Lewis Base Activation of Lewis Acids: Catalytic Enantioselective Allylation and Propargylation of Aldehydes

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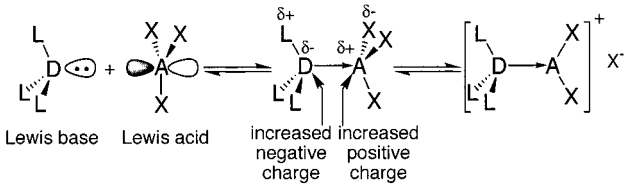
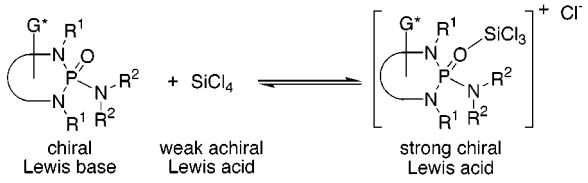
In the 22 years since the landmark report by Koga et al. of a catalytic enantioselective Diels−Alder reaction,[1] asymmetric catalysis by chiral Lewis acids has become one of the most heavily investigated fields of research.[2] Because of the central importance of carbon−carbon bond-forming reactions, a myriad of chiral Lewis acid catalyst systems have been developed for many transformations. Typically, these catalysts are generated by the combination of a strong Lewis acid with a chiral ligand either in situ or in a separate preparation. In nearly all examples of main group, early transition metal, and lanthanide-based Lewis acids, asymmetric modulation with chiral ligands leads to deactivation of the catalyst due to the basicity of the donor atoms of the ligand. An important consequence of this behavior is the need for either independent synthesis of the chiral Lewis acid or an excess of the ligand to ensure suppression of competitive, achiral background reaction from the nascent Lewis acid. Indeed, this deactivation of the parent Lewis acid by the ligand has been used to attenuate the activity of Lewis acid catalysts to increase selectivity.[3] Especially because of ligand substitutions, careful design of a chiral Lewis acid catalyst is needed if high selectivities are to be realized.

There are however, certain circumstances in which a Lewis basic donor ligand can *enhance* the activity of a Lewis acidic acceptor. This counter-intuitive situation is clearly anticipated, according to a set of empirical bond-length and charge-density variation rules formulated by Gutmann.[4] Specifically, Gutmann's fourth rule states that upon coordination of a polyatomic donor to a polyatomic acceptor there will be a net *increase* in electron density on the donor *atom* and a net *decrease* of electron density on the acceptor *atom*.[5] Thus, upon coordination of a Lewis base, the central atom of a Lewis acid becomes *more electrophilic* with the excess charge residing on the peripheral ligands! Taken to its logical limit, this transfer of electron density would result in an ionization of one of the ligands from the Lewis acid. Once the ligand is ionized, a full positive charge can be formally assigned to the central atom.[6]



The generation of a cationic species results in a significant increase in the Lewis acidity of the central atom; thus, the Lewis base has *activated* the Lewis acid.[7] The concept of Lewis base activation leads to intriguing possibilities for ligand-accelerated catalysis because the Lewis acid is most active when coordinated to the Lewis base.[8] Thus, by use of a chiral Lewis base, a highly active and chirally modified Lewis acid is generated. In this scenario a weak, achiral Lewis acid can be used in bulk without fear of a competing background reaction because the catalytically pertinent species always contains the chiral directing group.



In recent years the development and application of chiral Lewis base catalysis of aldol and allylation reactions have been investigated in these laboratories.[9] Mechanistic evidence supports the postulate that the chiral phosphoramide ionizes a chloride from the trichlorosilyl fragment in the enolate or allyl unit. The subsequent discovery that a catalytic amount of a chiral phosphoramide could activate silicon tetrachloride to open meso epoxides, thus forming enantioenriched chlorohydrins, suggested a more general application of the concept. We describe herein the demonstration that a weak Lewis acid, $SiCl_4$, can be activated by a chiral Lewis base to catalyze the allylation and propargylation of aldehydes, Scheme 1.[10,11]

Initial feasibility studies showed that the combination of $SiCl_4$ and HMPA could promote the addition of allyltributylstannane to benzaldehyde.[12] Control reactions revealed that there was no appreciable background reaction of these components in the absence of a Lewis base. Moreover, we also demonstrated that transmetalation from tin to silicon did not occur under the conditions of the reaction.[10]

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(4) (a) Gutmann, V. *The Donor-Acceptor Approach to Molecular Interactions*; Plenum Press: New York, 1978. (b) Jensen, W. B. *The Lewis Acid-Base Concepts*; Wiley-Interscience: New York, 1980; Chapter 4.

