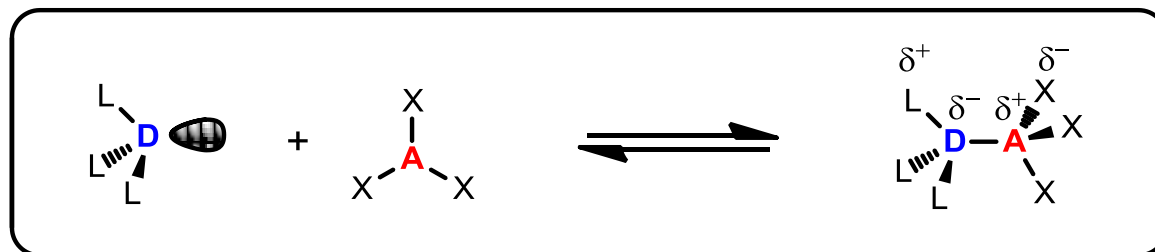


Lewis Base Catalysis in Organic Synthesis



Group Meeting

Yuwen Zeng

Sep. 28th, 2014

Presentation Outline

- Introduction
 - Definitions
 - Basic concepts
- Lewis base catalysis: $n-\pi^*$ Interactions
 - Electrophilic activation
 - Nucleophilic activation
 - Dual activation
- Lewis base catalysis: $n-n^*$ Interactions
 - Activation of boron
- Lewis base catalysis: $n-\sigma^*$ Interactions
 - Electrophilic activation
 - Nucleophilic activation
 - Dual activation
- Summary and Outlook

Comprehensive Reviews:

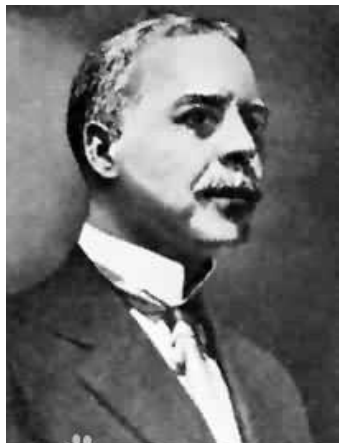
Dilman, A. D.; Loffe, S. L., *Chem. Rev.* **2003**, *103*, 733.

Rendler, S.; Oestreich, M. *Synthesis* **2005**, *11*, 1727.

Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560.

Gawronski, J.; Wascinska, N.; Gajewry, J. *Chem. Rev.* **2008**, *108*, 5227.

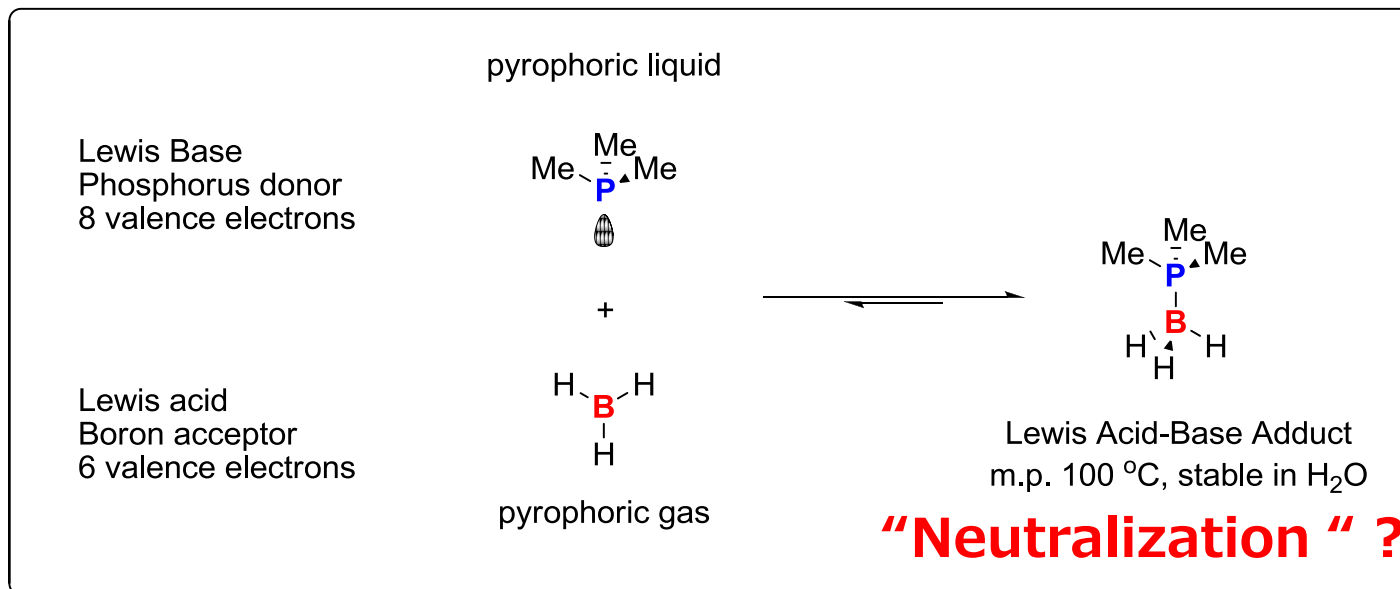
Introduction



Gilbert Newton Lewis
(1857-1946)

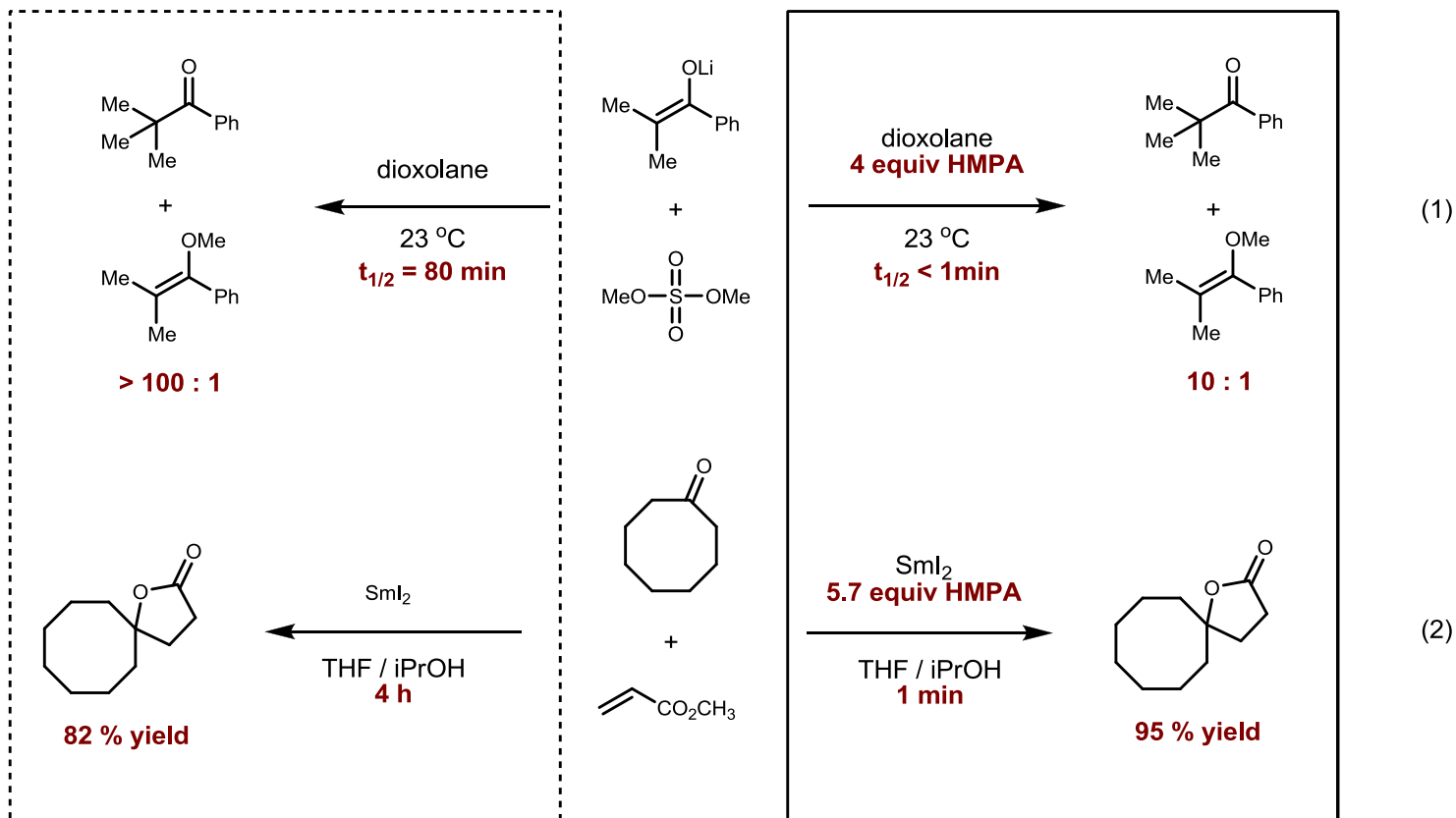
Was born in 1875, Massachusetts
1893-1896, Harvard University, B.S. Degree.
1897-1899, Harvard University, Ph. D. Degree
1916, published his classic paper on chemical bonding "The Atom and the Molecule", in which Lewis recognized that acid are not restricted to those substance that contain hydrogen (Bronsted acids), and helped overthrow the "modern cult of the proton".

