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Asymmetric Catalysis with Chiral Lewis Bases: A New Frontier in Main Group Chemistry

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Abstract: The concept of the electron pair bond formulated by G. N. Lewis provides the foundation for our understanding of chemical structure and reactivity. The consequences of the donor–acceptor interactions between bases and acids are manifest in the spectacular diversity of transformations that form the basis for chemical synthesis. By systematic analysis of the origins of these phenomena, it is possible to gain a unified picture of how electron pair donors (Lewis bases) can modulate and influence chemical reactions by enhancing either (or both) electrophilic or (and) nucleophilic character. This article provides a brief overview of the conceptual basis and theoretical foundation for these phenomena and illustrates a number of reactions primarily in Group 14 that are susceptible to catalysis by Lewis bases.

Keywords: Catalysis · Donor–acceptor · Electrophilic · Nucleophilic · Stereoselectivity

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, *inter alia,* the proton, electrolytes, and solvent interactions, the Lewis definitions provide a simpler, yet all encompassing, picture based on 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]

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 sub-unit. 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.

The nature of this effect for elements in the Main Group was first codified, by a set of empirical rules that described the changes in bonding and electronic distribution in Lewis acid/base complexes. Gutmann[4] recognized that formation of an acid–base adduct leads to an overall increase in 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 1). This redistribution of electron density has empirically observable consequences on bond lengths. These observations serve as the basis of Gutmann's four rules of molecular adduct formation.[5] The rules state that:

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 in order to compensate for the changes in electron density at D and A (Scheme 1).

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

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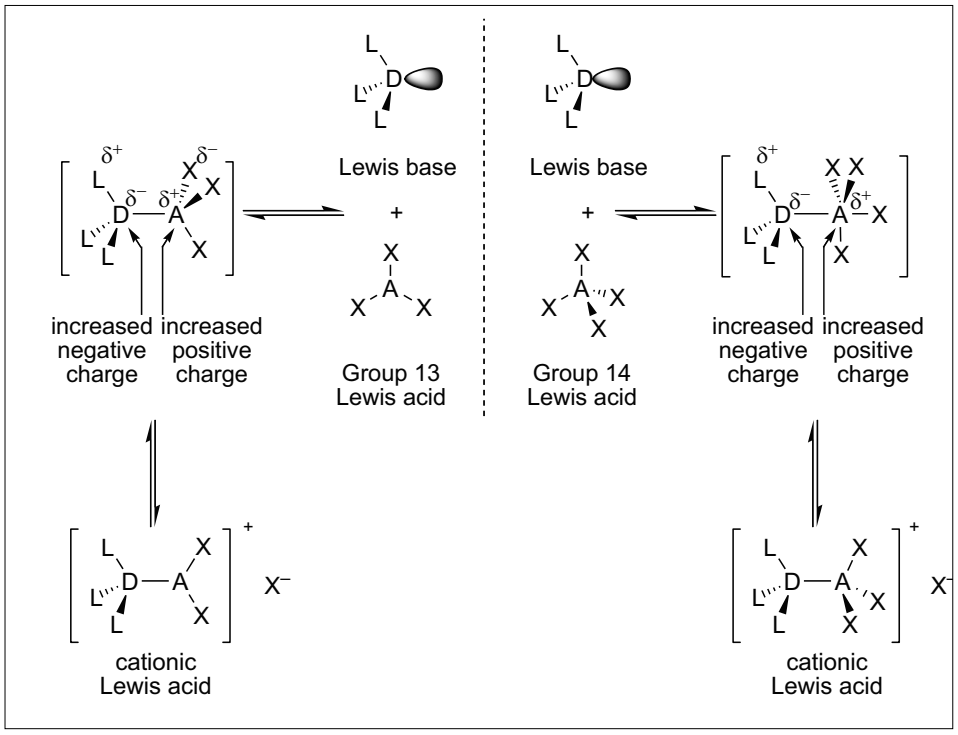
density from the donor species to the acceptor species, it will, in the case of polyatomic species, actually lead to a net increase or 'pileup' of electron density at the donor atom of the donor species and to a net decrease or 'spillover' of electron density at the acceptor atom of the acceptor species. 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."[5a]