(5) "...although a donor−acceptor interaction will result in a net transfer of electron density from a donor species to an 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." ref 4b, pp 136−137.

(6) (a) This is conceptually distinct from Bronsted acid activation of Lewis acids (Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561) or Lewis acid activation of Lewis acids (Ishimaru, K.; Monda, K.; Yamamoto, Y.; Akiba, K. *Tetrahedron* **1998**, *54*, 727). (b) For an example of a highly reactive Lewis acid in which a basic, peripheral ligand is cationic see: Hayashi, Y.; Rohde, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 5502.

(7) The ligand-ionization effect has been postulated in several reactions of Lewis base activation of Lewis acids. (a) Chojnowski, J.; Cypryk, M.; Michalski, J.; Wozniak, L. *J. Organomet. Chem.* **1985**, *288*, 275. (b) Corriu, R. J. P.; Dabosi, G.; Martineau, M. *J. Organomet. Chem.* **1980**, *186*, 25. (c) Bassindale, A. R.; Lau, J. C.-Y.; Taylor, P. G. *J. Organomet. Chem.* **1995**, *499*, 137.

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(11) For a review of Lewis acid-catalyzed, allylmetal additions see: Yanagisawa, A. In *Comprehensive Asymmetric Catalysis, Vol. II*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds. Springer-Verlag: Heidelberg, 1999; Chapter 27.

(12) Allyltrimethylsilane proved to be unreactive. Burfeindt, J.; Patz, M.; Müller, M.; Mayr, H. *J. Am. Chem. Soc.*, **1998**, *120*, 3629.

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Scheme 1

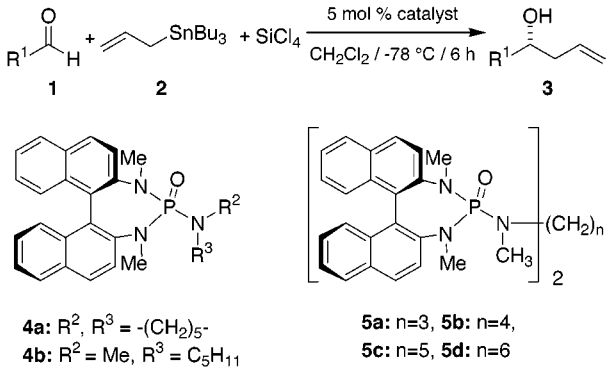


Table 1. Allylation of Benzaldehyde Promoted by Phosphoramides[a]

entry	promoter	tether length	yield, %[b]	ee, %[c]
1	**4a**[d]	-	85	79
2	**4b**	-	83	53
3	**5a**	3	81	84
4	**5b**	4	86	81
5	**5c**	5	89	93
6	**5d**	6	84	69

[a] All reactions employed 2.0 equiv of $SiCl_4$, 1.2 equiv of **2**, 0.05 equiv of promoter, at 0.5 M CH_2Cl_2 at −78 °C for 6 h. [b] Yield of chromatographically homogeneous material. [c] Determined by CSP−SFC. [d] 0.10 equiv of **4b** was used.

We next turned our attention to the potential for asymmetric induction. From the wide range of chiral phosphoramides at our disposal[13] several structural motifs were examined, and we were delighted to discover that a binaphthyl-based phosphoramide **4a** (the most selective catalyst for epoxide opening[9e]) could indeed produce the homoallylic alcohol **3a** with high yield and enantioselectivity with just 5 mol % of catalyst (Table 1, entry 1). Previous mechanistic studies revealed a second-order dependence on the phosphoramide in the allyl addition and aldol reactions, which led us to investigate alkyl-linked bis-phosphoramides as promoters.[9b,14] To determine the existence and optimal arrangement for cooperativity, several binaphthyl bis-phosphoramides with differing tether lengths were synthesized (Scheme 1, **5a**−**d**), and the results of their behavior as catalysts are collected in Table 1. Although all four bis-phosphoramides are effective catalysts for the allylation, **5c (**bearing a five-methylene linker) gave the highest enantioselectivity. The variation in selectivity among the dimers and their behavior compared to those of the control monomer **4b** strongly support the hypothesis of a "two-phosphoramide pathway".[9b,14]