"Simply put, a Lewis acid is an electron-pair acceptor and a Lewis base is an electron-pair donor."



Influence of Lewis Bases on reactivity Patterns

➤ Lewis bases have found important applications as promoters of a variety of diverse chemical processes

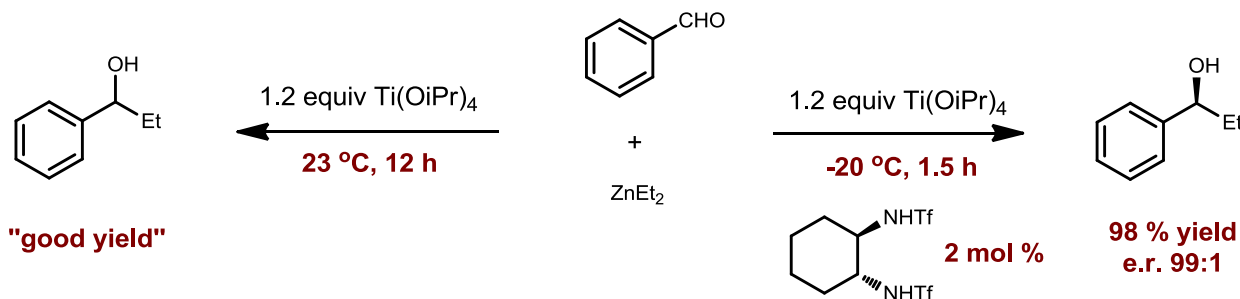


Definition of Lewis Base Catalysis

➤ Definition of Lewis base catalysis

- ◆ 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 electrophilic or(and) nucleophilic** character of the bound species.
- ◆ Furthermore, the Lewis base **should not be consumed** or altered during the course of the reaction.

➤ Difference between Lewis acid activation and Lewis base activation



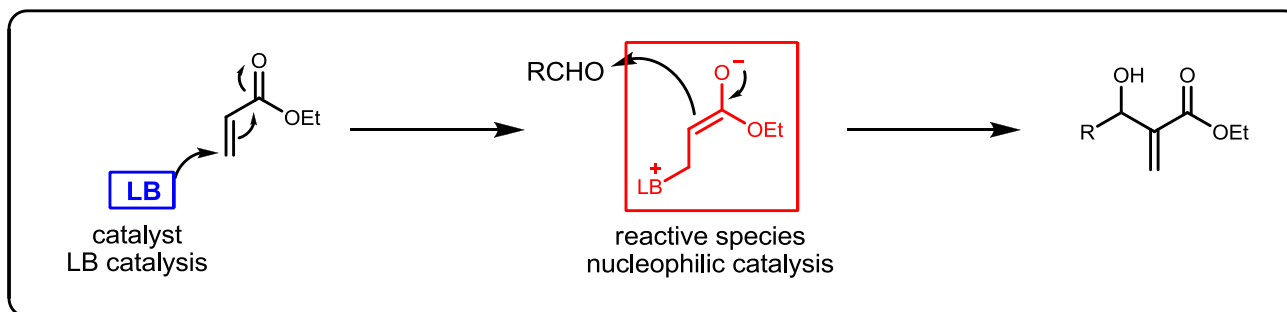
- ◆ Lewis acid activation **only enhance the electrophilic character** of substrate.
- ◆ Compared to Lewis acids, Lewis base effect a **much more diverse** array of reactivity patterns.

Definition of Lewis Base Catalysis

➤ Difference between Lewis base catalysis and nucleophilic catalysis




- ◆ The term nucleophilic and electrophilic should be used to describe those *characteristic of the reactive species* that are enhanced by the catalyst (and thus, tied to the mechanism).
- ◆ The term Lewis basic and Lewis acidic should be reserved for the *characteristic of the catalysts themselves*.
- ◆ The commonly used term “nucleophilic catalysis” is ambiguous, and thus the use of this term should be discouraged.

➤ Example



Lewis Base-Acid Interactions: Basic Concepts

➤ Jensen's orbital analysis of molecular interactions.

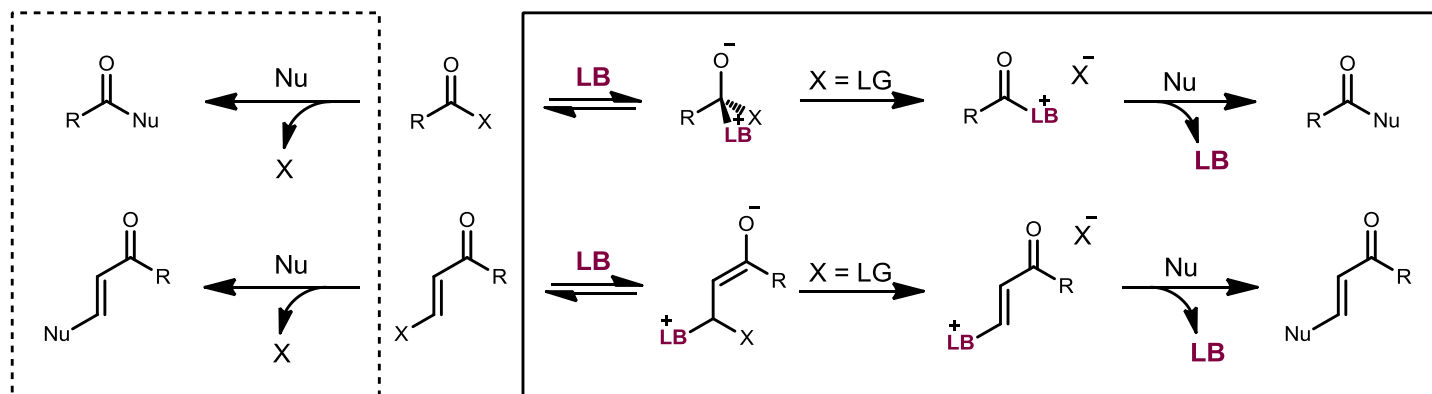
Donor	Acceptor		
	n^*	σ^*	π^*
 n	$n-n^*$	$n-\sigma^*$	$n-\pi^*$
 σ	$\sigma-n^*$	$\sigma-\sigma^*$	$\sigma-\pi^*$
 π	$\pi-n^*$	$\pi-\sigma^*$	$\pi-\pi^*$

➤ In practice, only three of these interactions are significant in terms of catalysis.

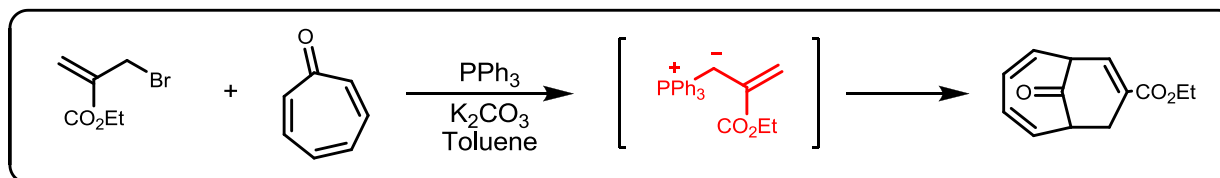
- Interactions between nonbonding electron pairs and anti-bonding orbitals with π character ($n-\pi^*$ interactions).
- Interactions between nonbonding electron pairs and anti-bonding orbitals with σ character ($n-\sigma^*$ interactions).
- Interactions between nonbonding electron pairs and vacant nonbonding orbitals with n character ($n-n^*$ interactions).

