads to the generation of a β-phosphonium ion pair (**XXXIII** or **XXVII**). In the case of the alkenoate, the intermediate **XXXII** does not possess significantly enhanced electrophilicity at C3 relative to that of the starting material. The alkoxide will then undergo conjugate addition to another molecule of alkenoate.

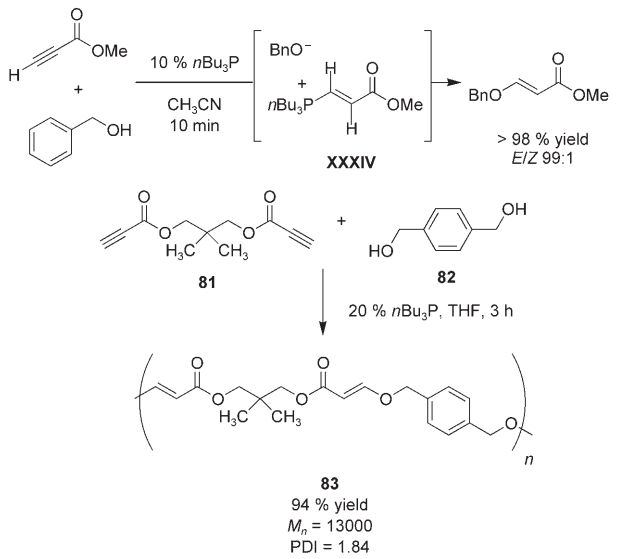



***Scheme 27.*** Phosphane-initiated versus phosphane-catalyzed reactions.

The resulting enolate then acts as a Brønsted base and deprotonates a second molecule of alcohol, thus completing the catalytic cycle. Therefore, it is believed that conjugate additions to alkenoates are only initiated by phosphanes. Strong support for the phosphane-initiation hypothesis has been derived from labeling experiments performed by Bergman and co-workers.[113]

On the other hand, the β-phosphonium species **XXVII** formed by the addition of a phosphane to an alkynoate does possess enhanced electrophilicity at C3 and it can react with nucleophiles. Therefore, it appears that these reactions are phosphane-catalyzed. The addition of malonates, alcohols, and thiols to alkynoates has been demonstrated using substoichiometric amounts of phosphanes (Scheme 28).[121] The method has been extended to an anionic group transfer polymerization strategy that has allowed for the synthesis of complex polymers with low polydispersity indexes.[122]

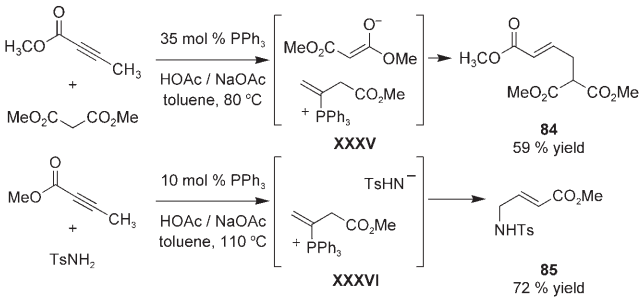
As access to unique reactive intermediates, such as the vinylphosphonium species **XXVII** involved in these catalytic conjugate additions is controlled by the relative rates of proton transfer and intermolecular reaction, modulation of experimental conditions can alter the partitioning of these intermediates and allow for access to additional reaction pathways. Under mildly acidic or buffered reaction condi-




***Scheme 28.*** Phosphane-catalyzed conjugate additions.

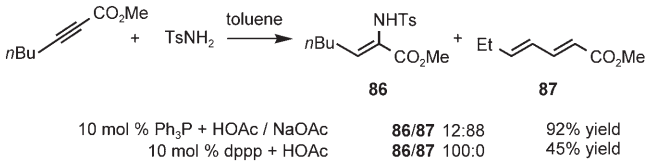
  

tions, wherein the rates of further proton transfers compete with intermolecular nucleophilic attack, the vinylphosphonium ion **XXVII** is in equilibrium with the species **XXVIII** (Scheme 25). This isomer has a unique pattern of umpolung reactivity because of the location of the vinylphosphonium moiety. The nucleophilic attack by an external reagent at the γ position of **XXVIII** is an interesting possibility because it represents $a^4$ umpolung reactivity of the starting alkynoate.[123] In the case of alcohols,[124] amines,[125] carboxylic acids,[126] malonates,[127] glycine imines, and nitroalkanes,[128] γ addition to **XXXV** or **XXXVI** occurs to give products **84** or **85**, respectively (Scheme 29).[129] The γ addition of bifunctional reagents such as diols, diamines, and amino thiols leads to novel methods for the phosphane-catalyzed synthesis of thiazoles, dihydrofurans, and a variety of other heterocycles.[130]



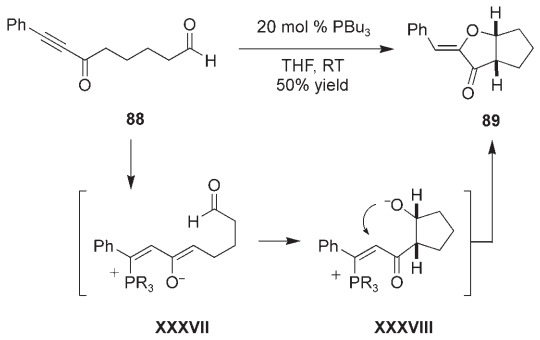

***Scheme 29.*** Phosphane-catalyzed umpolung γ additions.

In another example of how the relative rates of proton transfer and intermolecular nucleophilic attack can be balanced to generate novel forms of reactivity, a change of the reaction conditions can lead to a switch from $a^4$ to $a^2$ umpolung reactivity (Scheme 30).[131] The α-addition products **86** can generally be obtained in high selectivity with amines and malonates through addition at C2 to the β-phosphonium ion similar to **XXVII**. However, to obtain the α-addition products, substrates are commonly employed in which reaction is only possible at C2.




***Scheme 30.*** Phosphane-catalyzed umpolung α-additions. dppp = 1,3-bis(diphenylphosphanyl)propane.

The remarkable ability of these rapid proton-transfer equilibria to access a wide range of reactive intermediates with novel reactivity patterns is beautifully illustrated in the cascade cyclization of alkynoates recently demonstrated by Tomita and co-workers (Scheme 31).[132] Initial conjugate addition of tri-*n*-butylphosphane to **88** followed by proton transfer leads to the formation of the zwitterionic enolate

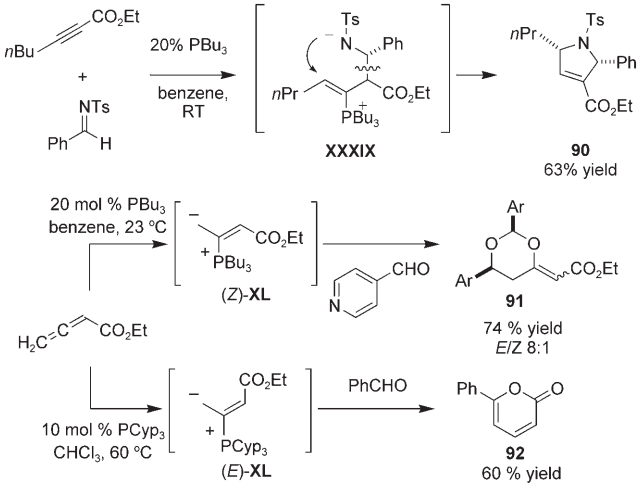



***Scheme 31.*** Phosphane-catalyzed cascade cyclization.

**XXXVII**, which can then undergo a facile, aldol cyclization. Subsequent α addition of the alkoxide group of **XXXVIII** to the β-phosphonium ion closes the bicyclic structure. After elimination of the catalyst, the highly functionalized bicyclic ketone **89** is produced in good yield and diastereoselectivity.

### *5.3.2. Phosphane-Catalyzed Cycloadditions*

Phosphane catalysis also plays an important role in catalytic cycloadditions. The same zwitterionic intermediates discussed in the preceding section undergo formal [3+2] cycloadditions with imines,[133] α,β-unsaturated ketones,[134] α,β-unsaturated nitriles,[135] and thioamides[130] (Scheme 32). These intermediates can be accessed either




***Scheme 32.*** Phosphane-catalyzed [3+2] cycloadditions. Cyp = cyclopentyl. Ar = 4-pyridyl.

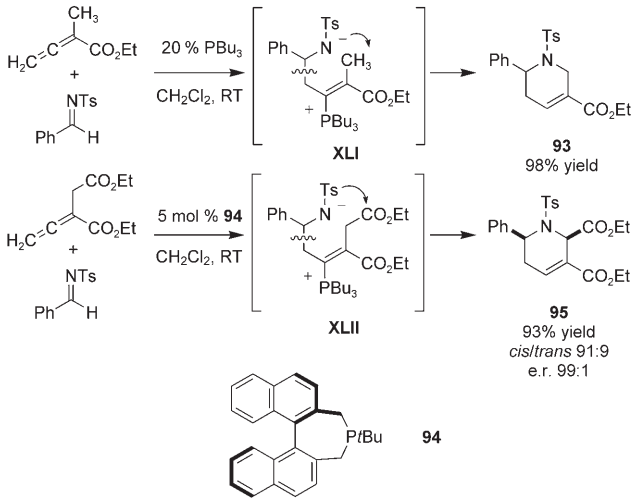
through reaction of an alkynoate or allenoate. The research groups of Zhang and Fu have extended this method by using chiral phosphanes that can induce high regio- and enantioselectivities in these cycloaddition reactions.[136] This strategy has been successfully applied to the total syntheses of hirsutene[137] and hinesol.[138]

Interestingly, Kwon and co-workers showed that the phosphane-catalyzed reaction of allenoates and aldehydes does not give the expected formal [3+2] cycloaddition products, 2,5-dihydrofurans. Depending on the catalyst struc-

ture and reaction conditions, 1,3-dioxan-4-ylidenes **91**[139] or 2-pyrones **92**[140] can be prepared with high selectivity (Scheme 32). This change in the reaction pathway is traced to the fate of the intermediate zwitterion **XL**. In the presence of a nonsterically demanding phosphane catalyst, such as tributylphosphane, (*Z*)-**XL** is favored for electrostatic reasons. The reaction of (*Z*)-**XL** with an aldehyde generates an alkoxide which then undergoes an Evans–Tischenko-type process prior to closure onto the phosphonium ion to form **91**. When a more sterically demanding phosphane catalyst, such as tricyclopentylphosphane, is employed, the *E* isomer of the intermediate zwitterion **XL** is preferred. The reaction of the aldehyde with (*E*)-**XL** generates an alkoxide which is in proximity to the ester group. Transesterification occurs which, after elimination of the phosphane catalyst, leads to the formation of the 2-pyrone **92**. Computational studies suggest that the dramatic differences between the reactivity of the zwitterion **XL** with aldehydes and imines (γ versus α addition, respectively) could be attributed to differences in the nature of stabilizing interactions engendered between the phosphonium group and the partial negative charge on the aldehyde or imine in the carbon--carbon bond-forming transition structure.[141]

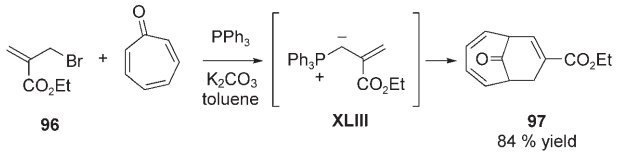
In another reaction that attests to the subtleties of phosphane catalysis, Kwon and co-workers have shown that a unique class of formal [4+2] cycloadditions with imines can also be accessed through Lewis base catalysis (Scheme 33).[142]




***Scheme 33.*** Phosphane-catalyzed [4+2] cycloadditions.

The initial step resembles that involved in the aforementioned [3+2] processes. However, the presence of acidic protons on the C2 substituent of the allenoate results in proton transfer in **XLI** being facile, and isomerization leads to formation of a vinylphosphonium species that can undergo intramolecular ring closure. This sequence represents a powerful method for the synthesis of highly substituted piperidines, and has recently been employed in the total syntheses of the alkaloids alstonerine and macroline.[143] Wurz and Fu have extended the method by demonstrating that the chiral phosphepine **94** is also an effective enantioselective catalyst for these [4+2] cycloadditions.[144]

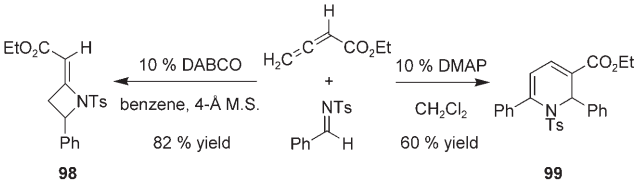
The ability of zwitterions such as **XLI** or **XLII** to act as partners in cycloadditions is not limited to common reaction manifolds such as the [3+2] or [4+2] combinations. Lu and coworkers have demonstrated that [6+3] cycloadditions are also possible by Lewis base catalysis (Scheme 34).[145] The zwitterion **XLIII**, generated from the allylic halide **96** under basic conditions, undergoes the [6+3] cycloaddition with tropone to provide **97** in good yield. This result is noteworthy because other cycloaddition pathways are generally favored over the [6+3] cycloaddition pathway with tropone.[146]




***Scheme 34.*** Phosphane-catalyzed [6+3] cycloadditions.

It is interesting to note that all the Lewis base catalyzed reactions discussed in the preceding section employed phosphanes. In contrast to the Morita–Baylis–Hillman reaction, which proceeds equally well with nitrogen and phosphorus Lewis base catalysts, these reactions appear to be uniquely susceptible to phosphane catalysis. In their studies on the α addition of malonates to alkynoates, Taran and coworkers showed that from a large number of amine and phosphane bases, only a limited number of phosphanes were effective catalysts.[131]

Therefore, the recent observations by Zhao and Shi of amine catalysis in a variety of Lewis base catalyzed reactions between allenoates and imines are particularly noteworthy (Scheme 35).[147] By changing the catalyst from DABCO to




***Scheme 35.*** Amine-catalyzed cycloadditions of allenoates.

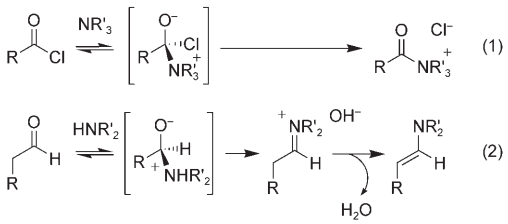
DMAP, different reactivity patterns can be accessed, allowing for the formation of both classes of products from the same starting materials. Clearly, the ability of nitrogen-centered Lewis bases to promote these reactions opens new opportunities for reaction development within this interesting class of Lewis base catalyzed reactions.

### *5.3.3. "Organocatalysis": n–π* Lewis Base Catalysis with Amines*

The role of proton transfer, either in the generation or stabilization of new reactive intermediates, is an important component to several Lewis base catalyzed reactions. In the

preceding sections, this aspect was clearly illustrated in the examples of Lewis base catalyzed acylations, Morita–Baylis–Hillman reactions and the numerous reactions grouped under "phosphane catalysis". Despite the vital contributions of hydrogen bonding and proton transfer to these processes, the primary contribution to catalysis is still the action of the Lewis base. In all cases, it is the highly reactive Lewis acid–base adduct that is the active catalytic intermediate.

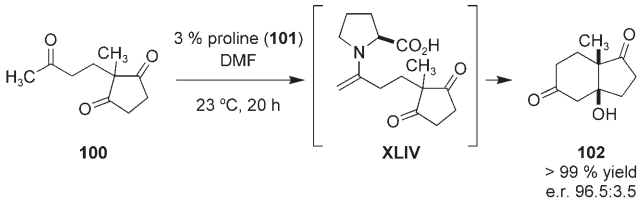
The addition of Lewis bases to unsaturated functional groups typically leads to the formation of charged intermediates such as the zwitterionic enolate **XVI** or the *N*-acylpyridinium ion **I**. In the case of ion **I**, this species is not the direct product resulting from the attack of the Lewis base, but rather a more stable species formed after collapse of a tetrahedral intermediate. In the case of the attack of a Lewis base on an acid chloride, the formation of a tetrahedral intermediate and subsequent collapse of this species with loss of chloride generates an *N*-acylammonium ion [Eq. (1) in Scheme 36]. If no easily ionized group is present, as is the case in the reactions of aldehydes and ketones, this mode of catalysis is not viable due to the reversible formation of the tetrahedral intermediate. However, this does not mean that Lewis base catalyzed reactions of these carbonyl compounds are not possible.




***Scheme 36.*** The fate of Lewis base adducts of various carbonyl compounds.

In the preceding examples of Lewis base catalysis with acid chlorides, anhydrides, and α,β-unsaturated carbonyl compounds, tertiary amines were often employed as catalysts. If a secondary amine is used instead, intramolecular proton transfer could lead to the formation of a neutral, resonance-stabilized amide and a loss of subsequent reactivity. Although this is a limitation with those substrates, it provides new opportunities for Lewis base catalysis with aldehydes and ketones that possess no leaving group in the absence of proton transfer. Attack of a secondary amine on an aldehyde or ketone generates a tetrahedral intermediate with an alternative pathway for collapse. After proton transfer and loss of water, an iminium ion is formed that possesses enhanced electrophilicity [Eq. (2) in Scheme 36]. Proton abstraction from the α-carbon atom can then lead to the formation of an enamine possessing enhanced nucleophilicity. Hence, the analogy between this and other types of n–π* catalysis is clear, and the dependence on the formation of a highly reactive tetrahedral intermediate is established for both. Just as in the case of the phosphane-catalyzed reactions, it is the intervention of additional proton-transfer steps after attack of the Lewis base that leads to new reactive intermediates with distinct reactivity patterns.

The highly reactive iminium ions and enamines have often been exploited as stoichiometric reagents. For example, Mannich reactions[148] as well as acyliminium ion cyclizations[149] have been used time and again as powerful transformations for synthesis. In addition, the utility of enamines as nucleophilic double bonds in alkylation and cycloaddition reactions is well documented.[150] In enzymatic catalysis, the formation of iminium ions, such as with tetrahydrofolate-dependent enzymes, has been recognized,[151] as has the role of enamines in Type I aldolases.[152] Despite this, the development of small-molecule catalysts that employ either iminium ions or enamines as intermediates has occurred only recently. In pioneering reports by Hajos and Parrish as well as Eder, Sauer, and Wiechert on the proline-catalyzed Robinson annulation of diketones it was demonstrated that high yields and selectivities could be obtained in the formation of a variety of bicyclic diketones.[153] The formation of an enamine intermediate similar to **XLIV** is key to this catalytic transformation.[154–156] Above and beyond the direct application of this process, this study firmly established the possibility of generating these highly reactive intermediates catalytically and under mild conditions (Scheme 37).




***Scheme 37.*** Proline-catalyzed Robinson annulations.

Remarkably, these observations lay more or less dormant until the turn of the 21st century, when a renaissance in the use of both iminium ion and enamine catalysis took place.[157] This field has increased dramatically in recent years and is still very much in the process of defining itself. Nevertheless, there are a number of very important processes that are now grouped under the rubric of "organocatalysis" that are in fact manifestations of both n–π* Lewis base catalysis as well as bifunctional catalysis.

Beginning in 2000, studies by MacMillan and co-workers revisited the area of iminium ion catalysis and greatly expanded its application to a number of well known synthetic transformations.[158] In the following years, interest in the use of chiral amines such as imidazolidinones and amino acids to promote carbon–carbon and carbon–heteroatom bond-forming reactions has grown exponentially and has led to the development of a structurally diverse group of catalysts (Figure 6). Careful consideration of this family of reactions reveals that they can be divided into two groups, much like the Morita–Baylis–Hillman reactions discussed previously. Reactions involving imidazolidinone catalysts and other catalysts devoid of additional Brønsted acidic sites are examples of simple n–π* Lewis base catalysis. Other reactions involving amino acid derived catalysts, such as the aldol and Mannich

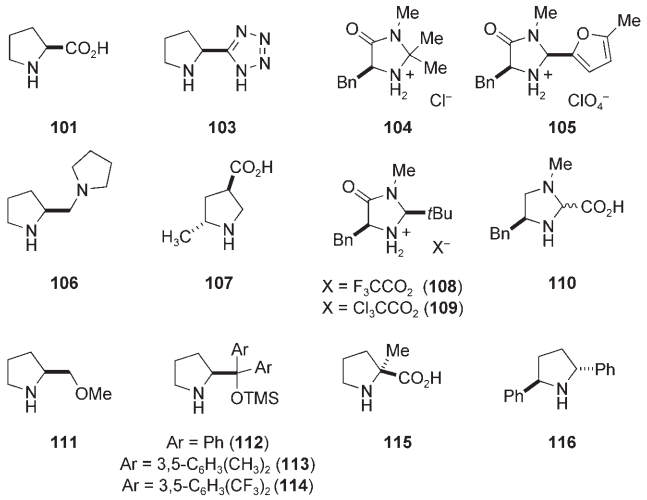


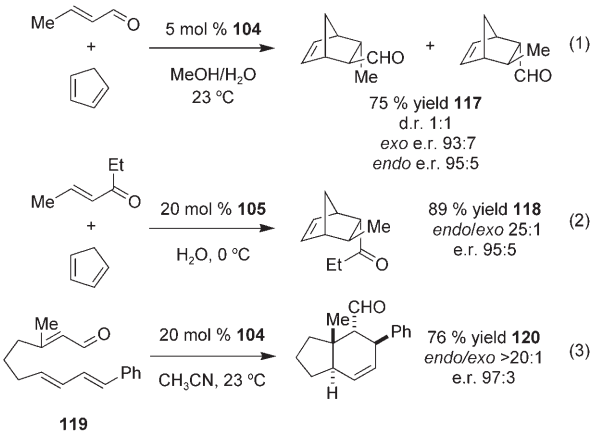

***Figure 6.*** Secondary amine catalysts for n–π* Lewis base catalyzed reactions.

reactions, have a vital Brønsted acid component that enhances the reactivity and selectivity. The reactions of these bifunctional catalysts will be discussed in Section 8. The decision whether or not to classify a particular amine-catalyzed reaction as simple n–π* or bifunctional catalysis can generally be made from the presence or absence of a Brønsted acidic site in the catalyst structure. In some cases, however, a product-based analysis proposed by Marigo and Jørgensen which is rooted in the relationship between catalyst structure and product stereochemistry can shed light on the operative mode of catalysis in a particular amine-catalyzed reaction.[159]

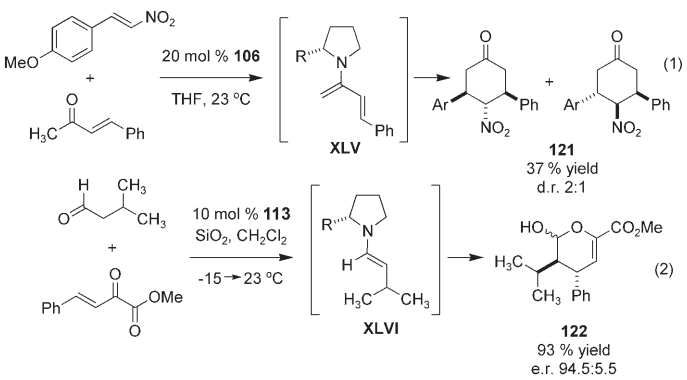
The initial report from MacMillan and co-workers in this expanding class of Lewis base catalyzed reactions with amines was the Diels–Alder reaction. In contrast to traditional modes of thermal or Lewis acid activation, these Lewis base catalyzed Diels–Alder reactions are driven by the formation of an iminium ion intermediate. With a chiral imidazolidinone salt, the reaction can be performed at room temperature, even with simple dienes, with good yields and enantioselectivities despite variable levels of diastereoselectivity [Eq. (1) in Scheme 38]. This initial report on the cycloaddition of simple dienes and aldehydes was followed by additional studies, some of which addressed several long-standing challenges in the area of asymmetric Diels–Alder reactions.[160] For example, it was shown that unsaturated ketones could can be used as dienophiles in a high-yielding and highly selective reaction [Eq. (2) in Scheme 38]. Whereas achieving high selectivity in [4+2] cycloadditions of ketones with chiral Lewis acids is complicated by the unselective formation of two Lewis acid–ketone adducts, good control over the iminium ion geometry is obtained with the imidazolidinone **105**, which directly translates to high enantioselectivity in the subsequent cycloaddition.[160g] In addition, the use of imidazolidinone catalysts leads to highly selective Type I and Type II intramolecular Diels–Alder reactions, even in cases where all-carbon quaternary centers are formed, as in **120** [Eq. (3) in Scheme 38].[160b]

The source of the dramatic rate enhancements in these Lewis base catalyzed Diels–Alder reactions is derived from the formation of a highly electrophilic α,β-unsaturated iminium ion. This process leads to a lowering of the LUMO of the dienophile and favors a normal electron demand Diels–Alder reaction. In fact, computational studies by Gordillo and Houk have shown that the activation energies for these Lewis base catalyzed Diels–Alder reactions are between 11–13 kcal $mol^{-1}$ lower than those for the corresponding thermal reactions.[161,162]

Much like many other Lewis base catalyzed processes, the enhanced electrophilicity observed in these Lewis base catalyzed Diels–Alder reactions is complemented by closely related processes where enhanced nucleophilicity plays a significant role. If an α,β-unsaturated ketone is exposed to a secondary amine, the initially formed iminium ion has the potential to be transformed by proton transfer into a conjugated enamine **XLV** which can participate as a diene in Diels–Alder reactions [Eq. (1) in Scheme 39].[163] In this case, it is the enhanced nucleophilicity of the intermediate **XLV** that accelerates the formation of **121**. The generation of enamines from aldehydes also allows for Lewis base catalyzed, inverse electron demand Diels–Alder reactions [Eq. (2) in Scheme 39]. Under amine catalysis, the hetero-Diels–Alder reactions of β,γ-unsaturated α-keto esters,[164] imines,[165] and nitroso alkenes[166] have all been realized. The combination of this kind of Diels–Alder reactivity with the Knoevenagel condensation allows for an equally efficient



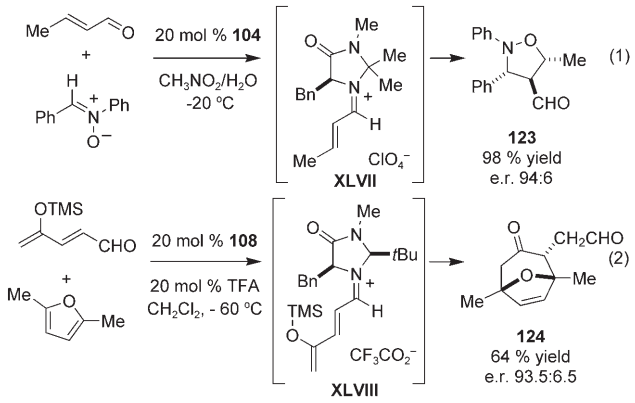

***Scheme 38.*** Amine-catalyzed [4+2] cycloadditions.




***Scheme 39.*** Amine-catalyzed [4+2] cycloadditions. Ar = 4-MeO$C_6H_4$.

three-component reaction between aldehydes, malonates, and α,β-unsaturated enones.[167]

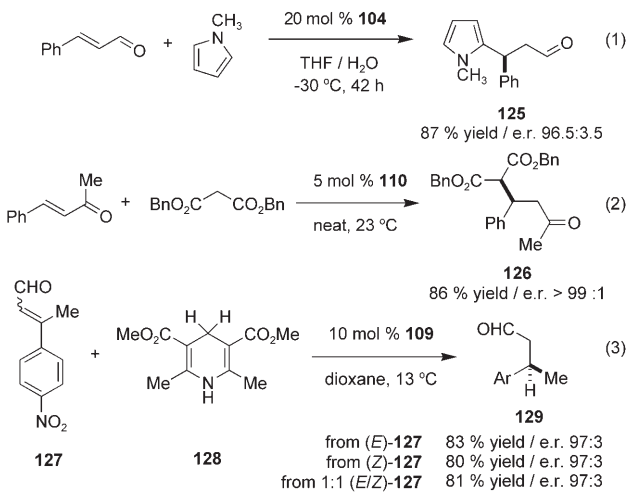
The Diels–Alder reaction is not the only cycloaddition that is amenable to this form of Lewis base catalysis. The electrophilic activation provided by the formation of an iminium ion intermediate plays a key role in the [3+2] cycloaddition of nitrones[168] as well as the [4+3] cycloaddition of furans[169] (Scheme 40).




***Scheme 40.*** Amine-catalyzed [3+2] and [4+3] cycloadditions. TFA = trifluoroacetic acid.

Since the initial report of the catalytic Diels–Alder reaction by MacMillan and co-workers, there has been an avalanche of publications in this area. New catalyst architectures and new reactions have been identified. The iminium and enamine intermediates formed through the action of chiral amine catalysts have found extensive application in a wide variety of carbon–carbon and carbon–heteroatom bond-forming processes. The formation of an iminium ion plays a key role in Lewis base catalyzed asymmetric Friedel–Crafts, Michael, and conjugate reduction reactions. Initially reported by Paras and MacMillan in 2001, the application of Lewis base catalysis to asymmetric Friedel–Crafts reactions has led to a considerable expansion in the scope of this process [Eq. (1) in Scheme 41]. A wide variety of electron-rich aromatic compounds, including pyrroles,[170] indoles,[171] furans, thiophenes, oxazoles, and substituted anilines,[172] all lead to the formation of the desired Friedel–Crafts reaction products in good yields and enantioselectivities. By this method, quaternary centers can be formed with good levels of diastereo- and enantioselectivity. Recent computational studies have confirmed that this reaction proceeds by a mechanism related to other Lewis base catalyzed reactions within this class.[173]

The enhanced electrophilicity exhibited in these asymmetric Friedel–Crafts reactions has played a major role in the development of a wide variety of Lewis base catalyzed Michael additions. The attack of malonates,[174] coumarins,[175] nitroalkanes,[176] siloxyfurans,[177] sulfides,[178] and amines[179] on chiral iminium ions allows for high levels of enantioselectivity to be obtained [Eq. (2) in Scheme 41]. These Lewis base catalyzed Michael additions also play a key role as the first step in a variety of Lewis base catalyzed cascade

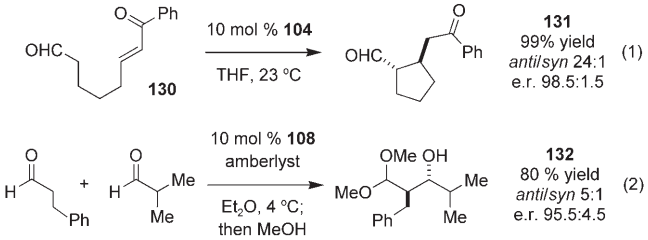



***Scheme 41.*** Electrophilic activation in amine-catalyzed reactions. Ar = 4-$NO_2C_6H_4$.

reactions, such as aldol–aldol,[180] Michael–Darzens,[181] cyclopropanation,[182] and epoxidation[183] processes.

Asymmetric conjugate reductions of carbonyl compounds, a challenging area for traditional catalysis, has also benefited from developments in this area of Lewis base catalysis. The attack of an organic hydride donor **128** on the intermediate iminium ion allows for high levels of enantioselectivity to be obtained in the conjugate reduction of α,β-unsaturated carbonyl compounds [Eq. (3) in Scheme 41].[184] It is interesting to note that these reactions are not sensitive to the alkene geometry in the substrate, a major challenge facing some transition-metal-catalyzed reductions.[185] Isomerization of the intermediate iminium ion allows for the reduction to proceed solely through a single isomer, thereby leading to consistently high levels of selectivity regardless of the substrate geometry or geometric purity.

The diversity of amine-catalyzed reactions that fall under the heading of n–π* catalysis (that is, not bifunctional catalysis with amino acids) encompasses numerous examples of nucleophilic activation. Through the intermediacy of a chiral enamine, Lewis base catalyzed Michael and aldol reactions as well as α-carbonyl functionalizations have been developed. The inter- and intramolecular Michael addition of aldehydes and ketones has been demonstrated, and occurs presumably through the attack of a highly nucleophilic, chiral enamine on a suitable acceptor [Eq. (1) in Scheme 42].[186] Aldol reactions between two aldehydes, a challenging process in the context of Lewis acid catalysis, has been performed

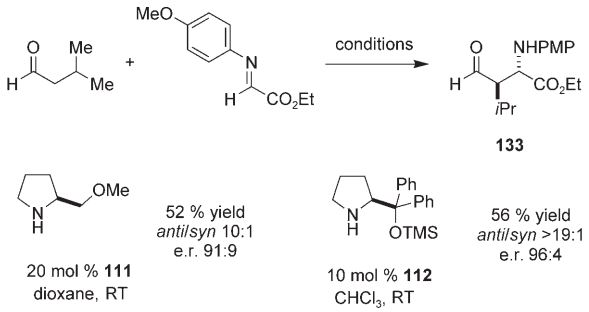



***Scheme 42.*** Nucleophilic activation in amine-catalyzed reactions.

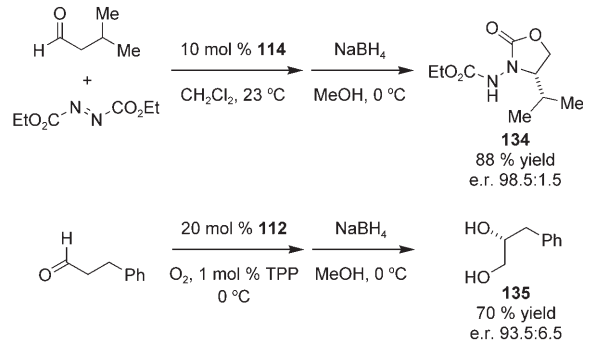
using chiral imidazolidinones as catalysts [Eq. (2) in Scheme 42].[187]

Although high yields as well as high diastereo- and enantioselectivities are obtained in these studies, imidazolidinones are not commonly used in amine-catalyzed aldol reactions. Proline is a much more versatile catalyst for these n–π* Lewis base catalyzed aldol reactions because of the vital influence of hydrogen-bonding interactions with the carboxylic acid moiety (see Section 8 on bifunctional catalysis). Lewis base catalysis of the Mannich reaction with chiral amines has also been explored, although again, the vast majority of examples employ bifunctional catalysts such as proline (Scheme 43). Notable exceptions involving the use of 2-methoxymethylpyrrolidine and the diaryl prolinol **112** have shown that high levels of enantio- and *anti*-diastereoselectivity can be obtained.[188] The diastereoselectivity of these Lewis base catalyzed Mannich reactions is particularly noteworthy because most proline-catalyzed reactions yield the *syn* product (Section 8.5).



