FOCUS ARTICLE

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Catalytic enantioselective allylation with chiral Lewis bases

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The advent of chiral Lewis base-promoted allylation of aldehydes has opened a new direction in the catalytic enantioselective construction of homoallylic alcohols. This short review outlines the conceptual framework for the creation of this new process and the interplay of mechanistic investigations and synthetic studies that have conspired to produce a useful new reaction. The current state-of-the-art in catalyst design and application of the reaction in synthesis are briefly illustrated.

The invention and development of catalytic enantioselective reactions are among the most challenging and intensively studied frontiers in organic synthesis.[1] The majority of catalytic asymmetric transformations employ chiral complexes based on transition metal or main group elements.[2] These complexes serve to activate and direct the course of reaction by coordination of the substrate in a Lewis acidic fashion.[3] There are, however, many reactions that are also susceptible to activation by Lewis bases. The process by which chiral Lewis bases enantioselectively promote organic reactions is conceptually distinct from that of chiral Lewis acids, and thus offers the opportunity of developing novel as well as synthetically useful transformations.

Over the last decade, we have been interested in developing chiral Lewis bases as activators for main-group organometallic reagents. In this brief account we outline the conceptual framework for this program and summarize our successes to date in the context of chiral Lewis base-catalyzed enantioselective allylation.[4]

The addition of allylic organometallic reagents to carbonyl compounds is an extremely important synthetic construct for a number of reasons. First, the homoallylic alcohol product is a versatile subunit in synthesis that can easily be converted to a number of other useful functions. In addition, two new stereogenic centers are created with the formation of a new carbon–carbon bond. Accordingly, both diastereo- and enantioselective variants have been thoroughly studied.

The traditional method for achieving catalytic enantioselective allylation relies on binding the electrophile (aldehyde) with a chiral Lewis acid which then activates it toward nucleophilic attack by the allylmetal reagent.[5] The advantages of catalytic method, namely the use of small amounts of chiral agents and high enantioselectivities are significantly offset by the lack of diastereoselectivity with substituted allylating reagents because of the non-rigid nature of the transition structure of the reaction.

In contrast, the chiral Lewis base-catalyzed allylation involves binding of the nucleophile (trichlorosilane, **1**) with the generation of reactive hypercoordinate silicon species, which can further coordinate the aldehyde. This dual mechanism of activation provides for high

The importance of catalytic enantioselective synthesis

There is an increasing demand for enantiomerically pure compounds in the pharmaceutical, fine chemical, and material science industries both for reasons of patient safety and to encourage the development of more efficient chemical processes. The development of chiral transition metal catalysts opened up a new field of chemistry – allowing the synthesis of pure enantiomers from achiral substrates. In such reactions, the formation of energetically favourable transition states between substrate and the catalyst allow the transfer of the desired stereochemical information from catalyst to product. The 2001 Nobel Prize for Chemistry was awarded to William S. Knowles and Ryoji Noyori for their work on catalysed asymmetric hydrogenation reactions and to K. Barry Sharpless for the development of catalysed asymmetric oxidation. Both are key reactions, allowing the synthesis of many more molecules of industrial and medical importance in pure enantiomeric form, such as the antibiotic levofloxacin and glycidol, a percursor of beta-blockers, which are widely used as cardiovascular drugs.

In this Focus article, an important new advance in catalytic enantiomeric synthesis is described. The addition of allylic organometallic reagents to carbonyl compounds creates versatile synthetic subunits. Traditionally, this reaction has been carried out under Lewis acid catalysis, but this has led to problems in creating the desired configuration of the product, because of the steric 'looseness' of the transition structure. Professor Scott Denmark and his team have pioneered a new approach, using chiral Lewis base catalysis. Mechanistic studies show that this leads to a much 'tighter' transition structure and products of high stereochemical purity. This approach has been applied to other carbon–carbon bond forming reactions. Future research may see this concept manifest in the chemistry of other main-group elements.

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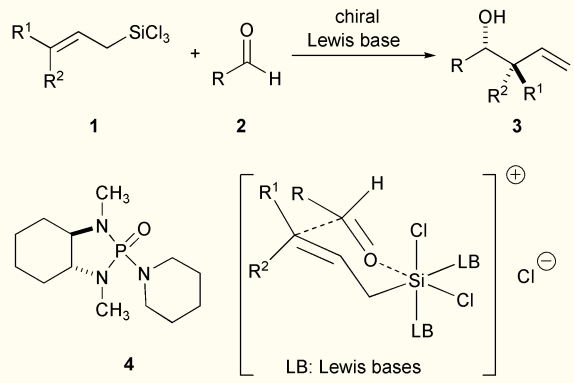
reaction rates and excellent transfer of stereochemical information because the reaction proceeds through a closed assembly of allyltrichlorosilane, aldehyde, and the chiral Lewis base. Thus, a high degree of diastereo- as well as enantioselectivity is expected. Furthermore, the noncovalent association between the chiral Lewis base and chlorosilane substrate makes possible the use of a catalytic amount of chiral activator.