Lewis Acid-Base Interactions: Basic Concepts

- The family of $n-\pi^*$ interactions represents the largest and most commonly recognized form of Lewis base catalysis.



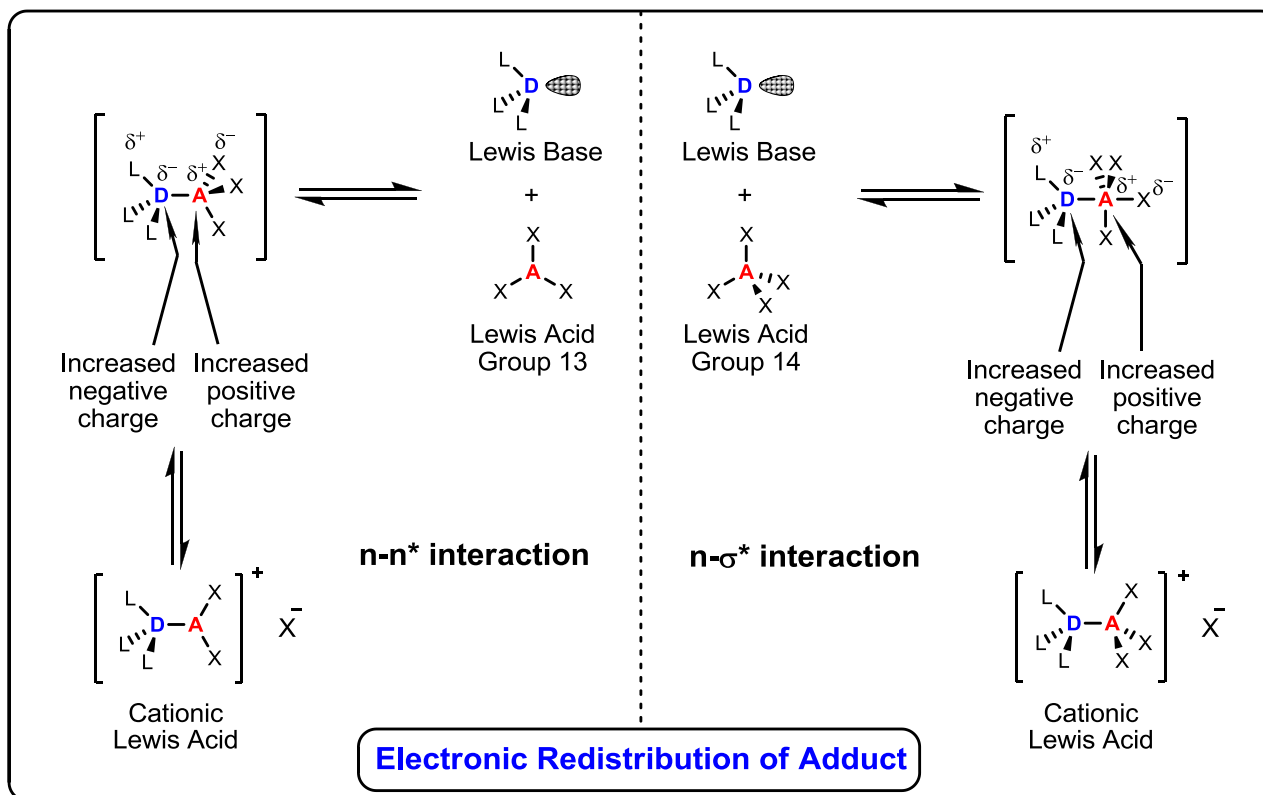
- Lewis base activation can provide both electrophilic and nucleophilic activation (ambiphilic).



Zwitterion
Both nucleophilic and electrophilic

Lewis Acid-Base Interactions: Basic Concepts

- The $n-\sigma^*$ and $n-n^*$ interactions, are less-well known, but equally versatile pathways for catalysis.
- An important requirement is that the Lewis acidic acceptor be able to expand its coordination sphere and attain a “hypervalent” state.

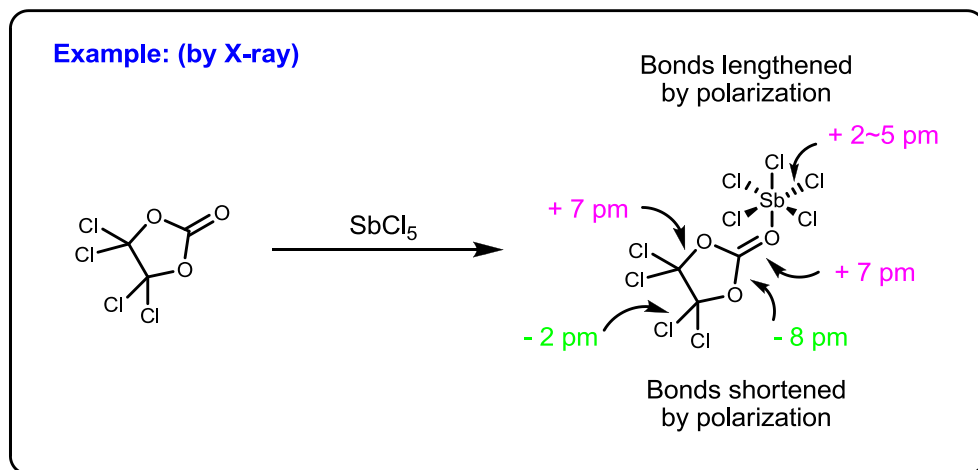


Lewis Acid-Base Interactions: Gutmann Analysis

➤ Gutmann recognized that formation of an adduct leads to an overall increase in the electron density of the acceptor fragment, but that the distribution of this electron density is not equal among the constituent atoms.

➤ Gutmann's four rules:

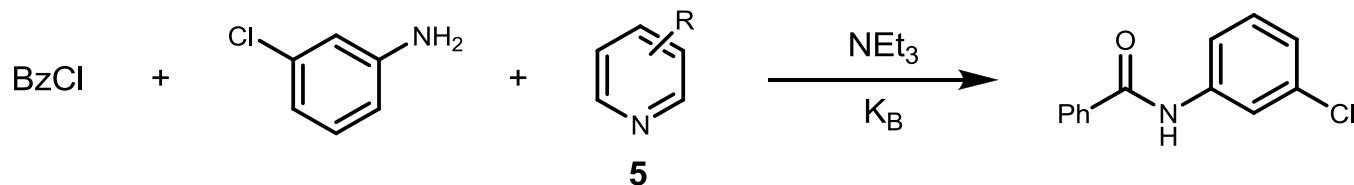
- 1) The smaller the intramolecular distance between D and A, the greater the induced lengthening of the peripheral bonds (A-X).
- 2) The longer the bond between D and A, the greater the degree of polarization of electron density across that bond.
- 3) As the coordination number of an atom increases, so do the lengths of all the bonds originating from that coordination center.
- 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.



Lewis Base Catalysis: n- π^* Interactions

Electrophilic Activation: Acylation

- n- π^* catalysis is representative of the chemistry of *unsaturated, carbon-centered* Lewis acidic functional groups.
- The acylation of alcohols and amines is a common transformation in Lewis base catalysis.

