Lewis-Base Catalysis

MacMillan Lab. Group Meeting
Anthony Mastracchio
November 5 2008

Lewis Base Catalysis

Presentation Outline

- Introduction

- Definitions and basic concepts of Lewis base Catalysis

- n–π^* interactions
  - Base catalyzed acylation of alcohols
  - Base catalyzed acylation of nucleophiles

- n–σ^* interactions
  - Polyhalosilanes
  - enoxyenolsilanes
  - $SiCl_4$ mediated processes

Relevant and Comprehensive Reviews:

Denmark, S. E.; Beutner, G. L., "Lewis Base Catalysis in Organic Synthesis." *Angew. Chem. Int. Ed.* **2008**, 1560

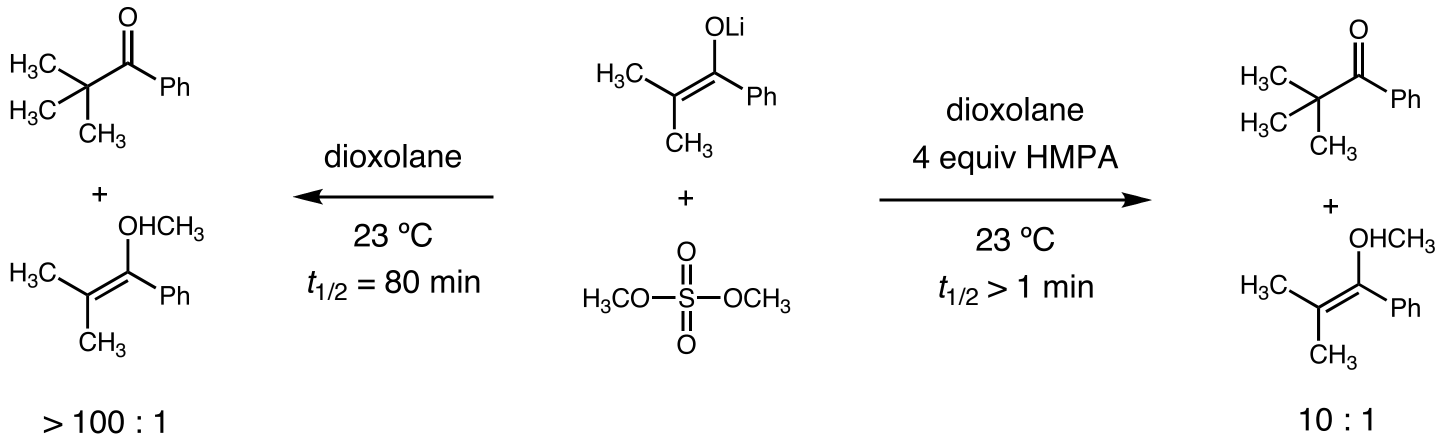
Gawronski, J.; Wascinska, N.; Gajewry, J. "Recent Progress in Lewis Base Activation and control of Stereoselectivity in the Additions of Trimethylsilyl Nucleophiles." *Chem. Rev. ASAP*

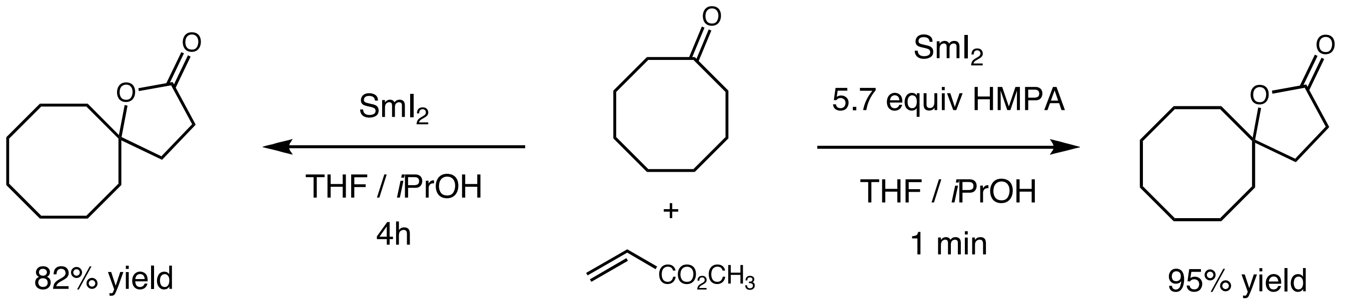
Rendler, S.; Oestreich, M. "Hypervalent Silicon as a Reactive in Site Selective Bond-Forming Processes" *Synthesis* **2005**, *11*, 1727

Storer, I. MacMillan Group Seminar " Hypervalent Silicon" July 2005

Lewis Base in Organic Synthesis

■ Strongly Lewis basic additive have found important applications as promoters of a variety of diverse chemical processes.





Lewis Base in Organic Synthesis

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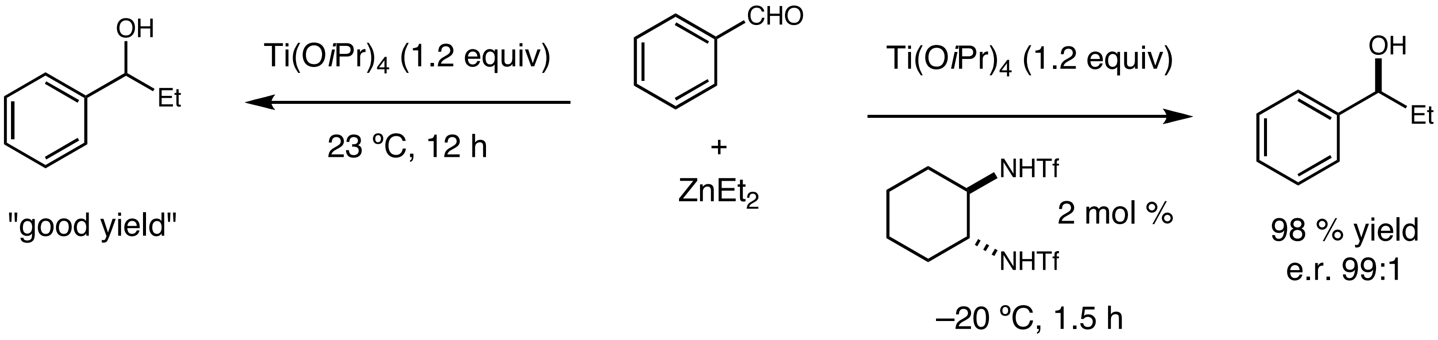
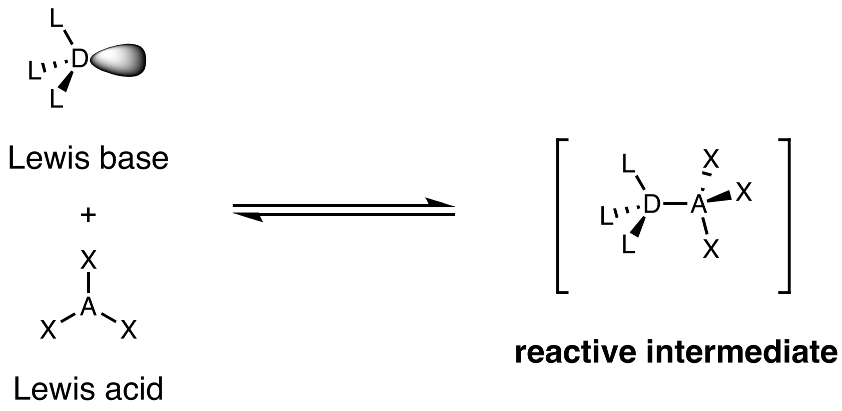


- When compared to the influence of Lewis acids, Lewis bases are seen to effect a much more diverse array of reactivity patterns.

- Lewis bases can enhance the chemical reactivity from increasing nucleophilicity or electrophilicity to modulation of electrochemical properties.

Some Definitions of Lewis Base Catalysis

- 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 reagent)

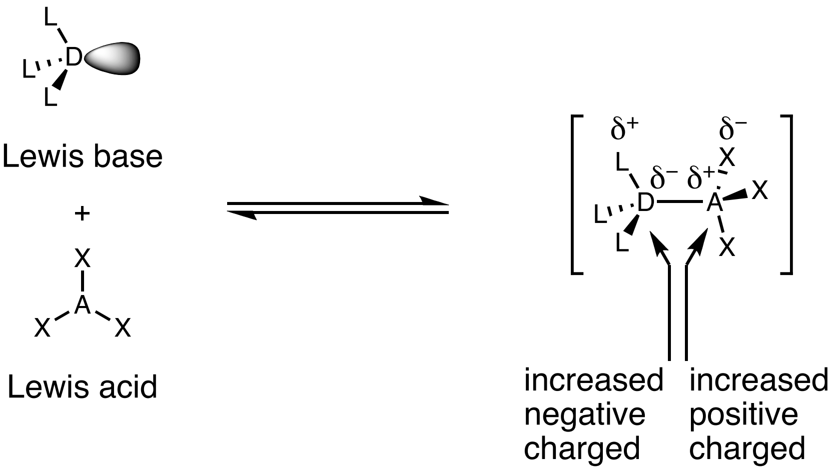


- In terms of reactivity, this increase in electron density normally translates to enhanced nucleophilicity of the acceptor subunit. However, this represent only one possible effect of the binding of a Lewis base.

- A much less appreciated and indeed, even counterintuitive consequence of the binding of a Lewis base is the ability to enhence the electrophilic character of the acceptor.