On the basis of this principle, as well as knowledge of the reactivity of allylic trihalosilanes,[6,7] the first examples of chiral Lewis base-promoted allylation were reported from these laboratories in 1994.[8] The addition of allylic trichlorosilanes **1** to aldehydes is promoted with stoichiometric amount of chiral phosphoramide **4** to give homoallyl alcohol **3** with modest enantiomeric ratio (4:1) (Scheme 1). More importantly, the addition of (*E*)- and (*Z*)-2-butenyltrichlorosilane provided the *anti*- and *syn*- product, respectively, with excellent diastereoselectivity, thus lending further support to the existing hypothesis of a closed, chair-like transition structure. Finally, the non-covalent association between the phosphoramide and chlorosilane substrate rendered it possible to use a catalytic amount of **4**, albeit with attenuated enantioselectivity.



Scheme 1.

The failure of empirical optimization to provide either a better catalyst or even a framework for structural modification stimulated an in-depth mechanistic study to probe into the origins of activation and stereoselection.[9a] A combination of nonlinear effect and kinetic studies revealed that the reaction was second order in phosphoramide **4**, though a first order, less selective pathway can be competitive at lower phosphoramide concentration. A second-order dependence on phosphoramide requires that the allylic trichlorosilane undergo ionization of a chloride anion to accommodate all of the reaction components. Thus, the aldehyde, two catalyst molecules, the allyl residue and two chloride ligands comprise a hexacoordinate array assembled around the cationic silicon center.[10] The origin of activation by phosphoramides is believed to be the enhanced Lewis acidity of silicon in the cationic complex together with the increased nucleophilicity of the allyl group.

Although mechanistically intriguing, the operation of dual pathways has undesirable effects on the rate and selectivity in the asymmetric catalysis. First, the second-order dependence on the catalyst, requires that the rate decreases as the square of catalyst concentration. Second, at lower catalyst loadings, a competing, less selective pathway can compromise the overall reaction selectivity. Both of these characteristics conspire to thwart the use of 'catalytic amounts' of the phosphoramide promoters. The solution to this problem was then formulated in the design, synthesis and application of dimeric bisphosphoramides wherein the effective concentration of the second catalyst molecule would be significantly increased through proximity. A systematic investigation of the tether revealed that the highest enantiomeric ratio (up to 6.1:1) was provided by bisphosphoramide **5d** in which the two base functions are separated by a five-methylene unit.[9]

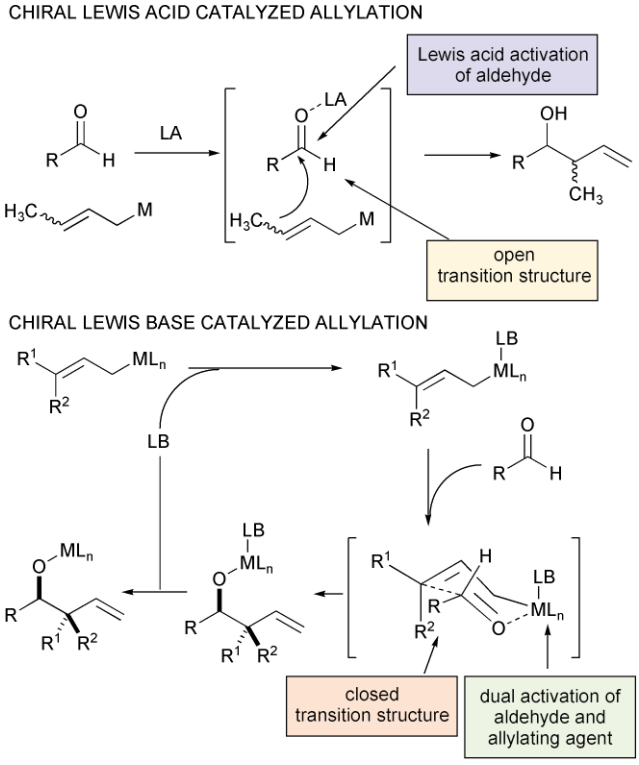
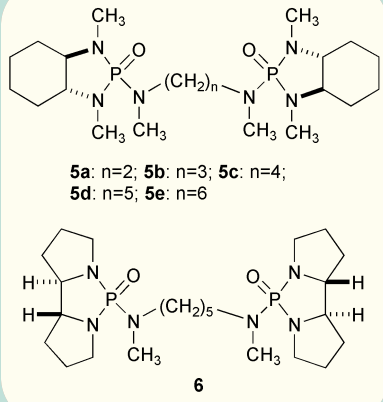


Fig. 1.