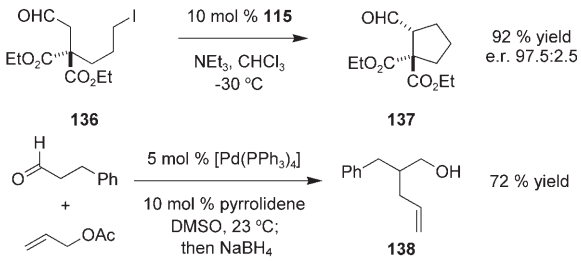

***Scheme 43.*** Nucleophilic activation in amine-catalyzed reactions.

A similar situation exists in α-carbonyl functionalizations in the presence of amine catalysts. A wide variety of carbon–heteroatom bond-forming processes have been investigated; some require bifunctional catalysts such as proline for high reactivity and selectivity while others do not. Amination reactions with azodicarboxylates and oxidation reactions with singlet oxygen have primarily been investigated with amino acid catalysts, but some excellent examples exist which fall under the heading of pure n–π* catalysis (Scheme 44).[189] Just as in the cases of the aldol and Mannich reactions, a highly



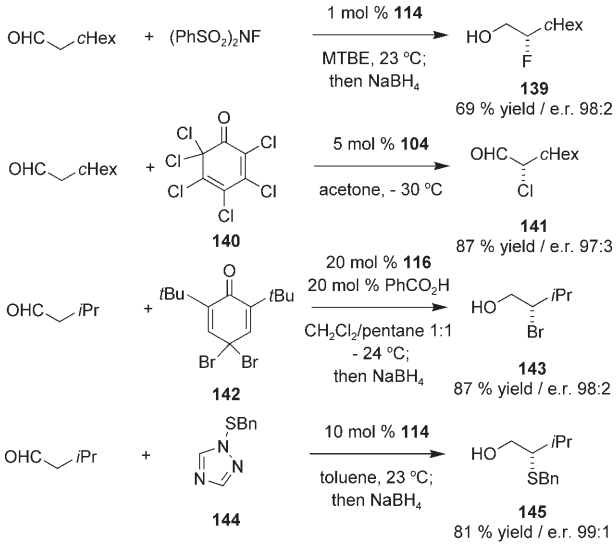

***Scheme 44.*** Amine-catalyzed α aminations and oxidations. TPP = tetraphenylporphine.

nucleophilic enamine is invoked in the carbon–heteroatom bond-forming step. Therefore, it is not surprising that alkylations can also be performed under amine catalysis (Scheme 45).[190] Intramolecular reactions lead to the formation of three- and five-membered rings with high levels of selectivity. Intermolecular alkylations have been achieved in combination with palladium catalysis.




***Scheme 45.*** Amine-catalyzed α alkylations.

In contrast to these carbon–nitrogen and carbon–oxygen bond-forming processes, α fluorinations,[191] chlorinations,[192] brominations,[193] iodinations, sulfenylations,[194] and selenylations[195] are all mediated through n–π* catalysis without the need for additional Brønsted acid catalysis (Scheme 46). High




***Scheme 46.*** Amine-catalyzed α functionalizations.

levels of enantioselectivity can be obtained with chiral imidazolidinones and silylated diaryl prolinols. The sense of the absolute asymmetric induction in these reactions is easily rationalized through consideration of a common enamine intermediate.

These examples show that a wide variety of organic reactions involving carbonyl compounds, some of which are typically catalyzed by chiral Lewis acids, can instead be promoted by chiral amine catalysts. The degree to which these catalysts are able to enhance the electrophilic character is truly remarkable considering their compatibility with a wide range of functional groups and solvents. Typically, the use of

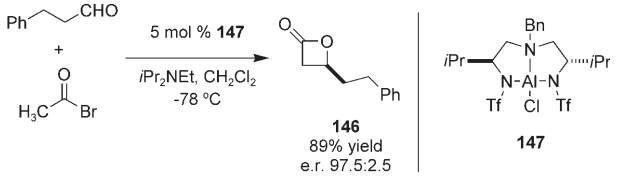
  

such strongly electrophilic Lewis acid catalysts would place severe limitations on the reaction scope and available experimental conditions.

Before leaving the section on n–π* activation, a comment is in order regarding the classification of these Lewis base catalyzed reactions involving iminium ion and enamine intermediates under the larger heading of "organocatalytic" processes. Comparison of the Lewis base catalyzed reactions discussed in this section with other "organocatalytic" processes, such as ketone-catalyzed epoxidations or phase-transfer-catalyzed alkylations,[157] reveals that a great diversity of reaction types have been grouped under this single, broad heading. The lack of specificity associated with this term persists whether one considers catalyst structure or even reaction mechanism. A higher level of precision is required in defining and applying such terms to aid in clearly classifying reactions. The current definition of "organocatalysis" is based on a lack of a certain structural component (a metal) with no overarching mechanistic continuity. Such a vague definition is too broad to be useful. On the other hand, the definition of Lewis base catalysis is based on a specific structural attribute of the catalyst (following Jensen, a nonbonding electron pair) and a specific mode of interaction of the catalyst with the substrate.

peripheral atoms. Thus, a hypervalent species is created with unique patterns of reactivity, where both the electrophilicity and nucleophilicity of the adduct are enhanced. Other cases exist where the binding of the Lewis base(s) generates such a strong polarization of the adjacent bonds that ionization occurs, thereby yielding an ion pair. In this ion pair, both the electrophilicity of the M center, and the nucleophilicity of the X unit are highly amplified, with attendant kinetic and stereochemical consequences.

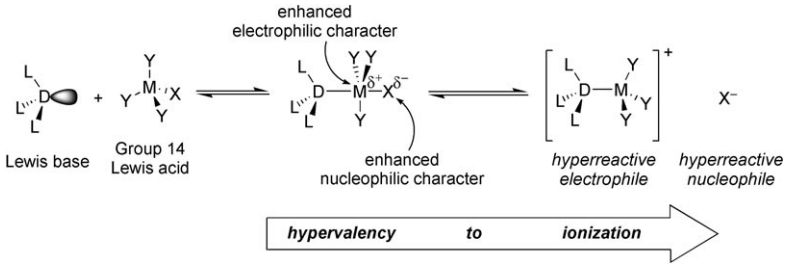
Examples of both families of species (hypervalent intermediates and ion pairs) that exhibit both electrophilic and nucleophilic activation are well known. An excellent illustration of the enhanced electrophilic reactivity of a hypervalent intermediate comes from the work of Nelson et al. on tetracoordinate aluminum complexes (Scheme 48).[196] In




***Scheme 48.*** Aluminum-catalyzed asymmetric [2+2] cycloadditions.

## 6. The n–σ* Interaction: Lewis Base Catalysis with Polarized and Ionized Intermediates

As demonstrated in the examples in Section 5, n–π* catalysis is representative of the chemistry of unsaturated, carbon-centered Lewis acidic functional groups. The higher stability of tetracoordinate carbon atoms compared to their tri- and pentacoordinate congeners, as well as the low polarizability of carbon–carbon σ bonds, limits the application of Lewis base catalysis to the chemistry of saturated, carbon-centered functional groups. The interaction of Lewis bases with more commonly recognized Lewis acids, such as transition-metal and electron-deficient main-group organometallic reagents, is representative of a fundamentally different class of catalysis: the n–σ* interaction. As in the n–π* Lewis base catalysis, the binding of the Lewis base to the Lewis acid induces a re-distribution of electron density in the newly formed adduct (Scheme 47). In the proposed model of the n–σ* interaction, this binding leads to a polarization of the adjacent bonds, thereby decreasing the electron density at the central atom and increasing the electron density at the




***Scheme 47.*** Reactivity continuum in n–σ* Lewis base catalysis.

studies of [2+2] cycloadditions, it was found that neutral tetracoordinate chiral aluminum complexes such as **147** mediate reactions that had earlier been performed with the highly electrophilic aluminum species $Al(SbF_6)_3$ with comparable levels of activity.[197] Illustrations of the enhanced nucleophilic reactivity of hypervalent species are found in the formation of silicates from trialkylsilyl reagents that lead to myriad carbon–carbon bond-forming reactions (see the next section).

Examples of ion pairs that manifest hyperreactive cationic or anionic intermediates are also known, mostly for organosilicon compounds. In this family, the primarily structural feature that distinguishes whether electrophilic or nucleophilic activation will be expressed is the nature of the spectator ligands on the silicon atom. Under Lewis base activation, trialkylsilanes exhibit enhanced nucleophilic character, whereas trihalosilanes exhibit enhanced nucleophilic and/or electrophilic character. This division will constitute the major organizational rubric for the next section.

### 6.1. Nucleophilic Activation through n–σ* Interactions: Trialkylsilanes and -stannanes

#### 6.1.1. Activation by Fluoride Ions: Lewis Base Catalysis or Anionic Initiation?

The earliest examples of Lewis base catalyzed reactions of the n–σ* type were found in the chemistry of silanes.[198] The ability of silicon to attain stable, hypervalent states has long been known and has attracted a great deal of attention, especially in the context of studies on the stereochemical course of nucleophilic

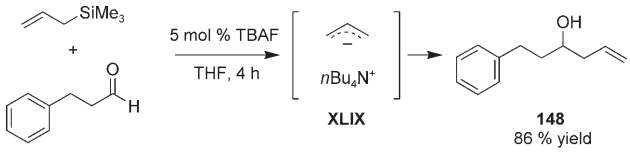
displacement at the silicon atom.[199] However, it was not until the mid-1970s that the unique reactivity of these structurally intriguing species was exploited in organic synthesis.[200] A crucial advance in the field, attributable to Corriu and co-workers, was the introduction of fluoride ions to promote the formation of a reactive, hypervalent silicate. The extremely high enthalpy of the silicon–fluorine bond (135 kcal mol$^{-1}$)[201] explains why fluoride is an effective promoter of a wide variety of silicon-based, carbon–hydrogen and carbon–carbon bond-forming reactions. Whereas Corriu and co-workers focused on the use of insoluble fluoride activators for a wide range of reactions,[202] it was the introduction of soluble fluoride sources, such as tetra-*n*-butylammonium fluoride (TBAF), that captivated the interest of the broader chemical community in using these transformations.[203]

A wide range of trialkylsilanes participate in fluoride-promoted processes including hydridosilanes for functional-group reductions, allylic and acetylenic silanes and a number of silylated pronucleophiles such as TMSCN, $TMSN_3$, and $TMSCF_3$ for carbonyl addition reactions, and various enoxysilanes for aldol and Michael addition reactions,. The preparative utility of these processes has raised interesting mechanistic questions about the nature of the fluoride activation and the actual involvement of hypervalent fluorosilicates. These issues are more than mechanistic curiosities, because the development of catalytic, enantioselective processes requires that the mechanism be clarified.

At its most basic level, the limiting scenarios for activation of trialkylsilyl species by fluoride ions are: 1) the intermediacy of a hypervalent fluorosilicate intermediate that combines with the substrate or 2) cleavage of a Si–X bond that leads to the formation of a reactive ion pair. To understand the circumstances that lead to either of these limiting cases (and the attendant stereochemical consequences), requires consideration of the identity of the silane and in particular its transferable ligand (Scheme 47). The intermediacy of hypervalent fluorosilicates is favored for bulkier trialkylsilanes bearing less electronegative or poorly delocalizing substituents that can stabilize the fluorosilicates. On the other hand, smaller trialkylsilanes bearing highly electronegative or strongly delocalizing substituents tend to be ionized to form a new ion pair. In this case, the hypervalent fluorosilicate is only a transition structure en route to the formation of the active, ionized species. Consideration of the identity of the transferable ligand is an important part in fitting the chemistry of trialkylsilanes into the picture of n–σ* Lewis base catalysis as developed by Gutmann and discussed in general terms in Section 3.1.2.

#### 6.1.1.1. *Allylation*

The first example of the use of homogeneous fluoride ion sources in carbon–carbon bond formation came from Sakurai and co-workers in 1978 with the report that TBAF induces the addition of allylic silanes to aldehydes (Scheme 49).[203] Along with the transfer of simple allyl units, 2-butenylsilanes can also be employed, and produce homoallylic alcohols with a high degree of *syn* diastereoconvergence. To rationalize this selectivity pattern, the original mechanistic proposal by




***Scheme 49.*** Fluoride ion initiated allylation with allyltrimethylsilane.

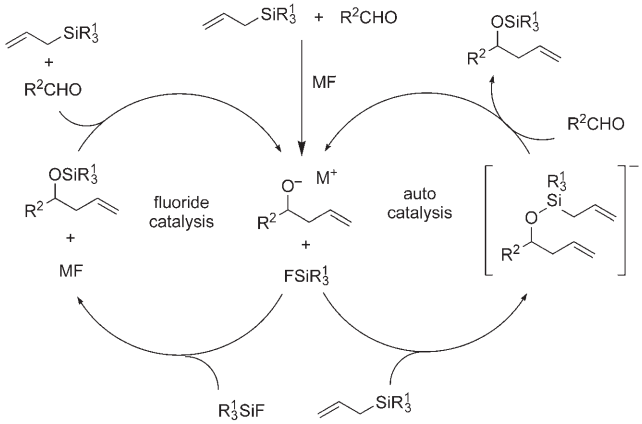
Sakurai and co-workers invoked a tetra-*n*-butylammonium ion pair as the active species.[204] It was clear that an open transition structure was operative, since a stereodivergent reaction would be expected if a closed, six-membered transition structure were involved.[205] This original proposal of a carbanion intermediate **XLIX** did not receive widespread support, primarily because of concerns regarding the high Brønsted basicity of such a carbanion intermediate.[206] However, recent studies by Biddle and Reich provide compelling evidence that an intermediate such as **XLIX** is active in this and other fluoride-initiated processes.[207] By examining the regio- and diastereoselectivity of reactions of well-defined allylic lithium ion pairs with those of allylic silanes in the presence of fluoride ions, conclusions can be drawn regarding the structure of the reactive intermediates. The fact that the selectivity observed in the fluoride-initiated reactions resembles that of solvent-separated lithium ion pairs strongly supports the intermediacy of a carbanion such as **XLIX**. Additional studies show that the structure of the silane moiety has little effect on the selectivity, and further support this conclusion. Nevertheless, some caution must be taken when considering the generality of these observations. The p$K_a$ value of the conjugate acid of the nucleofuge will have a strong effect on the partitioning of the reactive intermediate between a carbanion and a hypervalent silicate pathway. Whereas less basic species, such as those derived from acetylenic silanes,[208] certainly proceed through the carbanion mechanism, the situation may be different for more basic species.

It should be noted that care has been taken to differentiate whether a reaction is "initiated" or "catalyzed" by fluoride ions. The vital role of fluoride ions in forming active hypervalent fluorosilicates and ammonium ions is not in dispute, but the question of whether the reactions are truly catalytic in fluoride ions remains open.[209] In the critical turnover step, the product alkoxide must be silylated to release fluoride ions and regenerate the catalyst. In view of the strength of the silicon–fluorine bond,[201] some authors have disputed the role of TMSF as the active silylating agent. Corriu and co-workers suggest that trimethyldifluorosilicate ($TMSF_2^-$) is the active silylating agent rather than TMSF, but maintain that the processes are catalyzed by fluoride ions.[210]

Instead of invoking cleavage of the strong silicon–fluorine bond of either TMSF or $TMSF_2^-$ as being integral to the turnover step in the catalyst cycle, other pathways for activation have been proposed (Scheme 50). One pathway, originally suggested by Kuwajima and co-workers in their studies of the transsilylation of α-silyl esters, is a silicon-transfer pathway, wherein the anion formed after initial nucleophilic attack of a fluoride ion reacts directly with

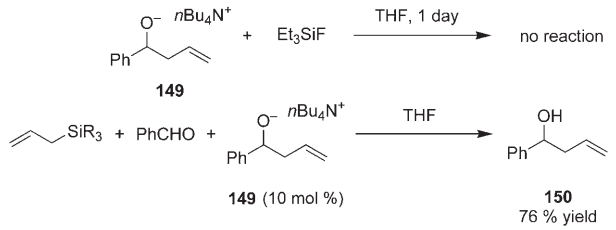
  

another silylated nucleophile, thereby completing the "catalytic" cycle.[211] Therefore, it is the enolate anion, or in this case the alkoxide anion, that is the true chain-carrying species.




***Scheme 50.*** Fluoride ion initiated versus catalyzed processes.

This kind of autocatalytic behavior is supported by the observation of an induction period in the reaction-rate profile. Thus, a slower initial phase of the reaction is promoted by fluoride ions while the faster, later phase is promoted by some other in situ generated anion. Studies by Hou and co-workers have shown that the ammonium alkoxides such as **149** that are produced in allylations with allyltrimethylsilane and tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) are in fact active catalysts for subsequent allylations (Scheme 51).[212] In addition, numerous examples of nucleophilic activation in the reaction of silyl nucleophiles with alkoxides exist, thus lending further support to the kinetic competence of this pathway. In-depth kinetic studies similar to those performed by Kuwajima and co-workers[211] are clearly warranted to establish the role of fluoride ions in the aldol and allylation reactions. However, this cannot alter the view that some form of Lewis base promotion leads to the pattern of nucleophilic reactivity observed in the fluoride-promoted reactions.[212,213]

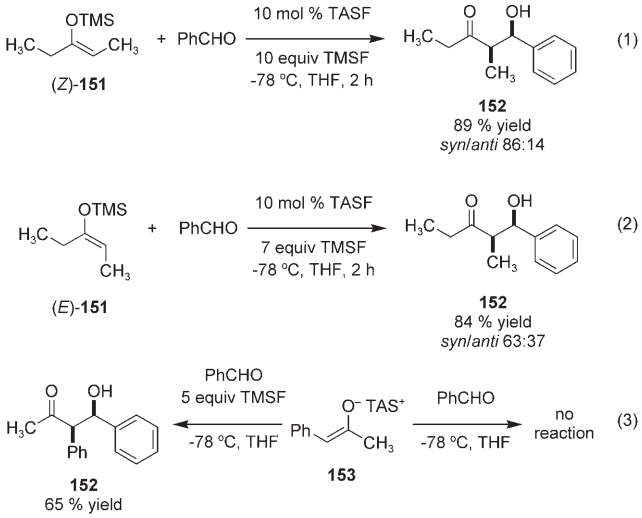



***Scheme 51.*** Reactivity of ammonium alkoxides.

#### 6.1.1.2. *Aldol Addition*

The impact of the silane structure on the mechanism and stereochemical outcome of fluoride-promoted reactions becomes more clear when considering silyl enol ethers and silyl ketene acetals. Initial studies by Kuwajima and Nakamura demonstrated that silyl enol ethers could be alkylated in the presence of benzyltrimethylammonium fluoride.[214] These authors proposed that the active species was an ammonium enolate. This proposal is consistent with a mechanism where a hypervalent fluorosilane is likely a transition structure. The preceding analysis suggests that facile ionization is reasonable because of the lower Brønsted basicity of ketone-derived enolates. Later studies described below would lend further support to this proposal. Still, this work did provide proof of principle for later studies on related aldol processes with carbonyl electrophiles.

The application of fluoride ions to promote aldol reactions was reduced to practice by Heathcock and co-workers several years later.[215] The use of stoichiometric amounts of a fluoride source allowed for highly *anti*-diastereoselective reactions between ketone-derived silyl enol ethers and aldehydes. It was only later, in a collaborative effort between the Kuwajima and Noyori research groups, that earlier observations were combined in the demonstration that only substoichiometric amounts of soluble fluoride sources were required to provide rapid and high yielding, *syn*-diastereoselective aldol reactions [Eqs. (1) and (2) in Scheme 52].[216] Again, the intermediacy of a "naked" ammonium enolate such as **153** rather than a hypervalent fluorosilicate is invoked in this process [Eq. (3) in Scheme 52].




***Scheme 52.*** Fluoride ion catalyzed aldol reactions of enoxysilanes.

This mechanism has gained support from studies on the reactivity of isolated ammonium enolates.[216b] Initial experiments demonstrated that despite their high reactivity, these species cannot undergo productive aldol reactions. The addition of a silylating reagent is required for high conversions. Although this may cast some doubt on the proposed mechanism, it must be remembered that under the actual reaction conditions described by Noyori and co-workers, the generation of the ammonium enolate would lead to the

formation of trimethylsilyl fluoride (TMSF), which could potentially act as a silylating reagent.

The requirement for an additional silylating reagent in the reactions of isolated ammonium enolates is readily explained by the established reversibility of the carbon–carbon bond-formation step in aldol reactions.[217] The ammonium aldolate must be trapped by a silylating agent to render the overall reaction thermodynamically favorable. In the reactions of an isolated tris(dimethylamino)sulfonium enolate **153**, the addition of five equivalents of TMSF to the reaction allows for high conversions [Eq. (3) in Scheme 52].[210] The release of a fluoride ion upon silylation of the aldolate can then complete the fluoride-catalyzed reaction. However, the possibility of fluoride ion initiation and enolate catalysis cannot be ruled out. In fact, Biddle and Reich have suggested that both may be operative in these aldol reactions.[207]

#### 6.1.1.3. Group-Transfer Polymerization and Michael Additions

The relatively low basicity of ketone-derived enolates allows for the facile ionization of silyl enol ethers by fluoride ions through the intermediacy of a hypervalent fluorosilicate. Therefore, if more basic enolates, such as ester- or amide-derived enolates, are employed, a change in the mechanism to one involving a hypervalent fluorosilicate and a different pattern of reactivity might be observed.[218] Although no demonstration of fluoride-catalyzed aldol reactions of silyl ketene acetals is on record, convincing evidence for the involvement of hypervalent fluorosilicates is found in studies of the fluoride-catalyzed silicon-group-transfer polymerization of silyl ketene acetals and α,β-unsaturated esters [Eq. (1) in Scheme 53].[219] This method provides access to a variety of acrylate polymers with low polydispersity indexes. This finding suggests a "living" polymerization in which chain-transfer processes are disfavored. The low polydisperisities observed in these reactions are proposed to arise from a closed, eight-membered-ring transition structure, **L**. The formation of highly reactive ammonium enolates in this process would lead to lower selectivities that could not generate the narrow ranges of molecular weights common to "living" polymers of this type.

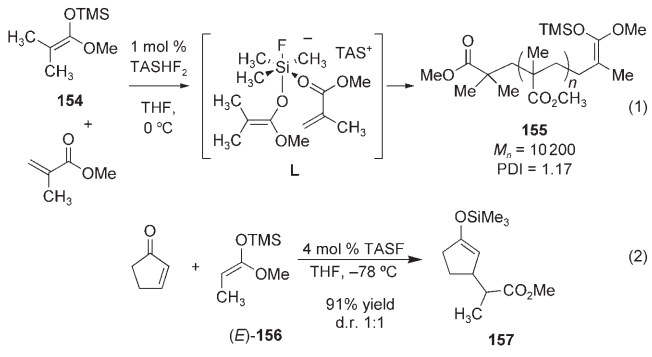
RajanBabu has expanded the use of TASF in group-transfer polymerization for Michael additions of silyl ketene acetals to enones [Eq. (2) in Scheme 53].[220] The reactions proceed rapidly at room temperature to afford silyl enol ethers such as **157**, which can be further manipulated. Unfortunately, diastereoselectivities were poor and the mechanism of the silicon-group transfer could not be elucidated.[221]

The plurality of mechanisms available in fluoride-promoted reactions of trialkylsilyl enol ethers and allylic silanes presents a serious challenge to the development of a catalytic enantioselective process. Some methods have been developed that employ chiral ammonium salts, but synthetically useful selectivities remain elusive.[222] Yamamoto and co-workers have had some success with a combined chiral Lewis acid/fluoride ion catalyst strategy which will be discussed in a subsequent section on bifunctional catalysis (see Section 8.3).

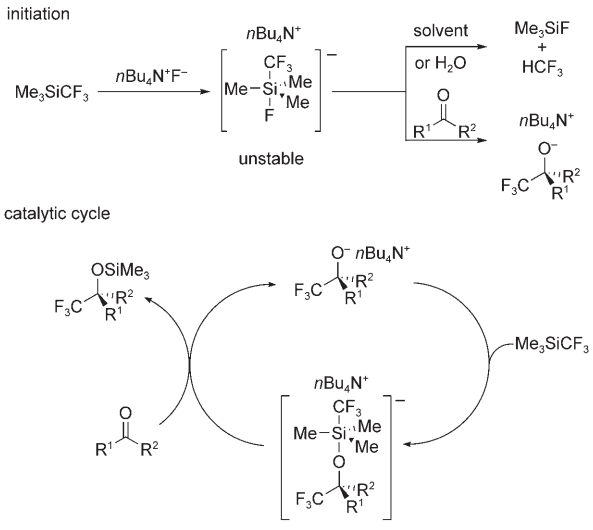
#### 6.1.1.4. Trifluoromethylation with Trifluoromethyltrimethylsilane[223]

The development of the Ruppert–Prakash reagent ($Me_3SiCF_3$) has revolutionized the nucleophilic introduction of trifluoromethyl groups into organic molecules.[224] In combination with a fluoride activator, usually TBAF, this reagent can efficiently add a trifluoromethyl group to myriad reactive functional groups including aldehydes, ketones, esters, amides, various azomethines, and other heteroatomic groups.[223c] Other anionic activators include KF[225a] CsF,[225b] $n$Bu$_4$N$^+$ Ph$_3$SnF$_2^-$,[225c] $n$Bu$_4$N$^+$ Ph$_3$SiF$_2^-$,[225d] and alkoxides.[225a] Although no detailed mechanistic or kinetic studies are on record, the reaction (with carbonyl compounds) is believed to be a fluoride-initiated/alkoxide-catalyzed process (Scheme 54).[224]

The nature of the interaction between fluoride ions and $TMSCF_3$ has been investigated by NMR spectroscopy.[226] Two species are detected upon mixing $TMSCF_3$ and $Me_4N^+F^-$ in different ratios at −60 °C (Scheme 55). Species **158** is seen when $TMSCF_3$ is in excess and **159** is seen when $Me_4N^+F^-$ is in excess. In fact, the related compound **160** has been isolated



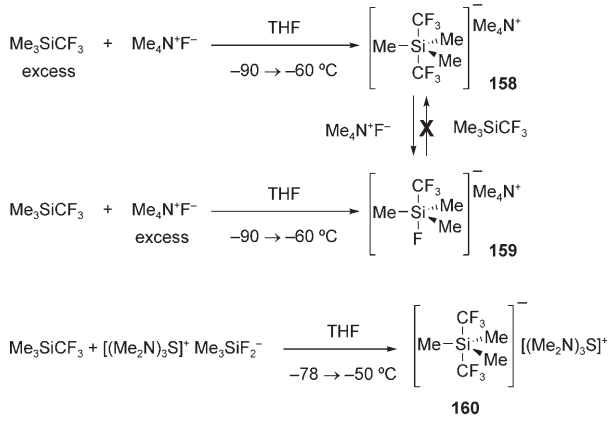

***Scheme 53.*** Fluoride ion catalyzed reactions of silyl ketene acetals (group-transfer polymerization and Michael addition).




***Scheme 54.*** Catalytic cycle for nucleophilic trifluoromethylation with $TMSCF_3$.

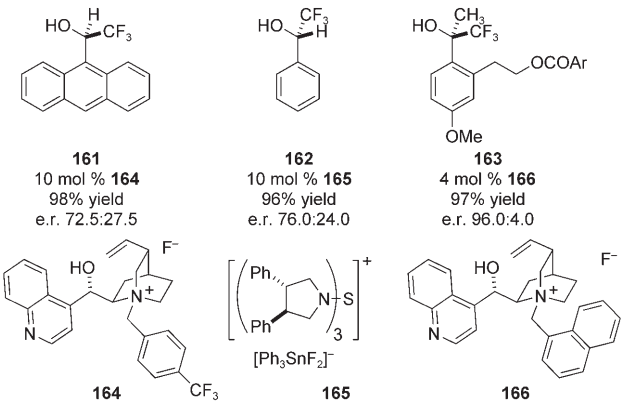
  

and crystallographically characterized as the $[(Me_2N)_3S]^+$ salt.[226b] These highly reactive compounds are known to be effective trifluoromethylating agents, but their role in the additions to carbonyl compounds under catalytic conditions has not been established.



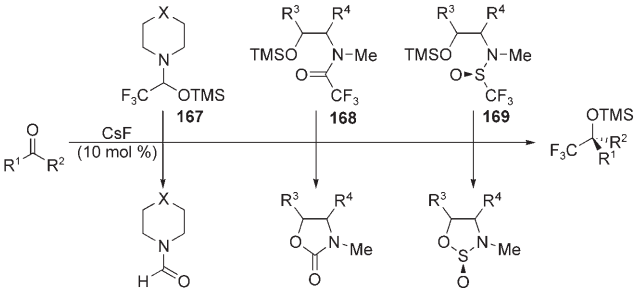

***Scheme 55.*** Hypervalent silicon intermediates from $TMSCF_3$.

Despite the lack of mechanistic insight and the possibility that these reactions are catalyzed by the alkoxide product and not the fluoride ion, enantioselective trifluoromethylation has been achieved with chiral ammonium fluorides. Iseki et al. described the use of a modified cinchoninium fluoride and found high yields but modest enantioselectivities in the trifluoromethylation of aromatic aldehydes to form the products **161** and **162** (Scheme 56).[227a] This research group also reported the preparation and survey of a family of chirally modified triaminosulfonium difluorotriphenylstannates as catalysts for enantioselective trifluoromethylation.[227b] The 3,4-diphenylpyrrolidino catalyst **165** is the most selective, and affords an enentiomeric ratio of 76:24 with benzaldehyde. The best catalyst for this process is the cinchoninium salt **166** reported by Caron et al. who also carried out an extensive optimization of solvent, temperature, and *N* substituent.[227c] This research group targeted the ketone-derived product **163**, and although the catalyst is not selective for other ketones, its efficiency and selectivity are still remarkable. These results encourage further exploration into a more detailed understanding of the actual intermediates in the reaction and the nature of the stereodetermining event.




***Scheme 56.*** Catalytic enantioselective trifluoromethylation.

Although the trifluoromethyl anion is inherently unstable, it is still a very good leaving group and as such can be generated by the breakdown of electron-rich species. Langlois and co-workers have developed a number of reagents **167**–**169** that carry a "$CF_3$ reservoir" in the form of hemiaminals, trifluoroacetyl derivatives, and trifluorosulfinamides.[228] These reagents can release the trifluoromethyl anion under both stoichiometric activation by bases, and also by the catalytic action of a fluoride ion on the silylated precursors (Scheme 57). The delivery of the trifluoromethyl group is fairly efficient, but unfortunately this process also most likely involves a fluoride-initiated, alkoxide-catalyzed mechanism with no opportunity for asymmetric induction, even with chiral reagents.



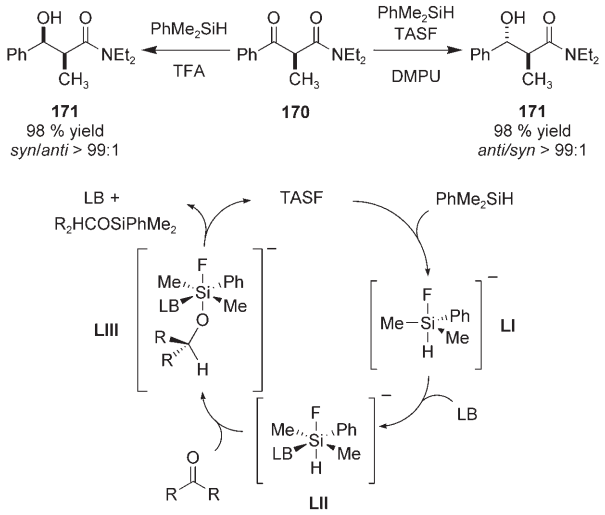

***Scheme 57.*** Reagents for catalytic nucleophilic trifluoromethylation.

### 6.1.1.5. *Reduction of Carbonyl Compounds with Silyl Hydrides*

The activation of hydridosilanes to function as reducing agents can be effected by Lewis bases, Lewis acids, and transition-metal species.[229] Although least common among the methods of activation, fluoride ions (as well as alkoxides) do offer unique chemical and stereoselectivity features. Initial reports showed that soluble fluoride sources such as TBAF could promote the reduction of a variety of carbonyl compounds with $Ph_2MeSiH$ (Scheme 58).[230] The active reagent, initially thought to be the fluorosilicate **LI**, showed excellent *anti* diastereoselectivity in the reductions of ketones bearing α-stereogenic centers, such as α-substituted β-keto amides. The selective formation of either the *syn* or *anti* reduction product could be achieved by adjusting the reaction conditions. This pattern of selectivity was rationalized through a change between an open, bimolecular transition structure and a closed, unimolecular assembly.

At an early stage in these studies, Fujita and Hiyama found that the addition of strongly Lewis basic cosolvents such as HMPA or DMPU also facilitated the reaction.[230e]




***Scheme 58.*** Fluoride ion catalyzed reductions with silanes. DMPU = *N*,*N*′-dimethylpropylene urea.

Kinetic studies on the reduction revealed a first order dependence on the concentration of the cosolvent, which suggests that these polar solvents play a role beyond simple solvation in the overall reaction. Accordingly, a revised mechanism involving a hexacoordinate silicate **LII**, bonded by both a fluoride ion and the neutral Lewis base, was proposed.[231]

Shibata and Baba have shown that the normal, radical-type reduction of organic functional groups with $n$Bu$_3$SnH can be altered to an ionic pathway in the presence of many different kinds of Lewis bases.[232] Specifically, TBAF was shown to give clean reduction of α-alkoxy ketones with high *syn*-diastereoselectivity arising from Felkin–Ahn-controlled addition.[233] Although a pentacoordinate fluorostannate was hypothesized as the intermediate, it could not be identified spectroscopically.[233b] As was also the case in the fluoride-activation of silanes, Shibata and Baba found that strong, neutral Lewis bases could play a similar role to that of anionic Lewis bases. However, with stannanes, neutral Lewis bases were highly effective in the absence of fluoride ions. The realization that neutral Lewis bases could activate silanes and stannanes generated new possibilities for mild catalytic methods (see the next section).[234]

### 6.1.2. Nucleophilic Activation with Other Lewis Bases

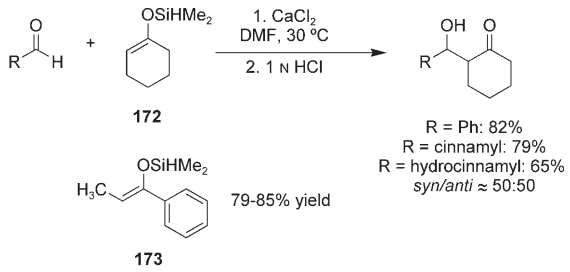
The development and impact of organosilicon chemistry in synthesis is historically tied to the use of fluoride ions as a Lewis base activator. Although catalysis with Lewis acids eventually superceded activation with fluoride ions, particularly for catalytic enantioselective variants, there are still many illustrations of non-fluoride Lewis bases (both anionic and neutral) that function in a variety of transformations that offer preparatively useful advances and mechanistically intriguing insights. These will be discussed below within the context of each chemical transformation.