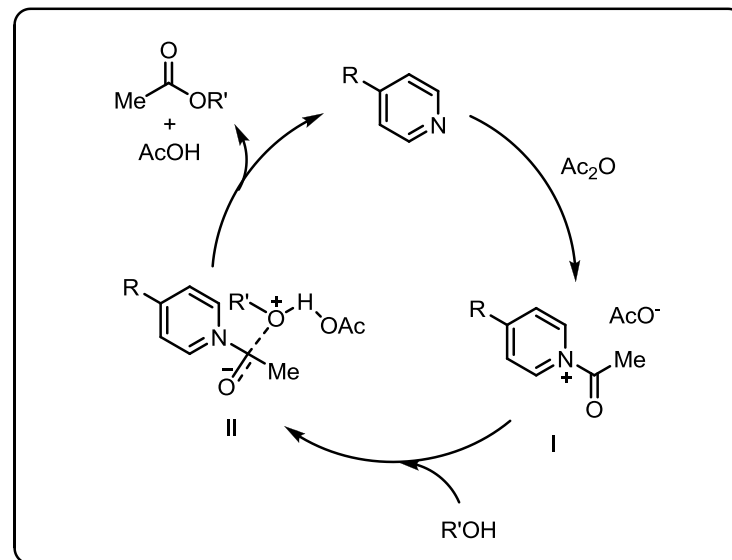


Kinetic Analysis

Entry	R	pK _a (H ₂ O)	K _B [L ² mol ⁻² S ⁻¹]	σ
1	3-NO ₂ (5a)	0.81	0.0231	0.710
2	3-Cl (5b)	2.84	0.0893	0.373
3	H (5c)	5.17	1.80	0
4	2-Me (5d)	5.97	0.0987	-0.170
5	3-Me (5e)	5.68	3.80	-0.069
6	4-Me (5f)	6.02	3.80	-0.170
7	4-NMe ₂ (5g)	9.58	10.0	-0.830

➤ The presence of a flanking 2-substituent creates unfavourable steric interactions and twists the acyl group out of the plane of the molecule.

Consensus Mechanism

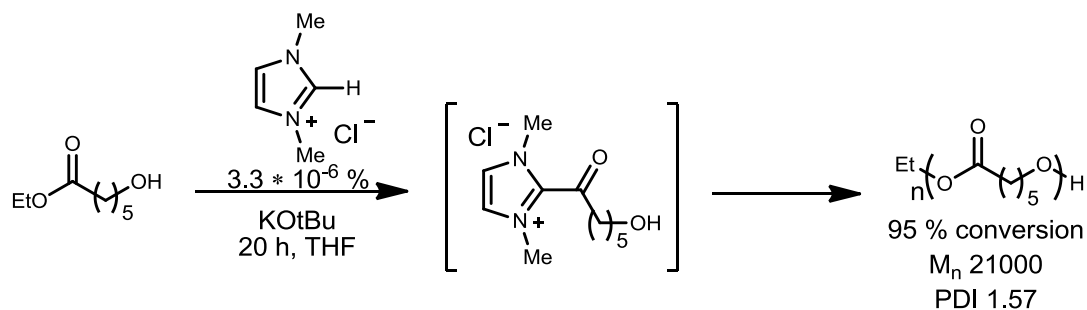


Lewis Base Catalysis: n- π^* Interactions

Electrophilic Activation: Acylation

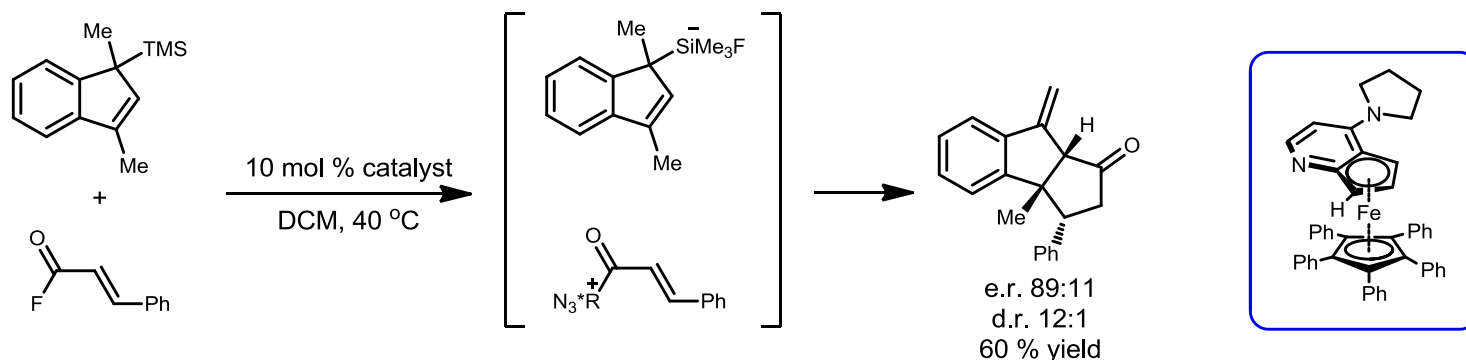
■ Extending the electrophilic reactivity of acylated Lewis Base catalysis.

➤ Lewis base catalyzed polymerizations of hydroxy esters.



E. F. Connor, G. W. Nyce, J. A. Lamboy, J. H. Hedrick, *J. Am. Chem. Soc.* **2002**, 124, 914.

➤ Lewis base catalyzed allylation/acylation cascade.

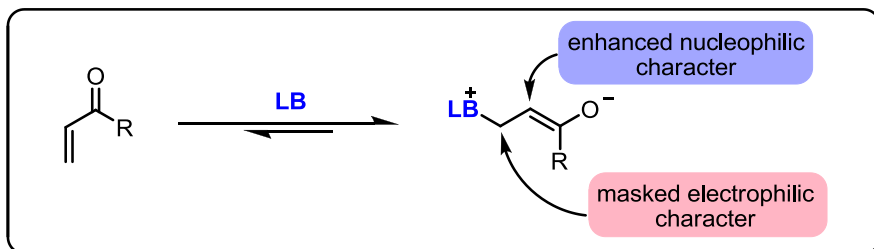
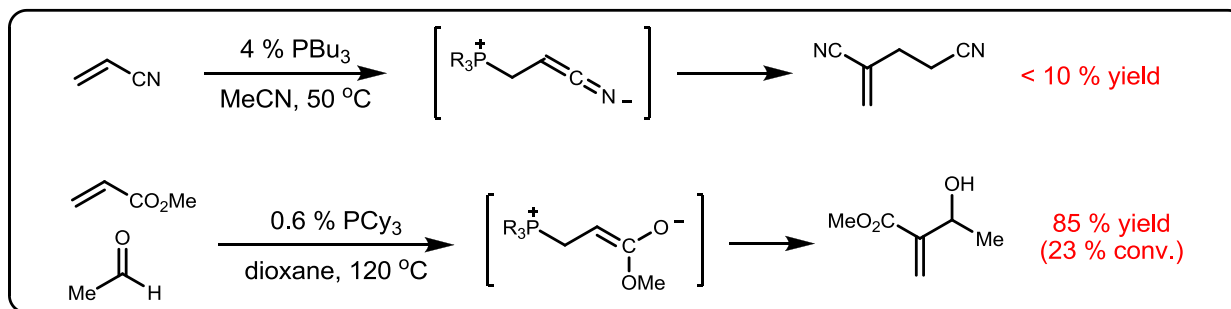


E. Bappert, P. Muller, G. C. Fu, *Chem. Commun.* **2006**, 2604.

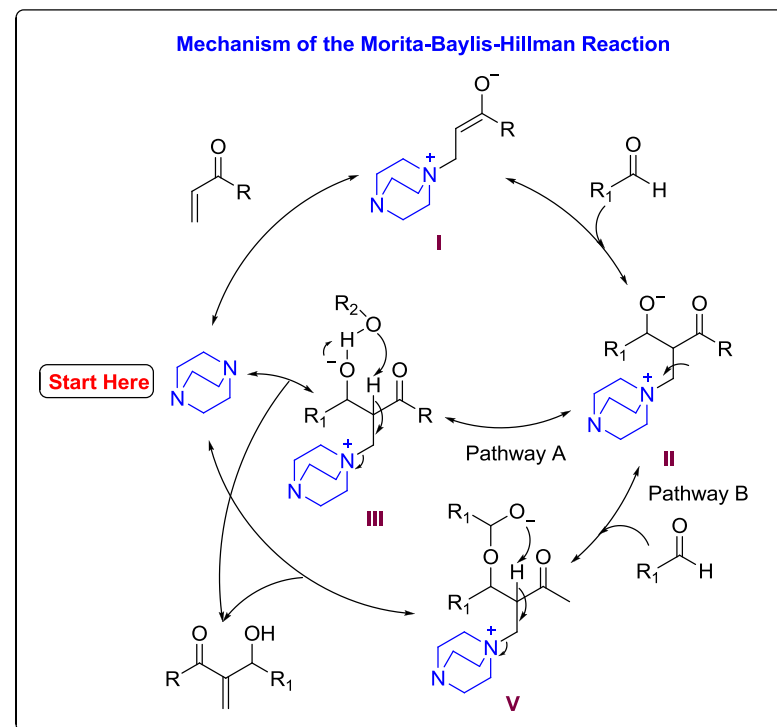
Lewis Base Catalysis: n- π^* Interactions