To further optimize selectivity, we recognized the unique structural features of the phosphoramide **6**, based on 2,2′-bispyrrolidine.[11] The *cis–anti–cis* fusion of the three five-membered rings creates a stair-like shape which provides a highly asymmetric environment. This property, along with the shape of the chiral environment crafted by the bidentate ligand is seen in the X-ray crystallographic analysis of the complex **6**•$SnCl_4$ shown in Fig. 2.[9b] To our delight, the bisphosphoramide **6** effectively catalyzed the addition of allyltrichlorosilane **1a** to unsaturated aldehydes with excellent selectivities (Scheme 2).[12] A more important demonstration of the scope was the extension to the reaction of γ-substituted allylic trichlorosilanes. The addition of (*E*)- or (*Z*)-2-butenyltrichlorosilanes was indeed found to be highly enantioselective and diastereoselective. Moreover, γ-disubstituted allylic trichlorosilanes could also react and provide prenylation products with excellent enantioselectivities.

To fully capitalize on the high asymmetric induction observed with **6** and the strong stereochemical coupling of silane geometry to the diastereoselectivity, we conceived an intriguing application in the stereoselective construction of quaternary stereogenic centers. Despite decades of activity in the area of asymmetric synthesis, there are still few methods that can accomplish this difficult task catalytically.[13] As test substrates, we chose trisubstituted silanes (*E*)- and (*Z*)-**7**, which were synthesized from geraniol and nerol, respectively, in geometrically pure form in two steps. The addition of these reagents to benzaldehyde, catalyzed by **6**, provided adducts *anti*-**8** and *syn*-**8** with excellent diastereo- and enantioselectivities (Scheme 3). To further illustrate the utility of this method, it was recently applied to the enantioselective synthesis of serotonin antagonists **10**. The key intermediate **9** was prepared with excellent selectivity by addition of a geometrically pure trichlorosilane to benzaldehyde catalyzed in the presence of *S*-(*l*,*l*)-**6**.[14]

In work from other laboratories, different phosphoramides,[15a–c] and Lewis bases such as formamides,[15d,e] N-oxides,[15f–h] ureas,[15i] and diamine,[15j] have also been used as catalysts. The mechanistic pathway involving two molecules of Lewis bases in the stereodetermining transition structure is most likely operative in these cases as well since good yields and excellent ees are obtained from the chiral didentated ligands such as **11**, **12**.

Although the primary goals of this program have been realized, there are still significant challenges remaining. In particular, this allylation method has yet to achieve satisfactory results with aliphatic aldehydes. Studies in these laboratories show that upon addition of chlorosilanes to