#### 6.1.2.1. Aldol Addition

##### 6.1.2.1.1. Anionic Lewis Bases

The high binding affinity of anionic Lewis bases for organosilicon moieties is not limited to fluoride ions.[201] Conjugate bases of various oxygen- and nitrogen-based functional groups also associate with organosilicon pronucleophiles such as enoxysilanes and can promote additions to carbonyl groups. However, as was the case with activation by fluoride ions, there is a mechanistic ambiguity as to the actual role of the added agent—either as an initiator or as a catalytic species.

A closely related aldol process promoted by chloride ions has been reported for dimethylsilyl enol ethers such as **172** and **173**.[235] A broad survey of metal halide salts as promoters of the aldol addition of **172** and **173** with benzaldehyde in DMF at 30 °C for 1 h produced the following trend in yields: $CaCl_2$ 95 %, LiCl 98 %, $n$Bu$_4$N$^+$Cl$^-$ 67 %, $CaBr_2$ 54 %, $MgBr_2$ 54 %, LiBr 52 %, $n$Bu$_4$N$^+$Br$^-$ 67 %, $CaI_2$ 32 %, LiI 34 %, NaI 35 %, KI 34 %, $n$Bu$_4$N$^+$I$^-$ 40 %. On the basis of the weak Lewis acidity of $CaCl_2$ and the promoting effect of tetrabutylammonium salts, the authors conclude that there is no contribution from the electrophilic activation of the aldehyde. Unfortunately, the reactions are completely unselective (Scheme 59).

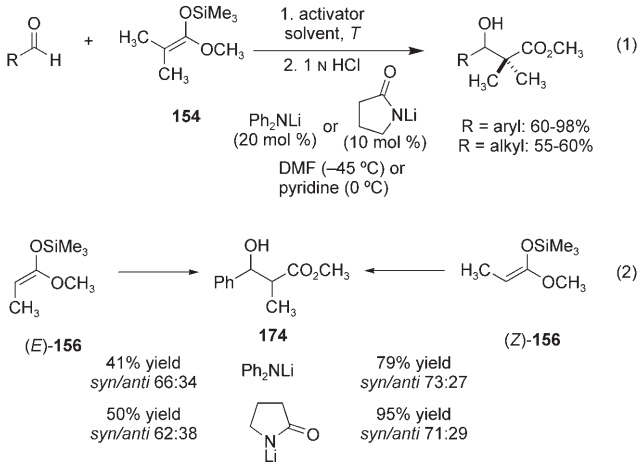



***Scheme 59.*** Calcium chloride catalyzed aldol addition of dimethylsilyl enol ethers.

In an extensive series of studies, Mukaiyama et al. have described the ability of both lithium diphenylamide (20 mol %) and lithium 2-pyrrolidinone (10 mol %) to promote the addition of TMS ketene acetals such as **154** to aldehydes [Eq. (1) in Scheme 60].[236] The reactions give high yields (most by NMR integration) in either DMF of pyridine. As a consequence of a strong solvent effect, the authors invoke a hexacoordinate adduct of the silyl ketene acetal bound to the anionic Lewis base and a solvent molecule, although this is most likely not the mechanism (see Section 6.1.1). The reactions of propanoate silyl ketene acetals (*E*)- and (*Z*)-**156** are diastereoconvergent and not selective, and therefore suggestive of an open transition structure [Eq. (2) in Scheme 60].

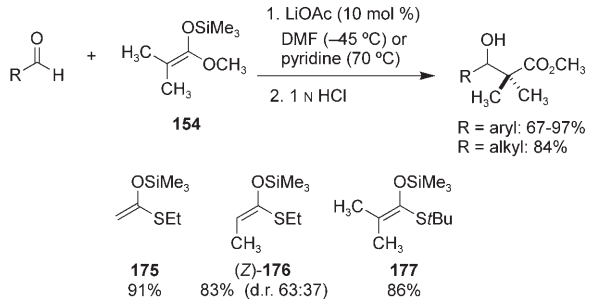
Mukaiyama and co-workers have also shown that alkali-metal carboxylates are effective catalysts for a similar range of enoxysilane nucleophiles and aldehyde electrophiles.[237] A broad survey of carboxylic acid, metal counterion, and solvent led to the finding that lithium acetate (10 mol %) in DMF, DMF/water (50:1), or pyridine serves most generally for this



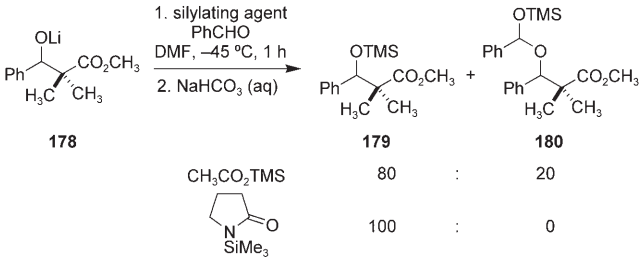

***Scheme 60.*** Amide-catalyzed aldol reactions of silyl ketene acetals.

transformation. Many aromatic and heteroaromatic aldehydes participate in high-yielding additions of silyl ketene acetals and ketene thio acetals (Scheme 61). Here again, the reactions of propanoate silyl ketene acetals are diastereoconvergent and not selective.



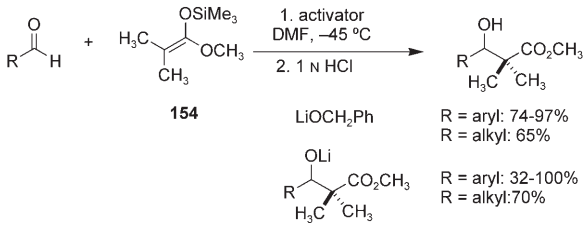

***Scheme 61.*** Lithium acetate catalyzed aldol reactions of silyl ketene acetals.

The authors suggest a similar mechanism as that for the amide-promoted reactions, with a minor modification to account for the formation of a small amount of a double adduct. In addition, they demonstrated that the intermediate aldolate (independently generated) can be silylated by both the TMS carboxylate and the *N*-TMS-2-pyrrolidinone, thus supporting (but not proving) the suggested catalyst turnover step (Scheme 62).




***Scheme 62.*** Demonstration of the turnover step for carboxylate- and amide-catalyzed aldol reactions.

Continuing this line of investigation, Mukaiyama and coworkers next evaluated the potential for alkali-metal alkoxides and phenoxides to promote the aldol additions shown previously.[238] Conjugate bases of nearly every alcohol investigated were effective at low loadings in DMF at −45 °C (Scheme 63). Lithium benzyloxide was selected and showed




***Scheme 63.*** Product-catalyzed aldol addition initiated by lithium benzyloxide.

good generality for aldehydes. Closer examination of this reaction reveals that it operates by the Lewis base initiated, product-catalyzed pathway discussed for fluoride-activated reactions (Section 6.1.1.1). This behavior is not surprising considering the greater basicity of alkoxides and the fact that the product aldolates themselves are alkoxides. Moreover, in contrast to silyl carboxylates and *N*-silyl-2-pyrrolidinone, TMS benzyloxide does not silylate the aldolate product, thereby precluding this as a catalyst turnover step.

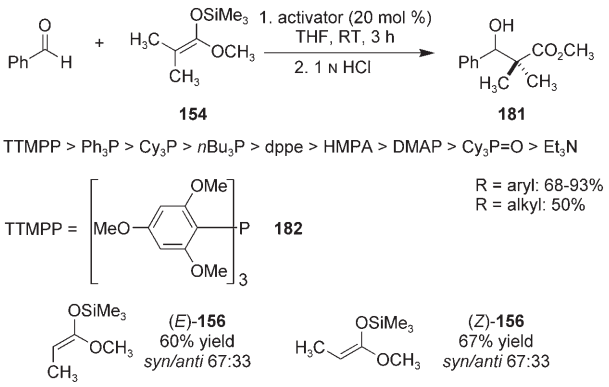
Tetraalkylammonium phenoxides have also served as activators to promote a *syn*-diastereoselective addition of propiophenone silyl enol ether and propanoate-derived thio ketene acetals. These reactions most certainly also proceed via open transition structures and the diastereoselectivity is likely an artifact of the specific enol silane structure.[239]

#### 6.1.2.1.2. Neutral Lewis Bases

The ability of neutral Lewis bases to interact with electrophilic trialkylsilyl species (triflates, perchlorates, halides) has been carefully studied by Bassindale and Stout in the context of the mechanism of nucleophilic substitution at a tetracoordinate silicon atom.[48] From the changes in the $^{29}$Si NMR chemical shifts and dissociation equilibrium constants, the following order of relative Lewis basicity was established: *N*-methylimidazole > DMAP > HMPA > dimethylimidazolone > *N*-methylpyridone > pyridine-*N*-oxide > triphenylphosphane oxide > DMPU > DMF > pyridine > triethylamine. Accordingly, it is not surprising that some of these and related Lewis bases have been tested for their ability to promote the aldol addition of enoxysilane species. Insofar as some of these species are (and have been used as) solvents for the addition reactions, they will be discussed as discrete additives first and then as bulk solvents second.

In 2000, Imamoto and co-workers surveyed a number of Lewis bases as promoters of the aldol addition of silyl ketene acetals (Scheme 64).[240] Among the Lewis bases surveyed (including phosphanes, phosphane oxides, and DMAP), the electron-rich triarylphosphane **182** affords the highest yields. The reaction with propanoate-derived silyl ketene acetals is




***Scheme 64.*** Phosphane-catalyzed aldol reactions of silyl ketene acetals. dppe = 1,2-bis(diphenylphosphanyl)ethane.

unselective, leading the authors to propose an open transition structure involving an enolate as the nucleophile.

A similar study with pyridine-*N*-oxide (10 mol% in conjunction with 20 mol% of lithium chloride) in DMF shows good catalytic activity for the addition to aromatic, olefinic, and aliphatic aldehydes (44–91% yield).[241a] Here as well, the addition of propanoate-derived silyl ketene acetals is not diastereoselective, again suggesting an open transition structure. Finally, as would be predicted from the Lewis basicity scale established by Bassindale and Stout,[48] *N*-methylimidazole shows excellent catalytic activity (again in the presence of 20 mol% of lithium chloride).[241b] Yields for the addition to a wide range of aldehydes are good (44–94%). Under microwave heating to 90°C, the TMS enol ether of acetophenone undergoes addition to a selection of aldehydes, although (as discussed below) the role of the solvent as a promoter at these temperatures cannot be ruled out.

The catalytic activity of DMF as a solvent[18] was first mentioned in a 1988 report from Kita et al. in which the addition of both acetate-derived and isobutyrate-derived silyl ketene acetals to isopropylidene glyceraldehydes was accomplished by heating in DMF at 70°C for 48 h.[242] These authors previously described a "noncatalyzed" Michael addition under similar conditions (Section 6.1.2.4.2) and were thus motivated to try the aldol addition. Subsequently, Hosomi and co-workers also investigated the "noncatalyzed" aldol addition of enoxydimethylsilanes in DMF at 50°C. These reactions give good yields for aromatic, olefinic, and aliphatic aldehydes (24–79%), however with no diastereoselectivity.[243] Interestingly, the C-bound nucleophile ethyl dimethylsilylacetate also underwent addition to aldehydes under these conditions (39–93% yield). It was surprising that the reactions were not diastereoselective given the expectation that the silicon atom would serve as an organizational center.

Finally, Génisson and Gornichon studied the effect of a number of dipolar aprotic solvents to effect the "noncatalyzed" aldol addition of silyl ketene acetals at room temperature.[244] They found that DMF, DMA, NMP, DMSO, sulfolane, and nitromethane all give aldolization products after 24 h, but that DMSO has the greatest ability to promote the reaction in the presence of 4-Å molecular sieves.[245] Only aromatic and olefinic aldehydes work well here, but again with no diastereoselectivity for propanoate-derived silyl ketene acetals.

The significance of all these experiments needs to be interpreted in the light of studies by Helmchen on the importance of solvent purities in reproducing the "catalytic effect" of the DMF in the Michael addition, and raises concerns regarding the role of the Lewis base in these reactions (Section 6.1.2.4.2).

#### 6.1.2.2. *Cyanomethylation with Trimethylsilylacetonitrile*

The addition of nitrile-stabilized anions to carbonyl compounds can afford both β-hydroxy- or unsaturated nitriles depending on the counterion and temperature.[246] In 1989, Palomo et al. found that under the influence of TBAF, trimethylsilylacetonitrile ($TMSCH_2CN$) could add smoothly to a variety of aldehydes.[247] Interestingly, these authors speculate that the reaction is fluoride ion initiated and product-catalyzed. The successful initiation of the reaction with potassium *tert*-butoxide supported their proposal.

Mukaiyama and co-workers have extended the use of Lewis base activation to the cyanomethylation of both aldehydes and imines, both in the presence of lithium acetate (10 mol%).[248] The addition to a range of aromatic, heteroaromatic, olefinic, and aliphatic aldehydes takes place in DMF at 0°C in good yields (42–98%). Substituted nitriles could also be employed, however, in these cases, cesium acetate (10 mol%) is required.

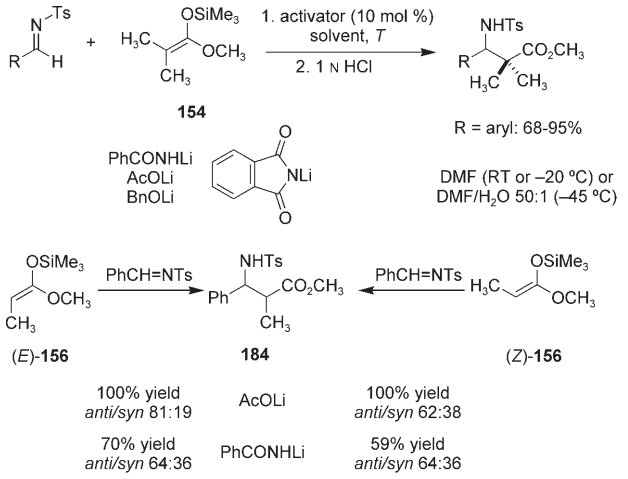
Shibasaki has also applied the $CuF/(EtO)_3SiF/Ph_3P$ system developed for catalytic aldol additions to the cyanomethylation of aldehydes and ketones with $TMSCH_2CN$, however this reaction will be discussed in the section on bifunctional catalysis (see Section 8.3).

#### 6.1.2.3. *Mannich Reaction*

Although the first illustration of a Lewis base activated Mannich reaction was described by Hosomi and co-workers as part of their investigation of enoxydimethylsilanes,[235] the majority of the work in this area comes from Mukaiyama and co-workers, who extended the evaluation of amides, carboxylates, and alkoxides as promoters for the addition of silyl ketene acetals and enol ethers to tosylaldimines (Scheme 65).[249] The additions are limited to aromatic aldimines, but still give excellent yields in DMF or DMF/water (50:1). As was found for the aldol additions, the Mannich reactions are also not diastereoselective with propanoate-derived silyl ketene acetals such as **156**, although a highly *anti*-selective addition was developed for other nucleophiles (see Section 8.5). The authors draw the same mechanisms as for the aldol addition, but change the nature of the intermediate, depending upon the Lewis base activator. Moreover, the reaction promoted by lithium benzyloxide was shown to be product-catalyzed.[249b] When *N*-phenylaldimines are employed under catalysis with lithium acetate, the immediate adduct cyclizes to a β-lactam in very good yield.[249c]

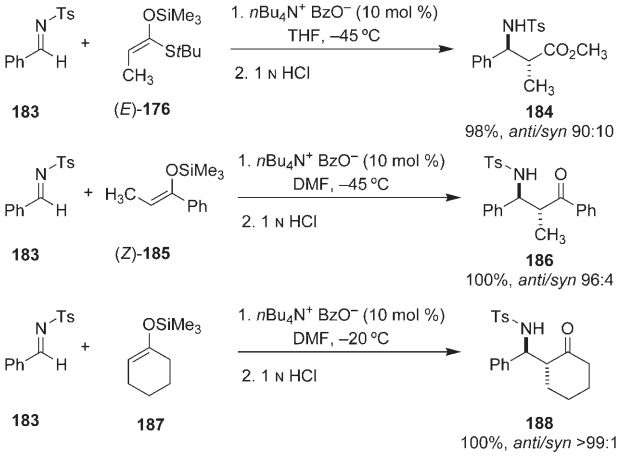
Interestingly, the use of silyl enol ethers and ketene thio acetals under catalysis with tetraalkylammonium carboxy-



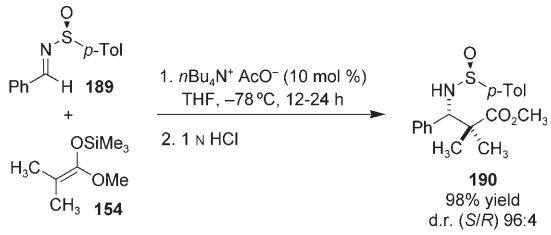

***Scheme 65.*** Amide- and carboxylate-catalyzed Mannich reactions.

lates affords Mannich addition products such as **184**, **186**, and **188** with extremely high *anti* diastereoselectivity (Scheme 66).[249d] However, this outcome is likely the result of a highly biased, open transition structure as the *anti* selectivity is stereoconvergent. This process has also been modified to produce β-lactams with high *trans* selectivity.[249e]




***Scheme 66.*** Tetraalkylammonium benzoate catalyzed *anti*-selective Mannich reactions.

*p*-Tolylsufinimines are useful substrates for highly selective additions of myriad nucleophiles to prepare enantiomerically enriched amines.[250] Mukaiyama and co-workers have taken advantage of the strong diastereoface-directing effect of the sulfur group to produce β-sulfinamido esters with high diastereoselectivity with tetrabutylammonium acetate as the catalyst (Scheme 67).[249f]




***Scheme 67.*** Diastereoselective Mannich reaction of *p*-tolylsufinimines.

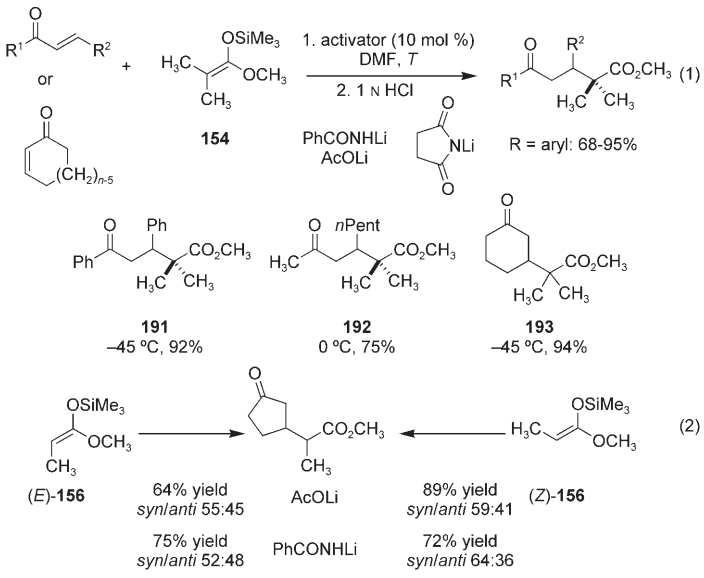
### 6.1.2.4. Michael Addition

#### 6.1.2.4.1. Anionic Lewis Bases

The ability to build rings, set multiple stereocenters, and engage a wide range of substrates has elevated the Michael addition to one of the most synthetically useful carbon–carbon bond-forming reactions.[251] The Michael addition can be performed using both preformed enolates and masked enolates, under catalysis by Brønsted acids and bases as well as Lewis acids. Curiously, the use of Lewis bases has been the slowest to emerge.[252]

The first report employed the reaction of the TMS enol ether of acetophenone under typical phase-transfer conditions (50% $NaOH/CH_2Cl_2/nBu_4N^+Br^-$) to afford a 77% yield of the Michael addition product.[253] Of perhaps greater synthetic utility is the use of $nBu_4N^+(PhCO_2)_2H^-$ for the addition of silyl ketene acetals to cyclic and acyclic enones. Sivaram and co-workers capitalized on the use of these unusual catalysts that were extensively developed in the context of group-transfer polymerization.[254] The catalyst provides high yields (87–95%) at room temperature and only 0.1 mol% loading.

Mukaiyama and co-workers have applied the now-familiar amides, carboxylates, and alkoxides to the Michael addition of silyl ketene acetals and silyl enol ethers to cyclic and acyclic ketones [Eq. (1) in Scheme 68].[255] Yields are generally good except with β-disubstituted acceptors. As in all previous cases, the reactions show poor and convergent diastereoselectivity [Eq. (2) in Scheme 68]. In what must be a product-catalyzed reaction promoted by lithium benzyloxide,

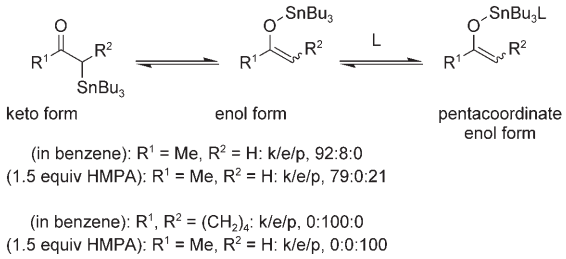



***Scheme 68.*** Amide- and carboxylate-catalyzed Michael additions.

*syn* diastereoselectivity could be achieved for the silyl enol ethers of propiophenone.[255b,256]

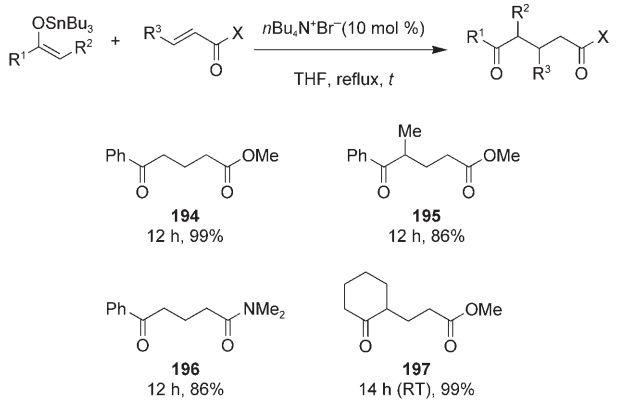
A mechanistically distinct and intriguing process involving the activation of enoxytributylstannanes has been developed and carefully investigated by Baba and co-workers (Scheme 69).[257] From earlier NMR investigations on the nature of the interaction of both anionic ($n$Bu$_4$N$^+$Br$^-$) and neutral (HMPA) Lewis bases with tin enolates, Baba and co-workers determined that pentacoordinate species are formed and that they express an enhanced nucleophilicity toward various electrophiles.[257c] The data show a clear shift in the equilibrium composition of the stannane in the presence of HMPA toward the pentacoordinate species. A more systematic study shows the change in the equilibrium population (as reflected in the change in $^{119}$Sn NMR chemical shift and $^1J_{C,Sn}$ coupling constant) for both HMPA and $n$Bu$_4$N$^+$Br$^-$.[257d]




***Scheme 69.*** Equilibrium composition of tin enolates.

The enhanced nucleophilicity of the tin enolate in the presence of either HMPA or $n$Bu$_4$N$^+$Br$^-$ is manifest in the ability to effect Michael additions to unsaturated ketones, esters, and amides to form 1,5-dicarbonyl compounds such as **194–197** (Scheme 70).[257a] For example, no reaction takes place between the tin enolate of acetophenone and methyl acrylate in refluxing THF for 12 h. However, in the presence of 10 mol % $n$Bu$_4$N$^+$Br$^-$, the adduct is isolated in 64 % yield after 12 h at room temperature. The reaction proceeds well for unsubstituted acrylates, β-substituted ketones, and nitroalkenes.[257b]

Ab initio calculations aided in the understanding of the accelerating effect of $n$Bu$_4$N$^+$Br$^-$ and also of the ability of the

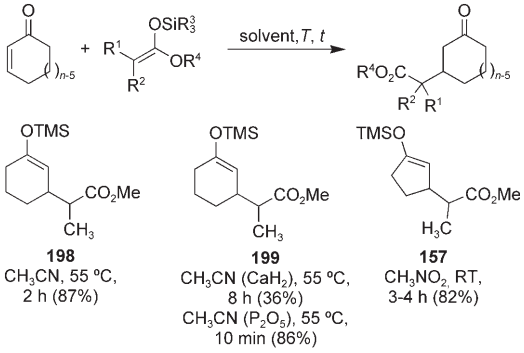



***Scheme 70.*** Tetrabutylammonium bromide catalyzed Michael addition of tin enolates.

salt to act as a catalyst.[257] A comparison of the ground-state structures of the free tin enolate and the pentacoordinate bromide adduct show: 1) the HOMO energy is raised 3.3 eV, 2) the Sn–O bond is lengthened by 0.167 Å, and 3) the activation energy for the addition is lowered by 7 kcal mol$^{-1}$. Most importantly, however, the immediate Michael addition product, which is also a stannyl ketene acetal, is unstable to isomerization to the α-stannyl ketone (by 5.3 kcal mol$^{-1}$), which had no affinity for the bromide ion and thus effects catalyst turnover. These characteristics will be revisited in the analysis of an alkylation of the tin enolate in Section 6.1.2.5.

#### 6.1.2.4.2. Neutral Lewis Bases

Apart from the acceleration of the Michael addition of tin enolates by HMPA noted above, there are several reports of "uncatalyzed" Michael additions of silyl ketene acetals in highly dipolar aprotic solvents. In 1982, Tamura and co-workers reported the ability to effect the Michael addition of silyl ketene acetals to cyclic enones to form silyl enol ethers such as **198**, **199**, and **157** by heating in acetonitrile at 55 °C for 2 h (Scheme 71).[258] Shortly thereafter, RajanBabu reported that similar additions proceeded even at room temperature in nitromethane.[220] In this study, a crossover experiment revealed full scrambling of the silyl substituents as part of the addition reaction.




***Scheme 71.*** Purported "uncatalyzed" Michael additions of silyl ketene acetals.

Although these results are intriguing, they have been called into question by Helmchen and co-workers, who reported that the original conditions described by Tamura and co-workers did not reproducibly lead to the adducts.[258b] Helmchen and co-workers discovered that the method used for the purification of the acetonitrile solvent was crucial. In acetonitrile distilled from calcium hydride, the reaction was extremely sluggish, whereas the addition reaction in acetonitrile distilled from phosphorus pentoxide was even faster than that reported by the research group of Tamura. Helmchen and co-workers also showed that the reactivity in acetonitrile distilled over calcium hydride could be restored by adding small amounts of phosphorus pentoxide to the reaction mixture. It should be noted that RajanBabu describes purifying the solvents used in his study by distillation from phosphorus pentoxide! Thus, unless further clarification is

forthcoming, reports of solvent-assisted or uncatalyzed Michael, aldol, and other reactions such as those from the Kita,[242] Hosomi[243] and Génisson[244] research groups should be viewed with caution.

#### 6.1.2.5. Alkylation of Enolates

As part of their extensive and thorough investigations on the nucleophilic activation of organotin compounds, the Shibata/Baba research groups discovered a striking dependence of the chemical reactivity of tin(IV) enolates on the additive. The uncatalyzed aldol addition and alkylation of tin(IV) enolates had been described and used in various synthetic endeavors.[259] However, in studying the reaction of tin(IV) enolates with α-bromo ketones, Baba and co-workers discovered that the chemical selectivity of the addition could be altered by changing the reaction conditions. For example, the thermal reaction of tin(IV) enolate **200** with bromoacetophenone affords exclusively the epoxy ketone **202** (Darzens reaction), whereas in the presence of 1.5 equivalents of HMPA (or triphenylphosphine oxide), the 1,4-diketone **203** (alkylation reaction) is the predominant product isolated [Eq. (1) in Scheme 72].[257c–e] A later competition experiment between the stannyl enol ether **204** and either an allylic bromide or a ketone showed the dramatic effect of added $n$Bu$_4$N$^+$Br$^-$ on the chemoselectivity [Eq. (2) in Scheme 72].

Preparatively, the alkylations only work well for activated halides (allyl halides, halo ketones, halo imines). On the basis of their previous spectroscopic studies (Scheme 69) that revealed a strong variation in the enolate structure in the presence of both HMPA and $n$Bu$_4$N$^+$Br$^-$, the authors suggested that the aldol addition requires vacant coordination sites on the tin center that are occupied in the presence of added ligands, thus disfavoring that pathway.[260]

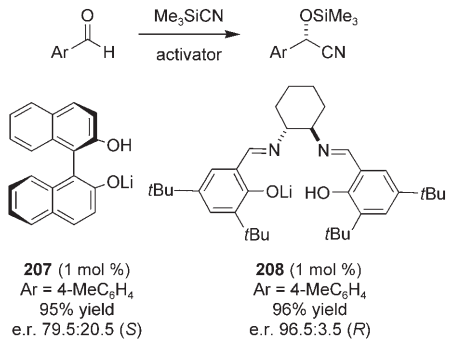
#### 6.1.2.6. Silylcyanation with Trimethylsilyl Cyanide (TMSCN)[261]

##### 6.1.2.6.1. Anionic Lewis Bases

Already in 1973, the Evans and Truesdale research groups described the potential for catalysis of the silylcyanation of ketones with TMSCN and cyanide ions.[262] Remarkably, this report lay dormant for decades before other anionic activators were investigated for this transformation.

For example, only in 2001 did Senanayake and co-workers report the potential of various lithiated heteroatom nucleophiles (LiOMe, LiO$n$Bu, LiNEt$_2$, LiPPh$_2$, LiSPh) for the catalytic, diastereoselective silylcyanation (with both TMSCN and TBSCN) of bicyclic ketones such as camphor, fenchone, and nopinone.[263] Although the catalytic efficiencies vary (4–24 h to completion), the similarity of the diastereoselectivities for a given ketone suggest that these catalysts are simply generating a common reactive species, which the authors propose is the hypercoordinate Me$_3$Si(CN)$_2^-$ ion.

Kagan and co-workers have extended the use of chiral anionic nucleophiles (previously employed for enantioselective reduction) for the enantioselective catalysis of silylcyanation.[264] Monolithiated (*S*)-binolate **207** catalyzes the formation of silyl cyanohydrins of aromatic aldehydes with only modest selectivity (e.r. < 79.5:20.5), whereas the monolithiated (*R*,*R*)-salen **208** generally affords higher, albeit rather variable, selectivities with aromatic aldehydes (Scheme 73). The dilithio derivatives are efficient catalysts, but are much less enantioselective.

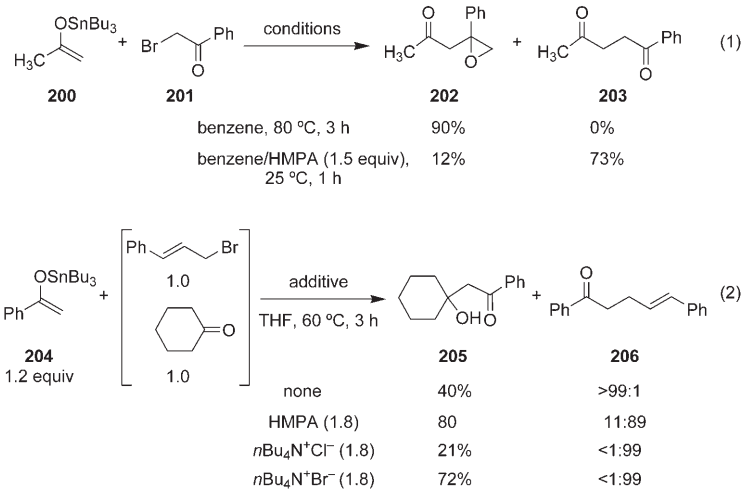



***Scheme 73.*** Chiral alkoxide catalyzed silylcyanation.

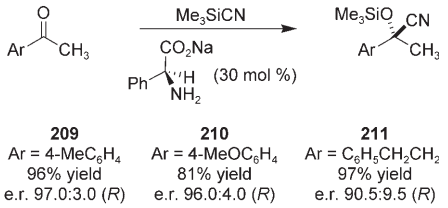
The enantioselective silylcyanation of ketones has been accomplished by the use of α-amino acid salts.[265] Although many α-amino acid salts are effective catalysts, sodium phenylglycinate is the most enantioselective (Scheme 74). Despite the high catalyst loading (30 mol%), the yields and selectivities for a number of aryl methyl ketones are high. Given the simplicity and ready availability of the catalyst, this method should find application in synthesis.

##### 6.1.2.6.2. Neutral Lewis Bases

The report of catalysis of a silylcyanation reaction with a phosphane by Evans and Wong in 1977 did not stimulate additional development for many years.[262b] However, in 1991, Mukaiyama and co-workers re-investigated this reaction, and examined the use of amines and phosphanes as catalysts (Scheme 75).[266,267] With a stannylated cinchonine catalyst **214**, good yields and enantioselectivities are obtained, albeit with a rather high loading of the

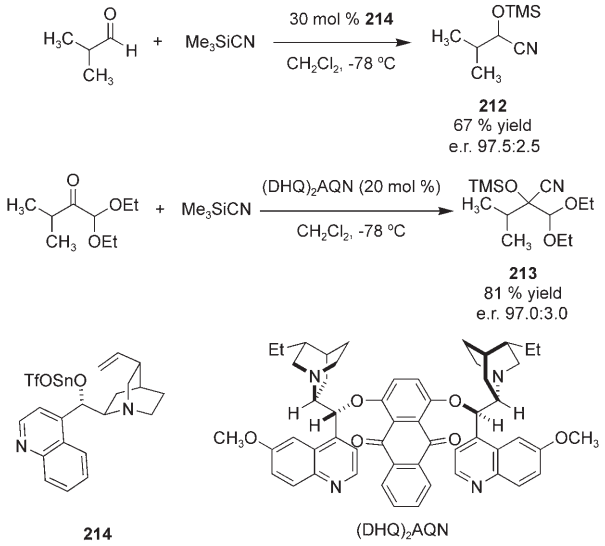



***Scheme 72.*** The effect of additives in the alkylation of tin(IV) enolates.




***Scheme 74.*** Silylcyanation of ketones catalyzed by sodium L-phenylglycinate.

catalyst (30 mol %).[266b] More recently, Deng and co-workers have employed Sharpless's dimeric cinchona alkaloids to effect a highly selective cyanosilylation.[268] However, the method is currently limited to the use of α,α-dialkoxy ketones. The mechanism of the reaction has yet to be clarified, but the intermediacy of either a hypervalent silicate or an ionized silyl cation–cyanide anion ion pair can be proposed.