Nucleophilic Activation

- The Morita-Baylis-Hillman Reaction (reaction driven solely by the enhanced nucleophilic character)



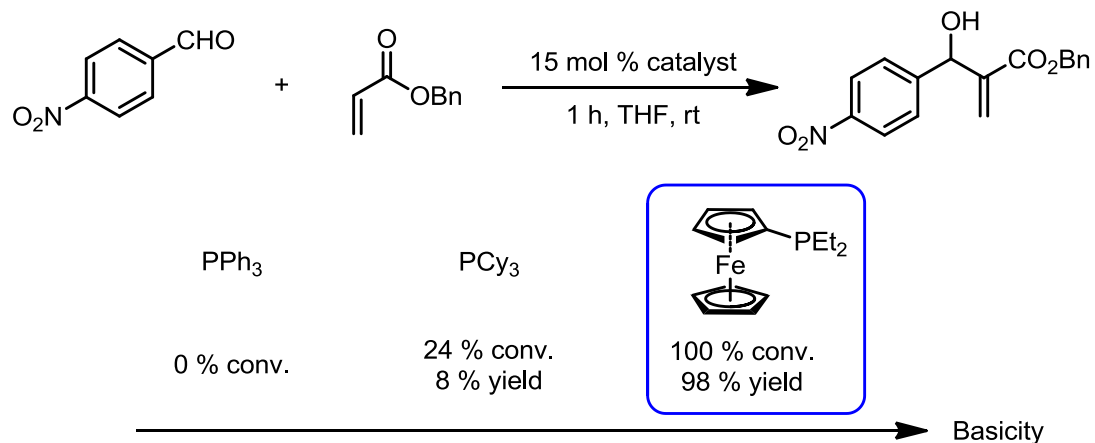
- The Morita-Baylis-Hillman reaction is commonly performed using highly Lewis basic phosphanes or amines as catalysts.
- These reactions are notoriously slow, often requiring days to reach useful levels of conversion.



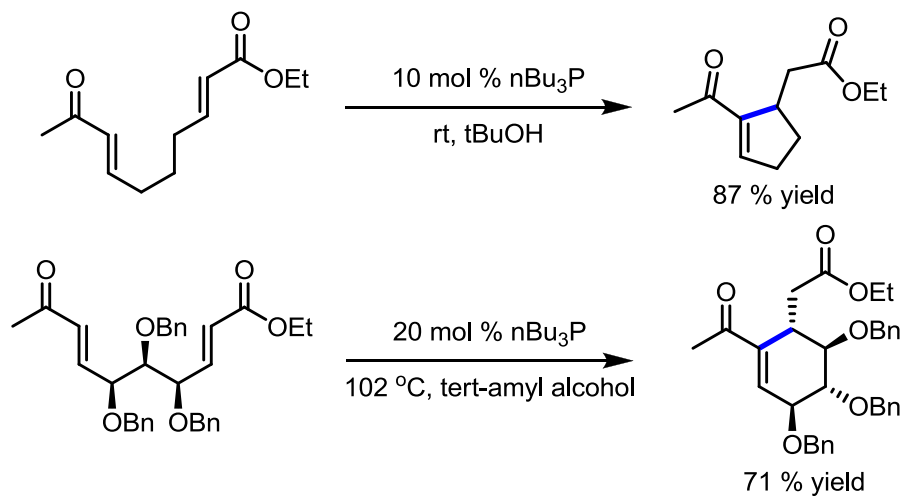
Lewis Base Catalysis: $n-\pi^*$ Interactions

Nucleophilic Activation

- Improve the reaction efficiency by introducing strong Lewis base



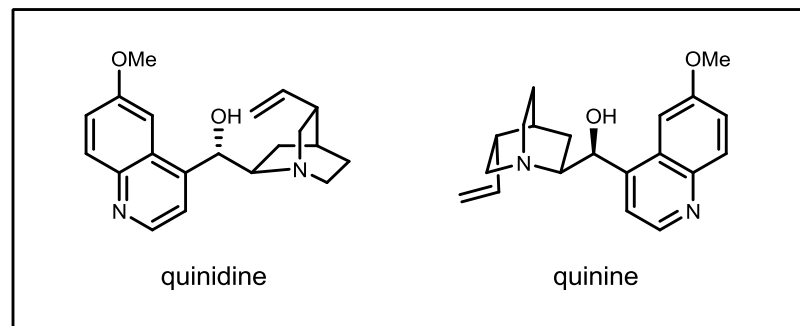
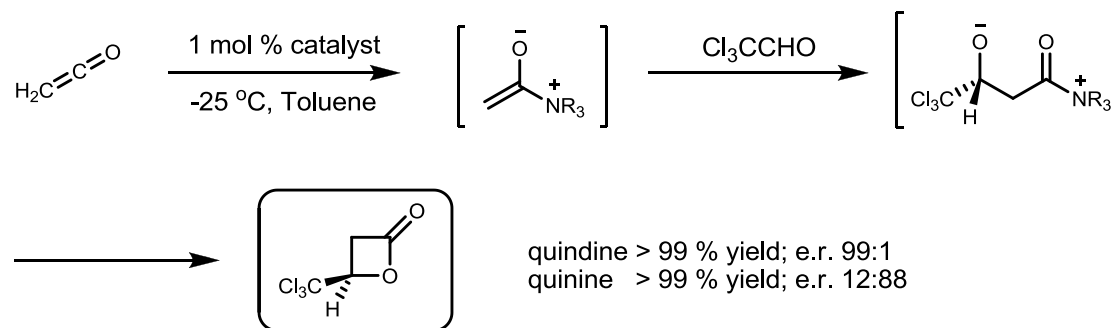
- The intramolecular Morita-Baylis-Hillman Reaction (Rahut-Currier Cyclization)



Lewis Base Catalysis: $n-\pi^*$ Interactions

Dual Activation

Reaction with Ketenes: Wynberg and Staring formal [2+2] cycloadditions



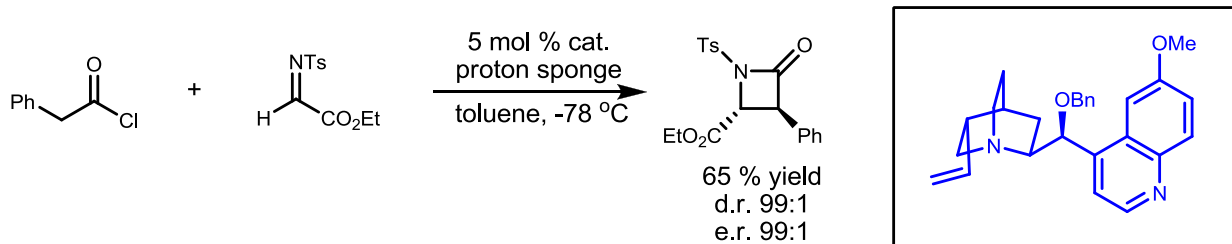
- The Lewis base catalyst enhances the nucleophilicity at C2 to enable the C-C formation but also enhances the electrophilicity at C1 to facilitate the final cyclization step.

Wunberg, H.; Staring, A. G. *J. Am. Chem. Soc.* **1982**, *104*, 166.

Lewis Base Catalysis: $n-\pi^*$ Interactions

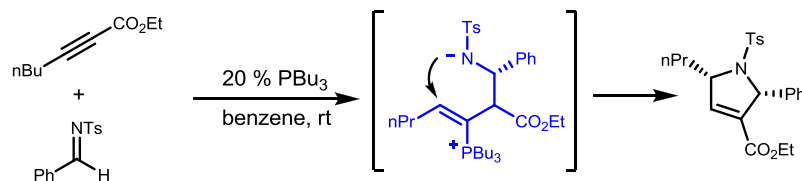
Dual Activation

■ Lewis Base Catalyzed [2+2] Cycloaddition: in situ generated ketenes



Calter, M. A.; Orr, R. K. Song, W. *Org. Lett.* **2003**, *5*, 4745.