The most 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 acceptor atom A increases by one and the bonds around it are lengthened, as predicted by the third and fourth rules. This corresponds to the 'spillover' effect where the augmented electron density around A is distributed to the more electronegative, peripheral atoms X. *A crucial consequence of the spillover effect is that the Lewis acidic center is often rendered more electrophilic compared to the parent Lewis acid while its ligands are rendered more nucleophilic.*

One of the simplest explanations for this phenomenon is found in the molecular orbital description of 3-center-4-electron (3C-4E) hypervalent bonds.[6] Hypervalent bonds are inherently electron-rich at the surrounding ligands and electron deficient at the central atom; combination of three atomic orbitals (AO) creates three molecular orbitals (MO), a bonding, a non-bonding and an anti-bonding orbital (Fig. 1). Mixing of the filled σ orbital on the acceptor with the filled n orbital on the donor generates a pair of hybrid orbitals. The HOMO of this hybrid orbital (Ψ^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 increases as does the energy gap between the Ψ^1 and Ψ^2 orbitals. In the extreme, this leads to ionization and generation of a cationic species (Scheme 1). Thus, the changes in bond order and the polarization of electron density that occurs in the formation of 3C-4E hybrids corresponds to Gutmann's four rules.

Over the past decade, a major focus of the research in these laboratories has been the experimental demonstration of this concept that we have termed 'Lewis base activation of Lewis acids'. The early illustrations involved the chemistry of allyltrichlorosilanes[7] and enoxytrichlorosilanes as reagents for carbonyl addition reactions under catalysis by strong, neutral Lewis bases.[8] However, in recent years, we have recognized a more general and practical manifestation in the use of (chiral) Lewis bases to activate weak main-group Lewis acids, such as silicon tetrachloride. Under the action of a strong, chiral Lewis base, the weak Lewis acid should be activated to carry out classical carbonyl addition reactions with enantiotopic face selectivity (Scheme 2).



Scheme 1. Electronic redistribution resulting from Lewis acid–base complexation

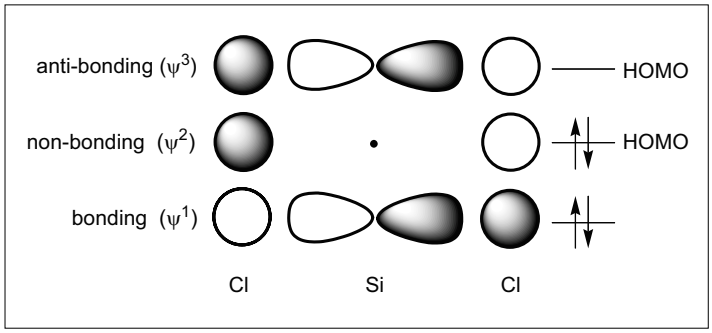
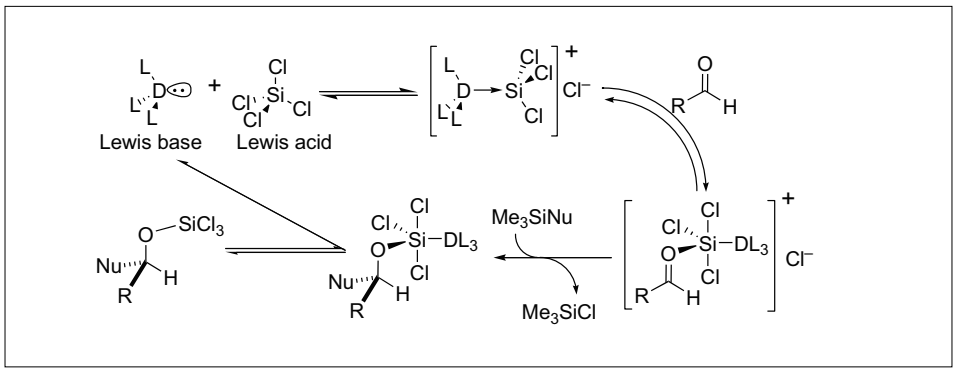
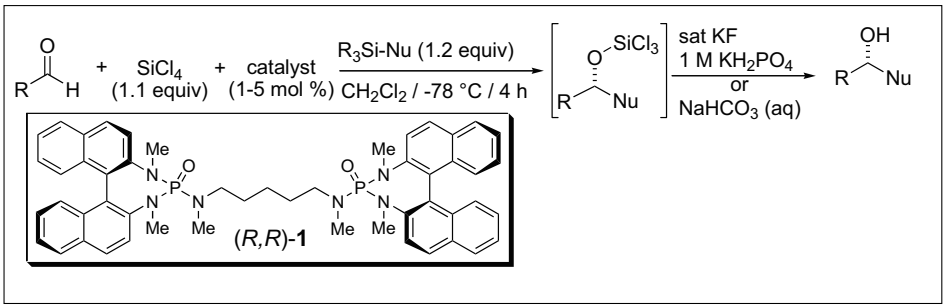