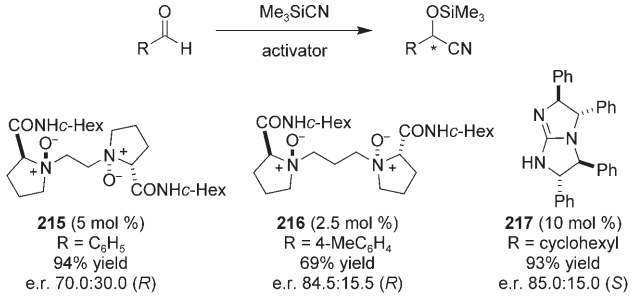



***Scheme 75.*** Cinchona alkaloid catalyzed asymmetric silylcyanations.

Among the most extensively investigated activators of silylcyanation in recent years are the phosphine oxides and amine *N*-oxides. These species have been employed as additives with chiral Lewis acidic complexes and have been incorporated into chiral ligands for binding to Lewis acids. These latter strategies fall under the aegis of multidentate "bifunctional catalysis" and are discussed separately in Section 7. However, amine *N*-oxides have been used by themselves as nucleophilic catalysts for silylcyanation.[269] Feng and co-workers developed a series of tethered, dimeric bis(proline amide *N*-oxide)s for this purpose (Scheme 76). The most selective catalysts **215** and **216** are connected by a trimethylene tether and bear cyclohexyamide units. Under optimized conditions, the yields are good, but the selectivities are modest for a series of aromatic aldehydes.

Other highly nucleophilic Lewis bases such as Verkade's phosphatrane[270] and N-heterocyclic carbenes[271] have been assayed for their ability to promote silylcyanation, thus far only with achiral catalysts.[272] Imidazol-2-ylidene derivatives bearing bulky substituents on the nitrogen atoms (*tert*-butyl, mesityl, adamantyl) are highly effective catalysts, less than 1 mol % is needed to convert both aldehydes and ketones rapidly into the TMS-cyanohydrins at room temperature.[273]

The high Brønsted basicity of guanidines makes them useful catalysts for a number of reactions, including asymmetric Strecker reactions.[274] Among a number of chirally modified guanidine derivatives, **217** displays the highest, albeit modest, selectivity for the silylcyanation of aliphatic aldehydes (Scheme 76).[274b]




***Scheme 76.*** Silylcyanation catalyzed by chiral amine *N*-oxides and guanidine **217**.

In 2006, our research group reported a direct kinetic comparison of the effectiveness of a variety of Lewis basic catalysts for the silylcyanation of four different classes of aldehydes in a number of different solvents.[275] Of all the Lewis bases surveyed, the following trend is seen: $n$Bu$_3$P > DMAP > Et$_3$N > NMI > HMPA (DMF, DMSO, pyridine-*N*-oxide, Ph$_3$P=O, tetramethylurea were much less effective). Among the phosphorus derivates, the order of reactivity is $n$Bu$_3$P ≈ HMPT > Ph$_3$P ≈ (MeO)$_3$P. With Et$_3$N as the catalyst, the reactions were fastest in acetonitrile by a wide margin over dichloromethane and other solvents. Chiral amines and phosphorus derivatives gave only poor enantioselectivity. The reaction shows first order behavior in the aldehyde and Et$_3$N, and zeroth order in TMSCN, which is consistent with two limiting mechanistic scenarios (Figure 7). Catalytic cycle A involves the activation of the aldehyde by a hypervalent complex of the Lewis base and TMSCN. The observation of a zeroth order dependence on TMSCN means that species **LIV** is formed irreversibly or that the Lewis base catalyst is saturated. In this cycle, binding of the aldehyde must be

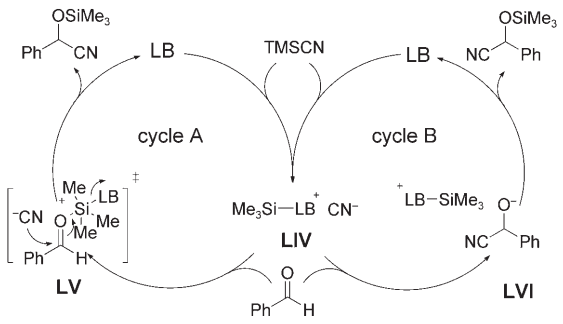



***Figure 7.*** Catalytic cycles for silylcyanation.

turnover-limiting to see first order dependence in both the aldehyde and Lewis base. In catalytic cycle B, the ion pair **LIV** serves as a cyanide source and must be formed under the same circumstances as in catalytic cycle A. However, in this cycle, the addition of the cyanide ion must be turnover-limiting to observe first order behavior in the aldehyde. Although the kinetic analysis of other Lewis base catalyzed silylcyanations has not been reported, catalytic cycle A seems much more likely given the proximity of the substrate to the chiral activator.

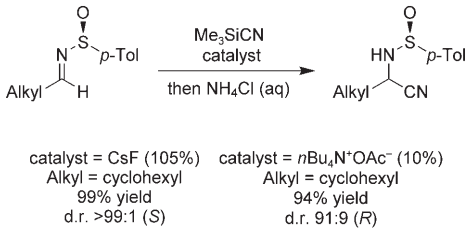
Clearly the nature of the adduct between the Lewis base and TMSCN will be very dependent on the structure of the Lewis base and the solvent. The operation of two pathways might explain the variable enantioselectivity observed in these reactions with small changes in the nucleophile structure or solvent.

#### 6.1.2.7. Strecker Reaction with TMSCN

The hydrocyanation of imines is one of the oldest carbon–carbon bond-forming reactions (Strecker amino nitrile synthesis).[276] Remarkably, despite its importance as a method for the synthesis of α-amino acids, the first example of a catalytic enantioselective Strecker reaction was not reported until 1996.[277] Since then, however, an extraordinary effort has been expended for the development of various catalytic methods, most of them employing chiral Brønsted bases, Lewis acids, or metal complexes. Aside from these traditional catalytic systems, there are a few reports of Lewis base catalysis of the Strecker reaction, one using a chiral *N*-oxide,[278] the others using achiral Lewis bases and a chirally modified sulfinylimine.[279] In the former case, (*R*) 3,3′-dimethyl-2,2′-biquinoline *N*,*N*′-dioxide is used in stoichiometric quantities to promote the addition of TMSCN to *N*-benzhydrylimines of aromatic aldehydes. Even with this loading of catalyst, the reactions required 1–4 days. The yields ranged from 67–96% and selectivities were in general good (e.r. 75.0–97.5:25.0–2.5).[278]

Hou and co-workers employed CsF to promote the addition of TMSCN to enolizable, aliphatic sulfinamines (aromatic sulfinamines fragment to 4-TolSCN).[279a] The yields are excellent and diastereoselectivities generally high, although the scope is still rather limited at this time (Scheme 77). In this case the induced selectivity is $S_S \rightarrow S_C$.

Interestingly, Mukaiyama and co-workers described the use of alkali-metal and tetraalkylammonium carboxylate salts to effect the same transformation on similar substrates and with similar selectivities, however with the opposite sense of induction ($S_S \rightarrow R_C$).[279c] No explanation is provided by the authors, but the outcome is reminiscent of the divergent, counterion-dependent behavior of the fluoride activation of silyl enol ethers observed by Chuit and Corriu (see Section 6.1.1.1.[210]




***Scheme 77.*** Diastereoselective silylcyanation of *p*-tolylsufinimines.

#### 6.1.2.8. Trifluoromethylation with $TMSCF_3$

##### 6.1.2.8.1. Anionic Lewis Bases

Following their development of anionic Lewis base activators for aldol, Michael, and Mannich reactions (Section 5.2), Mukaiyama and co-workers have applied alkali-metal and tetraalkylammonium carboxylates for the trifluoromethylation of aldehydes and ketones in high yield and good substrate scope.[280] Diastereoselective trifluoromethylation of chirally modified phenyl glyoxylates with lithium phenoxide afforded good selectivities (90:10) for the generation of Mosher acid analogues.[280b] Moreover, as was already described in the silylcyanation of *p*-tolylsulfinamines, these same carboxylate salts effect nucleophilic trifluoromethylation with $TMSCF_3$ in excellent yields and diastereoselectivities. The sense of asymmetric induction is the same as was observed with TMSCN.[280c,d]

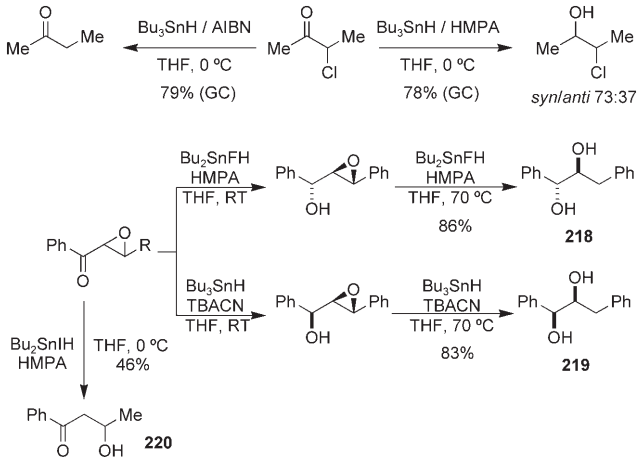
##### 6.1.2.8.2. Neutral Lewis Bases

Neutral Lewis bases are also effective in promoting the trifluoromethylation of carbonyl compounds. The effectiveness of a series of pnictogen-centered Lewis bases was surveyed in DMF with $TMSCF_3$ and benzaldehyde.[281] A rough trend emerged as follows: amines > phosphanes > arsines ≈ stibines. Within the amine class the order: TMEDA > $Et_3N \approx nBu_2NH$ > pyridine was found. With triethylamine (20 mol%), a selection of aromatic and aliphatic aldehydes and ketones underwent trifluoromethylation in modest yield. Attempts to effect catalytic enantioselective trifluoromethylation with chiral amines (alkaloids, amino acids) and chiral phosphanes were largely unsuccessful (e.r. < 55:45).

Prakash et al. described a survey of amine *N*-oxides for nucleophilic activation of $TMSCF_3$ and found that trimethylamine *N*-oxide could be used albeit in 50 mol% loading with aromatic, olefinic, and aliphatic aldehydes.[282] More recently, Song et al. reported that 1,3-diadamantylimidazol-2-ylidene is a highly effective catalyst (0.5–1.0 mol%) for the addition of $TMSCF_3$ to a wide range of aldehydes and ketones at room temperature in very good yield.[282b]

#### 6.1.2.9. Reduction of Carbonyl Compounds with Tin Hydrides

The Baba and Shibata research groups have extensively explored the modulation of the reducing properties of various tin(IV) hydrides by the addition of Lewis bases (as stoichiometric agents), including halides, HMPA, tripiperidinophosphoric amide (TPPA), and some phosphane oxides.[232] Three different types of reagents have been developed (Scheme 78). The first, $nBu_3SnH$/TBAF (or TBACl or TBACN), which works well for the chemo- and diastereoselective reduction of ketones, has already been discussed in Section 6.1.1.5.[233a] The second, $nBu_3SnH$/HMPA (or TPPA), is suitable for the




***Scheme 78.*** Chemical selectivities and stereoselectivities in reductions with tin(IV) hydrides and HMPA. AIBN = azoisobutyronitrile.

reduction of aldehydes, and also for the chemoselective reduction of α-halo aldehydes and ketones (at the carbonyl group).[283a,b] The third, $n$Bu$_2$SnXH/HMPA (where X = F, Cl, I), is useful for various reductions depending upon the identity of the X atom. For example, $n$Bu$_2$SnFH/HMPA is useful for the diastereoselective reduction of epoxy ketones to give *anti*-epoxy alcohol products,[283c] whereas $n$Bu$_2$SnIH/HMPA is useful for the reductive opening of epoxides and epoxy ketones to give β-hydroxy ketones such as **220**.[233c] On the other hand, Bu$_2$SnClH/HMPA is useful for the reduction of imines[283d] and the reductive amination of ketones and aldehydes.[283e]

Spectroscopic studies show that Lewis bases interact differently with all of these tin(IV) hydrides. No change in the $^{119}$Sn NMR chemical shift is seen for $n$Bu$_3$SnH or $n$Bu$_2$SnH$_2$ in the presence of HMPA. On the other hand, mixing $n$Bu$_3$SnH and TBAF led to a disappearance of the signal for $n$Bu$_3$SnH ($\delta = -90.3$ ppm) and the appearance of signals for ($n$Bu$_3$Sn)$_2$ and $n$Bu$_3$SnF$_2^-$, no evidence for the adduct $n$Bu$_3$SnHF$^-$ could be obtained. However, the association of $n$Bu$_2$SnFH and $n$Bu$_2$SnIH with HMPA are evident in the $^{119}$Sn NMR, $^{19}$F NMR, and IR spectra.[233c] The authors speculate that the Lewis bases play a role in enhancing the reducing ability of the hydrides in the complexes and altering the normal radical-based reduction pathways associated with this class of agents.

#### 6.1.2.10. *[2,3] Wittig Rearrangement*

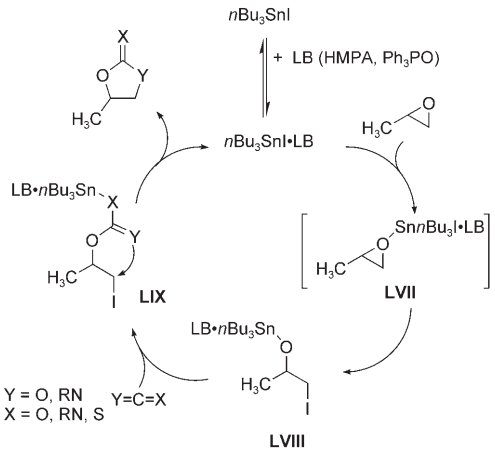
Enol derivates of α-allyloxy carbonyl compounds are known to undergo two competitive sigmatropic rearrangements; [3,3] Claisen and [2,3] Wittig rearrangements. Whereas silyl enol derivates undergo the (thermal) [3,3] rearrangement, metalloenolates undergo the (anionic) [2,3] rearrangement.[284] Mukaiyama and co-workers have shown that in the presence of lithio amides, ammonium carboxylates, or lithio alkoxides, the [2,3] rearrangement pathway predominates.[285] Thus far, the substrate scope is limited to 2-allyloxy-1-tetralones and allyloxy acetates.

### 6.1.3. *Ligand-Accelerated Catalysis with Trialkyltin(IV) Halides*

Although this form of Lewis base catalysis was intentionally excluded from coverage in this Review, there is one example that merits an exception because it represents a unique case of ligand-accelerated catalysis with main-group species.

The ability of main-group halides to open epoxides is one of their most defining characteristics,[286] and Lewis base catalyzed, enantioselective processes have been developed (Section 6.4). However, an intriguing process which is catalytic in both the metal halide and the Lewis base has been developed by the Nomura, Baba, and Shibata research groups.[287]

The insertion of carbon dioxide and isocyanides into oxiranes is a very well known process and is susceptible to catalysis by a number of different methods.[288] In an early study, Ratzenhofer and Kisch reported the accelerating effect of Lewis bases (Ph$_3$P and Et$_3$N) in combination with relatively hard Lewis acids (for example, AlCl$_3$, TiCl$_4$, and MoCl$_5$) to effect the insertion of carbon dioxide into propylene oxide at room temperature and pressure.[289] Following the lead from this study, Nomura et al. showed the high catalytic effect of many main-group Lewis acids (Ph$_3$SnX, Ph$_3$GeX, Ph$_3$SbBr$_2$, MeTeX$_2$) in combination with Et$_3$N, pyridine, and Ph$_3$P for the formation of cyclic carbonates.[287a,b] After considerable optimization, they settled on the combination of $n$Bu$_3$SnI and HMPA or triphenylphosphine oxide for the insertion of isocyanates, isothiocyanates, and carbodiimides into propylene oxide. These authors suggest a catalytic cycle on the basis of several lines of evidence (Scheme 79). The initial interaction between the Lewis base and the tin(IV) halide leads to an activation of the halide. From the Gutmann analysis or hypervalency analysis (Section 3.1.2), the polarization of $n$Bu$_3$SnI should simultaneously enhance the electrophilicity of the tin(IV) center and the nucleophilicity of the iodide ion: exactly what is needed to accelerate the epoxide opening. The insertion of a Sn–O bond into the heterocumulene is well documented and constitutes the next step.[290] The nucleophilicity of the tin carboxylate, carbamate, or isourea **LIX** is enhanced by coordination of the Lewis base and therefore can




***Scheme 79.*** Catalytic cycle for the insertion of heterocumulenes into epoxides.

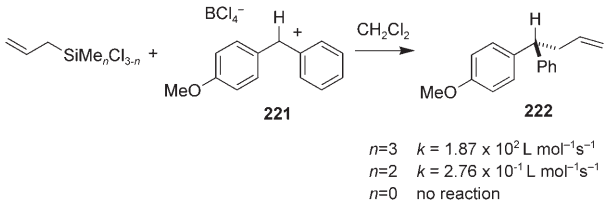
suffer internal displacement of the iodide, thereby forming the cyclic product and thus regenerating the $n$Bu$_3$SnI.

### 6.2. Electrophilic and Dual Activation through n–σ* Interactions: Polyhalosilanes

#### 6.2.1. Initial Studies

Whereas the preceding section focused on the chemistry of alkylsilanes, another class of organosilicon species that have demonstrated the potential for Lewis base catalysis through the n–σ* interaction are polyhalosilanes. The incorporation of electronegative substituents leads to a dramatic change in the chemistry of the silicon species. The use of strong, neutral Lewis bases in conjunction with these electrophilic silanes provides a preparatively useful and mechanistically novel alternative for the catalytic, asymmetric modification of the silicon reagents. Strong Lewis bases such as DMF and HMPA are capable of generating neutral hypervalent silanes that possess enhanced nucleophilicity at the peripheral groups (a consequence of the changes in the electron distribution caused by the formation of hypervalent bonds) and thus provide opportunities for the development of new reactions.

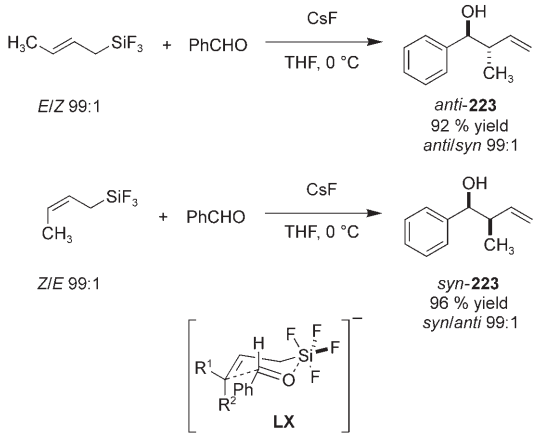
In the mid-1980s there was a growing interest in polyhalosilanes. The substitution of halogen atoms for alkyl and aryl substituents in allylic silanes renders these species much less nucleophilic. The dramatic effect of halogen substitution on the reaction rate was quantified by Mayr and et al. as part of their ongoing studies of π nucleophilicity (Scheme 80).[291] In the reaction of allylic silanes with diarylcarbenium ions such as **221**, replacement of a single methyl group by chloride renders allylchlorodimethylsilane 1000 times less nucleophilic than allyltrimethylsilane. Allyltrichlorosilane is so unreactive that its nucleophilicity could not be measured accurately by using this technique.




***Scheme 80.*** Nucleophilicity of allylic silanes on the Mayr scale.

From the kinetic analysis of the reactions of polyhalosilanes with diarylcarbenium ions, it is expected that they would be poor substrates for any allylation reaction. However, these reagents are not simple π nucleophiles like the related trialkylsilanes. Lewis base activation of these highly electrophilic silanes can lead to both enhanced nucleophilicity of the allyl fragment as well as enhanced electrophilicity at the silicon atom. Binding of the aldehyde to the electron-deficient silicon atom now transmits the decreased electron density at the silicon atom to the bound carbonyl group. Therefore, reaction through a closed transition structure provides a potent form of dual activation for both substrates. The enhanced reactivity of these bimolecular, hypervalent intermediates is in line with Gutmann's conclusions about the polarization of the peripheral bonds in a Lewis acidic acceptor upon formation of an adduct with a Lewis base (see Section 3.1.2.1).

Allyltrifluorosilane, which should be completely unreactive towards aldehydes in light of the analysis by Mayr et al., provides a dramatic illustration of the power of Lewis base activation (Scheme 81). Sakurai and co-workers have shown




***Scheme 81.*** Fluoride ion catalyzed allylations with fluorosilanes.

that, in the presence of cesium fluoride, a rapid reaction between allyltrifluorosilane and a wide range of aromatic, olefinic, and aliphatic aldehydes takes place.[292] In addition to the reactivity differences associated with dual activation, the stereochemical outcomes of two processes involving open and closed transition structures are different. The strict correlation of the silane geometry with the product configuration (diastereodivergent, $E \rightarrow anti$, $Z \rightarrow syn$) indicates that the reaction proceeds through a cyclic, chairlike transition structure (**LX**) organized around a hypervalent silicon atom. This stands in contrast to the *syn* stereoconvergence seen in the fluoride activation of allylic trialkylsilanes (see Section 6.1.1.1).

Computational studies on the electronic structure of a series of fluorosilanes and silicates provide a quantitative picture of how fluoride activation can enhance both the nucleophilic and electrophilic character in allyltrifluorosilane (Figure 8).[293] Whereas the degree of induced polarization, evidenced by increased electron density at C$_\gamma$ ($q$(C$_\gamma$)) and decreased electron density at the silicon atom ($q$(Si)), is small in changing from the tetracoordinate ground state to the

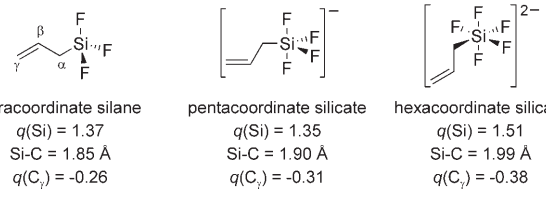
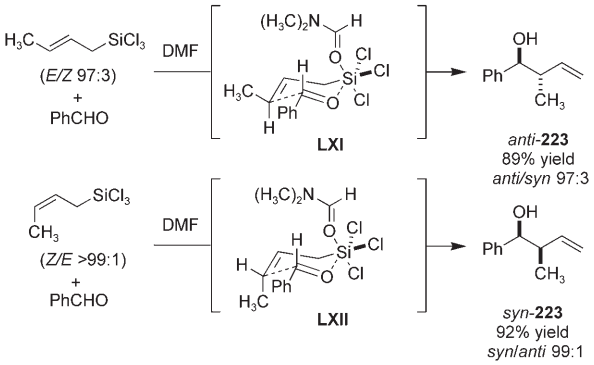



***Figure 8.*** Charge distribution in hypervalent fluorosilanes and silicates.

pentacoordinate intermediate ($\Delta q(C_\gamma) = -0.05$, $\Delta q(Si) = -0.02$), the change upon binding of a second fluoride ion is dramatic ($\Delta q(C_\gamma)) = -0.07$, $\Delta q(Si) = +0.14$). Although an allylpentafluorosilicate is probably not the active species in these reactions, it can be imagined that the binding of the aldehyde to the pentacoordinate silicate to a form a hexacoordinate, aldehyde-substituted tetrafluorosilicate may have a similar effect on the redistribution of electron density in the adduct and lead to a similar dual activation of both the aldehyde and allyl fragments of the complex.

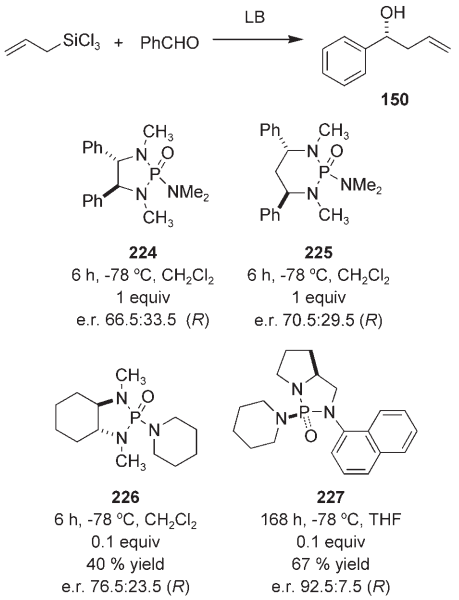
Kobayashi and Nishio provided an important preparative advance by demonstrating that highly Lewis basic solvents such as *N*,*N*-dimethylformamide (DMF) could promote the allylation of aromatic, olefinic and aliphatic aldehydes with allyltrichlorosilane in a manner analogous to the activation by fluoride ions (Scheme 82).[294] The diastereodivergent behavior observed in the addition of 2-butenylsilanes is consistent with the intermediacy of cyclic, chairlike transition structures **LXI** and **LXII**. Organization of the allylic fragment and the aldehyde around a formamide-bound, hypervalent silane finds support from the observation of the hexacoordinate silicon species $(DMF)_2SiCl_3(CH_2CH{=}CH_2)$ at $\delta = -170$ ppm in the $^{29}$Si NMR spectrum upon mixing allyltrichlorosilane and DMF. This signal falls squarely in the chemical shift range established for other, known hexacoordinate silicates.[295]




***Scheme 82.*** Lewis base promotion of allylations with allyltrichlorosilane.

### 6.2.2. *Lewis Base Catalyzed Allylation with Polyhalosilanes: Chiral Lewis Bases*

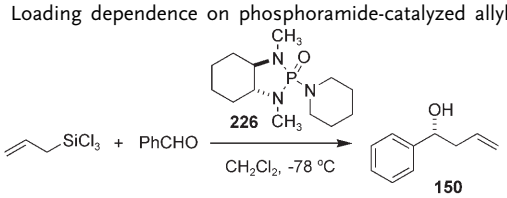
Although these allylation reactions are promoted by Lewis bases and represent important conceptual advances in the development of the field, the first neutral Lewis base catalyzed allylation did not appear until 1994. Our research group reported that the addition of a substoichiometric amount of a Lewis base catalyzed the allylation of aromatic and olefinic aldehydes with allyltrichlorosilane in the nonpolar solvent dichloromethane (Scheme 83).[296] Aliphatic aldehydes proved unreactive, despite their higher reactivity than conjugated aldehydes in other carbonyl addition processes.[217] An initial survey of Lewis bases (for example, DMF, DMSO, pyridine *N*-oxide) revealed that HMPA was the most effective promoter. In fact, no reaction was observed in the absence of a Lewis basic promoter. The addition was found to be diastereodivergent, consistent with the involvement of a cyclic, chairlike transition structure organized around a hypervalent silicon atom as suggested by Sakurai and co-workers.




***Scheme 83.*** Chiral phosphoramide catalyzed asymmetric allylations.

These patterns of reactivity and diastereoselectivity strengthened the analogy of these reactions to the fluoride-promoted reactions of allylic trifluorosilanes. It was only when the issue of enantioselectivity was assessed using a chiral Lewis base that the direct analogy between fluoride- and phosphoramide-promoted processes began to break down, thus suggesting the Lewis base may exert its influence by a unique mechanism. Using a structurally diverse group of $C_2$-symmetric and asymmetric phosphoramides **224**–**227**, our research group showed that moderate enantioselectivities could be achieved in the allylation.[297] However, a weak loading dependence on the enantioselectivity was observed in which lower loadings led to lower selectivities (Table 5). Considering the lack of a kinetically competent achiral background reaction, these results represented the first suggestion that there were two distinct pathways involving

***Table 5:*** Loading dependence on phosphoramide-catalyzed allylations.

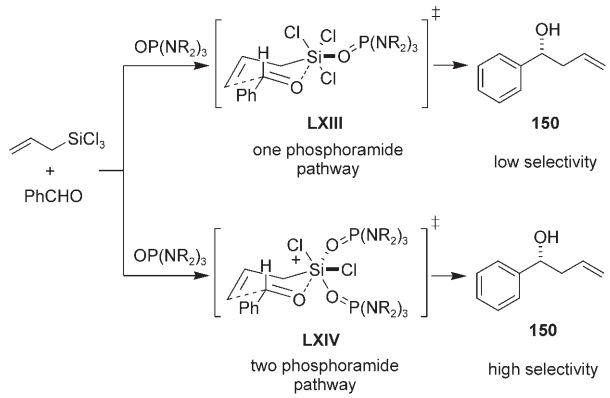



| Entry | Catalyst [equiv] | *t* [h] | Yield [%] | e.r. |
|---|---|---|---|---|
| 1 | 1.0 | 6 | 81 | 80.0:20.0 |
| 2 | 0.5 | 24 | 78 | 78.5:21.5 |
| 3 | 0.25 | 24 | 74 | 79.5:20.5 |
| 4 | 0.1 | 24 | 40 | 76.5:23.5 |

the chiral phosphoramide with different levels of enantioselectivity.

Subsequent kinetic studies showed a non-integral order dependence of 1.77 on the phosphoramide catalyst **226**.[298] This outcome can explain the loading dependence of enantioselectivity, and suggests that both a one- (**LXIII**) and a two-phosphoramide (**LXIV**) pathway are operating (Scheme 84). These results raised questions regarding the similarities between these reactions involving allyltrichlorosilane and earlier work by Sakurai and co-workers involving allyltrifluorosilane. The consideration of a closed transition structure where the allyl fragment, aldehyde, and three chloride ligands must be bound to the silicon atom, along with two molecules of phosphoramide catalyst, leads to the unlikely conclusion that a seven-coordinate silane must be involved.

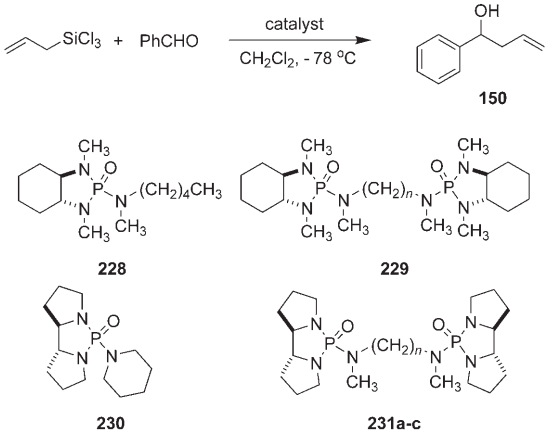



***Scheme 84.*** Divergent mechanistic pathways in reactions of allyltrichlorosilane.

In the previous discussion of fluoride-promoted reactions of trialkylsilanes, it was noted that when the silicon atom bore highly electronegative ligands, ionization to form a hypervalent, cationic silicate was possible. Although this is not the case in Lewis base catalyzed reactions involving trifluorosilanes, Berrisford and co-workers have suggested that ionization of the chloride ion from allyltrichlorosilane is possible in the presence of neutral Lewis bases.[299] This ionization implies that the reaction proceeding through a two-phosphoramide pathway involves a six-coordinate, hypervalent cationic siliconium ion. This kind of transition structure still provides nucleophilic activation in the allyl fragment because of the hypervalent nature of the silicon complex. However, the cationic silicate also provides potent electrophilic activation for the bound aldehyde, thus helping to rationalize the dramatic rate enhancement observed in these neutral Lewis base catalyzed processes. The ionization of chloride is an important factor that must be considered when rationalizing the low reactivity of aliphatic aldehydes under these conditions. An equilibrium exists between an ionic complex of the aldehyde with the cationic silicate and a neutral silylated chlorohydrin. The neutral chlorohydrin is clearly more favorable in the nonpolar environment provided by the solvent of choice for these reactions, dichloromethane.

Subsequent studies have shown that the generation of a cationic silicon species is an integral part of phosphoramide-catalyzed allylations that proceed through either a one- or a two-phosphoramide pathway.[298] The observation that high catalyst loadings and catalyst structures that favor the two-phosphoramide pathway are more enantioselective provided inspiration for the development of linked, dimeric phosphoramide catalysts (Table 6).[300] The use of a dimeric Lewis base catalyst has several advantages; it disfavors the less selective one-phosphoramide pathway and aids in overcoming the entropic disadvantage for the formation of the termolecular transition structure containing two Lewis bases. A survey of several linked catalyst structures revealed that there was a significant advantage in terms of reactivity and selectivity for a dimeric catalyst linked through a pentamethylene chain. Further optimization to incorporate the novel 2,2′-bispyrrolidine backbone[300] led to the development of a highly selective, dimeric allylation catalyst **231b** for allyltrichlorosilane. Unsubstituted and γ-substituted silanes could be employed in these reactions, and provided the products in good yields as well as high diastereo- and enantioselectivities. Moreover, the use of unsymmetrical γ,γ-disubstituted silanes was viable, and quaternary stereogenic centers could be formed with high selectivity.

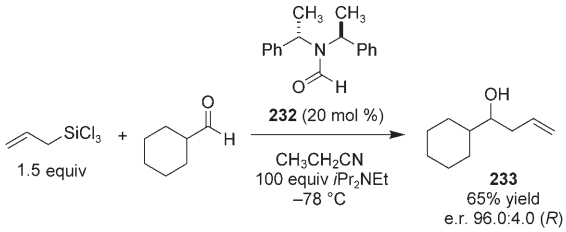
***Table 6:*** Dimeric phosphoramide catalyzed allylations with allyltrichlorosilane.




| Entry | Catalyst | *n* | Equiv | Yield [%] | e.r. (config.) |
|---|---|---|---|---|---|
| 1 | **228** | – | 1.0 | 73 | 75.5:24.5 (*R*) |
| 2 | **229** | 5 | 0.1 | 54 | 86.0:14.0 (*R*) |
| 3 | **230** | – | 0.05 | 56 | 78.0:22.0 (*S*) |
| 4 | **231a** | 4 | 0.05 | 54 | 59.0:41.0(*S*) |
| 5 | **231b** | 5 | 0.05 | 85 | 93.5:6.5 (*S*) |
| 6 | **231c** | 6 | 0.05 | 58 | 83.5:16.5 (*S*) |

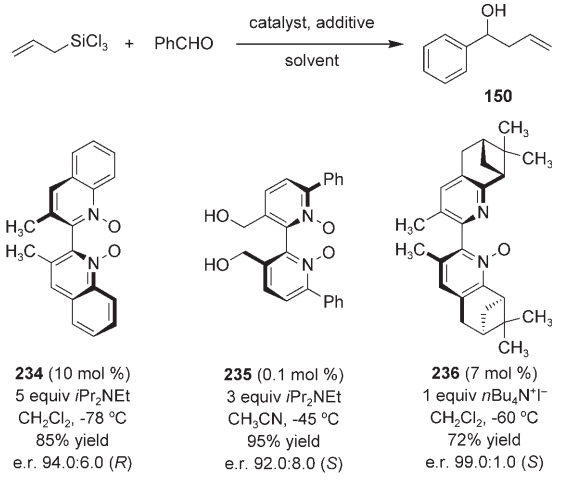
The success of chiral phosphoramide catalysis with allyltrichlorosilanes has prompted the search for other active and selective Lewis base catalysts.[301] Iseki et al. have also studied a number of chiral phosphoramides. However, selectivities with these catalysts remain low when compared to the dimeric phosphoramide **231b**.[302] Furthermore, publications on the use of chiral formamides,[303] *N*-oxides,[304] amines,[305] and ureas[306] have demonstrated that a wide variety of chiral, neutral Lewis bases are effective catalysts for this reaction (Scheme 85).