Some Definitions of Lewis Base Catalysis

- Electronic redistribution resulting from Lewis acid–base complexation



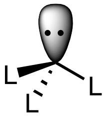
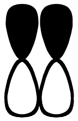
- Although the acceptor will possese an increased electron density relative to the parent Lewis acid, it is the distribution of the electron density among the constituent atoms that must be considered to rationalize the effect of adduct formation on reactivity

- To visualize this concept clearly, it is useful 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

Some Definitions of Lewis Base Catalysis

- 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 are significant in terms of catalysis. These are:

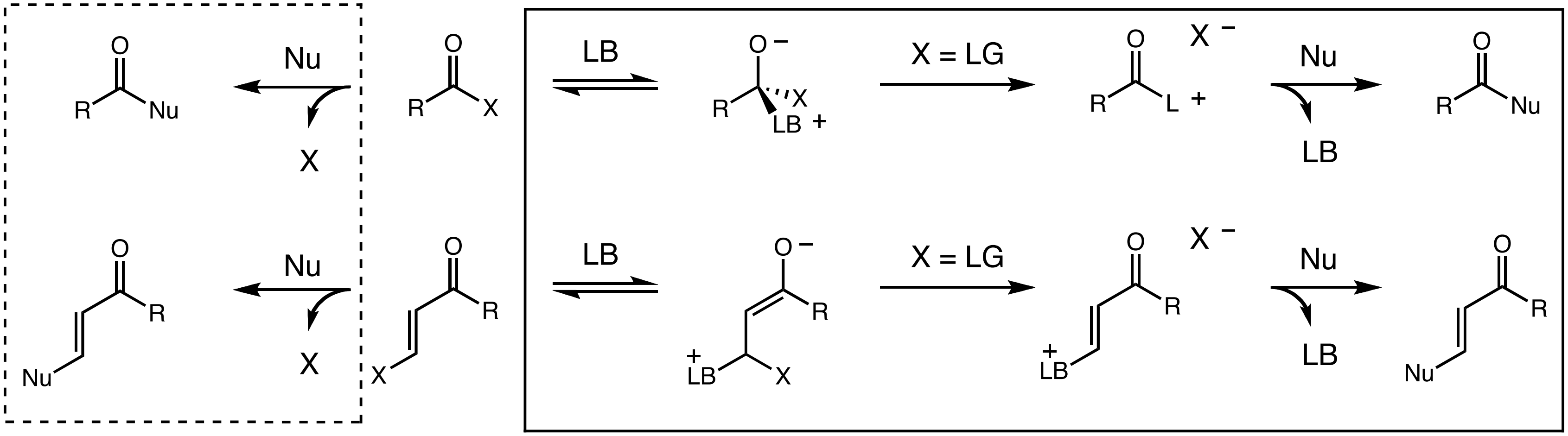
1) interactions between nonbonding electron pairs and antibonding orbitals with π character (n–π^* interaction)

2) interactions between nonbonding electron pairs and antibonding orbitals with σ character (n–σ^* interaction)

3) interactions between nonbonding electron pairs and vacant nonbonding orbitals with n character (n–n^* interaction)

Lewis Base Catalysis: n–π Interactions*

- Generally termed "nucleophilic catalysis", n–π* interactions represents the largest and most commonly recognized form of Lewis base catalysis.

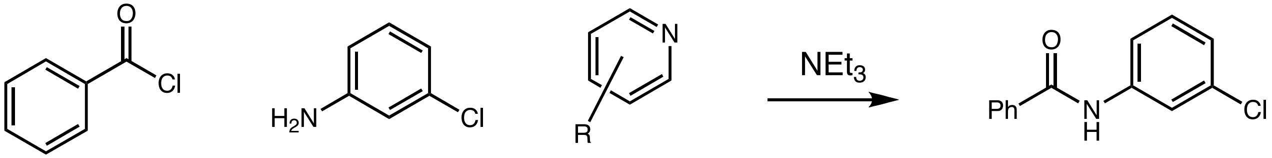


- These processes are the first clearly identified examples of Lewis base catalysis.

- In both cases the attack by the Lewis base leads to the formation zwitterionic intermediate with enhanced nucleophilic character at the oxygen atom. If a leaving group is present, this intermediate collapse to a new ionic species with enhanced electrophilic character.

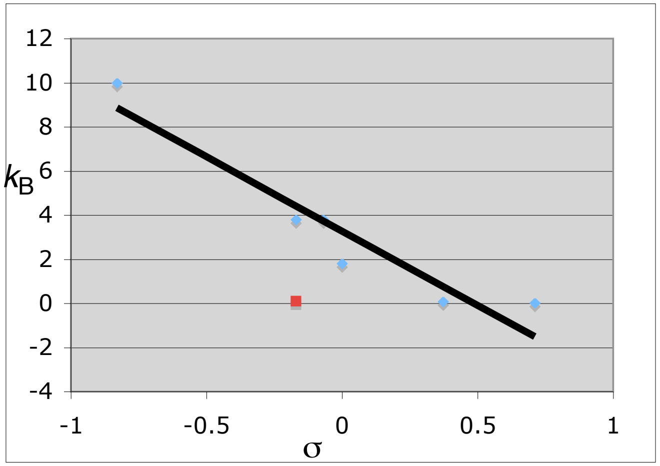
Lewis Base Catalysis: n–π Interactions*

- First study case of Lewis base catalysis: Base promoted acylation of alcohols



- Studies for the development of more active catalyst showed that donor substituent greatly enhanced the rates for acylation. These investigations led to the discovery of DMAP (entry 7)

Entry	**R**	**k_B [$L^2mol^{-2}s^{-1}$]**	**pK_a (H_2O)**	**σ**
1	3-NO_2	0.0231	0.81	0.710
2	3-Cl	0.0893	2.84	0.373
3	H	1.80	5.17	0
4	2-Me	0.0987	5.97	–0.170
5	3-Me	3.8	5.68	–0.069
6	4-Me	3.8	6.02	–0.170
7	4-NMe_2	10.0	9.58	–0.830



- Linear relationship were found between reaction rate, Hammett σ values, and pK_a values.

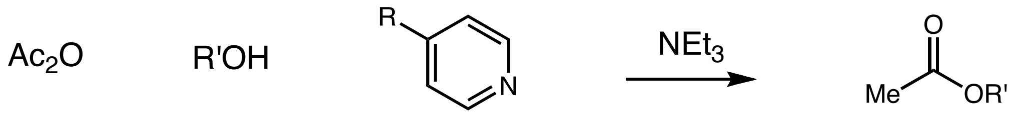
- Both relationships broke down with 2-substituted pyridines despite small change in σ and pK_a values.

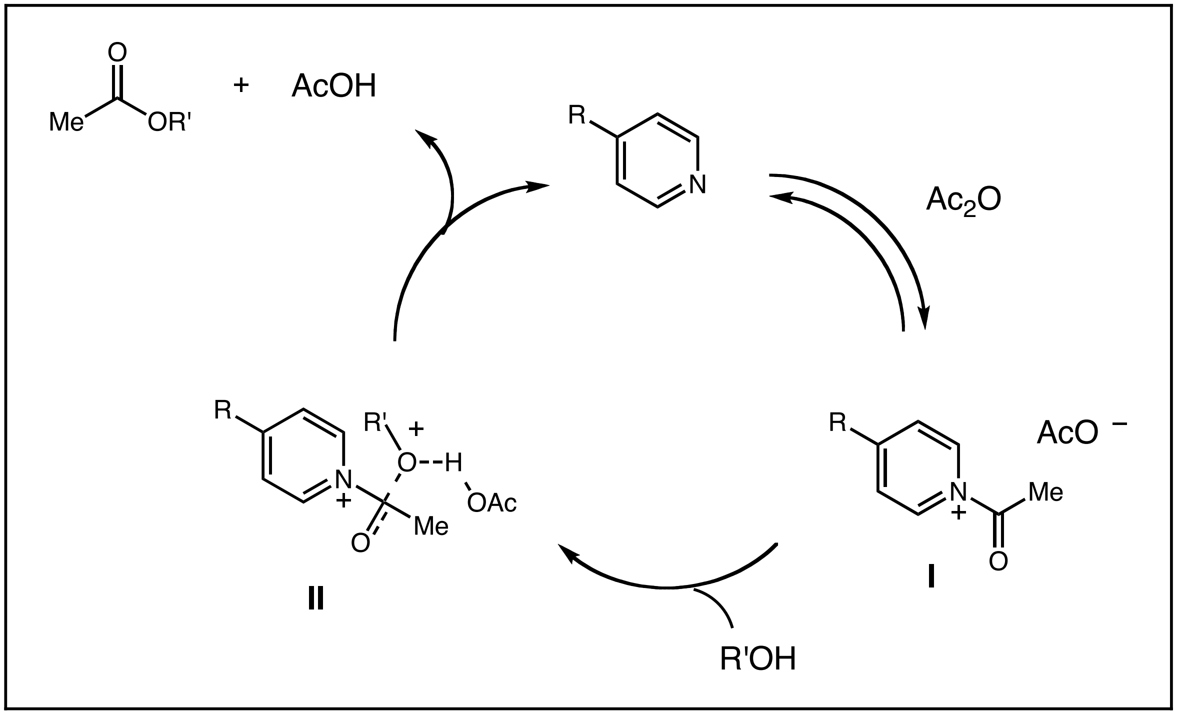
- This dramatic change in reaction rate between 4- and 2-methylpyridine is inconsistent with simple Brønsted base catalysis. New "consensus" mechanism involving Lewis base catalysis was formulated

Litvinenko, L.M.; Kirichenko, A.I.; *Dokl. Akad. Nauk. SSSR Ser. Chem.* **1967**, *176*, 197

Lewis Base Catalysis: n–π Interactions*

- Consensus mechanism for pyridine-catalyzed acylations.