Fig. 1. Molecular orbital diagram of three-center-four-electron hybrids



Scheme 2. Catalytic cycle for Lewis base activated carbonyl additions



Scheme 3. General reaction protocol for Lewis base activated addition with $SiCl_4$

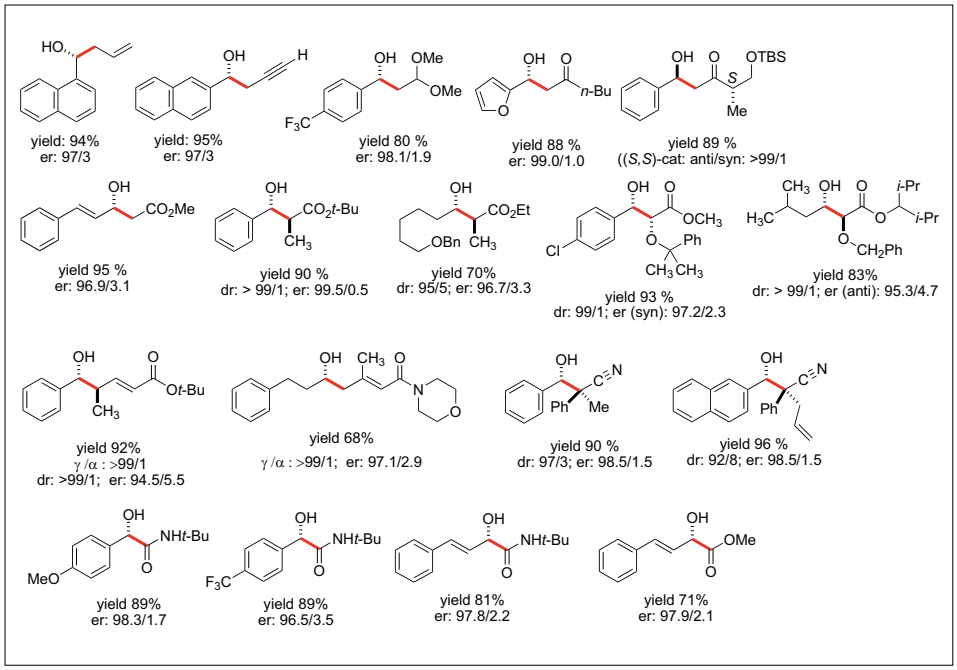


Fig. 2. Products of catalytic enantioselective additions using (*R*,*R*)-**1**

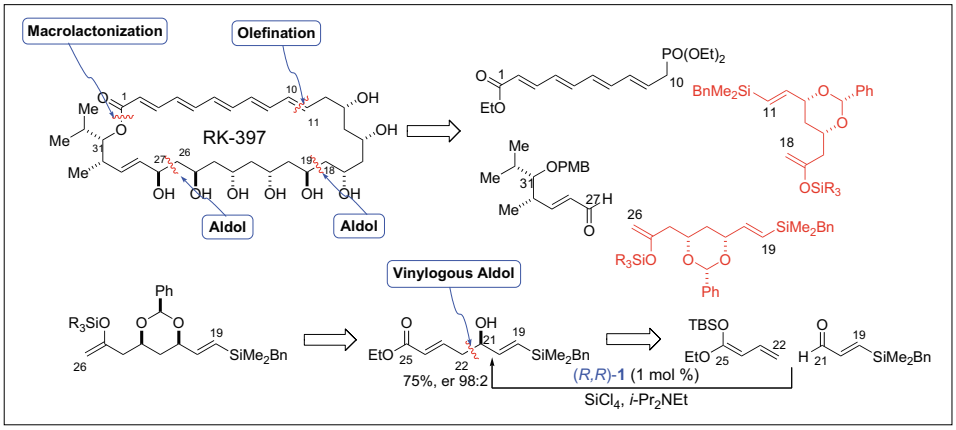


Fig. 3. Retrosynthetic analysis and key bond construction for RK-397

Preparative Carbonyl Additions

From earlier studies on the use of chiral Lewis bases in conjunction with trichlorosilyl reagents, we identified chiral phosphoramide (*R*,*R*)-**1** as a highly active and stereoselective catalyst for a wide range of carbonyl additions (Scheme 3).[9] Shown in Fig. 2 are the products of representative additions of allylic stannanes,[10] enol silyl ether derivatives of aldehydes,[11] ketones,[12] esters,[13] nitriles,[14] conjugated ketones,[15] esters,[16] conjugated amides,[17] and isonitriles.[18] The reactions require 1–5 mol % of the catalyst and enantio-, diastereo- and site selectivities are all very high. For propanoate silyl ketene acetals,[13a] a unique *anti*-convergent stereoselectivity is observed, whereas with glycolate silyl ketene acetals,[13b] either *syn* or *anti* diastereomers are accessible by adjusting the size of the ester and hydroxyl substituents. Conjugated silyl ketene derivatives give products from exclusive γ-addition also with high diastereo- and enantioselectivity.[15–17] The silyl ketene imines allow the enantioselective construction of quaternary stereogenic centers.[14] Finally, the addition of isonitriles forms either α-hydroxy esters or α-hydroxy amides, depending upon the workup.[18]