***Scheme 85.*** Formamide-catalyzed asymmetric allylations with allyltrichlorosilane.

However, of all of the catalyst structures that have been examined, only allylations promoted by *N*-oxides **234**–**236** (Scheme 86) have provided comparable levels of selectivity compared to phosphoramides such as **231**. The Nakajima[304k,l] and Hayashi[304h,i] research groups have both investigated the use of chiral 2,2′-bipyridyl bis-*N*-oxides in allylation. The strong basicity of the *N*-oxide oxygen atom along with their rigid, structures makes them extremely effective activators.[48] The observed enantioselectivities are high, although the scope of the reaction is limited to conjugated aldehydes. As in reactions catalyzed by phosphoramides, this process appears to involve an ionized, hexacoordinate siliconate. Kočovský and co-workers have examined the use of chiral bis-*N*-oxides and mixed quinoline/isoquinoline *N*-oxides.[304f,g,j] The yields and selectivities are comparable to those obtained in other catalyst systems. The use of catalyst **236** is intriguing because it promotes synthetically useful reactivity with aliphatic aldehydes. As expected, the reactions with (*E*)- and (*Z*)-2-butenylsilanes give excellent diastereoselectivity, but the yields are much attenuated (27–37%) and the enantioselectivities are diminished (e.r. 86:14–88:12).




***Scheme 86.*** *N*-Oxide-catalyzed asymmetric allylation with allyltrichlorosilane.

The study of the addition reactions of allylic trichlorosilanes has revealed a new class of Lewis base catalyzed processes. The involvement of two Lewis bases and the intermediacy of a hexacoordinate siliconium ion provides for an efficient and selective process. The involvement of a closed transition structure demonstrates how, in this case, the Lewis base is doing more than simply enhancing the nucleophilicity. Although the polarized bonds of the hypervalent silicate impart a larger degree of partial negative charge on the allyl fragment, the association of the aldehyde to the electron-deficient silicon atom also provides strong electrophilic activation for the carbonyl group. Hence, in these cases, it is clear that the n–σ* interaction provides a unique type of dual activation that includes both the electrophilic and nucleophilic components of the allylating reagent.

### 6.2.3. Lewis Base Catalyzed Allylation of Hydrazones

In an extension of these ideas, Kobayashi and co-workers have reported selective allylations and crotylations of benzoylhydrazones.[307] As was the case in aldehyde allylation, these investigators first established the suitability of highly Lewis basic solvents such as DMF or HMPA to effect the addition of allyl- and 2-butenyltrichlorosilane to aromatic and aliphatic aldohydrazones[307c] as well as aromatic ketohydrazones.[307d] The additions take place in good yield and high diastereoselectivity, but in this case, the correlation of silane geometry and product configuration is reversed from that of aldehydes, namely *E*→*syn*, *Z*→*anti*. This correlation is interpreted in terms of a chairlike transition structure with a pseudoaxially oriented substituent on the azomethine carbon atom.

The first successful enantioselective additions to benzoylhydrazones employed chiral sulfoxides as the promoters in excess amounts (3 equiv **237**/hydrazone).[308] Here again, the additions are high yielding and diastereo- and enantioselective (Table 7). For the addition to α-hydrazono esters (glyoxalate derivatives), Kobayashi and co-workers found that 4-Tol-binap(O)$_2$ **238** gives the highest yields and selectivities, again when used in excess amounts (2 equiv/hydrazone).[308b]

### 6.2.4. Lewis Base Catalyzed Propargylation and Allenylation of Aldehydes

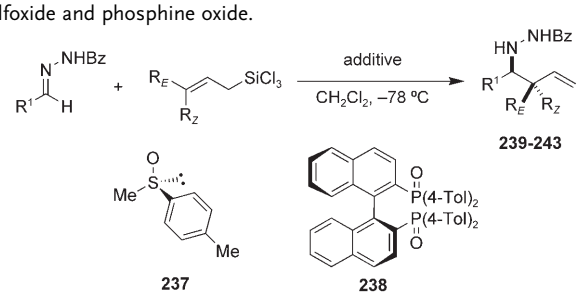
Other interesting extensions of this method are the reactions of allenyl- and propargyltrichlorosilanes with aldehydes and hydrazones (Scheme 87).[309] The ratio of the trichlorosilane isomers **244** and **245** is directly controlled by the choice of catalyst in the reaction of propargyl chloride.[309a] Propargylic silane **244** leads exclusively to allenyl alcohol **246** while allenic silane **245** leads to the corresponding propargyl alcohol **247**. Similarly, allenylation and propargylations of benzoylhydrazones have also been reported.[309b]

### 6.2.5. Lewis Base Catalyzed Reduction of Carbonyl Compounds and Imines with Silanes

Hydrosilanes are well known reducing agents, primarily for ionic hydrogenation or in transition-metal-catalyzed hydrosilylation. However, as first demonstrated by Corriu and co-workers,[310] reductions by hydrosilanes are susceptible to catalysis, particularly by fluoride ions. More recently, trialkoxy- and trichlorosilanes along with poly-

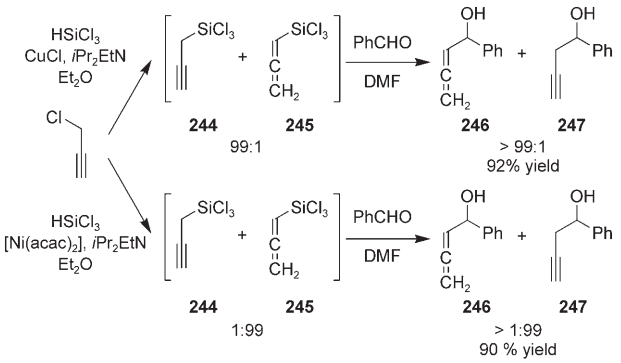
  

***Table 7:*** Allylation and crotylation of benzoylhydrazones with a chiral sulfoxide and phosphine oxide.




| Entry | $R^1$ | $R_E$ | $R_Z$ | Catalyst (equiv) | Yield [%] | d.r. (*syn*/*anti*) | e.r.[a] |
|---|---|---|---|---|---|---|---|
| 1 | $PhCH_2CH_2$ | H | H | **237** (3.0) | 73 (**239**) | – | 96.5:3.5 |
| 2 | *i*Pr | H | H | **237** (3.0) | 80 (**240**) | – | 99.0:1.0 |
| 3 | $PhCH_2CH_2$ | H | Me | **237** (3.0) | 60 (**241**) | <1/>99 | 95.5:4.5 |
| 4 | $PhCH_2CH_2$ | Me | H | **237** (3.0) | 58 (**241**) | >99/<1 | 94.5:5.5 |
| 5 | $EtO_2C$ | H | H | **238** (2.0) | 91 (**242**) | – | 99.0:1.0[b] |
| 6 | $EtO_2C$ | H | Me | **238** (2.0) | 92 (**243**) | 98/2 | >99:1[b] |
| 7 | $EtO_2C$ | Me | H | **238** (2.0) | 96 (**243**) | <1/>99 | 98.0:2.0[b] |

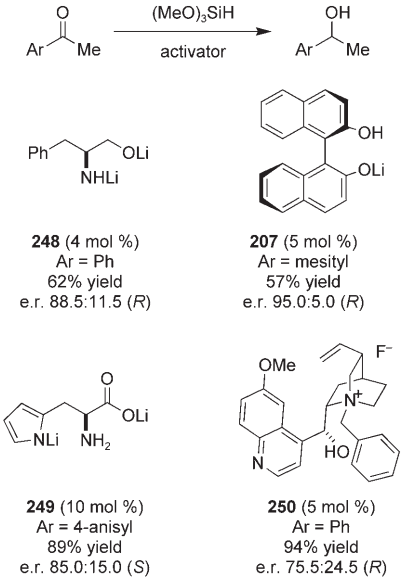
[a] Enantiomeric ratio for the major product. [b] The major product from (*S*)-**238** is enantiomeric to that shown.




***Scheme 87.*** Lewis base promoted allenylations and propargylations.

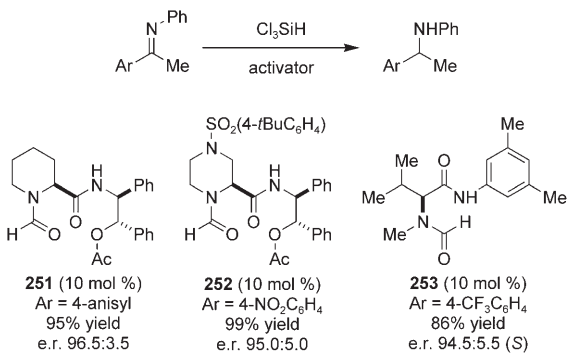
methylhydridosilane (PMHS)[311] have been employed particularly because of their propensity to form hypercoordinate silicate complexes which possess enhanced reducing capabilities. For example, trimethoxysilane can be activated by a variety of anionic chiral catalysts[312] to effect the enantioselective reduction of acetophenones (Scheme 88).

A conceptually distinct approach (which will be featured frequently in this section) is the use of chirally modified fluoride sources such as the *N*-benzylquininium fluoride **250** (Scheme 88).[313] At 10 mol% loading, this catalyst effected the selective reduction of a series of aryl ketones with respectable selectivity using $(MeO)_3SiH$. The hydroxide salt is also effective.




***Scheme 88.*** Reduction of ketones with trimethoxysilane.

In recent years, the use of trichlorosilane in combination with Lewis basic activators has gained in popularity, particularly for the reduction of ketones and imines.[314] In 1996 Kobayashi et al. first demonstrated the ability of trichlorosilane to reduce aldehydes and ketones in DMF; this reaction is analogous to the allylation with allyltrichlorosilane.[314c] Naturally, this observation led to the development of chiral formamide-based activators that could be used in substoichiometric quantities. Unfortunately, only modest enantioselectivities were obtained with *N*-formyl derivatives of proline amides (e.r. < 71:29).[314b] Only slightly better results (e.r. < 83:17) are obtained in the reduction of *N*-phenylketimines.[314a] However, very recently, *N*-formyl derivatives of pipecolinic acid and piperizine-2-carboxylic acid **251** and **252** have shown synthetically useful enantioselectivities in reductions of arylalkyl imines (Scheme 89).[314d,e] Finally, in an exhaustive survey of amino acid derived bisamides, the Malkov and Kočovský research groups have identified a number of important structural features that lead to high conversions and high enantioselectivities.[314f] The superior catalyst structure is an *N*-formyl,*N*-methylvalineamide **253** derived from a bulky aniline.




***Scheme 89.*** Reductions of imines with trichlorosilane.

### 6.2.6. *Lewis Base Catalyzed Aldolization with Enoxytrichlorosilanes*

In retrospect, the clear structural analogy between allylic silanes and silyl enol ethers made the extension of fluoride ion promotion from the original reports of Sakurai and coworkers to the later studies of the Noyori research group a logical one. The ability of the Lewis base to promote the formation of a hypervalent species in which the electron density at the peripheral ligands is increased provides an easy method for enhancing the nucleophilicity of the allyl or enolate fragment. In the case of polyhalosilanes, there is an added advantage of a closed transition structure involving a cationic siliconium ion that provides powerful electrophilic activation for the carbonyl substrate and a reliable pathway for control over the diastereoselectivity in the subsequent addition. This high level of preorganization proved important in our studies of allylations with γ,γ-disubstituted trichlorosilanes.[248]

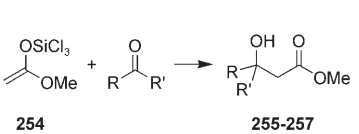
As control over enantio- as well as diastereoselectivity has always been a major concern in asymmetric aldol reactions, it was also logical to wonder what advantages a Lewis base catalyzed reaction with trichlorosilyl enol ethers might provide. In recent years, studies have demonstrated that similar mechanistic and stereochemical analyses can be employed for the phosphoramide-catalyzed allylations as well as for the aldol reactions.[315] However, the aldol reaction has several unique facets that add a level of mechanistic detail to the picture of Lewis base catalysis with polyhalosilanes.

The first report of a Lewis base catalyzed aldol addition with an enoxytrichlorosilane described the reactions of an acetate-derived trichlorosilyl ketene acetal **254** (Table 8).[316] Unlike allylic trichlorosilanes, these enol ethers possessed sufficient nucleophilicity to undergo rapid, uncatalyzed addition reactions with aromatic, olefinic, and aliphatic aldehydes as well as ketones. The binding of the weakly Lewis basic aldehyde provided sufficient activation for the aldol reaction. The addition of a chiral phosphoramide catalyst **258** did provide moderate levels of asymmetric induction with a limited number of substrates, but not at synthetically useful levels.

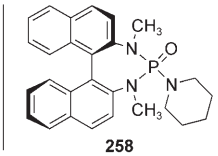
The reactions of ketone-derived trichlorosilyl enol ethers showed considerably more promise (Table 9).[317,318] In the uncatalyzed reaction, the diastereoselectivity indicated that it proceeds via a closed, boatlike transition structure. Both conjugated aromatic and olefinic aldehydes as well as nonconjugated aliphatic aldehydes were reactive, indicating the involvement of a hypervalent silane that is not ionized. Although a significant background reaction was still observed in the case of these less nucleophilic enol ethers, it was not competitive with the catalyzed process. In the presence of 10 mol% of the chiral phosphoramide **224**, good yields and enantioselectivities could be obtained. In analogy to catalyzed reactions with allylic trichlorosilanes, these results support a cationic siliconium ion and help to rationalize the dramatic rate enhancement. However, the situation was not so simple when the diastereoselectivity of the reaction was considered. It was shown that the catalyzed reaction can provide either the product expected from a closed, chairlike transition structure or a closed, boatlike transition structure, solely depending on the catalyst structure. When the phosphoramide derived from *N*,*N*′-dimethylstilbene-1,2-diamine **224** was employed, the *E*-enol ether gave high *anti* selectivities and hence, a chairlike transition structure appeared to be operative. When the phosphoramide derived from *N*,*N*′-diphenylstilbene-1,2-diamine **261** was employed, the *Z*-enol ether gave high *anti* selectivities, thus suggesting a boatlike transition structure was operative.

The high levels of enantioselectivity observed in the reactions catalyzed by **224** and **261** leave no doubt that the phosphoramide is involved in both processes. However, the dramatic difference between the observed diastereoselectivities indicates that they must participate in different manners.[319] Common ion effect studies, as well as the observed patterns of reactivity with aliphatic aldehydes, lead to the conclusion that, in both cases, an ionized cationic silicate was involved. Therefore, it was not surprising when kinetic

***Table 8:*** Phosphoramide-catalyzed asymmetric aldol reactions of trichlorosilyl ketene acetals.



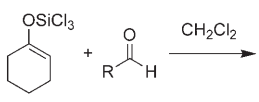

**254** **255-257**



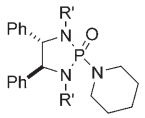

**258**

| Entry | R | R′ | Catalyst (mol%) | *T* [°C] | Yield [%] | e.r. (config) |
|---|---|---|---|---|---|---|
| 1 | Ph | H | – | 0 | 98 (**255**) | – |
| 2 | (*E*)-cinnamyl | H | – | 0 | 89 (**256**) | – |
| 3 | *tert*-butyl | H | – | 20 | 99 (**257**) | – |
| 4 | Ph | Me | HMPA (10) | 20 | 97 (**255**) | – |
| 5 | Ph | H | **258** (10) | −78 | 91 (**255**) | 61.5:38.5 (*S*) |
| 6 | *t*Bu | H | **258** (10) | −78 | 75 (**257**) | 74.5:25.5 (*S*) |

***Table 9:*** Phosphoramide-catalyzed asymmetric aldol reactions of trichlorosilyl enol ethers.




**259** **260a-b**



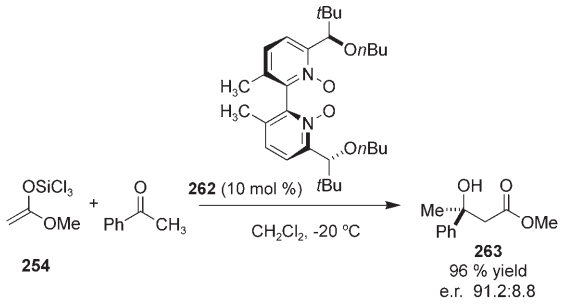

**224** R′ = Me
**261** R′ = Ph

| Entry | R | Catalyst (mol%) | *T* [°C] | Yield [%] | d.r. (*syn*/*anti*) | e.r. (config.) |
|---|---|---|---|---|---|---|
| 1 | Ph | – | 0 | 92 (**260a**) | 98:2 | – |
| 2 | *c*-$C_6H_{11}$ | – | 0 | 92 (**260b**) | 50:50 | – |
| 3 | Ph | **224** (10) | −78 | 95 (**260a**) | <1:99 | 96.5:3.5 (*R*,*S*) |
| 4 | Ph | **261** (10) | −78 | 94 (**260a**) | 99:1 | 76.5:23.5 (*R*,*R*) |
| 5 | *c*-$C_6H_{11}$ | **224** (10) | −78 | – | – | – |

studies[319] conducted with both **224** and **261** revealed a similar mechanistic rationale as was observed in the phosphoramide-catalyzed reactions of allyltrichlorosilane.[298] A first order dependence on the larger, more sterically demanding catalyst **261** was observed in the reaction of benzaldehyde and the cyclohexanone-derived trichlorosilyl ether **259**. This finding suggests the presence of a pentacoordinate, cationic siliconium ion in the carbon–carbon bond-forming transition structure **LXVI**. A second-order dependence on the smaller catalyst **224** was observed for the same process. As in earlier proposals, this finding suggests the presence of a hexacoordinate, cationic silicate in the carbon–carbon bond-forming transition structure **LXV**. On the basis of these observations, a revised catalytic cycle could be proposed for this Lewis base catalyzed process involving two mechanistically and kinetically distinct pathways (Figure 9). The high molecularity of the transition structures for these two processes is further supported by the large, negative entropies of activation observed for reactions catalyzed by both **224** and **261**.

The ability to select for a reaction through either a one- or a two-phosphoramide pathway with distinct stereochemical consequences through a simple change in the catalyst structure is noteworthy and demonstrates the level of control that can be exerted through the use of these in situ generated catalyst complexes. The unique nature of these Lewis basic catalysts not only has consequences on the stereochemical course of the reaction,[320] but also for the reactivity and the scope of existing asymmetric aldol methods.

Recent studies revisiting the chemistry of trichlorosilyl ketene acetals revealed that a high yielding and highly selective aldol reaction with ketones could be performed (Scheme 90).[321] The use of chiral phosphoramides gives poor selectivity when compared to bis-*N*-oxide catalysts such as **262**. Clearly, balancing the higher reactivity of the trichlorosilyl ketene acetal **254** with the lower reactivity of ketones toward nucleophilic addition allows the chiral catalyst to make a kinetically significant contribution to a selective catalytic process.




***Scheme 90.*** *N*-Oxide-catalyzed asymmetric aldol reactions of trichlorosilyl ketene acetals with ketones.

Another important advance provided by the use of trichlorosilyl enol ethers is the aldol reaction between two aldehydes. Typically, aldol reactions between two aldehydes are problematic since the product of the first aldol reaction is a viable substrate for further nucleophilic additions, thereby leading to unproductive oligomerization. However, in this case the aldehyde product is effectively protected through in situ formation of an inactive chlorohydrin such as **LXVII**. This process provides a serendipitous solution to the problem of the development of a catalytic, asymmetric aldol reaction between two aldehydes by capitalizing on the troublesome formation of chlorohydrins. In 2001, our research group reported that the use of aldehyde-derived trichlorosilyl enol ethers such as **264** allowed for a high yielding, highly enantio- and diastereoselective aldol process (Scheme 91).[322] Again, the diastereoselectivity of the reaction together with detailed mechanistic studies support the hypothesis that the reaction proceeds through a closed, chairlike transition structure.[323]

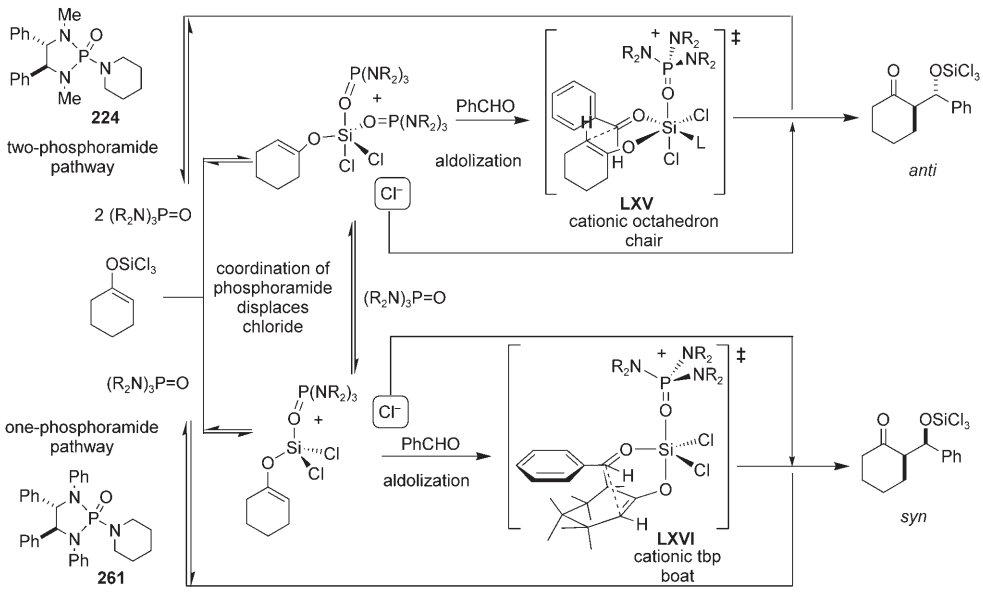
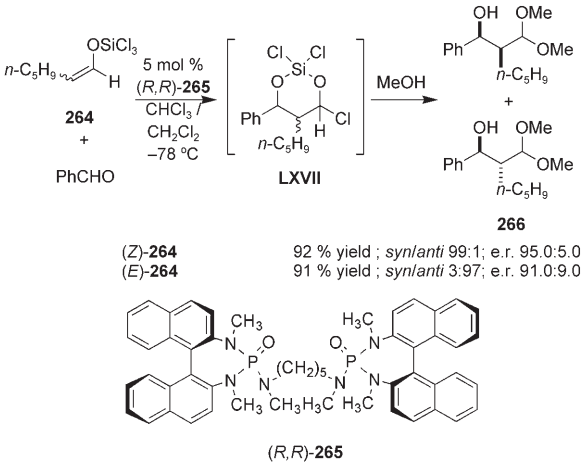



***Figure 9.*** Divergent mechanistic pathways in reactions of trichlorosilyl enol ethers. L = phosphoramide.

### *6.3. Lewis Base Catalyzed Epoxide Opening: The Trichlorosilyl Cation*

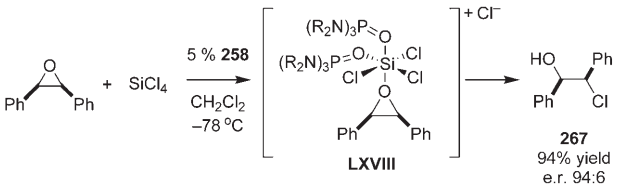
The foregoing example of aldol reactions between two aldehydes demonstrates that the presence of the chloride ion, which is formed as a consequence of Lewis base activation of the trichlorosilane, can also serve as a potent nucleophile. In an early study on the reactivity of trichlorosilyl enol ethers with other electrophiles, it was observed that epoxides react with trichlorosilyl enol ethers to yield vicinal chlorohydrins rather than the




***Scheme 91.*** Phosphoramide-catalyzed asymmetric aldol reactions between aldehydes.

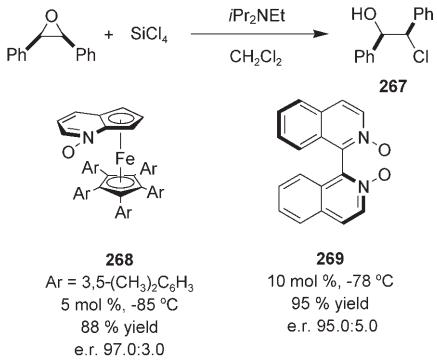
desired γ-hydroxy ketones.[324] This result suggested that the use of the parent halosilane, silicon tetrachloride ($SiCl_4$), may allow for the development of an effective method for an asymmetric epoxide opening catalyzed by chiral phosphoramides (Scheme 92). Although this was not a well-known method for chlorohydrin formation, studies conducted by Andrews et al. had already shown that triphenylphosphane was an active catalyst for the formation of chlorohydrins from epoxides and trimethylsilyl chloride (TMSCl).[325] We have shown that *meso*-epoxides are rapidly opened to the enantiomerically enriched vicinal chlorohydrins in good yields and selectivities in the presence of $SiCl_4$ and a substoichiometric amount of a chiral phosphoramide.




***Scheme 92.*** Phosphoramide-catalyzed desymmetrization of *cis*-stilbene oxide.

A similar catalytic cycle to those proposed for the reactions of allylic trichlorosilanes and trichlorosilyl enol ethers was envisioned, involving the intermediacy of an ionized chlorosilane. However, careful consideration of the catalytic cycle revealed a significant difference. In this case, the turnover-limiting step does not involve an intramolecular process. As the chloride ion is the active nucleophile, bond formation must be considered an intermolecular process between a trichlorosilyl cation bound electrophile and an exogenous nucleophile (as in **LXVIII**).[326] This realization served as a starting point for the development of other Lewis base catalyzed processes as well as a significant expansion of the scope of these reactions (Section 6.4). After the nucleophilic attack, the catalyst then dissociates from the resulting trichlorosilyl ether to complete the catalytic cycle. Therefore, each molecule of $SiCl_4$ (the source of the active Lewis acid in these reactions) that enters the catalytic cycle is incorporated into the product. Although it might appear so, this process cannot constitute ligand-accelerated catalysis, because $SiCl_4$ is a stoichiometric reactant. It is purely an example of Lewis base catalysis because only the Lewis base can participate in subsequent turnovers. Since the catalytically active species is a powerful Lewis acid generated by the action of a Lewis base, the process is most clearly described as "Lewis acid mediated and Lewis base catalyzed".

Other, structurally distinct Lewis bases are also useful in this reaction. The research groups of both Nakajima and Fu have employed chiral *N*-oxides to promote the opening of *meso*-epoxides in good yields and selectivities (Scheme 93).[327] In the case of the planar-chiral *N*-oxide **268**, initial kinetic studies demonstrate that the reaction is second order in the catalyst and zeroth order in $SiCl_4$ and therefore suggests a stoichiometric complexation of the catalyst and formation of the active intermediate. This result is particularly interesting as it demonstrates the subtle, often contradictory difference between the thermodynamic stability of Lewis base–acid adducts and their high reactivity.




***Scheme 93.*** *N*-Oxide-catalyzed desymmetrizations of *cis*-stilbene oxide.

Although the desymmetrization of epoxides is a well-studied reaction and a number of nucleophiles such as halides, alcohols, carboxylates, and cyanide ions have been employed,[328] the use of carbon-centered nucleophiles remains an underdeveloped area.[329]

### *6.4. Lewis Base Catalyzed, Lewis Acid Mediated Reactions*

The demonstration that a phosphoramide-modified trichlorosilyl cation is an effective chiral Lewis acid is intriguing and further investigations with other electrophiles allowed for the development of novel Lewis base catalyzed processes. The combination of silicon tetrachloride and a chiral phosphor-

amide catalyst to generate a strong, chiral Lewis acid is distinct from the vast majority of Lewis acid catalyzed processes used in asymmetric aldol and allylation methodologies. Instead of the formation of a covalent adduct between the chiral ligand and the Lewis acid precursor (which often leads to decreased reactivity for the resulting complex), Lewis base complexation activates the Lewis acid. This strategy avoids competition from achiral background reactions.

Studies by our research group have shown that an in situ generated, phosphoramide-bound trichlorosilyl cation is, in fact, capable of catalyzing a wide variety of reactions.[330] When combined with an aldehyde and a main-group organometallic reagent, this species promotes rapid carbon–carbon bond formation. A variety of structurally diverse nucleophiles can be used, ranging from allylic stannanes to a variety of enol ethers and even isocyanides. In a broad sense, the relative reactivity of these species is well understood in terms of the scale of π nucleophilicity developed by Mayr et al.[291b]

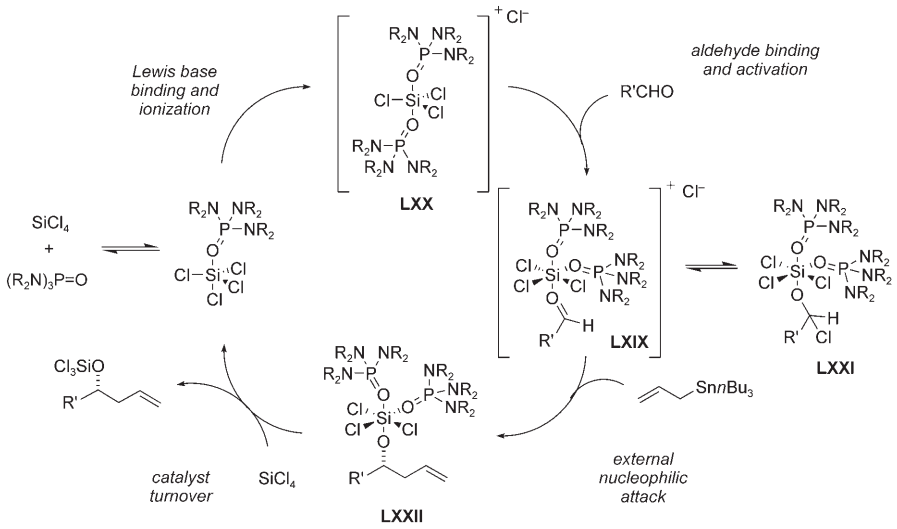
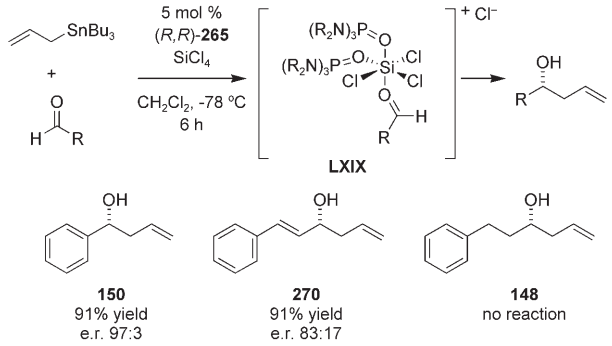



***Figure 10.*** Catalytic cycle for $SiCl_4$-mediated/phosphoramide-catalyzed reactions.

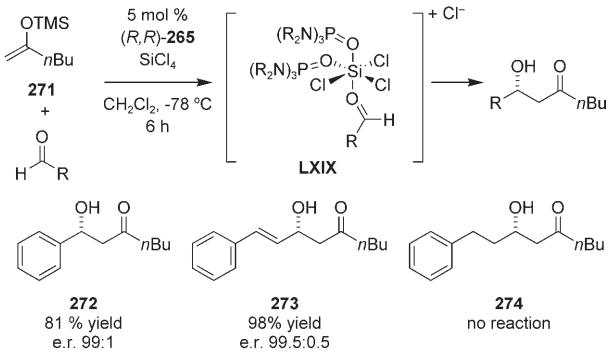
The first example of this catalyst system for the delivery of an external nucleophile was the addition of allyl tri-*n*-butylstannane to aldehydes (Scheme 94).[330a] The reactions were complete in several hours, and good yields and enantioselectivities could be obtained. However, only aromatic and olefinic aldehydes were reactive, again suggesting the involvement of an ionized siliconium species such as **LXIX**.



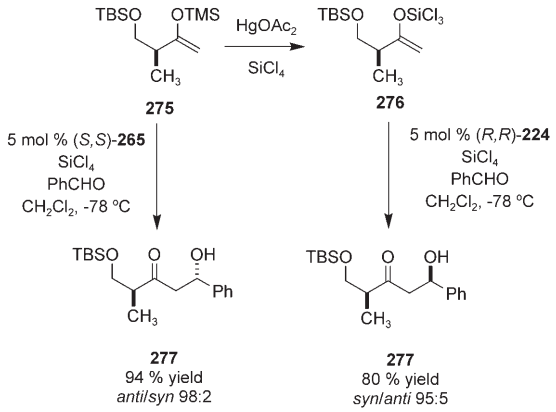

***Scheme 94.*** $SiCl_4$-mediated/phosphoramide-catalyzed allylations with stannanes.

A general catalytic cycle analogous to that proposed for the epoxide opening is applicable to the addition reactions of stannanes (Figure 10). The cycle is initiated by the binding of the phosphoramide to the weakly Lewis acidic $SiCl_4$. In line with Gutmann's analysis, binding leads to a polarization of the silicon–chlorine bond and eventually ionization to form the active catalyst species, the chiral trichlorosilyl cation **LXX**. This species can then bind the aldehyde to form **LXIX** and proceed through an intermolecular carbon–carbon bond-formation step. The product is formed as a trichlorosilyl ether **LXXII** and release of the catalyst completes the cycle. The lack of reaction with aliphatic aldehydes is explained through the unproductive equilibrium between **LXIX** and the unreactive chlorohydrin **LXXI**. With aliphatic aldehydes, this equilibrium lies far to the side of the chlorohydrin **LXXI**.[331] Weak nucleophiles, such as allylic stannanes, are unable to intercept the small equilibrium amount of **LXIX** present. More reactive nucleophiles, such as silyl ketene acetals and isocyanides can intercept this species, and thus both aromatic and aliphatic aldehydes are rendered reactive.