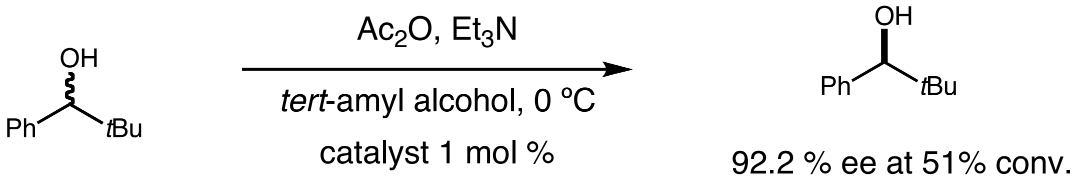


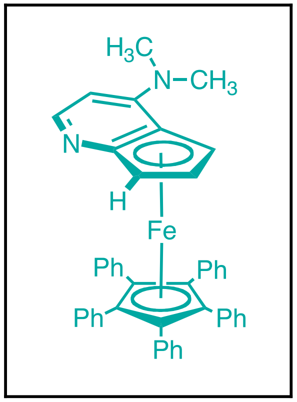
- Recent calculations suggest that **II** is the rate determining structure
- Support for the formation of the acylpyridinium intermediate has been found by IR and UV spectroscopy as well as crystallographic studies
- For maximum conjugation between the pyridine and the acyl group a fully planar conformation must be obtained. The presence of a flanking 2-substituent creates unfavorable steric interactions and twist the acyl group out of the plane destabizing the molecule. This explains low reactivity for 2-substituted pyridine.

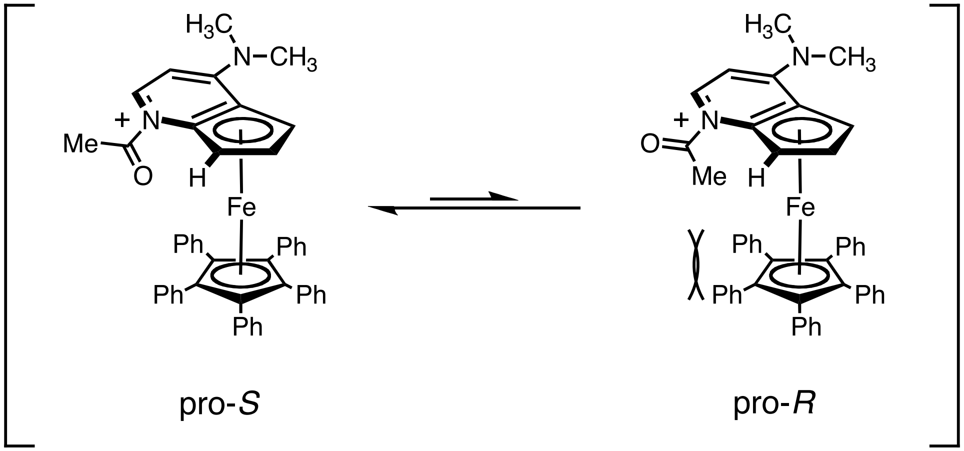
- Can catalytic enantioselective processes be developed?

Lewis Base Catalysis: n–π Interactions*

■ Fu's kinetic resolution of secondary alcohols







- 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

■ High levels of selectivity was obtained for the kinetic resolution of alkyl aryl and alkenyl secondary alcohols

Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492.

Lewis Base Catalysis: n–π Interactions*

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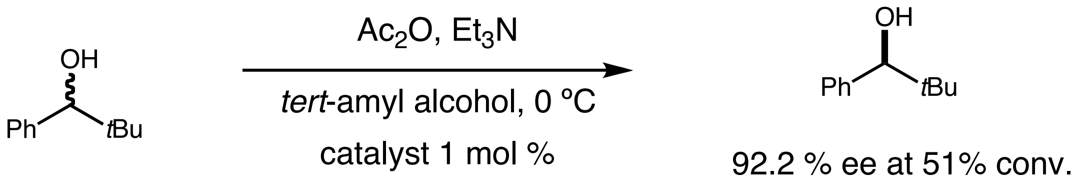

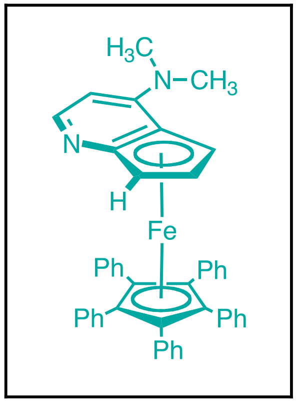

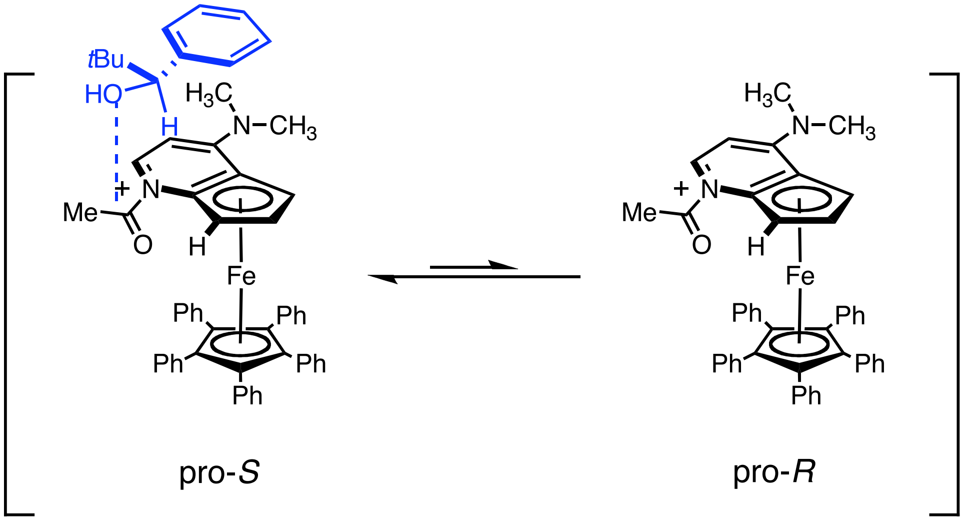

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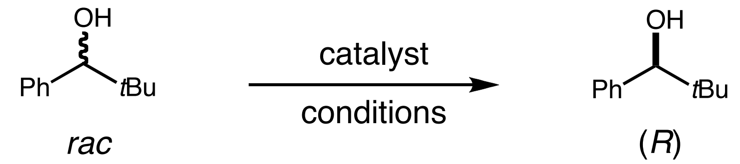
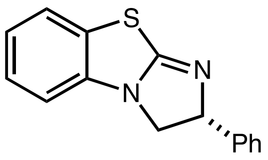
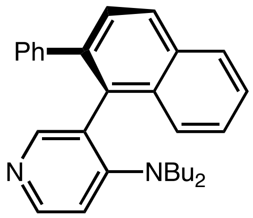
Lewis Base Catalysis: n–π Interactions*

- Chiral catalysts for the kinetic resolution of alcohols.

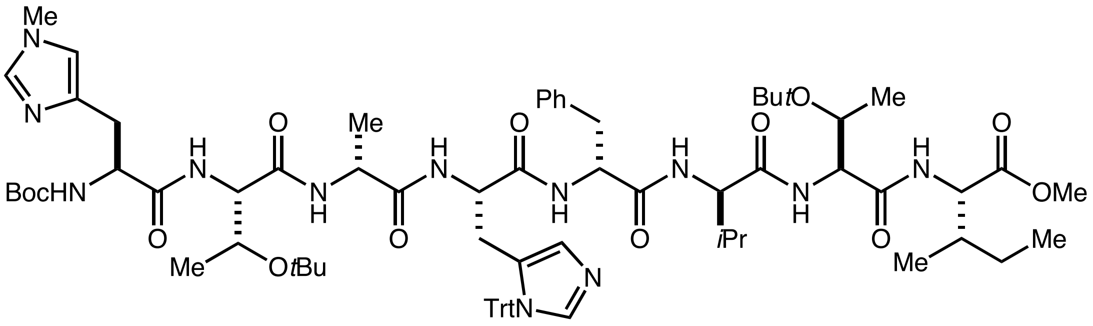




4 mol %, $CHCl_3$, 0 ºC
Na_2SO_4, N*i*Pr2Et, $(EtCO)_2O$
e.r. 99:1 at 51 % conv.
s = 166



1 mol %, toluene, –95 ºC
Et_3N, $(iPrCO)_2O$
e.r. 95.5:4.5 at 16 % conv.
s = 26



0.5 mol %, toluene, –65 ºC
$Ni Pr_2Et$, Ac_2O
e.r. >75:25 at 35 % conv.
s > 50

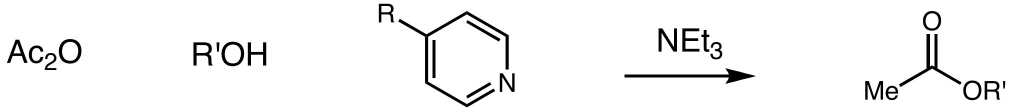
Kawabata, T.; Stragies, R.; Fukaya, T.; Fuji, K. *Chirality* **2003**, *15*, 71