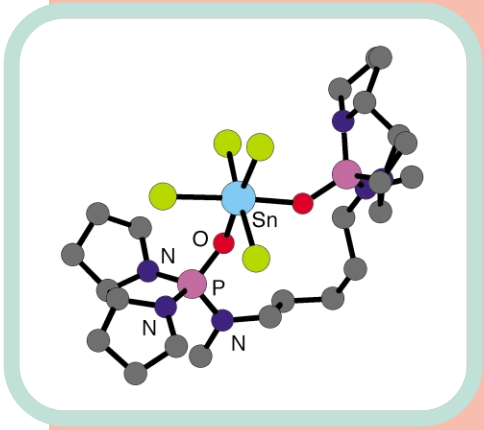
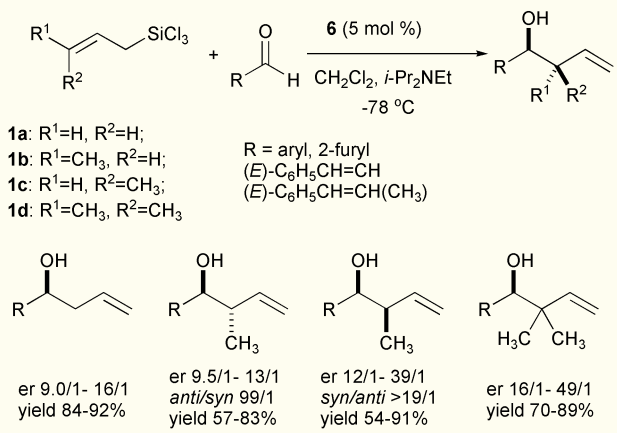
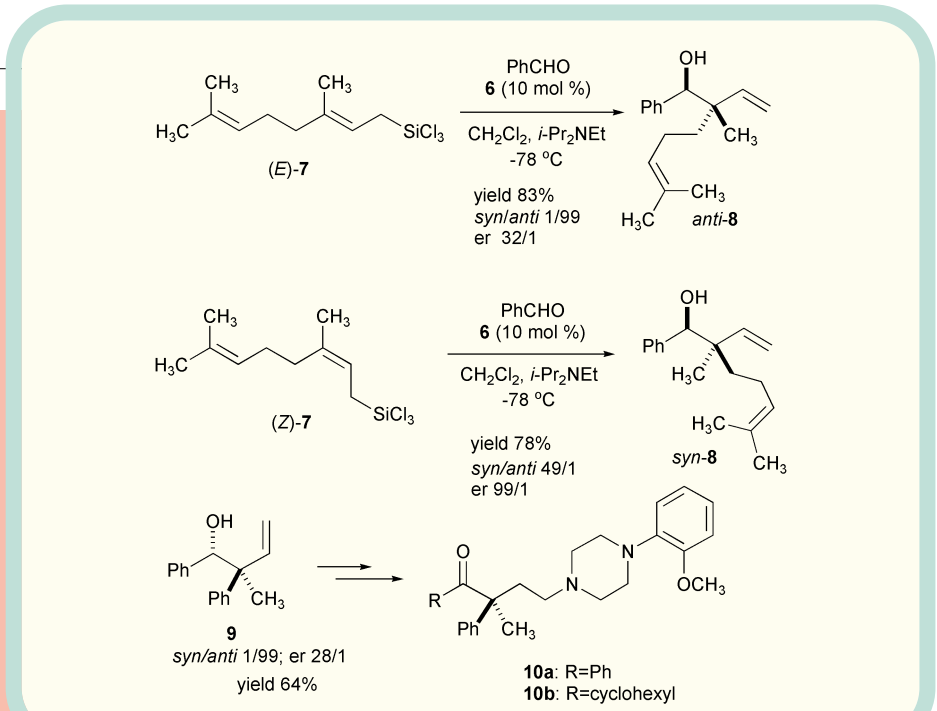


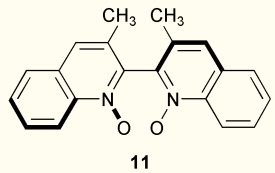
Fig. 2.

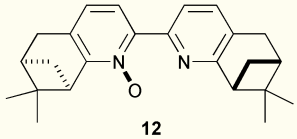


Scheme 2.



Scheme 3.





aliphatic aldehydes in presence of a Lewis base, an α-chloro silyl ether is formed. This species is very slow to react, and the product could be obtained after a prolonged time,[15d,e] but highly efficient reaction will require a way to bypass this intermediate or new ways of promoting its reaction.

Since our initial disclosure of the chiral Lewis base catalyzed allylation, significant progress has been made on the mechanistic understanding process, which has allowed for a rational improvement on the efficiency and selectivity of the catalyst. The successful implementation of the concept, namely the use of a main-group organometallic agent as an organizational center and a Lewis base as a chiral activator, bodes well for extension to other important carbon–carbon bond forming reactions.[16]

This paper is dedicated to Professor Ian Fleming F.R.S. of Cambridge University, on the occasion of his retirement and further pioneering studies in the application of organosilicon chemistry in organic synthesis.

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IN THIS ISSUE

Readers should note that there is a group of three communications in this issue of issue of *ChemComm* by Professor Ian Fleming (Department of Chemistry, University of Cambridge, UK) to whom this Focus article is dedicated:

- Further reactions of phenyldimethylsilyllithium with *N,N*-dimethylamides
- Reactions of phenyldimethylsilyllithium with β-*N,N*-dimethylaminoenones
- The reaction of phenyldimethylsilyllithium with *N*-phenylpyrrolidone

These communications illustrate well the work of Professor Fleming in the area of organosilicon chemistry in organic synthesis.