The use of a slightly more powerful nucleophile, such as the ketone-derived silyl enol ether **271**, provides both higher reactivity and enantioselectivity (Scheme 95). Methyl ketone-derived silyl enol ethers are reactive under these conditions, and give good yields of products with good levels of enantioselection.[330c] The influence of resident stereocenters on these aldol reactions has also been investigated (Scheme 96).[318] If the observed diastereoselectivities with these trimethylsilyl enol ethers are compared to those of the corresponding trichlorosilyl enol ethers,[318,319] the opposite sense of diastereoselection is observed, thus making this a



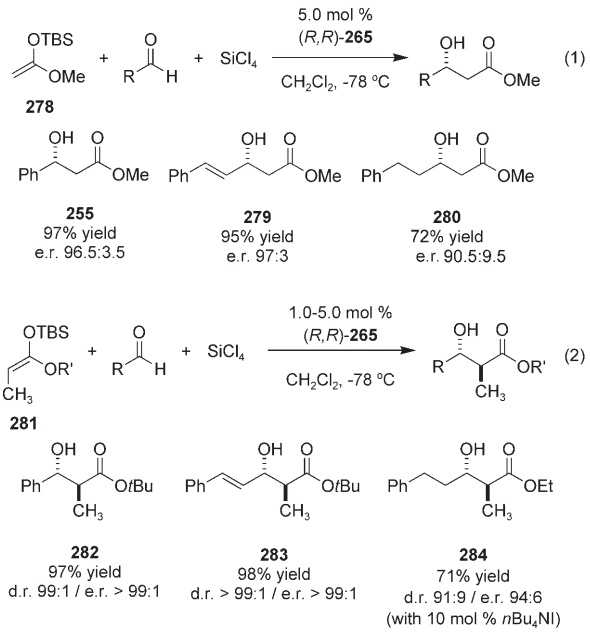

***Scheme 95.*** $SiCl_4$-mediated/phosphoramide-catalyzed asymmetric aldol reactions of silyl enol ethers.




***Scheme 96.*** Double diastereodifferentiation in $SiCl_4$-mediated/phosphoramide-catalyzed aldol reactions.

complementary method and allowing easy access to both diastereomers starting from the same synthetic precursor. However, despite the high utility and excellent selectivity observed with these systems, they are still limited to reactions of aromatic and other conjugated aldehydes.[332]

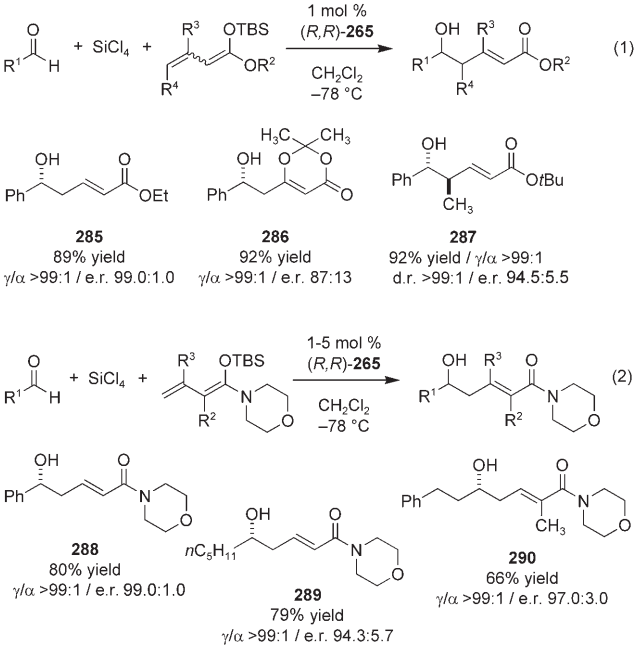
Silyl ketene acetals are a much more reactive class of π nucleophiles and consequentially show good reactivity under Lewis base catalysis, even with aliphatic aldehydes.[291c] The reactions of acetate-derived silyl ketene acetals are extremely rapid and high yielding, and afford the products from addition to aromatic, olefinic, and aliphatic aldehydes with good enantioselectivities [Eq. (1) in Scheme 97].[330b] Reactions performed with α-substituted silyl ketene acetals, such as the propanoate-derived species **281**, also provide high yields and enantioselectivities for a wide variety of aldehyde structures [Eq. (2) in Scheme 97]. However, in this class of nucleophiles, there is a unique advantage to the use of




***Scheme 97.*** $SiCl_4$-mediated/phosphoramide-catalyzed asymmetric aldol reactions of silyl ketene acetals

phosphoramide catalysis over other methods. A high level of *anti* diastereoconvergence is observed, which is indicative of an open transition structure, wherein the silyl ketene acetal attacks the trichlorosilyl cation bound aldehyde.

Extension of the scope of the nucleophile to include the additions of silyl dienol ethers has revealed that this catalyst system can mediate a highly γ-site-selective vinylogous aldol process.[333] These versatile reactions are general with respect to the nucleophile (ketene acetals and *N*,*O*-ketene acetals) as well as the aldehyde (aromatic, unsaturated, and aliphatic). The nucleophilicity of the N,O-ketene acetals has allowed for a general addition to aliphatic aldehydes with high selectivity using the silicon tetrachloride–phosphoramide system. (Scheme 98).[330d,e]

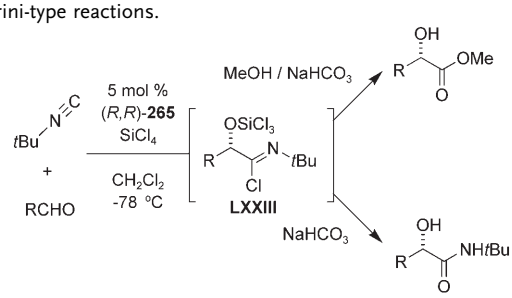



***Scheme 98.*** $SiCl_4$-mediated/phosphoramide-catalyzed asymmetric aldol reactions of silyl dienol ethers.

The development of the first catalytic, enantioselective Passerini reaction highlights the unique advantages of the silicon tetrachloride–phosphoramide catalyst system.[334] Earlier attempts using chiral metal species as Lewis acid catalysts were hampered by the inherent Lewis basicity of the isocyanide.[335] However, under the standard reaction conditions developed for the $SiCl_4$-mediated reactions of enoxysilanes, an isocyanide can add to aromatic, olefinic, and aliphatic aldehydes in high yields and high enantioselectivities (Table 10). After hydrolysis, either the amide or the ester product can be obtained selectively. The high reactivity of aliphatic aldehydes in these systems is thought to be a consequence of the unique nature of the isocyanide carbon–nitrogen bond. After the formation of the carbon–carbon bond, a nitrilium ion is generated. This highly electrophilic species can serve as a competitive trap for the ionized chloride ion, thereby forming the intermediate **LXXIII** and disfavoring formation of inactive chlorohydrins.

***Table 10:*** $SiCl_4$-mediated/phosphoramide-catalyzed asymmetric Passerini-type reactions.




| Entry | R | Quench | Product | Yield [%] | e.r. |
|---|---|---|---|---|---|
| 1 | Ph | $NaHCO_3$ | **291** | 96 | >99:1 |
| 2 | Ph | MeOH | **292** | 97 | >99:1 |
| 3 | (*E*)-PhCH=CH | $NaHCO_3$ | **293** | 81 | 98:2 |
| 4 | (*E*)-PhCH=CH | MeOH | **294** | 71 | 98:2 |
| 5 | $PhCH_2CH_2$ | $NaHCO_3$ | **295** | 92 | 82:18 |
| 6 | $PhCH_2CH_2$ | MeOH | **296** | 88 | 82:18 |

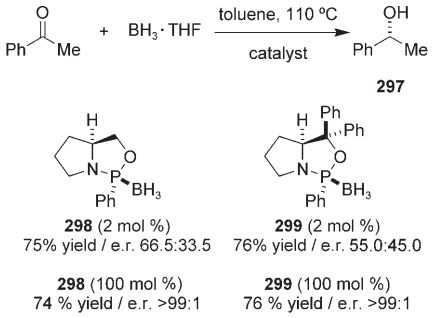
## 7. Lewis Base Catalysis Beyond Silicon: Novel Reactivity

Interest in the fundamental stereochemical and kinetic reactivity patterns of tetracoordinate silicon species led to the identification of the unique properties of hypervalent silicates that have served as an excellent testing ground for the novel concept of n–σ*-type Lewis base catalysis. However, now that this concept has been established and some understanding of its origin has been obtained, the search for Lewis base catalyzed reactions involving other elements has begun. Although very little research has been directed to this end, some notable examples exist that may represent the starting points for the development of novel Lewis base catalyzed processes.

### 7.1. Lewis Base Catalysis with Boron: An Example of the n–n* Interaction

The inherent Lewis acidity of trivalent boron compounds leads to the ready formation of Lewis acid–Lewis base adducts with many classes of donors. The parent compound in this family, borane, is generally employed in the form of a Lewis base adduct, thus making it an easily handled reagent. The identity of the Lewis base influences the reactivity of the borane adduct, and in some cases the choice of the appropriate Lewis base adduct can allow for highly selective reductions of functional groups.[336] The substitution of a strongly basic chiral species for one of the weakly Lewis basic additives may provide an attractive target for the development of a catalytic asymmetric process.

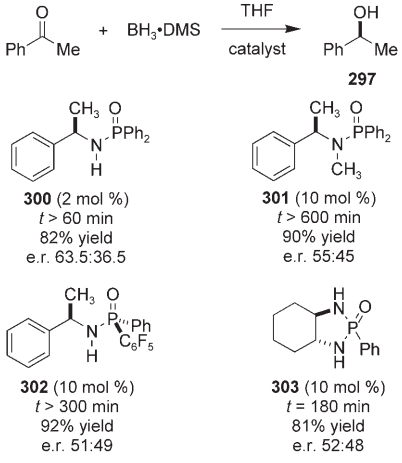
The addition of substoichiometric amounts of strong Lewis bases to borane reductions and hydroborations have been reported,[337] but it was only recently that chiral Lewis base catalysts were employed. In the early 1990s, Buono and co-workers found that borane complexes of chiral 1,3,2-oxazaphosphorinanes **298** and **299** derived from proline functioned effectively as catalysts for the reduction of ketones




***Scheme 99.*** Borane reduction of ketones catalyzed by chiral 1,3,2-oxazaphosphorinanes.

with borane (Scheme 99).[338] The characteristics of these reductions and the catalysts are remarkable: 1) the enantioselectivity increases with temperature (the best results are obtained at 110°C!); 2) the enantioselectivity also increases with catalyst loading (the highest selectivities are obtained with 1.0 equiv of the complex); 3) the borane complex alone does not reduce ketones; 4) reduction of acetophenone with a stoichiometric amount of the $BD_3$ complex in the presence of 1.0 equivalent of $BH_3$·THF gives enantiopure (*R*)-1-$^2$H-1-phenylethanol **297** quantitatively; 5) the reduction of acetophenone with 1.0 equivalent of the complex and 2.0 equivalents of $BH_3$·THF leads to a 20:80 mixture of enantiopure (*R*)-1-$^2$H-1-phenylethanol/(*R*)-1-phenylethanol; and 6) the labeled complexes **298** and **299** do not undergo isotopic exchange under the reaction conditions. No clear mechanistic picture has been formulated to account for these facts, but it is clear that the Lewis basic properties of the phosphorus donor enhance the reducing ability of the bound borane. However, the site of binding and the mechanism of the overall reaction remains obscure.

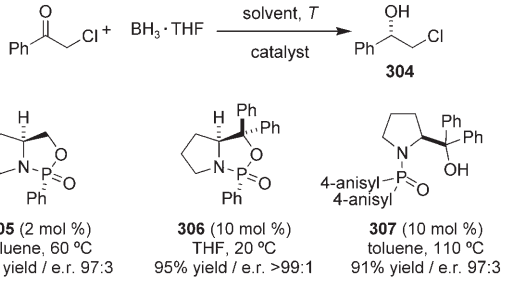
In studies on the chemistry of chiral phosphorus amides, Wills et al. found that phosphinamides, phosphonamides, and phosphoramides could promote an efficient and moderately selective reduction of ketones with borane (Scheme 100).[339] A dramatic rate enhancement is observed in the presence of only a small amount of this highly basic catalyst. The structure




***Scheme 100.*** Borane reduction of ketones catalyzed by chiral phosphoramides. DMS = dimethyl sulfide.

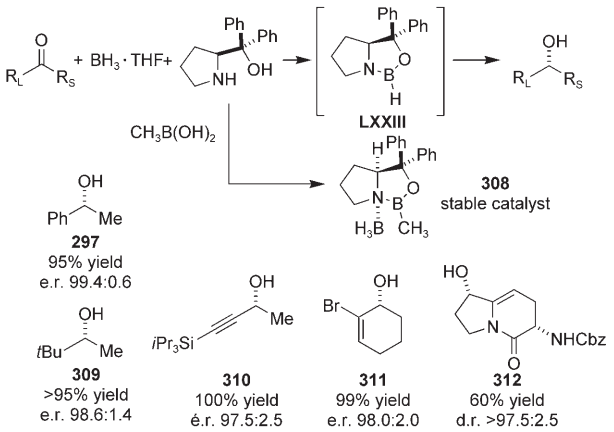
of the phosphorus amide has a strong, but not clearly understood, influence over its catalytic activity. The acyclic, monoamino compound **300** is the most effective catalyst. Although a Hammett-type study of the electronic influence of the aryl groups is consistent with the catalytic activity of these species being dependent on the Lewis basicity of the phosphoryl oxygen atom, the results obtained with the different phosphoramide structures present conflicting results. The use of a more basic cyclohexanediamine-derived phosphoramide **303**, which possesses two amine ligands rather than one, shows lower reactivity and selectivity. The proposed mechanism involving combined Lewis base/Brønsted acid catalysis in these systems remains unclear and further mechanistic studies are warranted.[339e]




***Scheme 101.*** Borane reduction of ketones catalyzed by chiral phosphorus(V) derivatives.

Following the inspiration from this class of catalysts, Buono and co-workers investigated the phosphorus(V) versions of **298** and **299** in the reduction of ketones (Scheme 101).[340] This class of Lewis basic species show similar behavior, but are more effective catalysts that do not require stoichiometric loadings for good selectivity. Variations on this theme have been reported by Peper and Martens[341a] and Wills and co-workers,[341b,c] with little improvement on the yields and selectivities. A large survey of structural permutations did not lead to improved selectivities. These catalysts are believed to act by a pathway mechanistically related to **300**–**303**, though no definitive studies are on record.

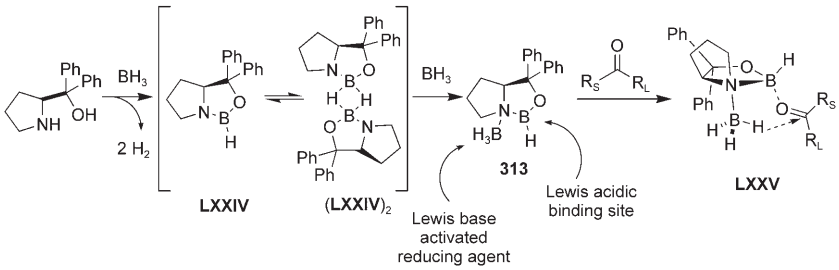
A more clearly defined example of a catalyst that effectively combines n–n*-type Lewis base and Lewis acid activation is provided by the catalytic enantioselective reduction of ketones by borane in the presence of chiral oxazaborolidine catalysts. The use of chiral amino alcohols in combination with boron- and aluminum-based hydride reducing agents has long been known as an effective method for stoichiometric asymmetric reductions.[342] However, building on the initial observation of Itsuno and co-workers, Corey and Helal have developed a well-defined catalyst system that functions with broad generality, high reaction rates, and enantioselectivities (Scheme 102).[343] Extensive variation of the amino alcohol structure and substituents led to a dazzling array of compounds, very few of which are superior to diphenylprolinol, except for specific substrate classes. The




***Scheme 102.*** Chiral oxazaborolidine catalyzed reductions of ketones. Cbz = benzyloxycarbonyl.

boron substituent plays a role in the stability and to a lesser extent the selectivity of the catalyst. The borane complex of the *B*-methyloxazaborolidine **308** is a stable, isolable, free-flowing solid that functions both as a catalyst and stoichiometric reducing agent.[344]

In a careful study of the reaction and the role of each of the reagents, it is observed that the combination of the amino alcohol with borane leads to the evolution of two equivalents of hydrogen gas (Scheme 103).[344] Examination of the




***Scheme 103.*** Mechanism of the oxazaborolidine reductions. $R_S$ = small substituent, $R_L$ = large substituent.

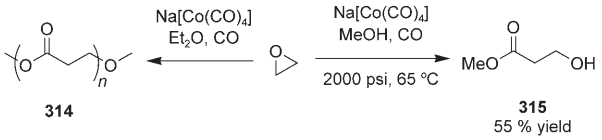
$^{11}$B NMR spectrum of this newly formed species suggests the existence of the oxazaborolidine **LXXIV**. By itself, the oxazaborolidine is not active in the reduction of ketones, but the addition of another equivalent of borane allows the reduction to proceed. Again, examination of the $^{11}$B NMR spectrum of this mixture shows the presence of a new boron species. The signal is assigned as the borane complex of the oxazaborolidine **313**. A mechanism wherein the *N*,*O*-substituted boron atom acts as a Lewis acid and the neighboring nitrogen atom serves as a Lewis base for the binding and activation of a second molecule of borane—the true hydride donor—has been suggested (**LXXV**). The proposal of a catalytically active tetracoordinate borane with highly polarized boron–hydrogen bonds clearly illustrates the concepts first outlined by Gutmann and then exemplified in the discussions of n–π* and n–σ* catalysis. The activation of both the electrophile and nucleophile by the oxazaborolidine has been examined intensively by using computational

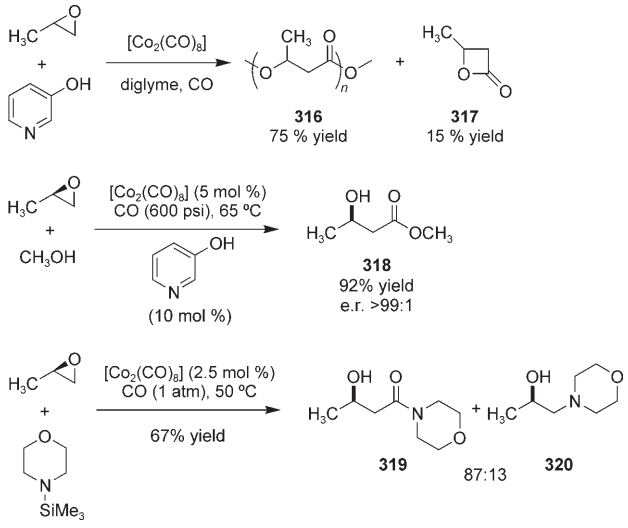
methods and is clearly consistent with the observed sense of asymmetric induction obtained in these reactions.[345] Further examples of these kinds of "bifunctional" catalysis will be discussed in Section 8.

### 7.2. Lewis Base Catalysis with Cobalt

As outlined earlier, transition-metal catalysis has intentionally not been considered in this Review. However, there is one group of transition-metal species that does merit some discussion in terms of Lewis base catalysis. The use of nucleophilic metal fragments, such as carbonylferrates and cobalt(I) complexes, has long been recognized as a unique method for nucleophilic substitutions. In organic chemistry, the use of cobalt complexes is primarily linked to the chemistry of the relatively unreactive dimetallic species, cobalt octacarbonyl [$Co_2(CO)_8$]. This compound is used for carbonylative reactions such as the Pauson–Khand reaction and hydroformylation.[346] Interestingly, the rate of several reactions catalyzed by cobalt octacarbonyl is greatly accelerated by the addition of strong Lewis bases.[347] For example, early studies by Heck demonstrated that sodium tetracarbonylcobaltate catalyzes a facile carbonylative ring opening of epoxides to generate either a polyester such as **314** or a β-hydroxy ester such as **315** in good yield (Scheme 104).[348] A 1994 patent reported the dramatic rate enhancement of the [$Co_2(CO)_8$]-catalyzed carbonylation in the presence of 3-hydroxypyridine (Scheme 105).[349] Careful control of the reaction conditions can allow for the formation of the β-lactone or polymerization to form polyesters. Jacobsen and co-workers have reported the use of this catalyzed carbonylation process as a useful adjunct to the hydrolytic kinetic resolution of epoxides. They demonstrated the ability to prepare β-hydroxy methyl esters such as **318** and morpholine amides such as **319** from enantiopure epoxides with the help of the 3-hydroxypyridine catalyst and TMS-morpholine, respectively (Scheme 105).[350]




***Scheme 104.*** Cobalt-catalyzed carbonylation of epoxides.




***Scheme 105.*** Lewis base catalyzed/cobalt-mediated carbonylative opening of epoxides.

From studies of the mechanism of disproportionation of $Co_2(CO)_8$ in the presence of Lewis bases, it is known that amines and phosphanes cleave this compound into homonuclear ion pairs (HNIPs) of the general formulation $[Co(CO)_3(LB)_n]^+[Co(CO)_4]^-$ **LXXVI**. It is thought that this reaction proceeds through the binding of at least two molecules of a Lewis base to one cobalt center followed by heterolytic cleavage of the cobalt–cobalt bond, thereby generating the homonuclear ion pair **LXXVI** (Figure 11).[347]

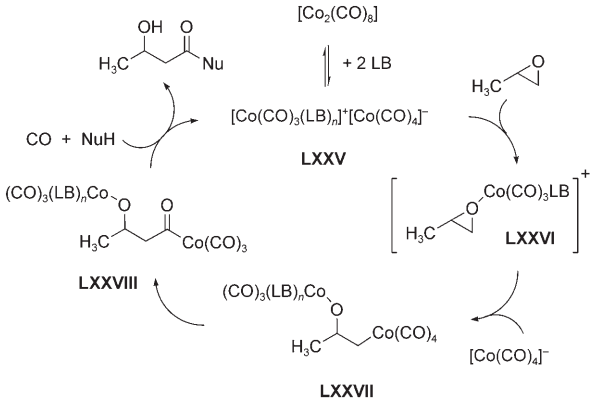
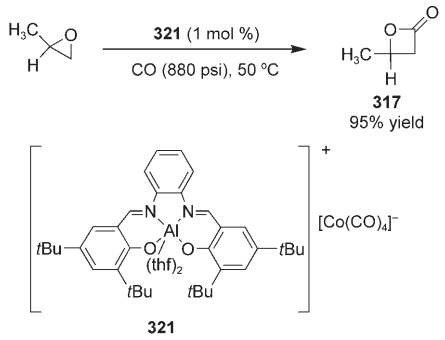



***Figure 11.*** Catalytic cycle for Lewis base catalyzed carbonylation of epoxides.

Binding of the Lewis bases polarizes the cobalt–cobalt bond, which is consistent with the Gutmann analysis. If the donor capacity of these ligands is sufficient, ionization can occur. Just as in the chemistry of $SiCl_4$, the newly generated ion pair possesses both Lewis acidic and Lewis basic fragments. Activation of the epoxide by the Lewis acidic cobalt(+1) fragment facilitates attack of the Lewis basic cobalt(−1) fragment to form **LXXVII**. Carbon monoxide insertion followed by capture of the acylcobalt species with an added nucleophile leads to the formation of the desired product and release of the catalytically active species. Recent theoretical and experimental studies have supported this mechanism, thus demonstrating the importance of both Lewis acid and base activation in the epoxide opening reaction.[351]

Alper and co-workers have extended this method through the combination of organic-soluble cobaltate salts and Lewis acids (LA), such as $BF_3{\cdot}Et_2O$.[352] Coates and co-workers have introduced a new class of catalysts of the general formula $[LA]^+[Co(CO)_4]^-$ where $[LA]^+$ is an aluminum(III)–salen, $Cp_2$titanium(III), or chromium(III)porphyrinate species.[353] The complex **321** shows excellent catalytic activity and site selectivity in the opening of epoxides, aziridines, and oxetanes (Scheme 106). This species, because of its dual properties as a Lewis acid and nucleophilic activator, should also be considered in the next section on bifunctional catalysis.

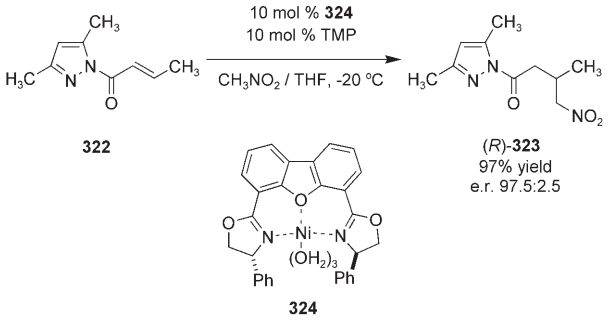



***Scheme 106.*** Ring-opening reactions of epoxides with mixed-metal catalysts.

## 8. Bifunctional Catalysis: Engineering Stereocartography[354]

Lewis base catalysis provides a unique form of catalytic "dual activation" wherein both the nucleophilic and electrophilic characteristics of a single species can be enhanced, either through polarization of bonds within the reagent or by ionization to form a highly active cationic species.

It is important to distinguish the kind of "dual activation" observed in Lewis base catalyzed processes from similar concepts that have been developed for other catalysts. One such important distinction is between what this Review has termed "dual activation" and what Itoh and Kanemasa has termed "catalytic double activation".[355] In a study of the Henry reaction between nitromethane and an α,β-unsaturated pyrazolyl amide catalyzed by a chiral nickel(II) complex, it was observed that addition of a basic amine co-catalyst was required for the reaction to proceed (Scheme 107). The




***Scheme 107.*** Catalytic double activation in the Henry reaction. TMP = 2,2,6,6-tetramethylpiperidine.

nickel species alone could not promote the reaction. Here the separate roles of the chiral Lewis acid catalyst **324** and an achiral Brønsted base (tetramethylpiperidine, TMP) are clear in promoting an efficient conjugate addition.

As Itoh and Kanemasa point out, "catalytic double activation" presents a major challenge. If the acid and base promoters can form a stable, inactive adduct, the opportunity for catalysis will be lost. In the nickel system, the steric demands of tetramethylpiperidine and the high lability of ligands at the nickel(II) center most likely preclude catalyst inhibition. An alternative solution to this problem is to constrain the Lewis basic and Lewis acidic sites within a single molecule. By attaching these mutually incompatible functional groups to a single catalyst scaffold, their geometry can be controlled and their orientations fixed in space. These molecules are intramolecular versions of systems exhibiting "catalytic double activation" and are true bifunctional catalysts.[356,357]

The analogy between such bifunctional catalysts and enzymes has been posited.[358] Just as enzymes employ entropic and enthalpic control to properly orient incoming reagents and catalytic residues in ideal geometries, the combination of basic and acidic sites within a small molecule could provide a similar benefit.[359] These bifunctional catalysts may represent the synthetic chemists' solution to the development of chemical catalysts with enzyme-like reactivities and selectivities. The power of using two modes of catalysis to promote a single reaction is clear when considering the enhanced reactivity of 3-hydroxyquinuclidine versus quinuclidine in the context of the Morita–Baylis–Hillman reaction (see Section 5.2.3).[103] An additional example of a bifunctional catalyst that combines Lewis base and Lewis acid catalysis in a single, small-molecule catalyst is the chiral oxazaborolidine used for the asymmetric reduction of ketones with borane (see Section 7.1). In view of certain limitations of enzymatic catalysis in organic reactions,[360] the development of small-molecule-based, bifunctional catalyst systems continues to attract a great deal of attention.

### 8.1. Asymmetric Alkylations with Diethylzinc: n–σ* Lewis Base–Lewis Acid Catalysis

When comparing the proposed mechanism of action of Lewis base catalyzed reactions exhibiting dual activation with bifunctional catalysis, it is immediately clear that they have similar effects: to simultaneously enhance the nucleophilic and electrophilic character of a reagent in the bond-forming transition structure. When seen in this light, it may be difficult to understand the need for a distinction between these two categories. However, it is important to remember that simply enhancing reactivity through changes in hybridization and bond polarity does not imply that the reacting groups are able to attain the geometry required by the transition structure. In the cases of the Lewis base catalyzed reactions of allylic polyhalosilanes, the six-membered-ring transition structure provides the perfect manifold to transmit both characteristics of the cationic silicate (Scheme 84). The electron-deficient, hypervalent silicon atom activates the aldehyde electrophilically. The increased electron density at the α-carbon atom is then transmitted through the conjugated system to the γ-carbon atom. The distal end of the allyl fragment is then able to attain the correct geometry for nucleophilic attack.

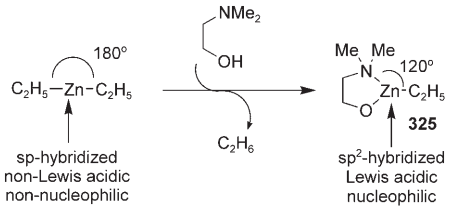
Gutmann's analysis of a Lewis base–Lewis acid adduct predicts that a decrease in electron density at one atom must be accompanied by a corresponding increase in electron density at neighboring atoms. Therefore, it may seem surprising that more cases of Lewis base induced, dual activation have not been found. Again, the constraints of the transition-structure geometry may provide sufficient grounds

for eliminating many candidates. Bifunctional catalysis avoids this problem because it separates the Lewis acidic and Lewis basic functionalities in a catalyst. The two moieties can then better position themselves in space, thereby allowing for this intermolecular "dual activation".

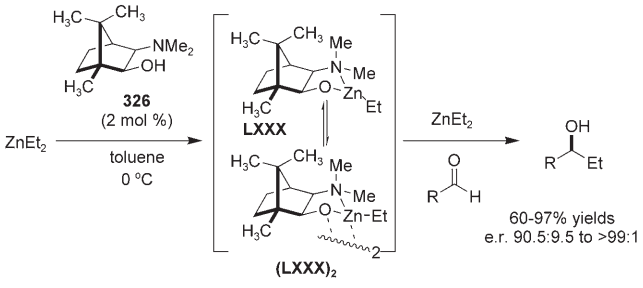
An excellent example of how bifunctional catalysis allows chemists to capitalize on Lewis base induced dual activation, even when the geometrical requirements of the reaction prevent it, is the amino alcohol catalyzed addition of dialkylzinc compounds to aldehydes.[361] Diethylzinc, by itself, is a relatively unreactive species toward carbonyl electrophiles. As a result of the low polarity of the sp-hybridized zinc–carbon bonds, these organometallic species are poor nucleophiles.[362] In fact, no reaction can be observed between benzaldehyde and diethylzinc under a variety of conditions.[361]

Reaction of a Lewis base such as dimethylaminoethanol with diethylzinc leads to the formation of a nonlinear, trimeric, trivalent zinc species **325**, in which the hybridization state of the zinc–carbon bonds is changed from sp to $sp^2$ (Scheme 108).[363] The electron density in the bond is now polarized toward the carbon atom because of its higher degree of p character. The presence of the more electronegative oxygen ligand also enhances the Lewis acidity of the zinc atom, as seen in the development of a LUMO on the zinc atom.[364] This simultaneously renders the zinc atom more electrophilic and the ethyl group more nucleophilic, which is consistent with the Gutmann analysis.




***Scheme 108.*** Effects of Lewis base binding to diethylzinc.

To capitalize on this redistribution of electron density, Noyori et al. employed the chiral, vicinal amino alcohol dimethylaminoisoborneol (DAIB, **326**) and diethylzinc to form a new trivalent complex **LXXX** in which the electrophilic and nucleophilic characters of the alkylzinc complex are enhanced in an asymmetric environment (Scheme 109). This in situ generated complex is an effective catalyst for the highly selective addition of diethylzinc to a variety of aldehydes, to afford the corresponding secondary alcohols (Scheme 109).[365] The use of nonpolar solvents is essential to high reaction rates, presumably because more basic solvents such as tetrahydrofuran may interfere with the binding and electrophilic activation of the aldehyde.




***Scheme 109.*** DAIB-catalyzed additions of diethylzinc to aldehydes. DAIB = dimethylaminoisoborneol.

On the basis of the preceding analysis of the trivalent complex **325**, one could propose that **LXXX** could activate the aldehyde and deliver the ethyl group through a four-membered-ring transition structure. Yet experiments performed with a stoichiometric amount of preformed complex **LXXX** did not lead to the formation of secondary alcohol products.[365c] The addition of a second equivalent of diethylzinc to the catalyst was required for high conversions. This finding suggests that although it seems possible for **LXXX** to complete the reaction, the required transition-structure geometry disfavors reaction through this bimolecular manifold. Further support for this conclusion was gained from matrix-isolation studies on the reaction conducted by Itsuno and Frechét.[366]

A mechanism has been proposed that involves a bifunctional n–σ* Lewis base–Lewis acid activation rather than dual activation of a single alkylzinc molecule (Figure 12).[365d] In this mechanism, the aldehyde is activated by the complexed zinc atom ($Zn_A$), but the ethyl group is delivered from a second molecule of diethylzinc which is complexed to the vicinal ethereal oxygen atom ($O_A$). Complexation between $O_A$ and the second molecule of diethylzinc ($Zn_B$), reminiscent of the activation of a second molecule of borane in the Corey–Itsuno catalyst (Section 7.1), accelerates nucleophilic addition through rehybridization. Complexation may also contribute to the higher electrophilicity of the complexed zinc atom ($Zn_A$) by removing electron density provided by the vicinal lone pair of electrons on the oxygen atom ($O_A$). The reaction finally proceeds through a closed, six-membered-ring tran-

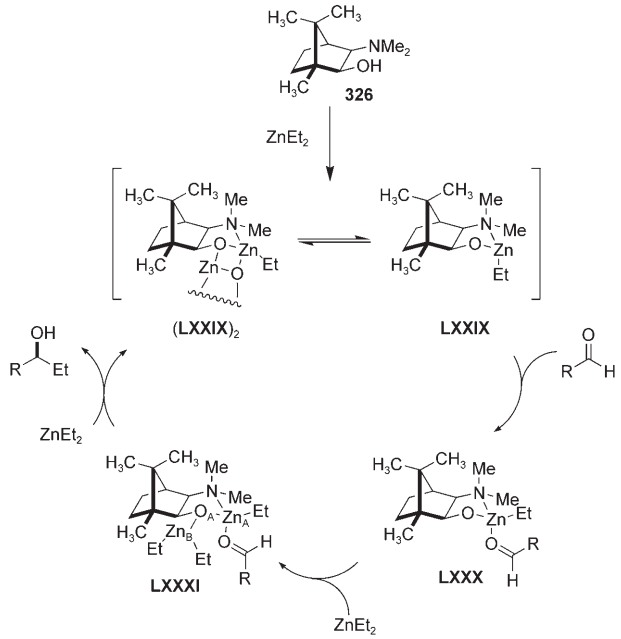
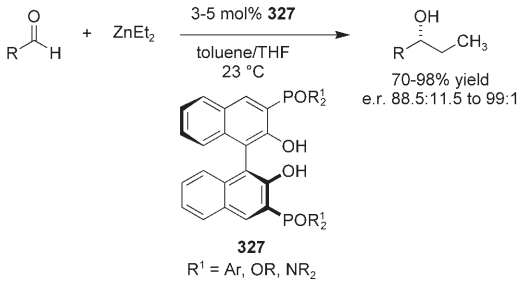



***Figure 12.*** Proposed mechanism for diethylzinc additions to aldehydes.

sition structure to complete the reaction. Catalyst turnover is facilitated by transmetalation with another molecule of diethylzinc.