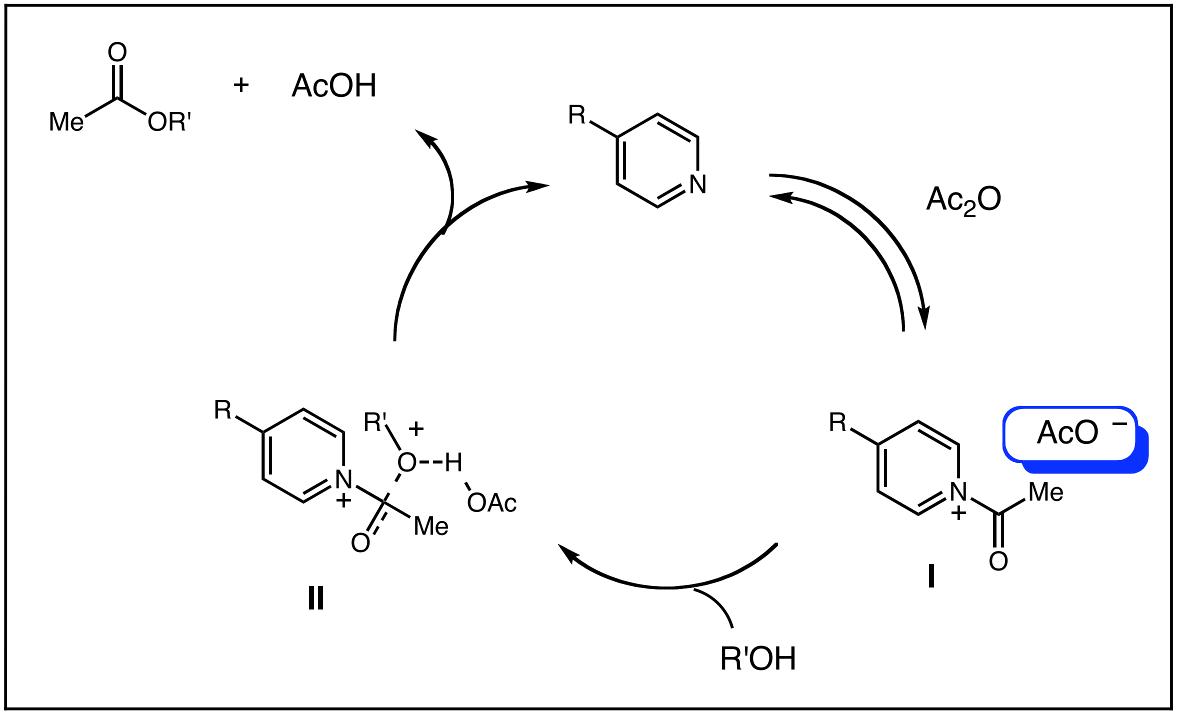
Birman, V.B.; Jiang, X.; Li, X.; Guo, L.; Uffman, E.W. *J. Am. Chem. Soc.* **2006**, *128*, 6536

Miller, S.J.; *Acc. Chem. Res.* **2004**, *37*, 601

Lewis Base Catalysis: n–π Interactions*

- Consensus mechanism for pyridine-catalyzed acylations.

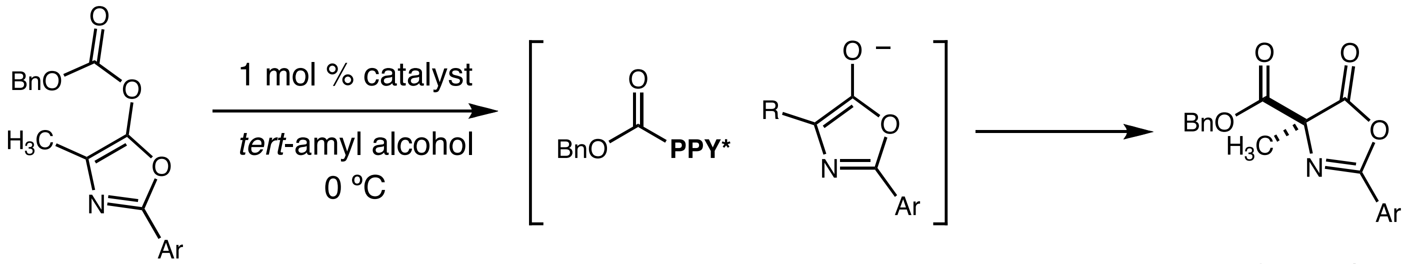




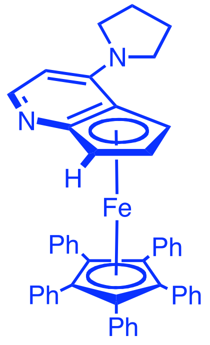
- Can we utilize the nucleophile produced in asymmetric transformation?

Lewis Base Catalysis: n–π Interactions*

■ Extension to acylation of nucleophiles



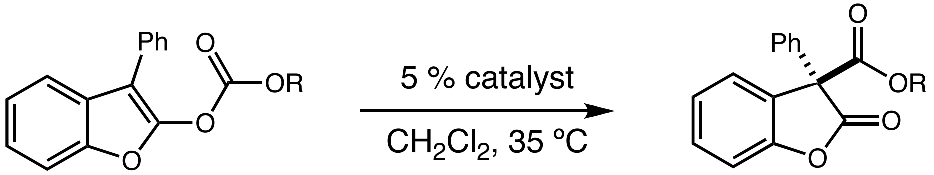
e.r. 95.5 : 4.5
94 % yield



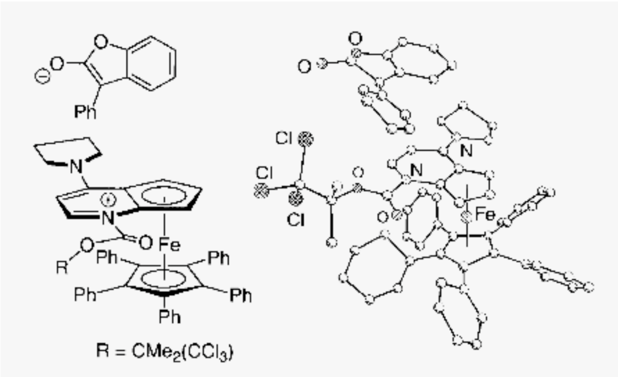
PPY*

Ruble, J.C.; Fu, G.C. *J. Am. Chem. Soc.* **1998**, *120*, 11532

- This method has been further expanded to furanones, benzofuranones, and oxindoles.



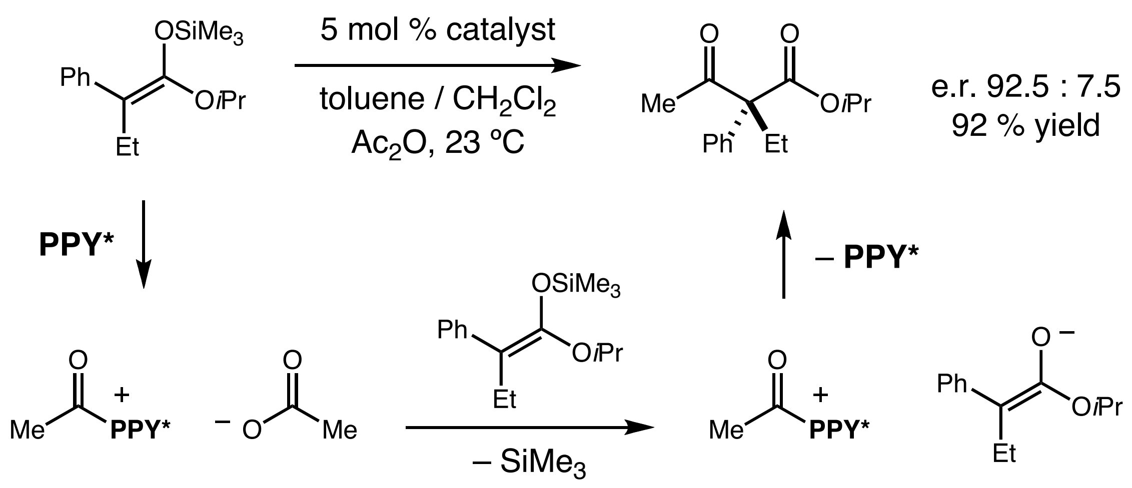
97 % ee
81 % yield



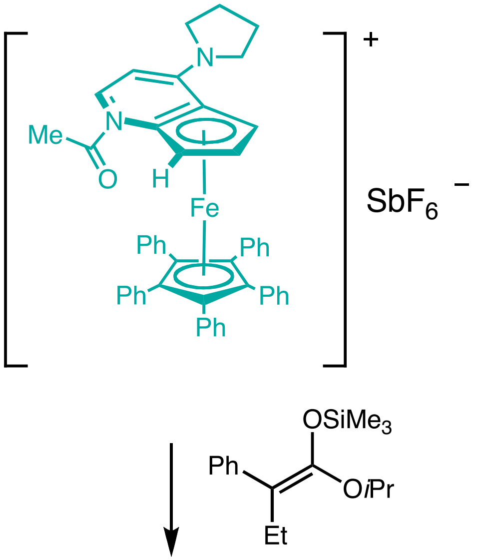
Hills, I.D.; Fu, G.C. *Angew. Chem. Int. Ed.* **2003**, *42*, 3921

Lewis Base Catalysis: n–π Interactions*

Fu's C-acylation of silyl ketene acetals



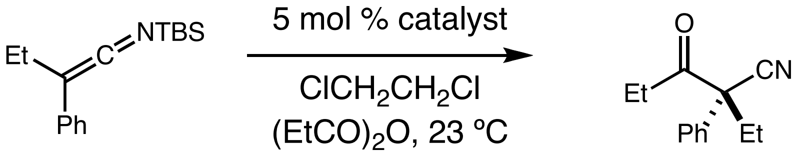
e.r. 92.5 : 7.5
92 % yield



no reaction

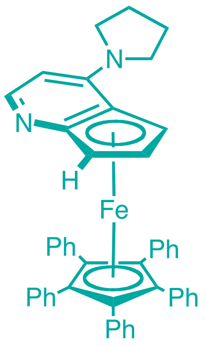
- It is believed that the reaction involves activation of both the anhydride (formation of an acylpyridinium ion) and the silyl ketene acetal (generation of an enolate). This was concluded in part because the acylpyridinium SbF_6 salt was unreactive towards the silyl ketene acetal.