Application in Synthesis

The utility of the enantioselective vinylogous aldol addition has been demonstrated in the context of a total synthesis of the polyene-polyol antifungal agent, RK-397.[19] The retrosynthetic analysis revealed the common subunit **2** that represents C(11)–C(18) and C(19)–C(26), (Fig. 3). The construction of this subunit was achieved through the selective addition of the TBS ketene acetal of ethyl crotonate (**3**) to the 3-silylpropenal **4** catalyzed by (*R*,*R*)-**1**. Subsequent elaboration allowed for the installation of the remaining stereocenters from C(13) to C(27). This variant of the vinylogous aldol addition possesses high synthetic potential because of the high site and enantioselectivity and the latent functionality of the products.[20]

Mechanistic Studies

Over the past five years, extensive mechanistic investigations have begun to clarify the origin of catalytic activity and stereoselectivity. Kinetic analysis using a Rapid Injection NMR apparatus have revealed a rate equations that shows a striking ½ order dependence on (*R*,*R*)-**1** (Eqn. (1)).

$$\frac{d\text{Aldolate}}{dt} = \frac{k_3 k_4 [\text{cat}]^{0.5}_{\text{total}} [\text{RCHO}] [\text{ketene acetal}]}{k_{-3} + k_3[\text{RCHO}]} \quad (1)$$

Moreover, natural abundance silicon-29 and phosphorus-31 NMR studies have identified a number of dimeric resting states from the silicon chemical shifts and $J^2_{\text{Si-P}}$ coupling constants. This picture supports the notion that the catalyst resting state contains two bisphosphoramides and two $SiCl_4$ molecules and these assemblies must dissociate to the active catalyst upon interaction with the aldehyde.