■ Phosphane-Catalyzed [3+2] Cycloadditions



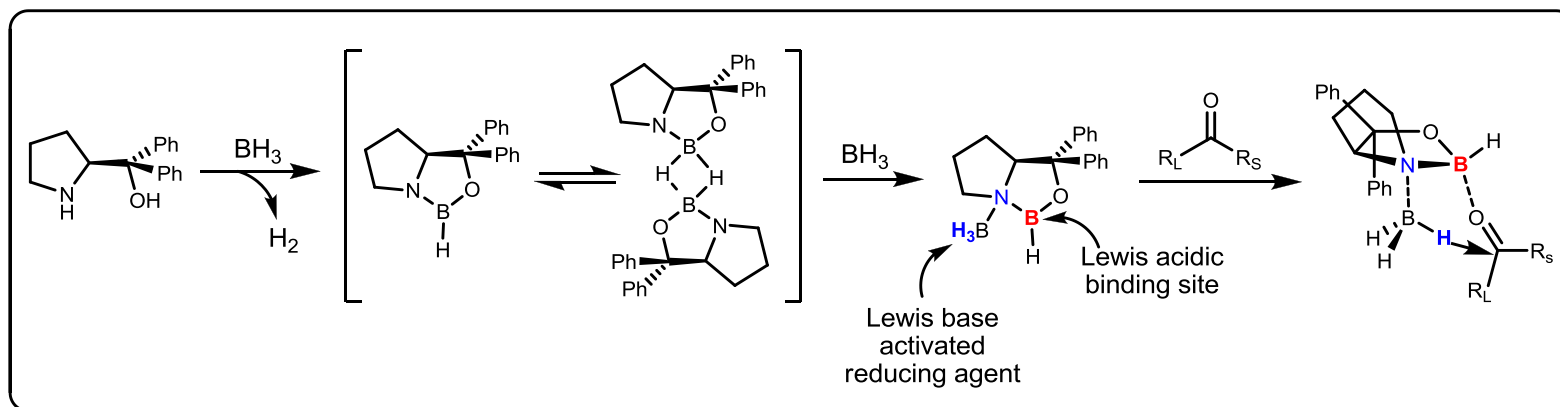
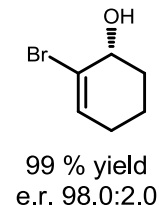
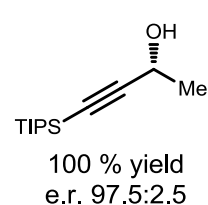
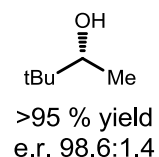
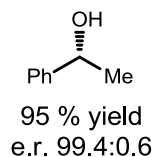
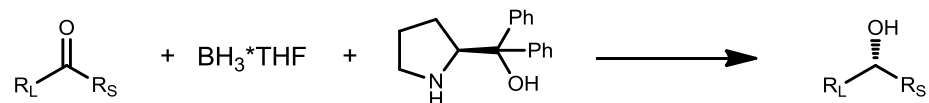
C, Zhang, X. Lu, *J. Org. Chem.* **1995**, *60*, 2906.

- The same zwitterionic intermediates also undergo formal [3+2] cycloadditions with α,β -unsaturated ketones and nitriles.
- The reaction has been extended by using chiral phosphanes and reached high regio- and enantioselectivities.

Lewis Base Catalysis: n-n* Interactions

Activation of boron

- Lewis base catalysis with boron: An example of the n-n* interaction.

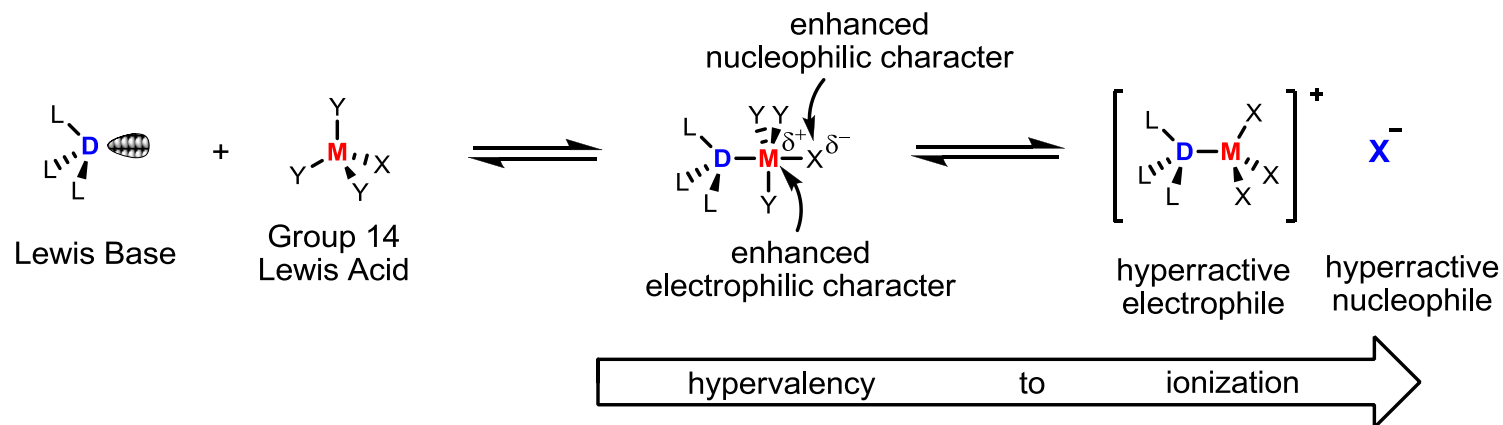


Lewis Base Catalysis: $n-\sigma^*$ Interactions

Polarized and Ionized Intermediates

■ $n-\sigma^*$ catalysis is representative of the chemistry of more commonly recognized Lewis acid, such as *transition-metal* and *electron-deficient main-group organometallic reagents*.

■ re-distribution of electron density in the newly formed adduct.



■ DFT calculation of partial atomic charges.

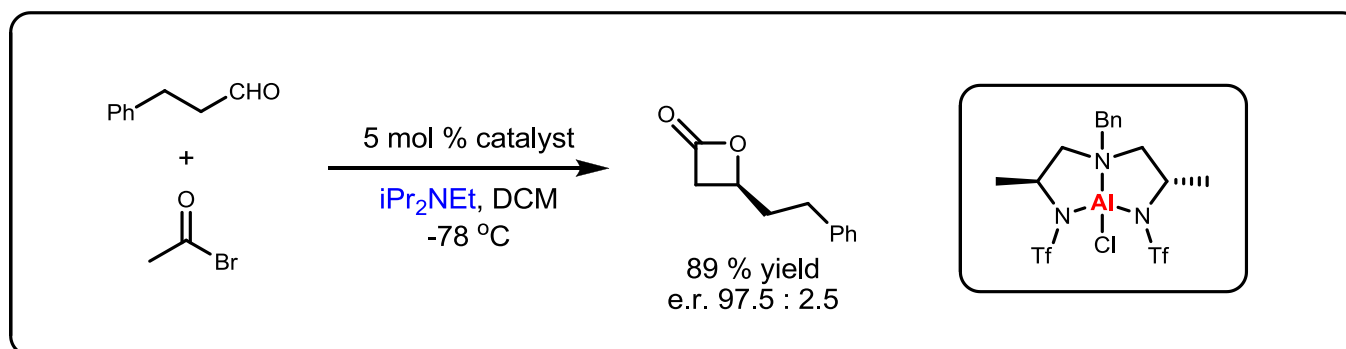
	SiF ₄	SiF ₅ ⁻	SiF ₆ ²⁻	SiCl ₄	SiCl ₅ ⁻	SiCl ₆ ²⁻
Mulliken charges: (at the Si atom)	+ 1.19	+ 1.14	+ 2.12	+ 0.178	+ 0.279	+ 0.539

Lewis Base Catalysis: $n\text{-}\sigma^*$ Interactions

Electrophilic Activation

■ Enhanced electrophilic reactivity of a hypervalent intermediate.