Fu's C-acylation of silyl ketene imines



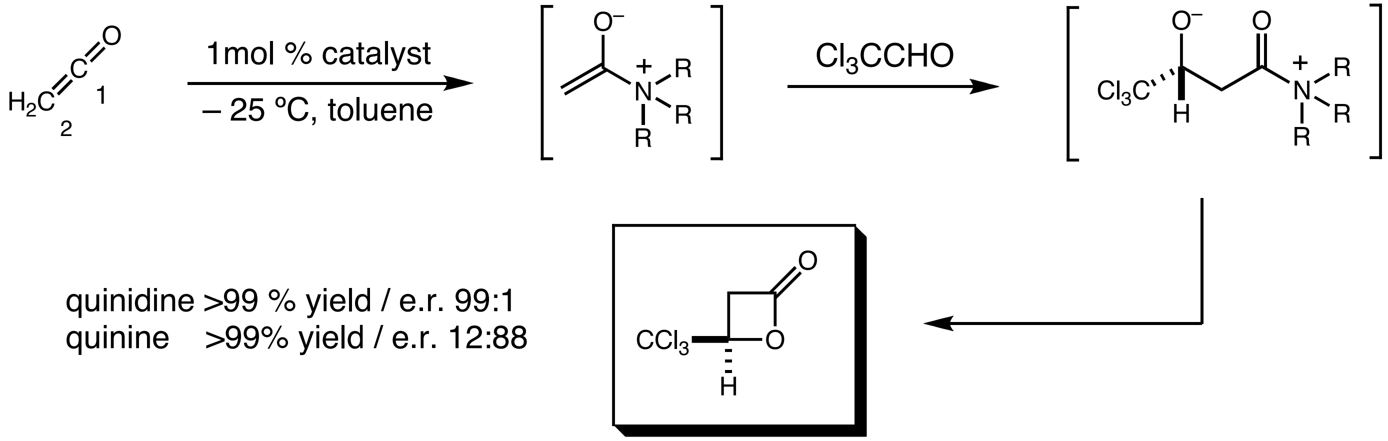
e.r. 90.5 : 9.5
85 % yield

PPY* =

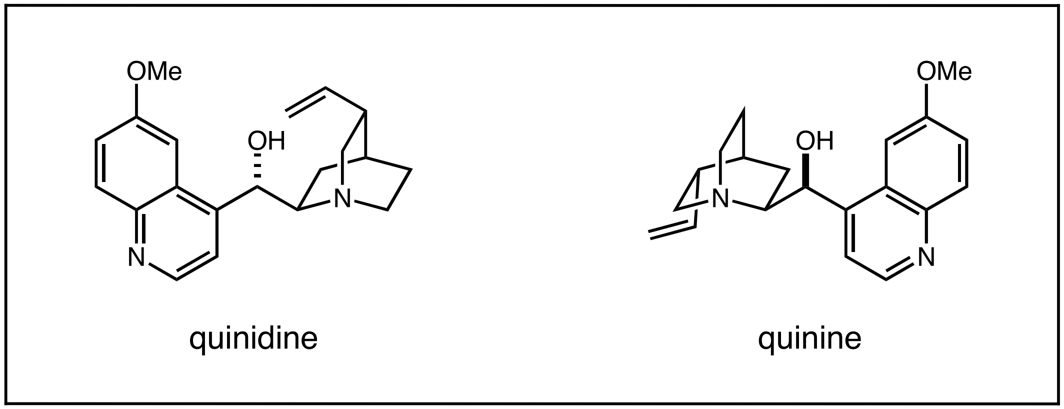


Lewis Base Catalysis: n–π Interactions*

Lewis base catalyzed reactions of ketenes: Wynberg and Staring formal [2+2] cycloadditions



quinidine >99 % yield / e.r. 99:1
quinine >99% yield / e.r. 12:88



quinidine

quinine

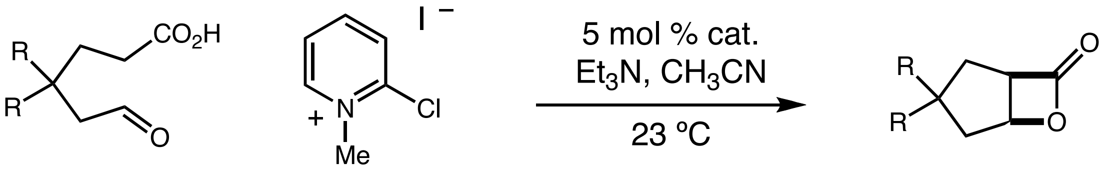
- The Lewis base catalyst enhances the nucleophilicity at C2 to enable the C–C formation but also enhances the electrophilicity at C1 to facilitate the final cyclization step.

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

Can the Lewis Base be use to both form the ketene an to perform the asymmetric transformation?

Lewis Base Catalysis: n–π Interactions*

■ Lewis base catalyzed [2+2] cycloadditions with in situ generated ketenes.



5 mol % cat.
Et_3N, CH_3CN

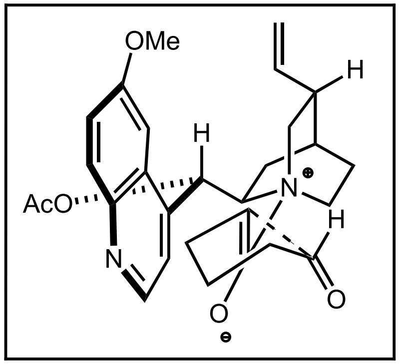
23 °C

37-55 % yield
90-92 % ee

- It was observed that blocking the hydroxyl group with different carbonyl derivatives did not affect enantioselectivity very much, and thus the following stereochemical rationale was proposed

- Once the acylammonium enolate is formed, the aldehyde approaches the enolate from the *si* face, away from the quinoline

Cortez, G. S.; Tennyson, R.L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123,* 7945



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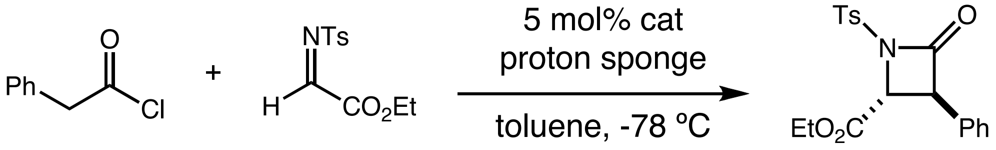
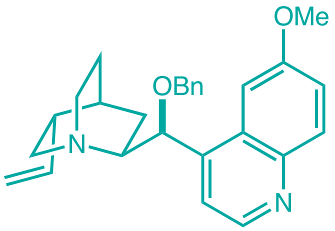


5 mol% cat
proton sponge

toluene, -78 °C

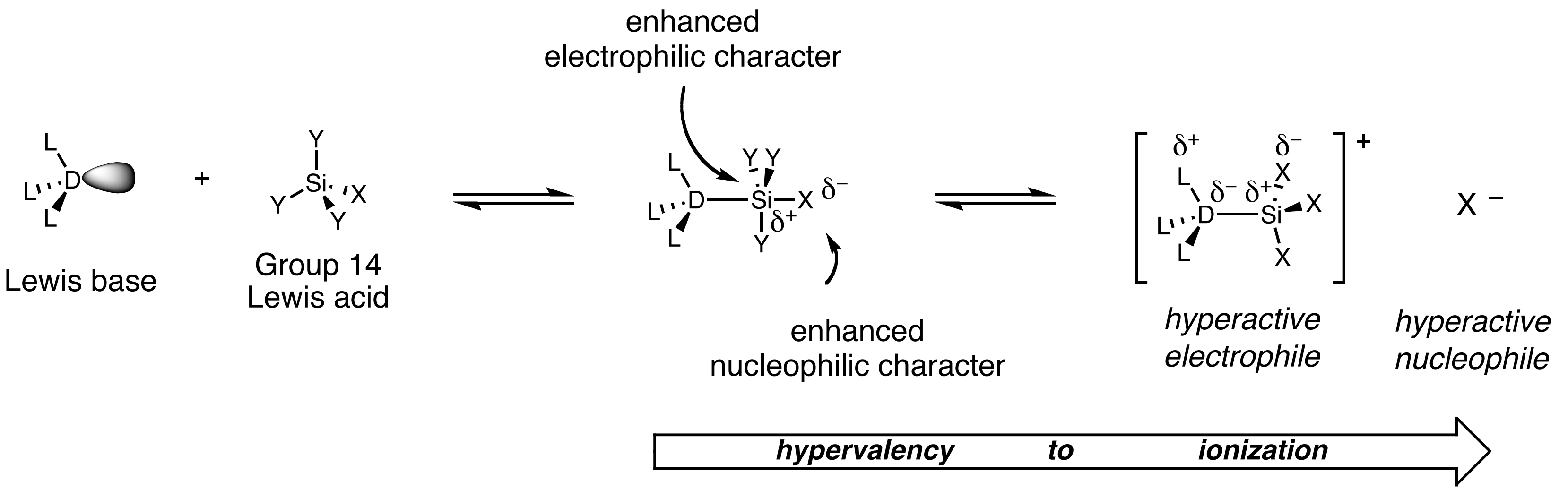
65 % yield
d.r. 99:1
e.r. 99:1



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

Lewis Base Catalysis: n–σ Interactions*

- Lewis acids, such as transitionmetal 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.

- In the proposed model of n–σ* interaction, this binding leads to a polarization of the adjacent bonds, thereby increasing the electron density at the peripheral atoms. Silicon has shown great success in this type of process.

- Increase electrophilicity of the Metal center is supported by computational studies.

series	$SiCl_4$	$SiCl_5^-$	$SiCl_6^{-2}$
Mulliken charge	+0.178	+0.279	+0.539

- What causes the enhanced electrophilicity of the metal and what makes silicon prone for hypervalency?

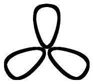
Bonding to Silicon - How are 5 or 6 Bonds Accommodated?