Solution NMR and X-ray studies of the complexes formed from HMPA and

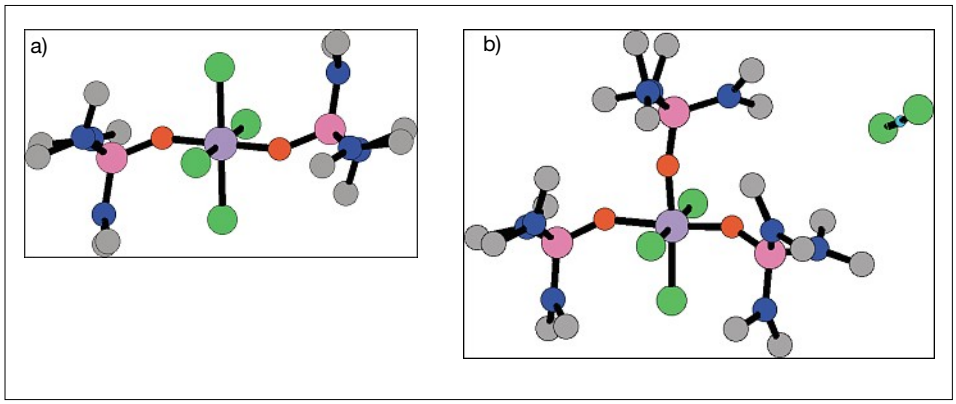


Fig. 4. X-ray crystal structures of (a) 2HMPA•$SiCl_4$ and (b) [3HMPA•$SiCl_3$]$^+$ HCl_2^-

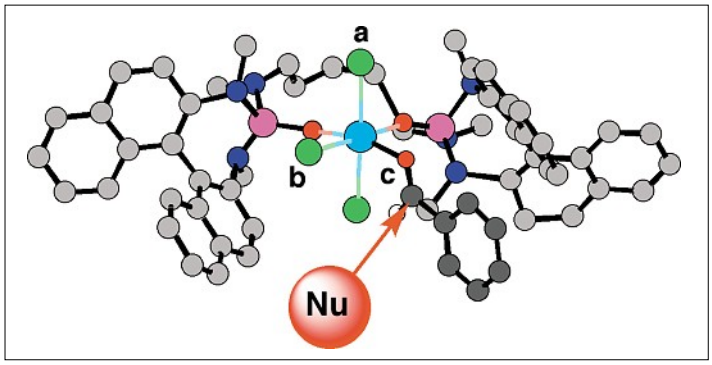


Fig. 5. Putative reactive complex between (*R*,*R*)-**1**, $SiCl_4$ and benzaldehyde

$SiCl_4$ support these conclusions (Fig. 4).[21] The single crystal X-ray structures of the 2HMPA•$SiCl_4$ and the [3HMPA•$SiCl_3$]$^+$ HCl_2^- complexes demonstrate the ability of $SiCl_4$ to bind phosphoramide, undergo ionization and also exist in solution as both 2-phosphoramide and three phosphoramide hexacoordinate species.

Finally, computational modeling of the putative reactive complex formed from (*R*,*R*)-**1** and benzaldehyde has identified the most favorable position of binding and that of greatest electronic activation of the aldehyde (Fig. 5).[13a] The binding position **a** *trans* to chlorides is not suitable because of the high electron density at the 3C-4E bond and the position **b** *trans* to the phosphoramide oxygen is sterically encumbered by the face of the naphthalene ring. Position **c** is both electronically activated and occupies a vacant space that shields the *Si* face of the bound aldehyde. Accordingly, all nucleophilic additions to aldehydes occur on the *Re* face using the (*R*,*R*) catalyst.

Conclusion and Outlook

The successes reported over the past ten years have clearly demonstrated the potential for Lewis base catalysis, particularly for the activation of weak Lewis acids. Although the applications illustrated in this brief review all involve silicon-based reagents, these principles are generally applicable to nearly all of the elements in the Main Group of the periodic table. The ability of these elements to form hypervalent complexes combined with the richness of the chemistry of the p-block elements augur well for the development of new catalytic versions of the powerful synthetic reactions characteristic of the Main Group.[22]

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