➤ Aluminum-catalyzed asymmetric [2+2] cycloadditions



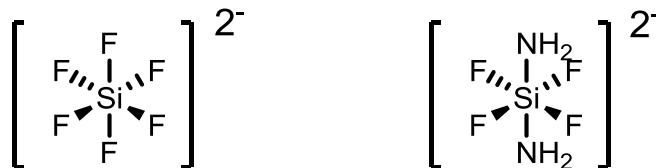
➤ The combination of neutral chiral aluminum catalyst and Lewis base gave a comparable levels of activity with the highly electrophilic aluminum species $\text{Al}(\text{SbF}_6)_3$.

S. G. Nelson, C. Zhu, X. Shen, J. Am. Chem. Soc. 2004, 126, 14.

Lewis Base Catalysis: n-σ* Interactions

Nucleophilic Activation: Trialkylsilanes

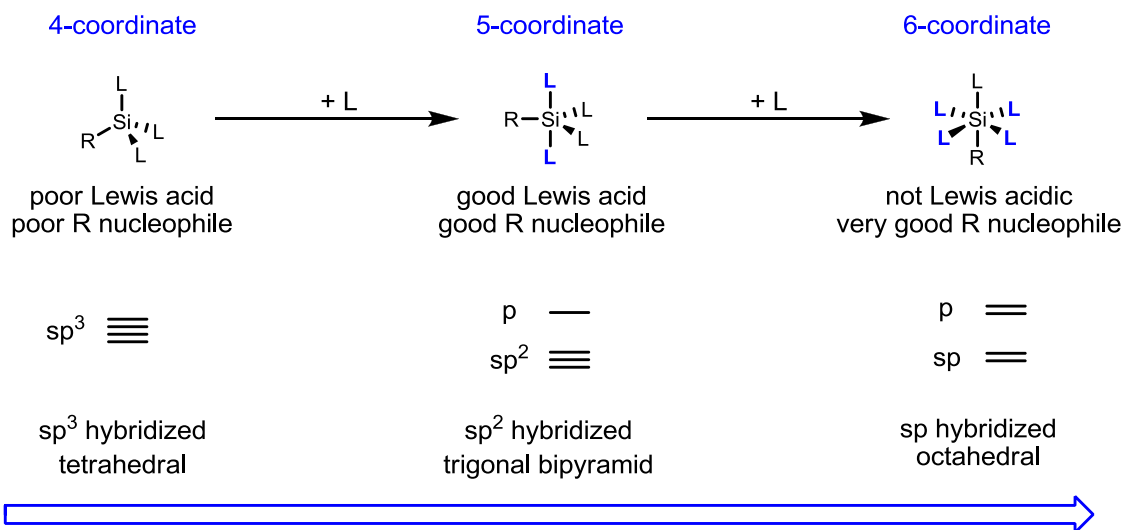
- The earliest examples of n-σ* type of Lewis base-acid interactions were found in the chemistry of silanes (since the early 19th century).



Gay-Lussac, J. L.; Thenard, L. J. *Memoires de Physique et de Chimie de la Societe d'Arcueil*, **1809**, 2, 317.

Davy, J. *Phil. Trans. Roy. London*, **1812**, 102, 352.

- Hybridization and orbital picture of silicon complexes.

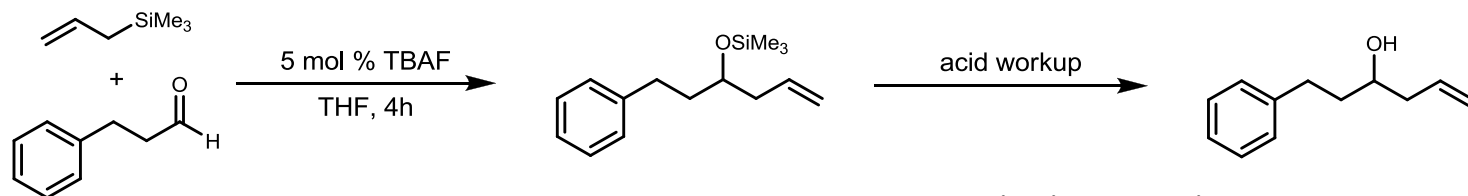


- Increasing δ^+ at silicon
- Increasing δ^- at ligands L and R
- 6-coordinate species not Lewis acidic because it has no room for binding

Lewis Base Catalysis: n- σ^* Interactions

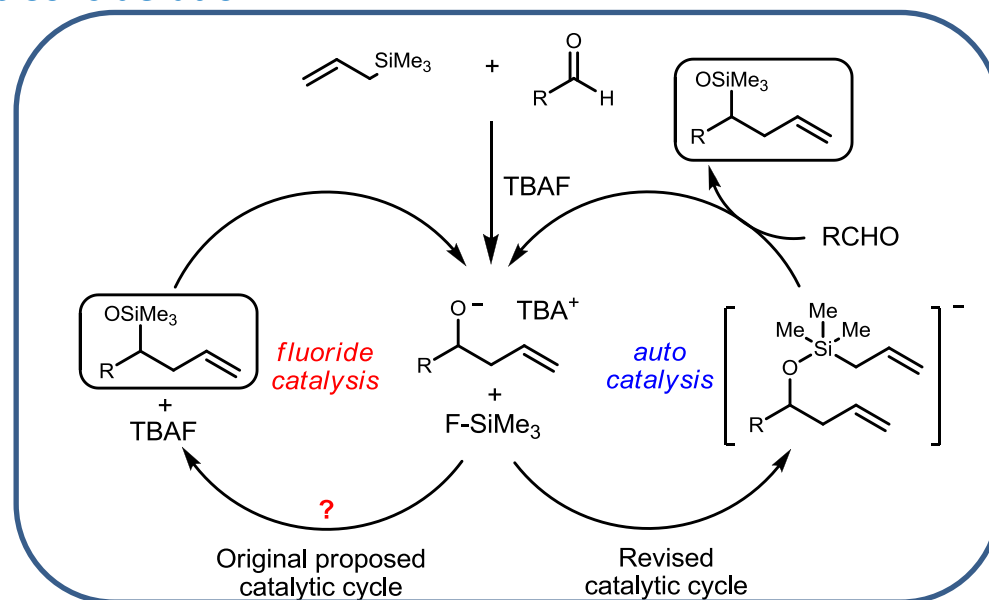
Nucleophilic Activation: Trialkylsilanes

- Until mid-1970s, Fluoride ions were first introduced by Corriu to promote the formation of a reactive, hypervalent silicate.
- First example of the use of homogeneous fluoride ions in C-C bond formation came from Sakurai.