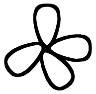
Valence Shell Electron Pair Repulsion Theory (VSEPR)

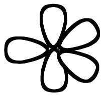
Theory to account for molecular bond geometries

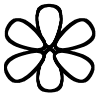
- Predicted hybrid orbitals for 2–6 coordinate compounds


linear
sp

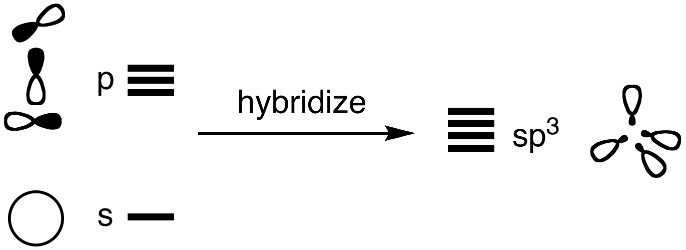

trigonal planar
sp^2

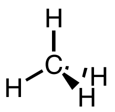

tetrahedral
sp^3


trigonal bipyramid
sp^{3d}

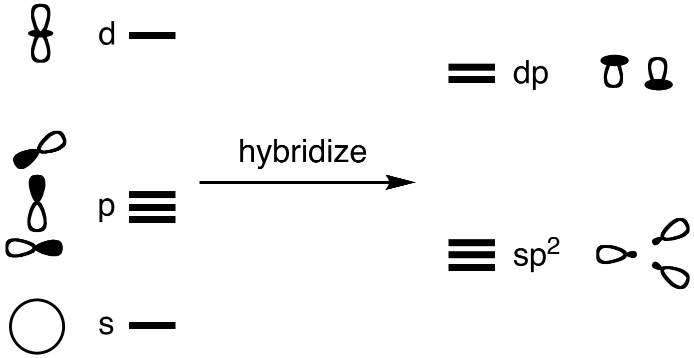

octahedral
sp^3d^2

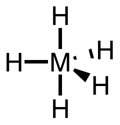
Tetrahedral coordination – sp^3 rehybridization




sp^3
tetrahedral

Trigonal bipyramidal – sp^3d rehybridization?



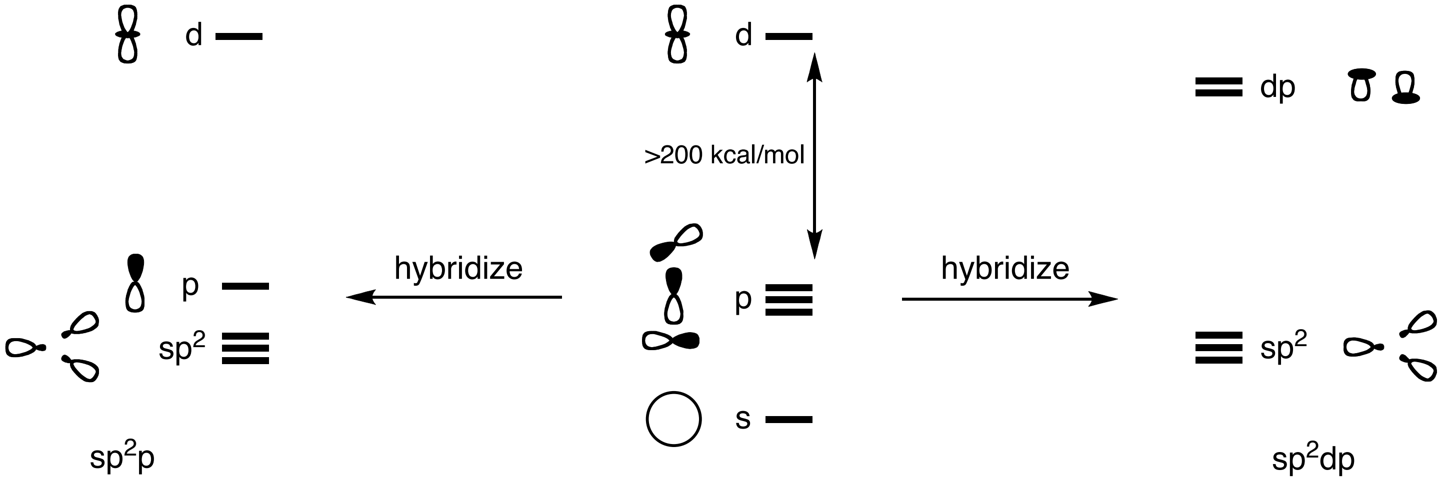

sp^2dp
trigonal bipyramid

Gillespie, R. J. *Chem. Soc. Rev.*, **1992**, *21*, 59.
Storer, I. *MacMillan Group Seminar: Hypervalent Silicon*, **2005**.

The Role of d–Orbitals in Main-Group Compounds

pentavalent compounds

How do 3s, 3p and 3d orbitals really hybridize to permit pentavalency?

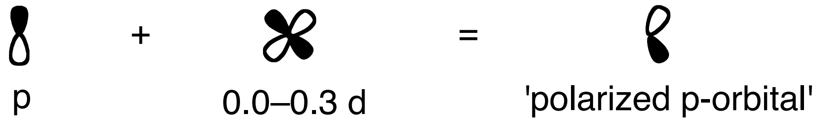


- The d-orbitals must be close enough in energy to the s and p orbitals to mix favourably

- The 3sp^{2}dp hybridization would come at a massive energetic cost of >200 kcal/mol rendering this unlikely to ever occur – sp^{2}p hybridization is likely to occur preferentially

3d orbitals are still involved to a limited extent

- The d-orbitals have been essential for complete computation of all main group compounds
- Their role appears to be confined to that of polarization of the p-orbitals – d-orbital occupation of <0.3e

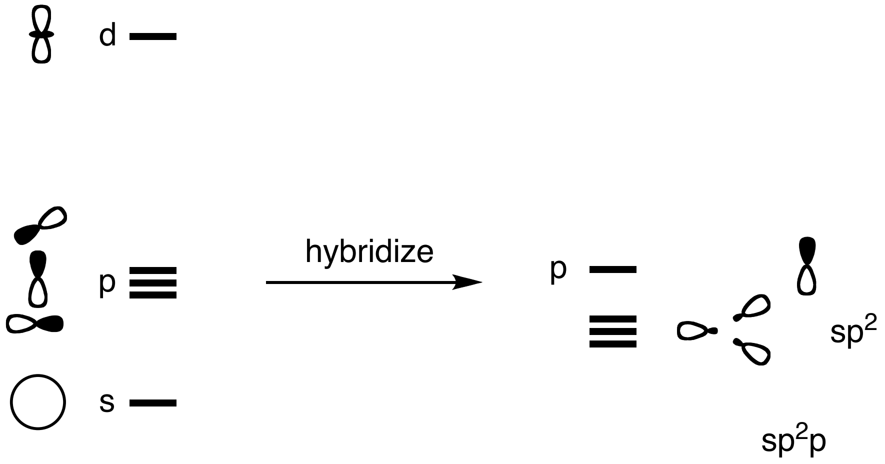


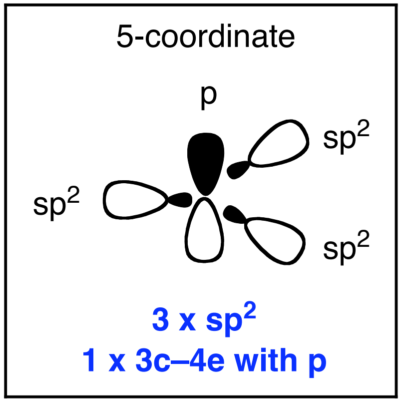
Storer, I. *MacMillan Group Seminar: Hypervalent Silicon*, **2005**.

Hypervalent Main Group Complexes

The Existence of 3c–4e Bonds

How do 3s, 3p and 3d orbitals really hybridize to permit pentavalency?





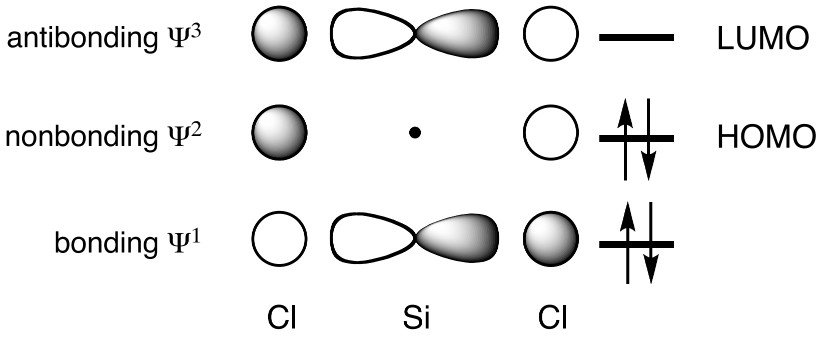
3 x sp^2
1 x 3c–4e with p

The 3c–4e bond – MO consideration

- Mixing of the filled σ orbital of the acceptor with the filled n orbital of the donor generates a pair of hybrid orbitals