Further optimization of the allylation with **5c** focused on the effects of solvent, halosilane source, and loading. Simple replacement of one chlorine led to dramatic differences in reactivity in the order $HSiCl_3 > SiCl_4 \gg MeSiCl_3 \approx PhSiCl_3$. Even though $HSiCl_3$ was nearly as effective, silicon tetrachloride was selected as the optimal silicon source. A survey of the $SiCl_4$ loading revealed only a modest dependence of enantioselectivity on stoichiometry, but more importantly that the reaction proceed to only 50% completion with 0.5 equiv. This suggested that the product alkoxytrichlorosilane was not capable of participating as a Lewis acid precursor.

With an optimized procedure in hand, we next examined the scope of the reaction with various aldehydes (Table 2). A variety of unsaturated aldehydes were found to react under these conditions, but the enantioselectivities were highly dependent on the aldehyde structure.[15] Aromatic aldehydes gave the best results followed by olefinic and then propargylic aldehydes. No obvious trend in electronic or steric contributions is readily apparent. For example, the effect of substitution next to the aldehyde was inconsistent: 1- and 2-naphthaldehyde both gave similarly high

Table 2. Allylation of Aldehydes with **5c**[a]

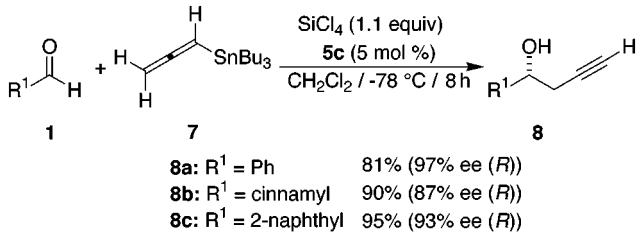
entry	R^1	product	yield, %[b]	ee, %[c]
1	C_6H_5 (**1a**)	**3a**	91	94
2	4-$NO_2C_6H_4$ (**1b**)	**3b**	90	83
3	(*E*)-$C_6H_5CH{=}CH$ (**1c**)	**3c**	91	65
4	(*E*)-$C_6H_5CH{=}C(CH_3)$ (**1d**)	**3d**	75	11[d]
5	$C_6H_5C{\equiv}C$ (**1e**)	**3e**	92	22
6	1-naphthyl (**1f**)	**3f**	94	94
7	2-naphthyl (**1g**)	**3g**	92	93
8	2-furyl (**1h**)	**3h**	65	62

[a] All reactions employed 1.1 equiv $SiCl_4$, 1.2 equiv of **2**, 0.05 equiv **5c**, at 0.5 M in CH_2Cl_2 at −78 °C for 6 h. [b] Yields of chromatographically homogeneous material. [c] Determined by CSP-SFC. [d] Configuration not determined.

selectivities, substitution in the cinnamyl series (**1c** vs **1d**) led to a dramatic decrease in selectivity. The absolute configuration of all products was shown to be *R* by correlation (see Supporting Information).

Finally, we have briefly explored the scope of the nucleophile. Whereas, the use of (*Z*)-2-butenyltributylstannane yielded a disappointing 2/1 mixture of *anti/syn* homoallylic alcohols, allenyltributylstannane **7** showed very promising results (Scheme 2). Under the standard reaction conditions, **7** afforded homopropargyl alcohols in excellent yields and enantioselectivities with several aldehydes. In no case was the isomeric allenyl alcohol detected. These reactions were generally slower than the allyl additions due to the lower reactivity of allenylstannanes compared to that of allylstannanes.[16] As in the allylation process, only 1,2-addition was observed with cinnamaldehyde.

Scheme 2



In summary we have demonstrated a new concept for the generation of a chirally modified and activated Lewis acid by Lewis base-promoted ionization of a weak Lewis acid. This method of catalyst generation precludes the need for independent preparation of the ligated Lewis acid and allows for the use of stoichiometric amounts of the precursor which enhances reaction rate. This chiral phosphoramide·$SiCl_4$ system successfully catalyzed the addition of allyl- and allenylstannes to aldehydes with high yields and good to excellent stereoinduction. Application of this catalyst system to other carbon−carbon bond-forming reactions and development of new base-activated Lewis acids are in progress.

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Supporting Information Available: Full characterization of all catalysts and products along with representative procedures for the addition reactions (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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