Hosomi, A.; Shirahata, A.; Sakurai, H. *Tett. Lett.* **1978**, *19*, 3043

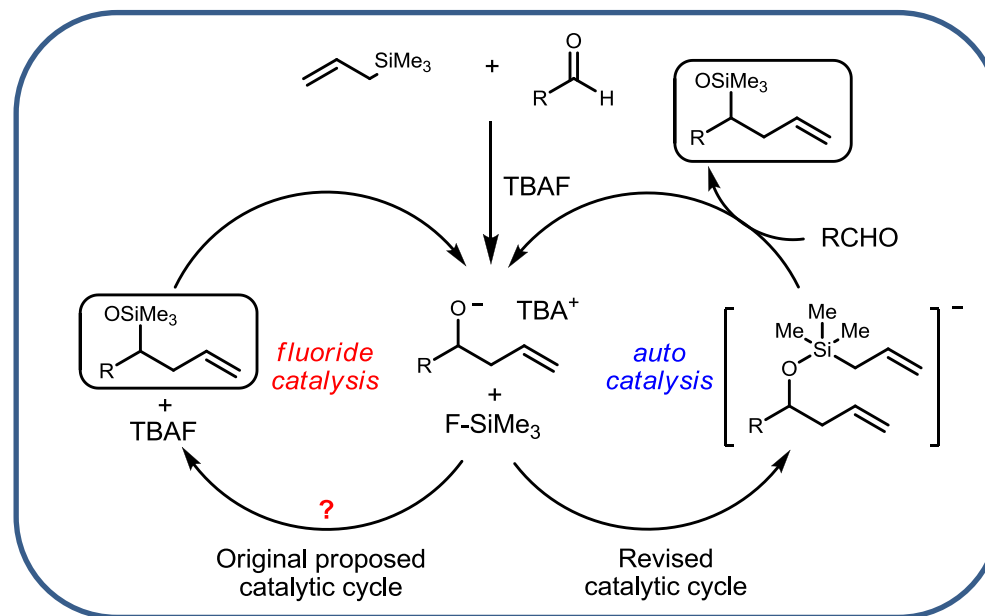
➤ Mechanistic Consideration



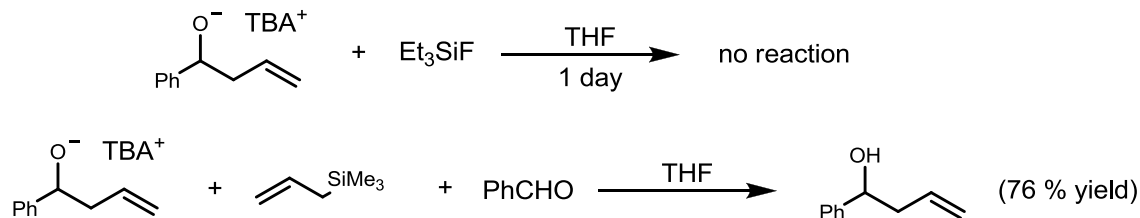
Lewis Base Catalysis: n-σ* Interactions

Nucleophilic Activation: Trialkylsilanes

➤ An induction period in the reaction-rate profile was found, which supported the autocatalytic mechanism. 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.



➤ Hou has demonstrated that alkoxides, not fluorides, are in fact active catalysts for subsequent allylation.

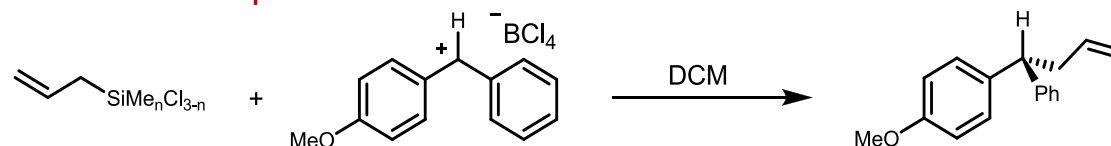


Wang, D.-K.; Zhou, Y.-G.; Tang, Y.; Hou, L.-X. *J. Org. Chem.* **1999**, *64*, 4233.

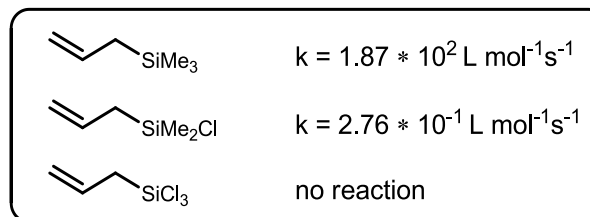
Lewis Base Catalysis: n-σ* Interactions

Dual Activation: Polyhalosilane

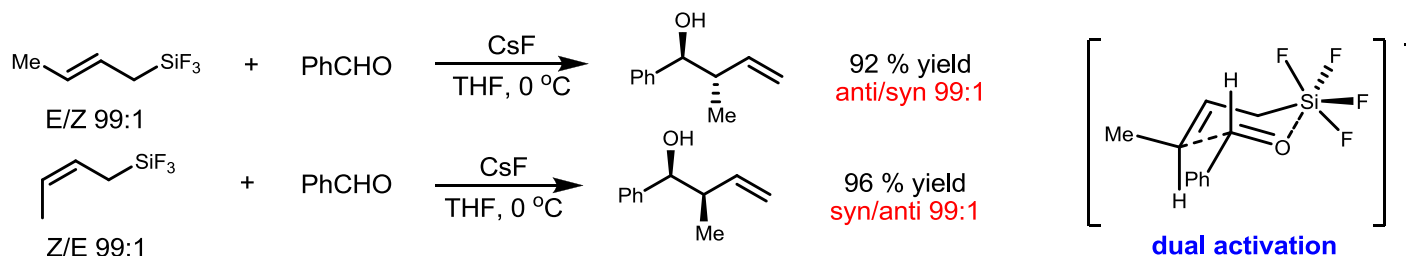
■ The incorporation of electronegative substituents leads to a dramatic change in the chemistry of the silicon species.



➤ The substitution of halogen atoms for alkyl substituents in allylic silanes renders these species much less nucleophilic.



■ However, 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.



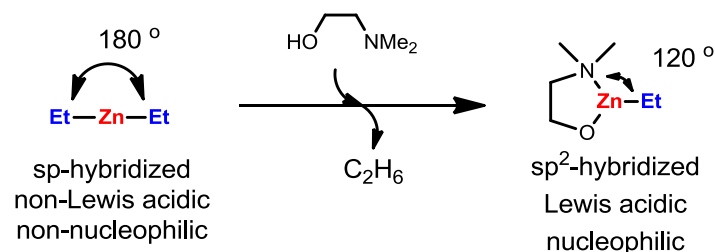
➤ The high selectivity indicates that reaction through a closed chair-like transition structure, with dual activation of both nucleophile and electrophile.

Kira, M.; Kobayashi, M.; Sakurai, H. *Tett. Lett.* **1987**, *28*, 4081.

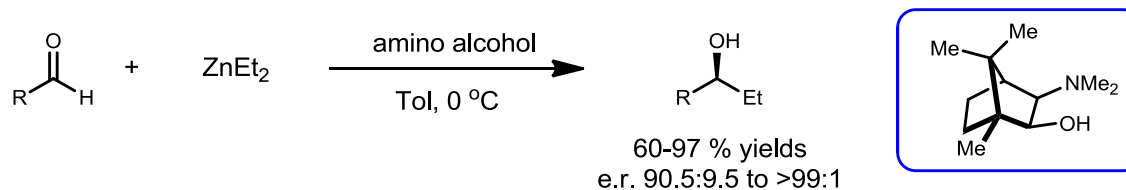
Lewis Base Catalysis: n-σ* Interactions

Dual Activation: dialkylzinc

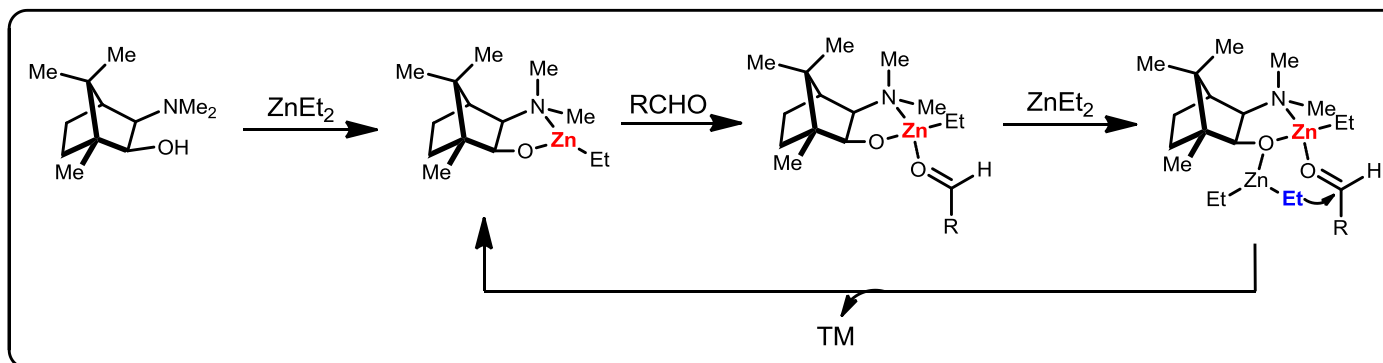
- Reaction of Lewis base with dialkylzinc: Addition to aldehyde.



- Lewis base induced dual activation with dialkylzinc: Addition to aldehyde.



- Proposed mechanism of Lewis base induced dual activation with dialkylzinc: Addition to aldehyde.



Summary and Outlook

- In contrast to the more familiar paradigm of Lewis acid catalysis, Lewis base catalysis can provide enhancements in nucleophilic and/or electrophilic character.
- The precise nature, coordination and conformation of the active catalyst have not been fully recognized.
- A more central focus must be the development of fundamentally new mechanisms for catalysis.

Thank you for your attentions!