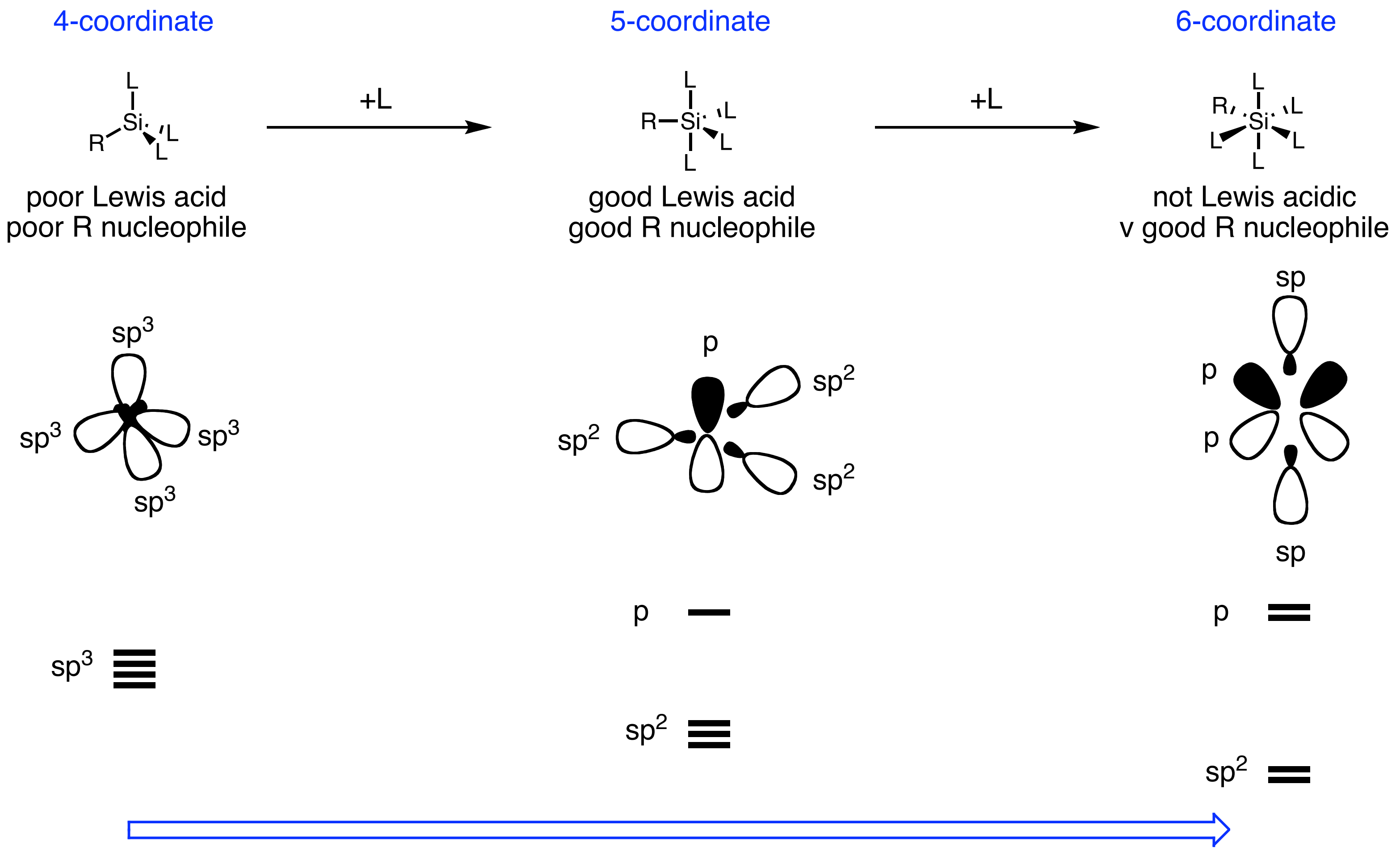
- The HOMO of this hybrid orbital (Ψ^2) contains a node at the central atom and localizes the electron density at the peripheral atoms

- This explains the enhances electrophilicity of the metal center while increasing the nucleophilicity of the ligands. This also explains why virtually all hypervalent compounds bond with electronegative F, Cl and O.



Chemical Reactivity of Hypervalent Silicon

■ Hybridization scheme and orbital picture of silicon complexes



4-coordinate

poor Lewis acid
poor R nucleophile

5-coordinate

good Lewis acid
good R nucleophile

6-coordinate

not Lewis acidic
v good R nucleophile

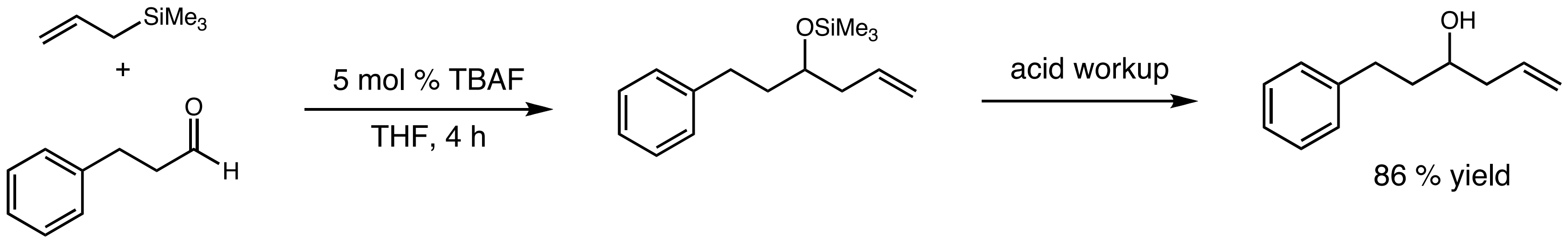
- Increasing δ^+ at silicon
- Increasing δ^- at ligands L and R
- 6-coordinate species not Lewis acidic because it has no room for binding

■ Electron density at Si decreases with increased coordination, causing the electropositive character (Lewis acidity) of the Silicon centre to be increased.

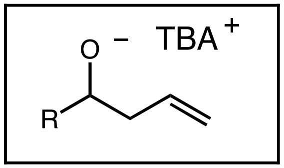
Lewis Base Catalysis: n–σ Interactions*

- Corriu first introduced fluoride ions to promote formation of hypervalent silicate in the mid-1970s. However, it was the introduction of soluble fluoride sources that later captivated the chemical community

- First example of the use of homogeneous fluoride ions in C–C bond formation by H. Sakurai



- The process involves the formation of an alkoxide



- In the critical turnover step, the alkoxide must be to release fluorides and regenerate the catalyst.

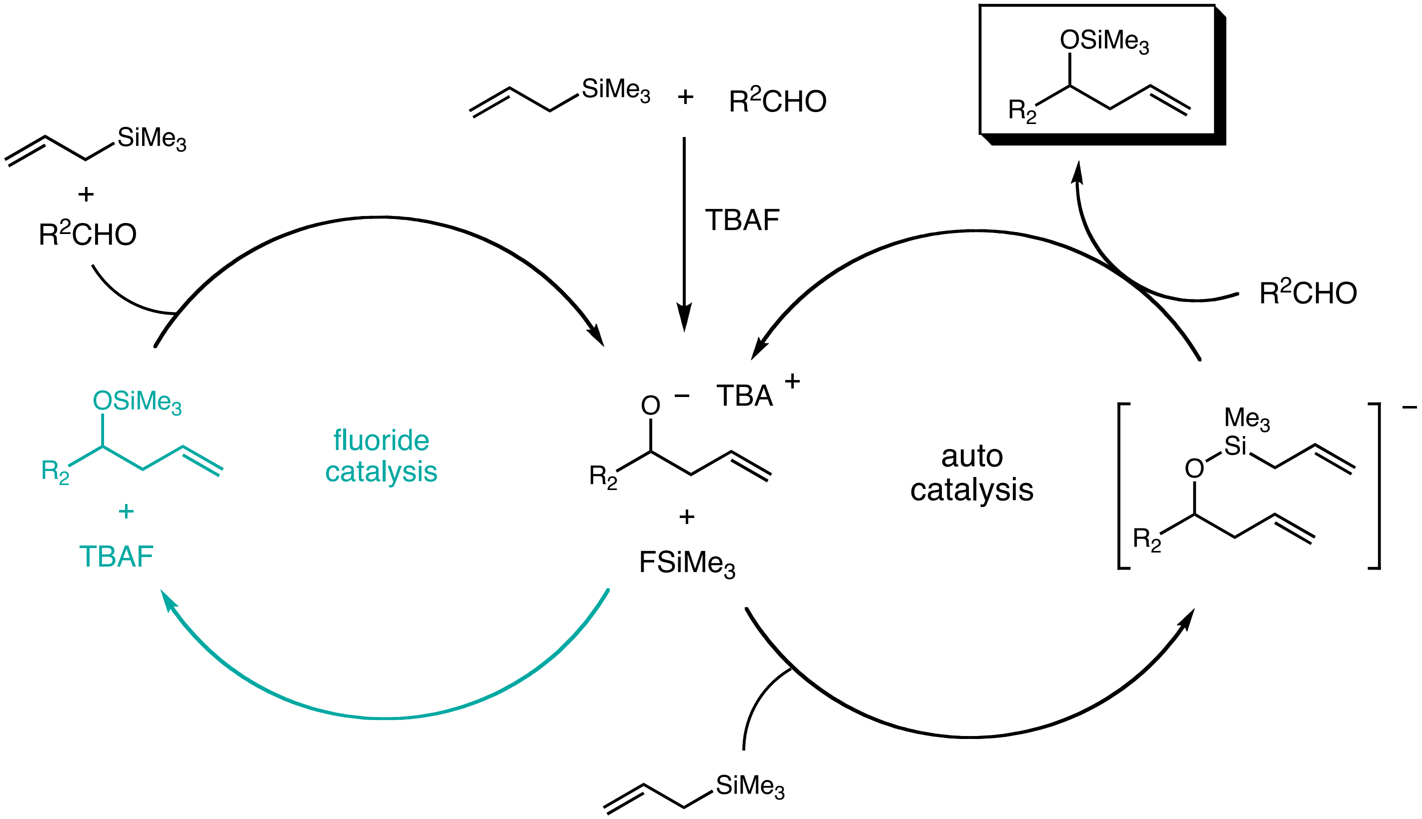
- In view of the strenght of the Si–F bond (135 kcalmol^{-1}), many have disputed the role of TMSF as the active silylating agent