The proposed catalytic cycle for these reactions includes several features that highlight the bifunctional nature of these catalysts. The complex **LXXX** is believed to exist as part of an equilibrium between an unreactive dimer $(\mathbf{LXXX})_2$ and a reactive monomer **LXXX** on the basis of a strong $ML_2$-type nonlinear effect.[367] The intermolecular interaction between the two units of **LXXX** occurs precisely in the same manner as in the alkylation transition structure discussed above.

This catalyst system, much like the oxazaborolidine developed by Corey and co-workers, separates the nucleophilic and electrophilic functionalities in a single reagent and gives those two roles to closely placed functional groups in the complex. This juxtaposition allows the polarized nature of the Lewis base adduct to be exploited, despite restrictive geometrical requirements. A similar concept has been applied in the design of a binol-based ligand for the addition of diethylzinc to aldehydes by Ishihara and co-workers (Scheme 110).[368] The phenolic oxygen atom serves a similar role to that of the alcohol in **326** while the nearby phosphine oxide mimics the role of the dimethylamino group in **326**. The high selectivity observed in the reactions discussed in this section is likely due to the constrained conformation of the complex and bound substrates. However, as will be seen in the following example, greater separations between the two, activating functional groups are also possible and can provide for highly tunable catalysts.

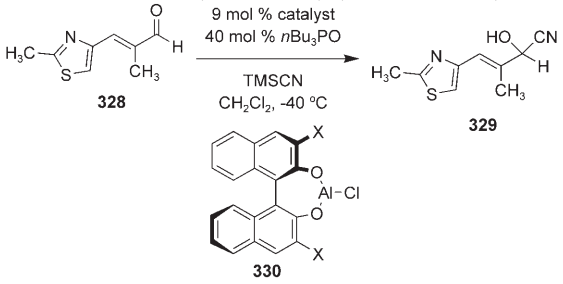



***Scheme 110.*** Alternative Lewis base catalysts for diethylzinc addition to aldehydes.

### *8.2. Silylcyanation Revisited: n–σ* Lewis Base–Lewis Acid Catalysis*

The ability to engineer a catalyst that will simultaneously provide both nucleophilic and electrophilic activation of a single reagent, despite the constraints imposed by the transition-structure geometry, is represented in the asymmetric additions of diethylzinc to aldehydes discussed above. The design of a system that exhibits simultaneous activation of two separate reagents has found another solution through catalyst design. Shibasaki and co-workers have investigated the use of carefully designed bifunctional catalysts containing Lewis acidic metal sites in proximity to Lewis basic, phosphine oxide moieties. The position of the groups in space could be optimized to obtain high stereoselectivity, but also to prevent catalyst inactivation. Their initial report on this design strategy described the addition of TMSCN to aldehydes. High yields and selectivities could be obtained in the silylcyanation of a wide variety of aldehyde substrates (Table 11).[369] A comparison of the two catalysts **330** and **331** with differing linker lengths between the aluminum center and the pendant phosphane oxide illustrates how careful conformational control is key to the success of a bifunctional catalyst which is prone to self-inactivation.

***Table 11:*** Bifunctional catalysis in the silylcyanation of aldehydes.




| Entry | Catalyst | X | Yield [%] | e.r. (*R*/*S*) |
|---|---|---|---|---|
| 1 | **330** | $CH_2POPh_2$ | 91 | 98.5:1.5 |
| 2 | **331** | $CH_2CH_2POPh_2$ | 4 | n.d.[a] |
| 3 | **332** | $CHPh_2$ | 50 | 44:56 |

[a] Not determined.

The mechanism formulated by Shibasaki and co-workers suggests that the aluminum atom binds the aldehyde, activating it electrophilically, while the phosphane oxide binds the TMSCN, activating it nucleophilically through an n–σ*-type Lewis base interaction (Figure 13). A transition structure **LXXXIII** was proposed that rationalized the observed sense of asymmetric induction in these addition reactions and combined both of these interactions.

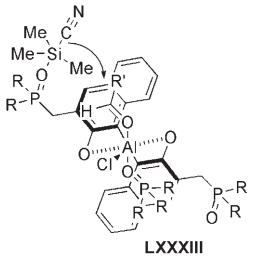



***Figure 13.*** Proposed transition structure for silylcyanation of aldehydes.

The unprecedented nature of this mode of catalysis has resulted in additional studies having been undertaken to support the involvement of both Lewis acid and base catalysis. Several interesting observations suggest that these systems truly function as n–σ* Lewis base–Lewis acid catalysts. In control experiments, it was shown that under the optimal reaction conditions neither the parent complex formed from binol and $EtAlCl_2$, not tri-*n*-butylphosphane by itself was able

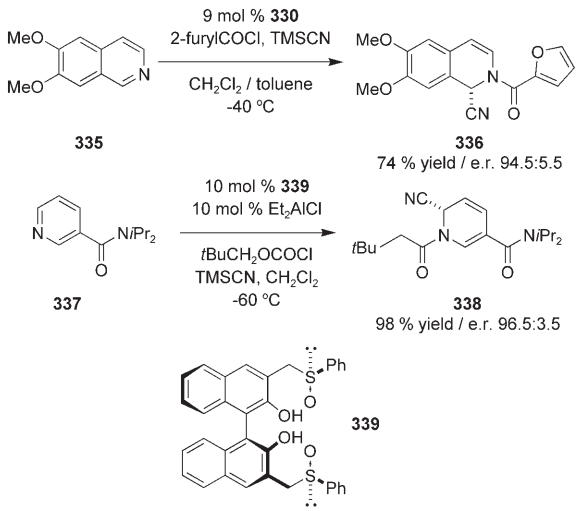
to promote the cyanation. Enhancing the Lewis basicity of the phosphane oxide moiety by exchange of the phenoxy groups for more electron donating *p*-$(Me_2N)C_6H_4$ groups leads to an observable rate enhancement, in agreement with the idea that these Lewis basic moieties are intimately involved in catalysis.[369b]

Additional support is garnered by comparing catalysts **330** and **332**. In the reaction of TMSCN with aldehyde **328**, the optimal catalyst leads to the formation of (*R*)-**329**, while the diphenylmethyl-substituted catalyst **332** leads to the formation of (*S*)-**329** (Table 11, entry 3). This reversal in the sense of asymmetric induction suggests that steric shielding provided by the 3,3′ substituents should favor attack on the pro-*S* face of the complexed aldehyde. The formation of the (*R*)-**329** with the phosphine oxide containing catalyst **330** supports the formation of a catalyst–TMSCN complex and the n–σ* Lewis base interaction proposed by Shibasaki and co-workers in their stereochemical analysis.[369b]

Recent in situ IR studies of this catalyst system have lent additional support to the existence of this n–σ* interaction between the catalyst and TMSCN.[370] The combination of either the catalyst **330** or tributylphosphine oxide with TMSCN led to the appearance of a new band in the IR spectrum that was tentatively assigned as either a cyanide ion or a trimethylsilyl isocyanide. The equilibrium between silyl cyanides and isocyanides is known to be sensitive to the addition of Lewis acids and the nature of the silyl substituents,[371] but studies on the influence of Lewis bases on this equilibrium have not been conducted. The interaction of the TMSCN with the aluminum center was precluded through in situ IR studies of a binol complex of $Et_2AlCl$. All these observations support the bifunctional nature of these catalysts and the role that the phosphine oxide moiety plays in **330** in the n–σ* type Lewis base activation of the TMSCN.

This bifunctional catalyst has also found application in two other, closely related cyanation reactions: the Strecker and Reissert reactions.[372] Shibasaki and co-workers have demonstrated that the addition of TMSCN to fluorenylimines can be effected in the presence of catalyst **330** (Table 12).[373] However, these reactions were extremely sluggish, requiring days to reach high conversion (entry 1). The addition of a substoichiometric amount of an alcohol (entry 2) or HCN (entry 3) provided for a considerable rate enhancement. This finding suggests that the proton source increases the reaction rate by facilitating catalyst turnover. This discovery led to the development of an efficient and highly selective catalytic system that employs a substoichiometric amount of TMSCN and a stoichiometric amount of HCN. Although the addition of HCN would appear to open a competitive pathway for cyanation, control experiments have demonstrated that the reaction with TMSCN is considerably faster. Therefore, the Strecker reaction proceeds through a Lewis acid–Lewis base rather than a Lewis acid–Brønsted base assisted mechanism.

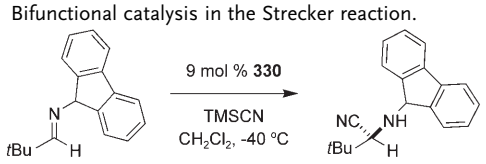
The Reissert reaction of isoquinolines and pyridines is another reaction that can be promoted by a bifunctional, Lewis base–Lewis acid catalyst. Shibasaki and co-workers have shown that in the presence of a stoichiometric amount of an acid chloride, **330** promotes the addition of TMSCN to isoquinolines in high yields and selectivities (Scheme 111).[374] In the case of pyridines, higher selectivities are obtained with the sulfoxide-containing catalyst **339**.[375] Despite these changes, it still appears that the same kind of Lewis acid–Lewis base catalysis discussed in the case of the silylcyanation of aldehydes is applicable to these reactions.




***Scheme 111.*** Bifunctional catalysis for cyanide addition to isoquinolines and pyridines.

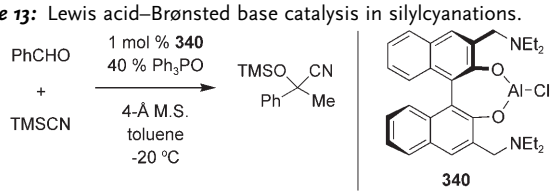
In 2002, Saá and co-workers disclosed their studies on a catalyst related to **330** that incorporates tertiary amines as the Lewis basic moieties (Table 13). Although this catalyst promotes silylcyanations with similar levels of reactivity and selectivity, careful mechanistic studies revealed that the

***Table 12:*** Bifunctional catalysis in the Strecker reaction.




| Entry | TMSCN [Equiv] | Additive (equiv) | *t* [h] | Yield [%] | e.r. |
|---|---|---|---|---|---|
| 1 | 2.0 | - | 192 | 94 | 87.5:12.5 |
| 2 | 2.0 | PhOH (0.2) | 44 | 97 | 89:11 |
| 3 | 0.2 | HCN (1.2) | 36 | 98 | 88.5:11.5 |

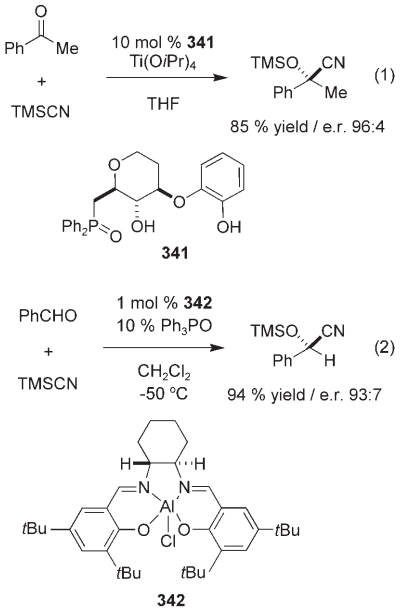
***Table 13:*** Lewis acid–Brønsted base catalysis in silylcyanations.




| Entry | Catalyst | Additive (equiv) | *t* [h] | Yield [%] | e.r. |
|---|---|---|---|---|---|
| 1 | **340** | – | 6 | 99 | >99:1 |
| 2 | (*R*)-binol–AlCl | – | 24 | 9 | – |
| 3 | (*R*)-binol–AlCl | $NEt_3$ (0.2) | 9 | 99 | 40:60 |

reaction did not proceed by a similar mechanism.[376] Instead, silylcyanations with this catalyst appear to proceed through a Lewis acid–Brønsted base assisted mechanism. Trace amounts of HCN contained in the TMSCN are needed in the initiation step. Whereas the parent binol–aluminum complex could not promote the reaction by itself, the addition of triethylamine recovered the cyanosilylation activity. However, the sense of asymmetric induction with **340** and (*R*)-binol was reversed, similar to what had been observed by Shibasaki and co-workers when investigating catalysts **330** and **332** (Table 11). Furthermore, substrates containing basic nitrogen substituents, such as 3-pyridylcarboxaldehyde, gave racemic products as a result of the introduction of competitive, achiral Brønsted basic site. The involvement of Lewis acid–Brønsted base catalysis in cyanoformylations and cyanophosphorylations with catalyst **340** has also been demonstrated.[377]

The significant change in mechanism caused by exchanging the phosphine oxide moiety contained in **330** for the tertiary amine moiety contained in **340** demonstrates the difficulty associated with correctly identifying Lewis base catalyzed reactions. Just as in the case of the fluoride-initiated reactions of silanes discussed in Section 6.1.1, mechanistic studies are required to accurately identify Lewis base catalyzed reactions. Therefore, care must be taken when discussing other related bifunctional catalyst systems for silylcyanation, especially when the mechanism is not yet clearly defined. Several examples of such catalyst systems have recently appeared. The Gd and Ti complexes of **341** developed by Shibasaki and co-workers for silylcyanation of aldehydes and imines and opening of aziridines seem a clear choice for this category when one considers the structure of the ligand. However, the lack of a detailed solution structure of these catalysts complicates a straightforward analysis [Eq. (1) in Scheme 112].[378] A number of other closely related systems that contain both Lewis acidic and Lewis basic species have been reported for the asymmetric silylcyanation of aldehydes, but their mechanisms have not yet been investigated [Eq. (2) in Scheme 112].[379]

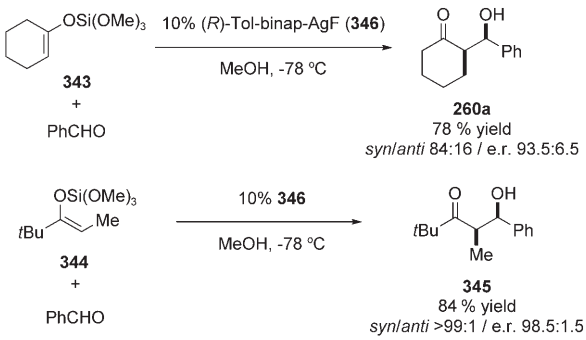



***Scheme 112.*** Potential bifunctional catalysts for silylcyanation with aldehydes.

### *8.3. Bifunctional Catalysis with Fluoride Sources: Combined n–σ* Lewis Base and Lewis Acid Catalysis*

The development of asymmetric fluoride-catalyzed reactions of silylated pronucleophiles has proven to be a significant challenge. Despite the high activity of fluoride salts as catalysts for carbon–carbon bond-forming processes, the peculiarities of the mechanisms of fluoride-catalyzed reactions have thwarted the most direct approaches. The issue of whether a particular reaction is fluoride-initiated or fluoride-catalyzed presents a separate challenge in addition to the problem of how one might create a "chiral fluoride ion". As it is impossible to covalently attach a chiral ligand to a fluoride ion, chiral ammonium and sulfonium fluoride salts have been developed with some success.[222,227a–b,314]

An alternative strategy for developing an asymmetric, fluoride-catalyzed reaction of silylated pronucleophiles would be to combine the achiral, n–σ* catalysis provided by fluoride ions with traditional chiral Lewis acid catalysis. This strategy has been reduced to practice in aldol reactions,[380] allylations,[381] cyanomethylations,[382] vinylations, and phenylations[383] with silylated pronucleophiles. The most thoroughly investigated examples in this class of reactions are silver(I) fluoride and copper(I) fluoride catalyzed aldol reactions. Studies by Yamamoto and co-workers with the *p*-Tol-binap–AgF complex **346** showed high levels of enantioselectivity in the addition of trialkoxysilyl enol ethers to aromatic and α,β-unsaturated aldehydes when the reaction was performed in a protic solvent such as methanol (Scheme 113).[380d] Yamagishi and co-workers had shown other silver salts, including acetates and tertafluoroborates, did yield the desired aldol products, but with lower levels of enantioselectivity.[380e,f] These reactions of **343** and **344** showed a high degree of *syn* diastereoconvergence. Yamamoto and co-workers suggest a closed, six-membered-ring transition structure with an additional intramolecular silicon–fluoride interaction. A flip between a boat and chair transition structure is proposed to account for the observed diastereoconvergence.




***Scheme 113.*** Bifunctional catalysis in the aldol reaction.

Although this conformational flip does rationalize the observed result, a simpler explanation may come through a mechanism that involves an open transition structure. In detailed studies that probed the mechanism of these aldol reactions catalyzed by a silver–diphosphane complex, Yamagishi and co-workers found that mixing binap–AgOAc with a silyl ketene acetal does not lead to the formation of a silver enolate, although changes in the $^1$H NMR spectrum of the silyl enol ether do occur.[384] Therefore, the authors propose the formation of a hypervalent silicate **LXXXIV** that may or may not remain associated with the silver complex (Figure 14). This complex then undergoes an aldol reaction through an open transition structure to give the observed aldol products. Yamagishi and co-workers also show that the nature of the anionic ligand in the silver complex has a strong impact on the reaction. Coordinating anions, such as acetate and chloride, behave similarly while weakly coordinating anions, such as tetrafluoroborate, show different reactivity patterns. Even though Yamagishi and co-workers did not investigate the silver(I) fluoride complex employed by Yamamoto and co-workers, a similar mechanism involving an open transition structure seems likely.

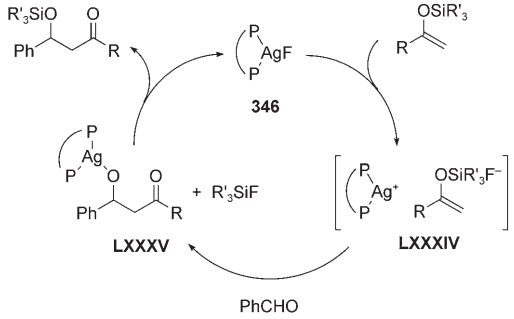
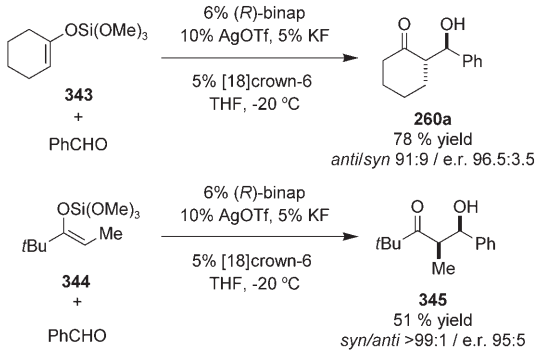


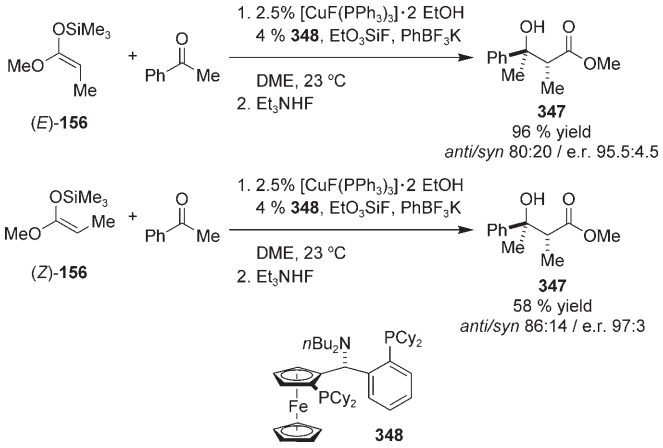

***Figure 14.*** Proposed catalytic cycle for silver(I)-catalyzed aldol reactions. $\widehat{PP}$ = *p*-Tol-binap.

Additional studies by Yamamoto and co-workers further support the notion that these silver fluoride catalyzed aldol reactions proceed through an open transition structure. Attempts to find an alternative catalyst system that would allow the reaction to proceed in aprotic solvents led to the examination of a binap/AgOTf/KF/[18]crown-6 catalyst mixture. This reaction can be performed in THF, rather than methanol, with equally high levels of enantioselectivity (Scheme 114).[385] Unlike the reactions of the silver fluoride catalyst **346**, the scope of this reaction now includes both aromatic and aliphatic aldehydes. Furthermore, the reaction is shown to be diastereodivergent. This is suggestive of a closed, chairlike, six-membered-ring transition structure and a switch in the mechanism of the reaction from that catalyzed by **346**. Fluoride most likely still plays a role in activating the trialkoxysilyl enol ether, but the nature of that interaction has changed.

Although these studies with silver(I) catalysts established the separate roles played by the Lewis basic and Lewis acidic portions of these catalyst systems, the question of whether the reactions were fluoride-initiated or fluoride-catalyzed was not addressed. In their extension of these reactions to copper(I) fluoride-phosphine catalysts, Shibasaki and co-workers begin to address this issue and provide support for the conclusion that these are truly fluoride-catalyzed reactions. With copper(I) fluoride, triphenyl phosphane, and ethanol as the catalyst, the addition of silyl ketene acetals to ketones can be accomplished in good yield (Scheme 115).[380a–c] The use of the




***Scheme 114.*** Silver(I)-catalyzed asymmetric aldol reactions.




***Scheme 115.*** Copper(I)-catalyzed asymmetric aldol reactions.

chiral bisphosphane **348** allows for high levels of enantioselectivity. When α-substituted silyl ketene acetals are employed, moderate levels of diastereoselectivity are obtained and, similar to Yamamoto and co-workers studies of the binap/AgOTf/KF/[18]crown-6 system for aldol reactions, these reactions are also diastereoconvergent.

Although the separate roles of the fluoride and copper ions are not disputed in these reports, the question of whether the reactions are fluoride-initiated or -catalyzed remains. Carreira and co-workers have shown in a closely related catalyst system that the reactions are merely fluoride-initiated.[386] To address the issue with this system, Shibasaki and co-workers investigated the catalytic activity of a copper(I) alkoxide in the aldol reaction. These alkoxide species, which were meant to mimic the copper aldolates **LXXXIX** formed in the aldol addition, are not effective catalysts (Figure 15).

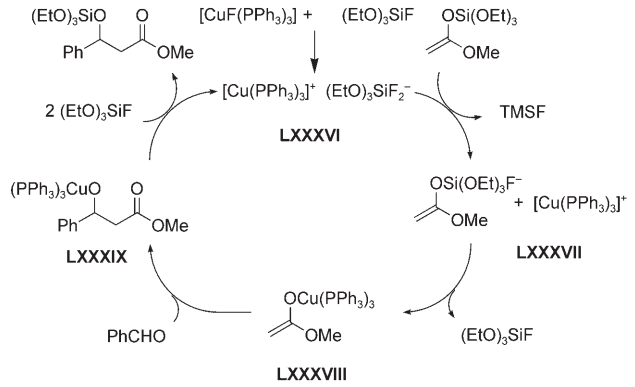
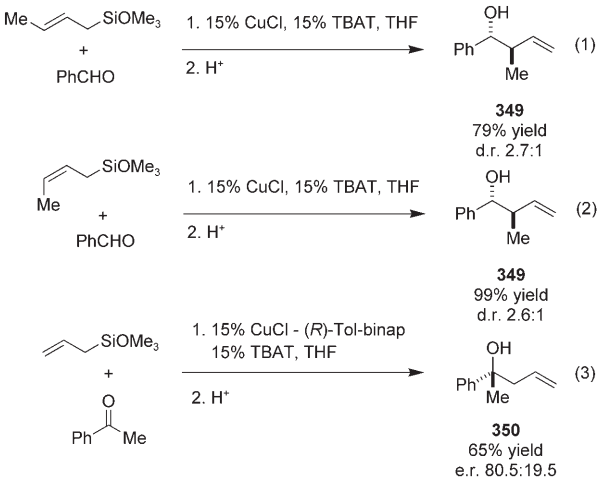



***Figure 15.*** Proposed mechanism of copper(I)-catalyzed aldol reactions.

Since autocatalysis by the copper(I) alkoxide is not operative, the role of the fluoride ions was investigated more thoroughly. In analogy to the beneficial effect provided by the addition of TMSF in the fluoride-catalyzed aldol reaction,[216b] the addition of triethoxysilyl fluoride is also observed to accelerate this aldol reaction. Since transmetalation of **LXXXIX** with this silylating reagent releases fluoride ions, the role of the fluoride ions in the initial steps of the catalytic cycle seems consistent with this analysis. The use of a more electrophilic difluoride such as dimethoxydifluorosilane provides further rate enhancements. Taken together, these observations strongly suggest that fluoride is the true chain-carrying species. As such, these reactions should be categorized as examples of bifunctional catalysis.

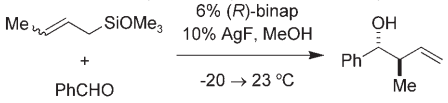
The exact mechanism, and therefore the involvement of combined n–σ* Lewis base/chiral Lewis acid catalysis, is less clear in the case of asymmetric allylations with allyl trialkoxysilanes promoted by silver(I) and copper(I) fluorides **346**. However, the close mechanistic similarity between these systems warrants further discussion. Enantioselective allylation with a silver(I) fluoride catalyst was first reported by Yamamoto and co-workers in 1999 (Table 14).[381c] In the presence the *p*-Tol-binap–AgF complex **346**, high levels of enantioselectivity are obtained in the addition of trialkoxysilanes to aromatic and α,β-unsaturated aldehydes. Allylations with 2-butenylsilanes give high *syn* diastereo- and enantioselectivity, regardless of the geometry of the allylic silane. Little mechanistic information was provided at this point, other than the observation by $^1$H NMR spectroscopy that the combination of **346** with the 2-butenyltrimethoxysilane in [D$_7$]DMF/CD$_3$OD leads to the disappearance of the signals corresponding to the silane. The authors propose the intermediacy of an allylsilver(I) complex. The diastereoconvergence of the reaction is rationalized through the assumption that isomerization of the allylic silver species is faster than allylation. No studies on whether or not the fluoride ions act as an initiator were presented.

Shibasaki and co-workers have extended bifunctional catalysis of allylation by using a copper(I) fluoride catalyst, and in doing so provided additional insights into the mechanism of the reaction which support the hypothesis that these are truly n–σ* Lewis base/chiral Lewis acid catalyzed reactions.[380a–c,381a,b] The exchange of copper(I) for silver(I) allowed for a significant expansion in the scope of this method to include the allylation of ketones and imines.[381b] A high degree of *syn* diastereoconvergence is observed in the reactions of (*E*)- and (*Z*)-2-butenylsilanes [Eq. (1) and (2) in Scheme 116]. It was also demonstrated that the reaction could be rendered enantioselective through the use of the chiral phosphine (*R*)-Tol-binap [Eq. (3) in Scheme 116]. The mechanism of the reaction was not explicitly investigated, but the diastereoconvergence of the reaction, in conjunction with the observation that additional triethoxysilyl fluoride accelerates the reaction, suggests a mechanistic analogy between these reactions and the aldol reactions described previously. Still, further investigations are warranted because some evidence of fluoride initiation has been reported in related reactions with *N*-benzoylhydrazones.[387]




***Scheme 116.*** Copper(I)-catalyzed asymmetric allylations of ketones. TBAT = tetrabutylammonium triphenyldifluorosilicate.

***Table 14:*** Bifunctional catalysis in allylations of aldehydes.




| Entry | *E*/*Z* | Yield [%] | d.r. | e.r. (*anti*) |
|---|---|---|---|---|
| 1 | 83:17 | 77 | 92:8 | 98:2 |
| 2 | <1:99 | 82 | 94:6 | 97:3 |
| 3 | 45:55 | 99 | 93:7 | 97:3 |

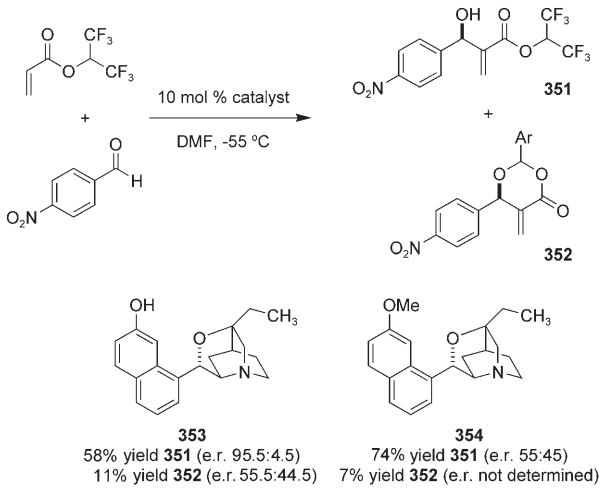
### *8.4. Bifunctional Catalysis in the Morita–Baylis–Hillman Reaction: n–π* Lewis Base and Brønsted Acid Catalysis*

Bifunctional catalysis can provide for a novel and effective method to introduce a chiral environment into an existing Lewis base catalyzed process. The additional activation by a Lewis acid can provide important contributions to reactivity and selectivity. However, Brønsted acid catalysis can also play an important role in bifunctional catalysis. Major

advances in the development of enantioselective Morita–Baylis–Hillman reactions (Section 5.2.3), originally classified as an example of n–π* Lewis base catalysis, have come through the application of bifunctional catalysts which combines Lewis basic and Brønsted acidic sites in a single structure. As proton transfer in the zwitterionic aldolate intermediate **XVI** makes a significant contribution to the overall reaction rate (Figure 5),[99,101,102] the addition of hydrogen-bonding substituents to a specific catalyst provides a novel opportunity to influence the rate and selectivity of this important carbon–carbon bond-forming reaction. Inspired by the effect of protic solvents on the rate of the reaction, several researchers have devised catalysts that include both Lewis basic and Brønsted acidic moieties. Some systems combine a Brønsted acidic site with a chiral Lewis basic site in the same molecule. Others employ a chiral Brønsted acid with an achiral Lewis base as separate entities.

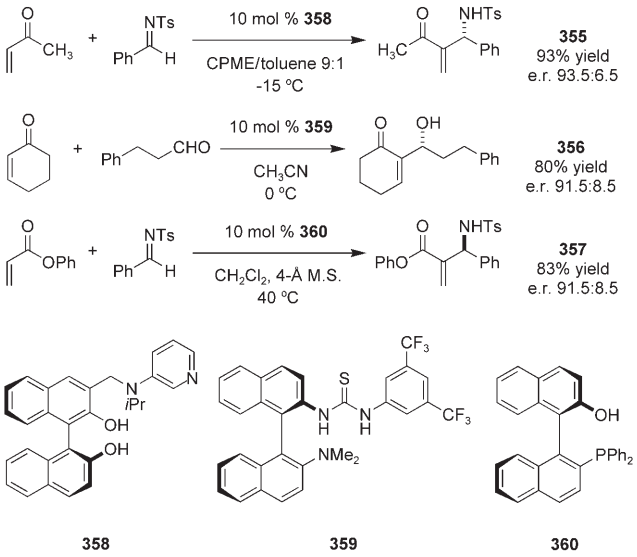
The first major breakthrough in the enantioselective Morita–Baylis–Hillman reaction came from Hatakeyama and co-workers in 1999 (Scheme 117).[388] The use of β-isocuperidine (**353**) as a catalyst for the reactions of hexafluoroisopropyl acrylates gives good yields and selectivities, despite the fact that previous studies had shown a variety of cinchona alkaloids to be ineffective catalysts for these reactions.[389] The product is generally formed as a mixture of the desired β-hydroxy ester **351** along with small amounts of the dioxanone **352**. The observation of dioxanone-containing products is supportive of the mechanism proposed by McQuade and co-workers involving a hemiacetal intermediate in the crucial proton-transfer step.[99] The research groups of Hatakeyama and Shi have employed this and other closely related catalysts for the reactions of numerous aldehydes and imines as well as to the total synthesis of several natural products.[390]




***Scheme 117.*** Centrally chiral, bifunctional catalysis in the Morita–Baylis–Hillman reaction. Ar = 4-$NO_2C_6H_4$.

This system incorporates two interesting features: 1) the use of a highly electrophilic acrylate and 2) a remote phenol group. The fluorinated ester is essential for rapid rates in the carbon–carbon bond formation.[391] Other fluorinated esters, such as trifluoroethyl acrylate and hexafluoro-*n*-propyl acrylate, showed dramatically decreased reaction rates when compared to the hexafluoroisopropyl acrylate. In line with the observation that Brønsted acids are crucial to obtaining high yields, Hatakeyama and co-workers have shown that the remote phenolic oxygen atom plays a significant role in obtaining high levels of selectivity. Analogous catalysts that contain methylated phenols (such as **354**) perform poorly when compared to **353**.[388]

In addition to the use of cinchona alkaloids as scaffolds for bifunctional Brønsted acid/Lewis base catalysts, several different catalysts have been built around the axial chirality present in conformational restricted binaphthyl derivatives (Scheme 118). Using a modified binol derivative, Sasai and co-workers found that the pyridine-containing Lewis base **358** performed well in the reaction of methyl vinyl ketone with imines.[392] Wang et al. also investigated an *N*,*N*-dialkylaniline-containing Lewis base **359** that incorporates a thiourea as a Brønsted acid co-catalyst. This catalyst performed well in the reaction of 2-cyclohexenone with a variety of aldehydes.[393]



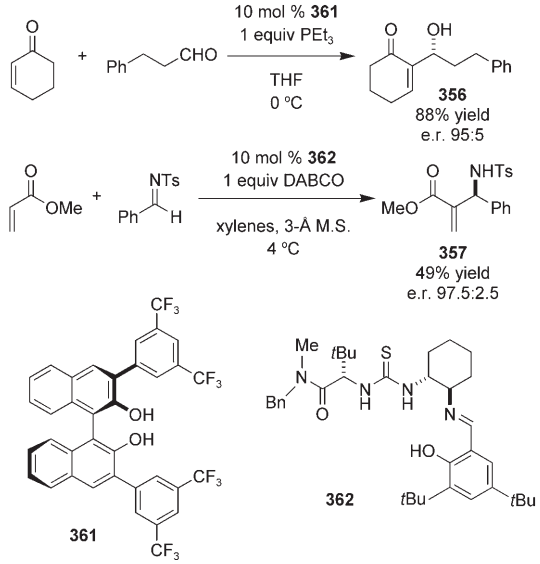

***Scheme 118.*** Axially chiral, bifunctional catalysis in the Morita–Baylis–Hillman reaction. CPME = cyclopentyl methyl ether.

Bifunctional catalysts based on phosphanes have also been developed for the enantioselective Morita–Baylis–Hillman reaction. The first successfully employed asymmetric phosphane catalyst is the commonly available dimeric Lewis base binap.[394] Although selectivities are not high, subsequent publications from the research groups of Shi and Sasai demonstrated that selectivity can be greatly enhanced by replacing one of the phosphane units with a hydroxy group, as in **360**.[395] Other phosphane-based chiral catalysts have also benefited from the introduction of hydrogen-bonding substituents.[396]

The combination of Lewis basic and Brønsted acidic sites in a single chiral scaffold is clearly a successful strategy for obtaining high reactivity and selectivity. Still, it is not the only strategy that has proven successful. Two catalyst systems, both

of which employ an achiral Lewis base and a chiral Brønsted acid, have further expanded the scope of this important reaction (Scheme 119). During studies of Lewis acid/Lewis base co-catalyzed Morita–Baylis–Hillman reactions with lanthanide–binol complexes, Schaus and co-workers recognized that binol by itself was an effective Brønsted acid co-catalyst for the reaction with α,β-unsaturated ketones.[397] Further examinations of catalyst structure led to the identification of **361** as an optimal catalyst. Unlike the examples of chiral Lewis bases discussed above, the chiral axis in the Brønsted acid catalyst is proximal to and can influence the formation of the new stereocenter by hydrogen bonding during the crucial proton-transfer step.

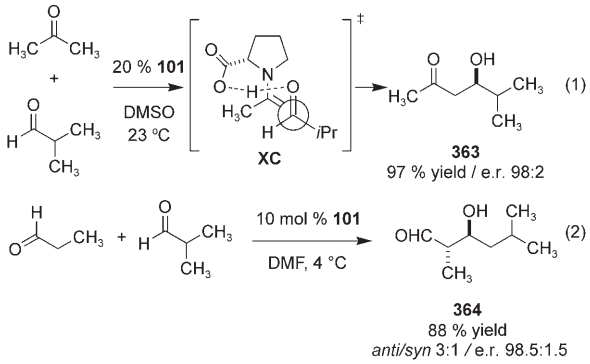



***Scheme 119.*** Binary, bifunctional catalysis in the Morita–Baylis–Hillman reaction.

A similar strategy involving separate Brønsted acid and Lewis base co-catalysts has recently appeared. Thioureas are effective catalysts for several enantioselective carbonyl and imine addition reactions.[398] Therefore, it is not surprising that catalyst **362** could also provide high levels of selectivity in the enantioselective Morita–Baylis–Hillman reactions with a wide variety of aldehydes and *N*-nosylimines.[399] A similar role for the Brønsted acid co-catalyst is proposed, wherein it likely plays a role in the final, proton-transfer step from the zwitterionic alkoxide **XVII** (Figure 5).

### *8.5. Bifunctional Catalysis with Amino Acids: Combined n–π* Lewis Base and Brønsted Acid Catalysis*

The resurgence of interest in secondary amines as Lewis base catalysts for the reactions of aldehydes and ketones has led to a variety of new methods for performing cycloadditions, Friedel–Crafts reactions, and α-functionalizations as well as Michael, Mannich, and aldol additions (Section 5.3.3). These methods provide a practical alternative to reactions which would typically be conducted using Lewis acid catalysts. The examples discussed in Section 5.3.3 employed imidazolidinone- and pyrrolidine-derived catalysts such as **104** and **116** that exert their catalytic effect through an n–π* interaction. Although these catalysts provide high selectivities, benefits can still be gained from the use of related catalysts that incorporate a Brønsted acidic site. Proline (**101**) is an excellent example of such a bifunctional secondary amine catalyst. It was the original catalyst employed by Hajos and Parrish as well as Eder, Sauer, and Wiechert in their pioneering studies on the Robinson annulation (Scheme 37),[153] and it remains broadly applicable in a wide variety of other transformations. The formation of the enamine **XLIV** is central to the success of these reactions, and hydrogen bonding between the carboxylic acid and the electrophile provides additional activation and control over the relative geometry of the reactants in transition structure **XC** (Scheme 120).[154–156]

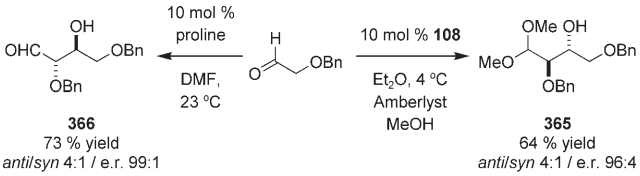



***Scheme 120.*** Proline-catalyzed aldol reactions.

The application of combined n–π* Lewis Base and Brønsted acid catalysis to the aldol reaction has had a significant impact on the scope of this important carbon–carbon bond-forming process.[400] The interaction of the secondary amine catalyst with either an aldehyde or a ketone leads to the formation of an iminium ion intermediate which is rapidly transformed into a nucleophilic enamine. This species is the true active intermediate in these Lewis base catalyzed aldol reactions.[154–156] Highly functionalized ketones and aldehydes, both of which are difficult substrates for Lewis acid catalyzed reactions, have been used as substrates in these reactions. Initial studies focused on the use of acetone as a nucleophile [Eq. (1) in Scheme 120],[401] but the scope soon expanded to other substrates. Dimerization of aldehydes as well as crossed aldehyde–aldehyde aldol reactions[402] can be performed with equal facility, comparable yields, and selectivities [Eq. (2) in Scheme 120].

In the case of the aldol reaction, similar diastereo- and enantioselectivities can be obtained with both simple n–π* and bifunctional catalysts (Scheme 121). The catalyst **108** leads to the formation of (2*R*,3*R*)-**365** through steric shielding of the *Si* face of the enamine by the bulky benzyl and *tert*-butyl substituents on the catalyst.[187] In contrast, the use of proline (**101**) leads to the formation of (2*S*,3*S*)-**366** through hydrogen bonding of the aldehyde to the carboxylic acid moiety of the *E* enamine.[403] This comparison also makes clear that larger, higher molecular weight catalysts such as **104**



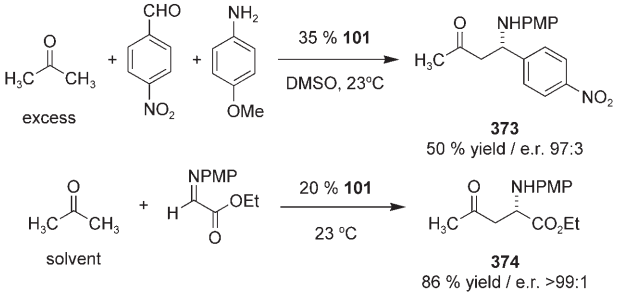

***Scheme 121.*** Comparison of n–π* and bifunctional catalysis with secondary amines.

or even **114** must be employed if stereocontrol is to be maintained in the absence of the coordinative interactions provided by simpler bifunctional catalysts such as **101**.

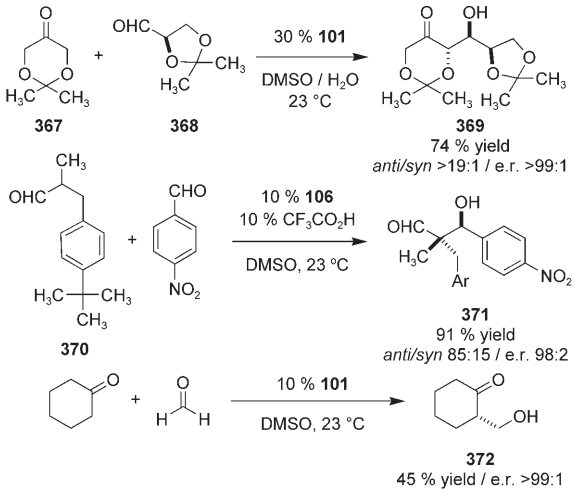
The intramolecular aldol reaction initially investigated by Hajos and Parrish as well as Eder, Sauer, and Wiechert has also been further investigated and shown to provide highly functionalized five- and six-membered rings.[404] The mechanism of these reactions has been studied extensively by using both experimental and computational methods. Despite early studies that suggested two catalyst molecules were involved in the carbon–carbon bond-forming step,[405] subsequent investigations have ruled out this possibility in favor of a simple enamine mechanism.[406] These results also lend support to the importance of the carboxylic acid/aldehyde hydrogen bond in determining the stereochemistry of the product.[407] The *anti* diastereoselectivity of these aldol reactions is a result of the selective formation of the *E* enamine and the formation of a hydrogen bond *anti* to the aldehyde substituent.

High yields and selectivities can be obtained, even when highly functionalized substrates are employed (Scheme 122).[408] Stereogenic quaternary centers can be formed through the use of unsymmetrically α,α-disubstituted aldehydes such as **370**.[409] Simple substrates such as formaldehyde even perform well under these conditions.[410] These highly functionalized products have attracted a great deal of synthetic interest since they can be easily transformed into a variety of carbohydrates.[411] It has also been shown that a wide variety of amino acids are capable of promoting these reactions with high selectivities, including simple amino acids (such as alanine) as well as dipeptides.[412] Some authors have suggested that this facile synthesis of carbohydrates in the presence of amino acids may provide clues to gluconeogenesis and the origins of biomolecular homochirality.[413]

The success of these bifunctional catalysts in the aldol reaction is mirrored in the closely related Mannich reaction of imines (Scheme 123).[414] Again, a wide variety of amino acid derived catalysts can be used to effect this transformation with high yields and selectivities, although proline remains the most common choice as the catalyst.[415] These secondary amine catalysts exert their effect through the formation of a nucleophilic enamine that participates in the carbon–carbon bond-forming process. Both aldehydes and ketones can be used as donors in these reactions with a wide variety of imine substrates.[416] Depending on the structures of the reacting partners, the reaction can be performed with preformed imines or as a direct, three-component reaction where the imine is formed in situ. Quaternary centers can be formed with high levels of selectivity in the reactions of α-ketimino esters as well as in the reactions of α,α-disubstituted aldehydes.[417] Amino methylations can even be performed in a direct Mannich reaction using formaldehyde and an aniline.[418]

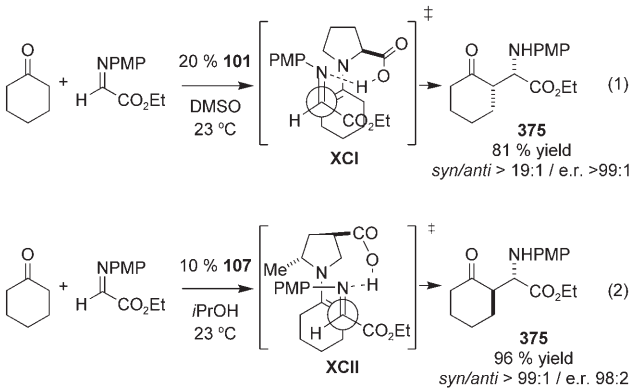



***Scheme 123.*** Bifunctional catalysis in the Mannich reaction. PMP = 4-methoxyphenyl.




***Scheme 122.*** Bifunctional catalysis in the aldol reaction.

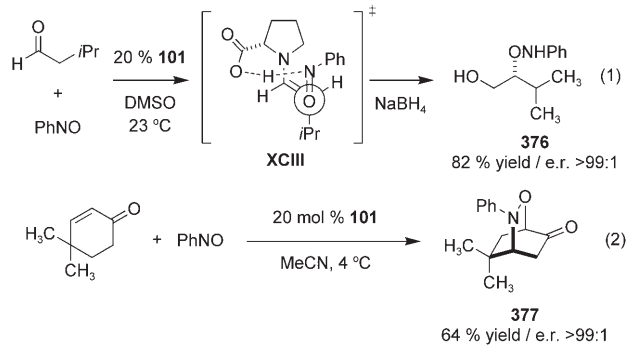
Unlike the related aldol reaction, the *syn* diastereomer is generally obtained in these Lewis base catalyzed Mannich reactions [Eq. (1) in Scheme 124]. Computational modeling studies suggest that this relative stereochemistry arises from attack of the *E* enamine on the *E* imine (as shown in **XCI**).[419]




***Scheme 124.*** Control over diastereoselectivity in the Mannich reaction.

Access to the *anti* diastereomer can be achieved through careful design of the Lewis base catalyst. Barbas and co-workers have shown that shifting the position of the carboxylic acid group from the 2- to the 3-position of the pyrrolidine leads to a dramatic shift in the diastereoselectivity of the reaction [Eq. (2) in Scheme 124].[420] High levels of *anti* diastereoselectivity can be obtained in the reactions of aldehydes and ketones with imino glyoxylates when **107** is employed as a catalyst.

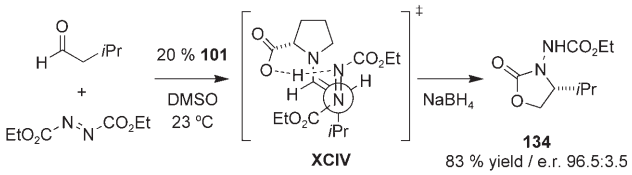
The role of the hydrogen bond between the carboxylic acid moiety and the electrophilic aldehyde or imine in aldol and Mannich reactions primarily controls which of the enantiotopic faces of the reaction partners will combine in the carbon–carbon bond-forming step. However, this hydrogen-bonding interaction can also play an important role in determining the site selectivity of the reaction. In the α functionalization of aldehydes and ketones with nitrosobenzene, the formation of a hydrogen bond between the lone pair of electrons on the nitrogen atom of nitrosobenzene and the carboxylic acid contained in the enamine intermediate provides high levels of constitutional- and enantioselectivity for the α-oxygenation product [Eq. (1) in Scheme 125].[421] The higher basicity of the nitrogen atom




***Scheme 125.*** Bifunctional catalysis in α oxygenations.

favors its protonation and leads to a transition structure resembling **XCIII**.[422] The use of α,β-unsaturated ketones as substrates led to the identification of a [4+2] cycloaddition process which yields the bicyclic compounds **377** with high levels of enantioselectivity [Eq. (2) in Scheme 125].[423] A formal [4+2] cycloaddition process can also be performed by linking α-aminooxylation with a Wittig rearrangement in a one-pot process.[424]

The use of bifunctional catalysts, such a proline, for α functionalization has allowed for the development of highly selective α oxygenations with other reagents as well. The addition of singlet oxygen, iodosobenzene, and oxaziridines can also be performed using these bifunctional catalysts.[425] Extension to other heteroatom additions is also possible under proline catalysis. The reaction of aldehydes and ketones with diazodicarboxylates leads to the formation of α-amination products in high yields and selectivities (Scheme 126).[426] Tertiary centers can be formed with high levels of selectivity when α,α-disubstituted aldehydes are employed.[427] Studies on the mechanism of this α amination




***Scheme 126.*** Bifunctional catalysis in α aminations.

have revealed interesting autocatalytic effects, similar to those observed in α aminooxylations catalyzed by proline.[428] Subsequent transformation of these products to amino alcohols and α-amino acids demonstrates the potential of bifunctional catalysis. However, it should be remembered that despite the importance of hydrogen bonding in the mechanisms of these reactions (cf. **XCIV**), all the reactions discussed in this section are still driven by the formation of reactive enamine intermediates accessed through the same kind of n–π* Lewis base catalysis (see Section 5).

## 9. Carbenes: Lewis Base Catalysis with Dual Activation

As mentioned in preceding sections, the use of Lewis bases can open up possibilities for novel modes of catalysis, either through dual activation or through bifunctional catalysis. In both cases, simple Lewis bases are involved which act as solely electron-pair donors. The existence of another class of Lewis bases that combines π acidity with the σ basicity of more common Lewis bases such as amines and phosphanes has long been known. Carbonyl, nitrosyl, and N-heterocyclic carbene ligands (NHCs), play an important role in inorganic coordination chemistry.[429] Such species are still Lewis bases, despite these additional characteristics. Recently, the use of NHCs as simple n–π* and n–σ* catalysts has been demonstrated in acylations (Section 5.1.1) as well as silylcyanations and trifluoromethylations (Section 6.5.1–6.5.2).

NHC catalysis of these reactions, although noteworthy, only capitalizes on the σ-donor properties of the NHCs. Application to reactions in which the both the σ-donor and π-acceptor properties of the NHC are involved has opened ûp the possibility for the development of a distinct class of catalytic processes. The great structural diversity of NHCs has allowed for the extension of these reactions into the realm of asymmetric synthesis (Figure 16).[430] The earliest application of this particular kind of Lewis base catalysis to an organic reaction came in pioneering studies of the benzoin reaction (Figure 17).[431] Whereas early methods for this umpolung reaction of a $d^1$ synthon employed cyanide ions as a catalyst, thiazolium ions were also recognized as effective catalysts for this carbon–carbon bond-forming reaction.[432] The elucidation of the special role of the thiazolium ion in the benzoin reaction by Breslow was an important step, not only for understanding the mode of action of a large family of enzymes, but also for the development of new catalytic processes.

The mechanism of this reaction is well established and supported by isotopic labeling, kinetic isotope effect studies,

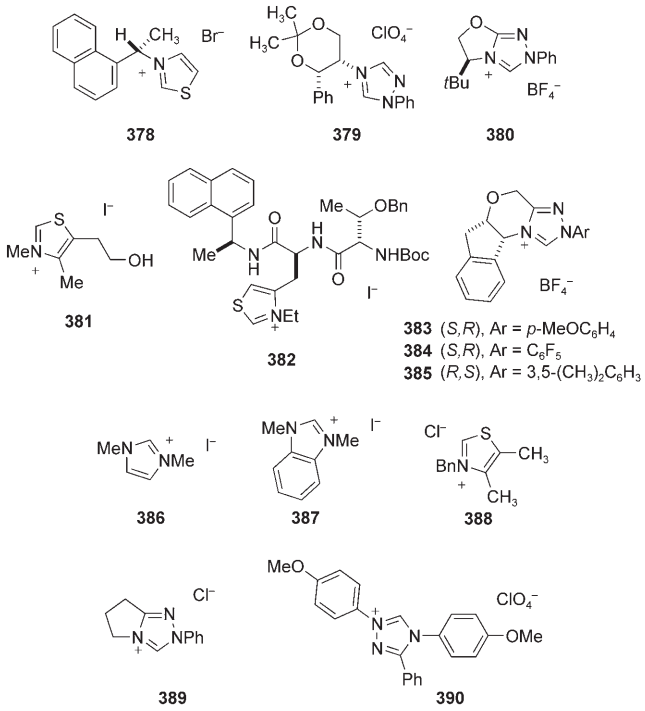



***Figure 16.*** Structurally diverse NHCs for Lewis base catalysis.

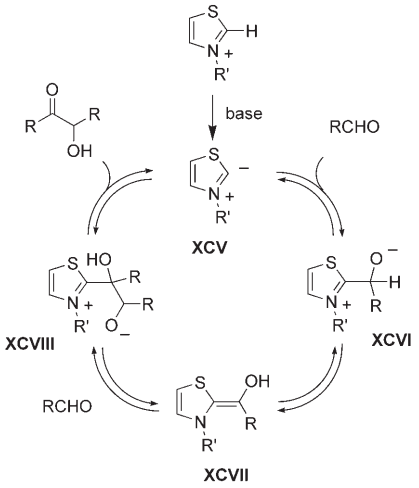
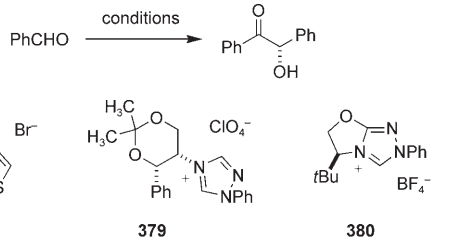



***Figure 17.*** Proposed mechanism of the benzoin reaction.

and computational analysis.[433] In the thiazolium ion catalyzed benzoin reaction, the active intermediate **XCV** is easily formed from a thiazole because of the low p$K_a$ value of the C2 proton. The newly formed, neutral species **XCV** is actually a stable NHC, as a result of π donation from the neighboring nitrogen atom. Although this species is a potent σ donor that can participate in subsequent steps as a strong Lewis base, it is also a π acid. It is exactly this unique kind of dual activation that makes thiazolium ions so effective in this particular carbon–carbon bond-forming reaction. Attack of the thiazolidine carbene on an aldehyde leads to the formation of an alkoxide **XCVI**, which after proton transfer, can be converted into a heteroatom-substituted enol **XCVII**. This species now possesses $d^1$ umpolung reactivity[123] derived from the latent enamine formed after proton transfer. Attack on a second molecule of aldehyde followed by release of the catalyst generates the observed product.

The success of thiazolium ions as catalysts for the benzoin reaction heralded the development of an NHC-catalyzed, enantioselective benzoin reaction (Table 15).[434] Initial studies by Sheehan et al. and others focused on chiral thiazolium ions such as **378** but were unable to provide high levels of selectivity.[435] Still, the observation of even moderate levels of enantioselectivity indicated the potential of this strategy. Improvements in selectivity only came after the recognition that thiazolidine carbenes are not unique in their ability to promote the benzoin reaction. Studies by Miyashita et al. demonstrated that imidazolium and benzimidazolium ions such as **386** and **387** could be used as catalysts for the benzoin reaction, although an asymmetric version of this reaction was not investigated.[436] Enders et al. finally succeeded in the development of an asymmetric NHC-catalyzed benzoin reaction by employing chiral triazolium ions such as **379** and **380**.[437] Good yields and enantioselectivities are obtained in the homobenzoin reaction of aromatic aldehydes. The mechanism of the reaction has been probed computationally and a model has been constructed which correctly predicts the absolute configuration of the benzoin products.[438] Aldehyde–ketone crossed benzoin reactions have also been accomplished using chiral triazolium salts.[439]

***Table 15:*** NHCs in the enantioselective benzoin reaction.

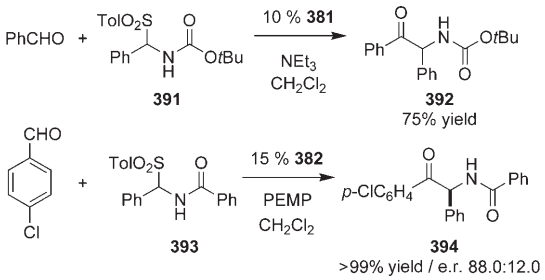



| Entry | Catalyst [%] | Solvent | Base | Yield [%] | e.r. |
|---|---|---|---|---|---|
| 1 | **378** (10) | MeOH | $NEt_3$ | 6 | 76:24 |
| 2 | **379** (1.25) | THF | $K_2CO_3$ | 66 | 12.5:87.5 |
| 3 | **380** (10) | THF | KO*t*Bu | 83 | 95:5 |

The ability of NHCs to generate $d^1$ umpolung reactivity has found applications beyond the well-known benzoin reaction of aldehydes. The $d^1$ addition of aldehydes to in situ generated imines has been investigated, with both achiral and chiral thiazolium ions (Scheme 127).[440]

The $d^1$ addition of aldehydes to α,β-unsaturated carbonyl compounds (Stetter reaction)[441] is another area which has expanded greatly because of the advent of NHC catalysis. The fundamental mechanism of the reaction is the same as was discussed in the benzoin reaction, although the nature of the electrophile has changed. Chiral triazolium ion catalysts are the most general asymmetric catalysts for this process, although some examples of chiral thiazolium ion catalysis have appeared.[442] Rovis and co-workers have shown that

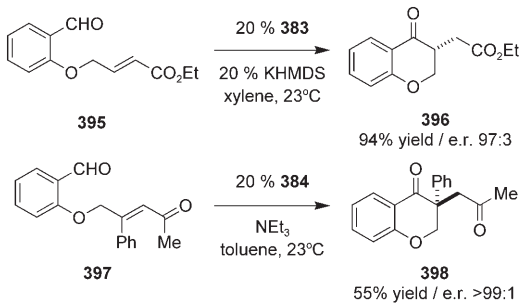
  




***Scheme 127.*** NHC-catalyzed umpolung additions of aldehydes to ketones. PEMP = 1,2,2,6,6-pentamethylpiperidine.

five- and six-membered rings can be formed in good yields and enantioselectivities (Scheme 128). Quaternary centers can be formed as well, although a specific geometry of the α,β-unsaturated ester is essential to obtaining high selectivity.[443]

The NHC-catalyzed umpolung reactions of aldehydes have also been extended beyond carbonyl electrophiles. Miyashita et al. have performed extensive studies on the umpolung

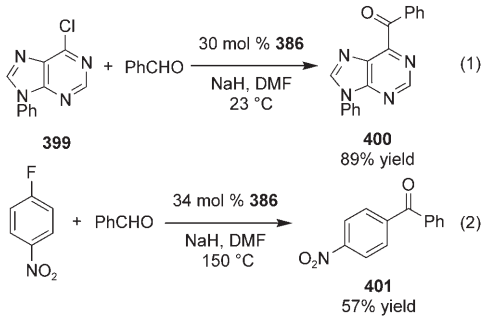



***Scheme 128.*** NHC-catalyzed enantioselective Stetter reaction. KHDMS = potassium hexamethyldisilazide.

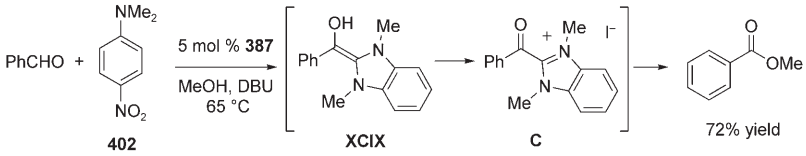
addition of aldehydes to a wide variety of aromatic and heteroaromatic compounds. In the presence of either **386** or **387** as the catalyst, quinoxalines, quinazolines, phthalazines, cinnolines, and several fused pyrimidines can all be acylated with aromatic aldehydes in good yield under mild conditions [Eq. (1) in Scheme 129].[444] Nucleophilic aromatic substitutions with electron-deficient aryl fluorides are also possible, although yields are only moderate [Eq. (2) in Scheme 129].[445]

In a completely different kind of reaction, it has been shown that the highly nucleophilic heteroatom-substituted enol formed upon addition of an NHC to an aldehyde can be oxidized in the presence of nitro aromatic compounds and flavins. In the presence of a nitro compound such as **402**, the heteroatom-substituted enol **XCIX** is transformed to the activated acyl compound **C**. In the presence of an alcohol, acylation occurs leading to the formation of the esters in moderate yields (Scheme 130).[446]

Although this NHC-catalyzed oxidation is a unique method for the oxidation of an aldehyde, it produces large quantities of by-products derived from the nitroaniline **402**.

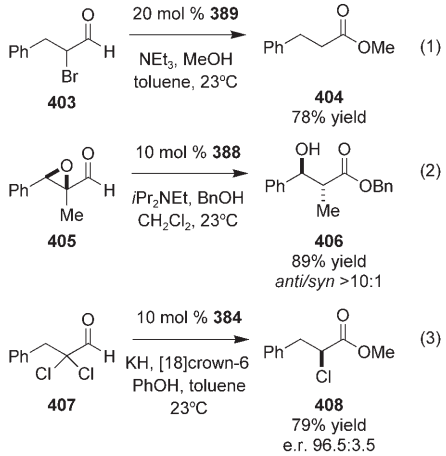



***Scheme 129.*** NHC-catalyzed umpolung additions to aromatic electrophiles.




***Scheme 130.*** NHC-catalyzed aldehyde oxidations with nitro compounds. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

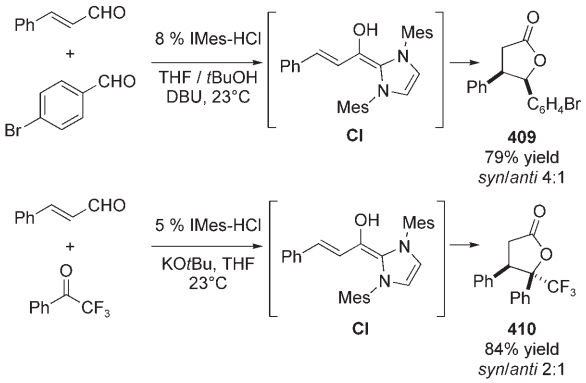
Several other, NHC-catalyzed oxidation reactions have been disclosed which do not rely on the addition of external oxidants and avoid this complication. Internal redox processes are possible when the aldehyde substrate bears a suitable leaving group adjacent to the carbonyl group. The reaction of NHC **388** with α-halo and α,β-epoxy aldehydes leads to the formation of the ester products in good yield [Eqs. (1) and (2) in Scheme 131].[447] In these cases, the oxidation is effected by displacement of the α substituent with concomitant formation of an enolate. Proton transfer then generates an active acylating agent that reacts with an alcohol to yield the product. In the case of substituted α,β-epoxy aldehydes, high levels of diastereoselectivity are obtained in the formation of the *anti*-β-hydroxy ester. When α,α-dichloroaldehydes such as **407** are employed, high levels of enantioselectivity are seen in the formation of the α-chloro ester **408** with triazolium catalyst **384** [Eq. (3) in Scheme 131].[448]




***Scheme 131.*** NHC-catalyzed aldehyde oxidations.

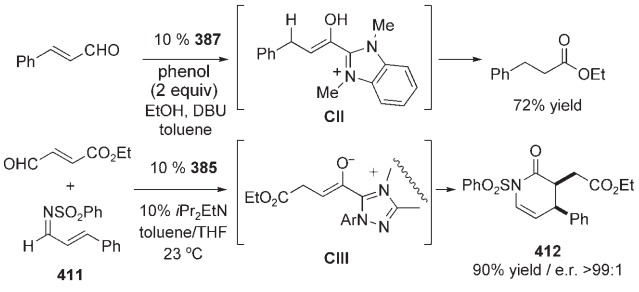
  

The high reactivity of heteroatom-substituted enol intermediates in these NHC catalyzed reactions is not limited to a $d^1$ umpolung. When α,β-unsaturated aldehydes are employed as substrates, the nucleophilic reactivity of the latent enamine can be transferred through the conjugated system to give **CI**, thereby generating a new form of $d^3$ umpolung activity. The research groups of Bode and Glorius have shown that a wide variety of aldehydes and α,β-unsaturated aldehydes react under NHC catalysis to give the substituted lactones in good yields and diastereoselectivities (Scheme 132).[449] Imines and trifluoromethyl ketones have also been shown to undergo this reaction.[450] The use of chiral triazolium ions as catalysts for this reaction gave low levels of enantioselectivity.



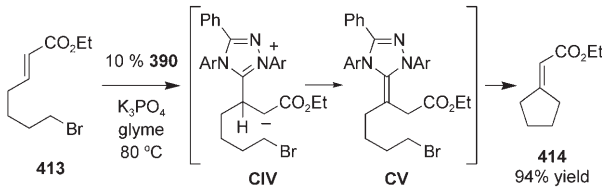

***Scheme 132.*** NHC-catalyzed lactone and lactam formations.

Additional forms of reactivity can be coaxed from highly reactive Lewis base adducts such as **CI** under the appropriate reaction conditions. Both Bode and Sohn as well as Scheidt and Cahn have shown that changes in the amine base and structure of the alcohol leads to the formation of esters (Scheme 133).[451] Under these conditions, protonation of the intermediate **CI** again leads to the formation of an enol **CII** which can be trapped by an alcohol to form an ester. Bode and co-workers have also shown that this enol intermediate can be trapped by electrophiles.[452] If a sulfonylimine is added to the reaction mixture in place of a proton donor, the potential for the intermediate **CIII** to form is present. A subsequent Diels–Alder reaction through an *endo* transition structure leads to formation of the observed product **412**. High yields as well as high diastereo- and enantioselectivities can be obtained using the chiral triazolium catalyst **385**.




***Scheme 133.*** NHC-catalyzed oxidation and formal cycloaddition.

Much as in the case of the n–π* phosphane-catalyzed reactions discussed in Section 4.3.1, control over the relative rate of the proton transfer in these systems opens up new synthetic possibilities. Fu and co-workers recently demonstrated a new form of $d^3$ umpolung activity mediated by NHCs.[453] When α,β-unsaturated esters with pendant alkyl halides were mixed with imidazolium carbenes under basic conditions, five- and six- membered ring exomethylene compounds were obtained (Scheme 134). The authors propose a mechanism which begins with the conjugate addition of the NHC to **413**. The intermediate enolate **CIV** then undergoes intramolecular proton transfer to generate the ylide **CV**. Nucleophilic attack then closes the ring and elimination of **390** generates the observed product **414**.




***Scheme 134.*** NHC-catalyzed carbocyclizations through ylides.

## 10. Lewis Base Catalysis: Quo Vadis?

The continuing quest for more efficient and selective catalytic processes calls for the development of reactions that operate with greater atom economy, under milder reaction conditions, and without highly sensitive and often toxic reagents. The chemical literature is replete with studies that focus on modifying or adapting existing methods to fulfill these demanding criteria. However, in our view, a more central focus must be the development of fundamentally new mechanisms for catalysis. Beyond the search for solutions to the inherent problems of existing methods of catalysis, the discovery and invention of fundamentally new avenues constitutes an attractive solution. The primary objective of this Review is to provide a conceptual foundation for new opportunities presented by recognizing the unique characteristics of Lewis base catalysis. A secondary objective is to illustrate how these characteristics have already been manifest in ways that have not been fully recognized with the hope that additional insights will emerge.

The fact that still in 2007, G. N. Lewis's landmark insights continue to stimulate those in search of new avenues of chemical reactivity and new opportunities for inventing catalytic processes is fitting testimony to the enduring legacy of this giant of research.[454] Through careful analysis of the chemical consequences of donor–acceptor interactions, it can be seen that Lewis base catalysis, either through n–π*, n–σ*, or n–n* interactions is a much more pervasive phenomenon than commonly thought. In contrast to the more familiar paradigm of Lewis acid catalysis, Lewis base catalysis can provide enhancements in nucleophilic and/or electrophilic character. This versatility has made it applicable to a wider range of reactions, from simple esterifications to carbonylations, and even a variety of cycloadditions.

Future applications of this novel form of catalysis are clearly promising. Considering the different ways in which electron-pair donors can enhance chemical reactivity through various mechanisms, the opportunities for invention seem limitless. Most importantly, the unifying ideas that form the basis for Lewis's theory of donor–acceptor interactions provide a foundation for the development of catalytic processes for chemical transformations heretofore inaccessible in the current paradigms. Chemical catalysis is indeed a perpetual frontier.[455]

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[454] Indeed, a special issue of the *Journal of Computational Chemistry* was dedicated to chemical bonding in honor of the landmark contributrions of Gilbert Newton Lewis: *J. Comput. Chem.* **2007**, *28(1)*, 1 – 466.

[455] As an epilogue, it should be mentioned that Lewis, a giant of physical chemistry, recognized the importance of asymmetric catalysis, particularly in the context biomolecular homochirality. In 1926 he made this prophetic statement: "It has long been known that chemical processes are sometimes enormously accelerated by minute traces of foreign substances. Such remarkable action is named catalysis, but this, as Poincaré would say, 'is not to solve the difficulty, but only to baptize it.' Nevertheless, giving a name to a phenomenon does indicate that we have recognized its existence and its generality, and when we state a problem clearly we are already part way toward its solution. Now one of the most interesting kinds of catalysis is the one in which a reaction is accelerated by one of its own products, so that a long time may elapse before anything happens, but if that product begins to form, or is introduced from without, the reaction goes faster and faster. This autocatalysis had not long been known, but we already realize that it is of extremely frequent occurrence, and doubtless we shall know much more about it in the near future." G. N. Lewis, *The Anatomy of Science*, Yale University Press, New Haven, **1926**, p. 181.

  