- Most generally accepted pathway was first suggested by Kuwajima

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

Lewis Base Catalysis: n–σ Interactions*

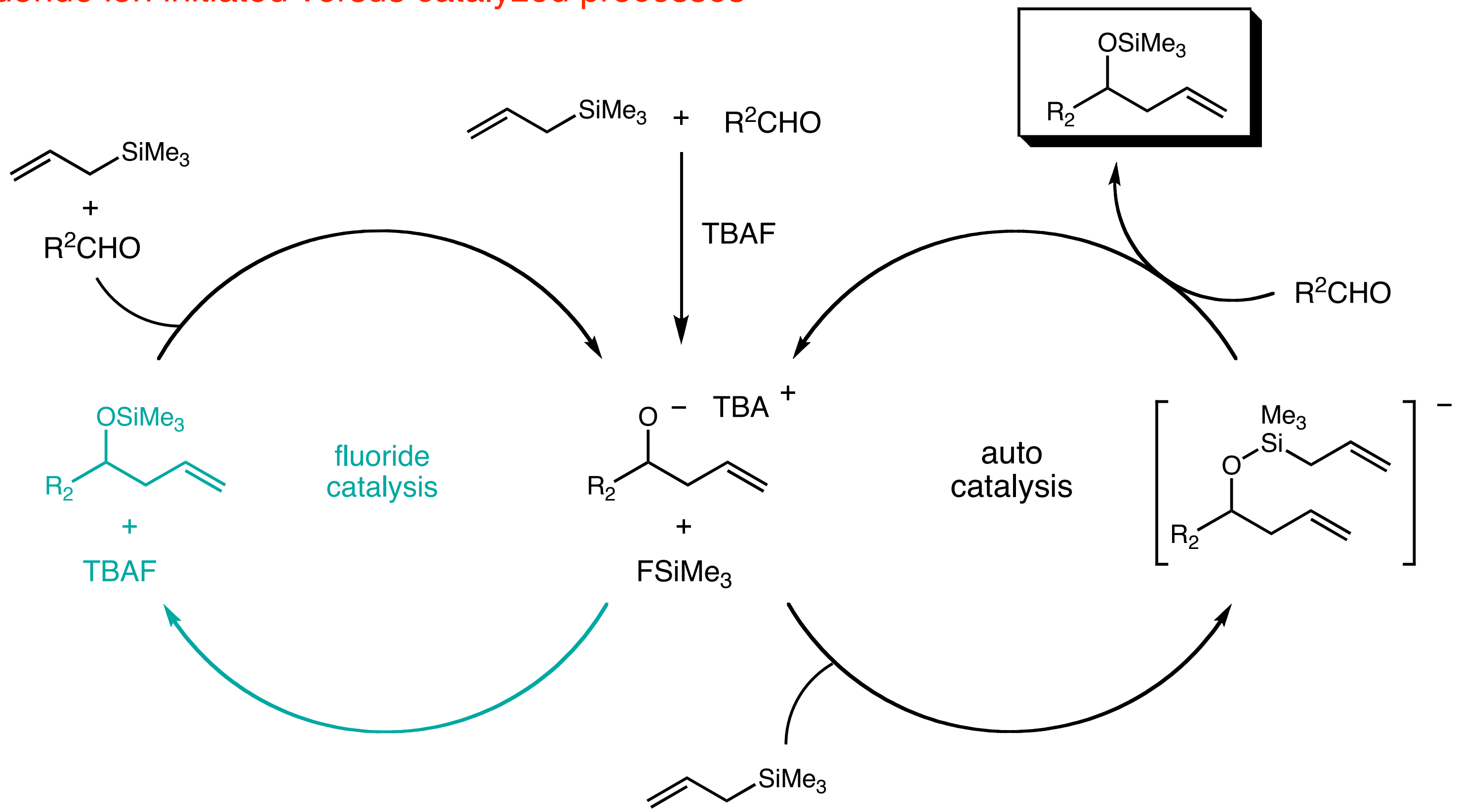
■ Fluoride ion initiated versus catalyzed processes



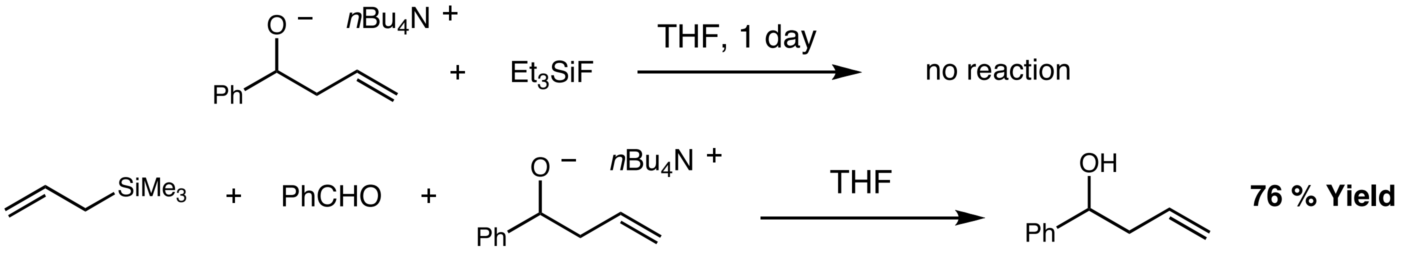
- This kind of autocatalytic behavior is supported by the observation of an induction period in the reaction-rate profile. Thus, a slower initial phase of the reaction is promoted by fluoride ions while the faster, later phase is promoted by some other in situ generated anion.

Lewis Base Catalysis: n–σ Interactions*

- Fluoride ion initiated versus catalyzed processes



- Hou has shown that the ammonium alkoxides generated are active catalysts for subsequent allylations

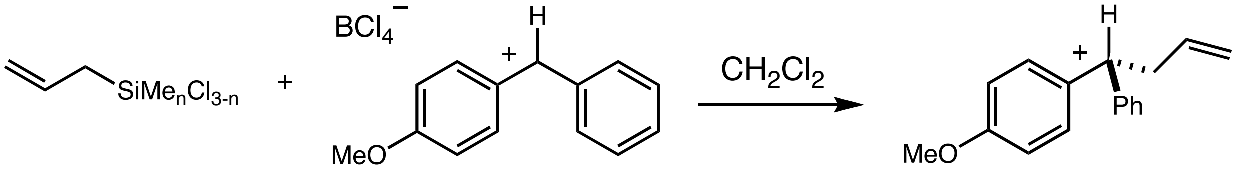


Wang, D.-K.; Zhou, Y.-G.; Tang, Y.; Hou, L. -X. *J. Org. Chem.* **1999**, *64*, 4233

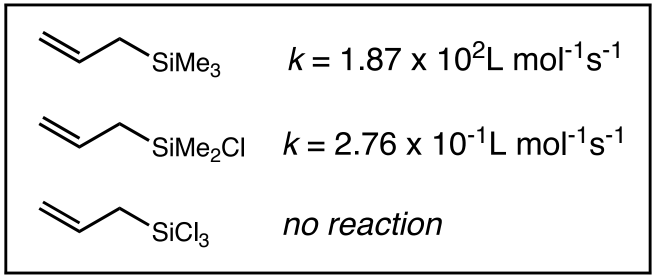
Lewis Base Catalysis: n–σ Interactions*

Polyhalosilanes

🟥 Nucleophilicity of allylic silanes on the Mayr scale



🟩 In light of the analysis by Mayr et al., allyltrifluorosilane and allyltrichlorosilane should be completely unreactive towards aldehydes. This provides adramatic illustration of the power of Lewis base activation

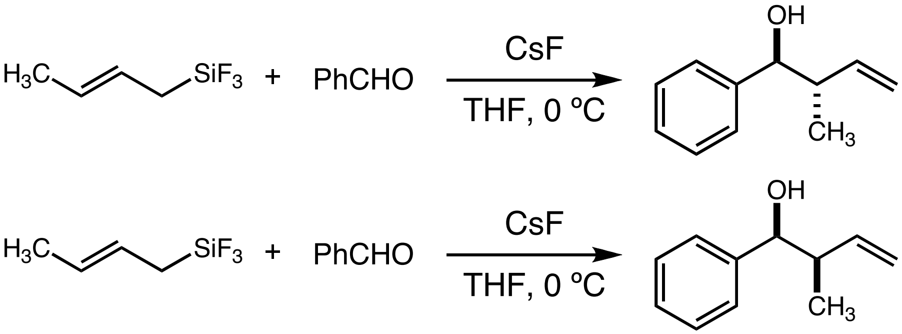


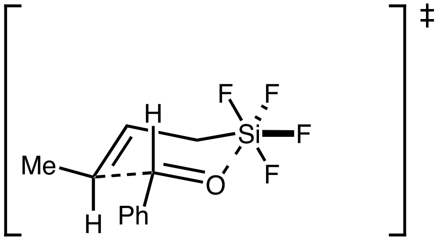
$k = 1.87 \times 10^{2} L\ mol^{-1}s^{-1}$

$k = 2.76 \times 10^{-1} L\ mol^{-1}s^{-1}$

no reaction

🟥 Fluoride ion catalyzed allylations with fluorosilanes





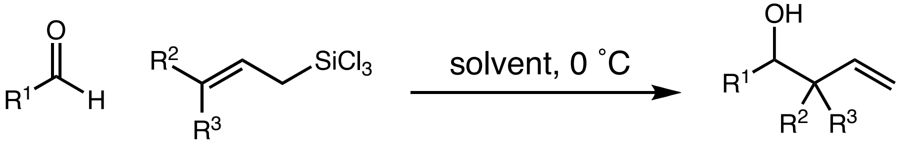
🟩 The strict correlation of the silane geometry with the product configuration (*E -->anti, Z -->syn*) indicates the reaction proceeds through a cyclic chair like transition structure, with dual activation of both nucleophile and electrophile

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

Lewis Base Catalysis: n–σ Interactions*

Polyhalosilanes

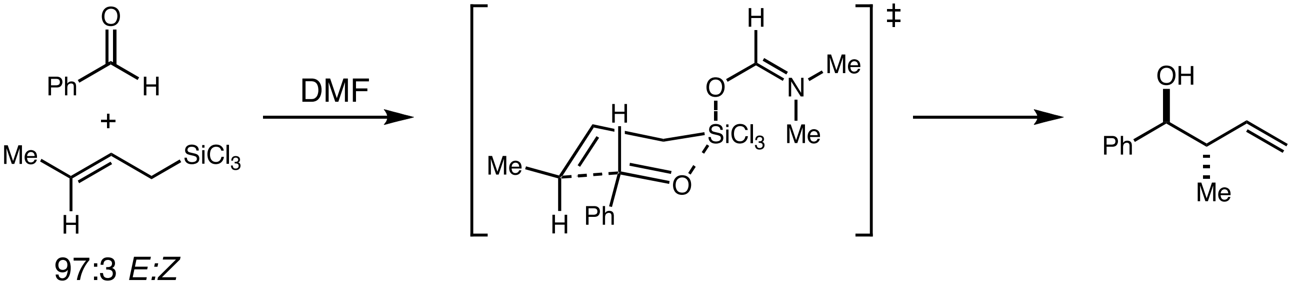
■ Lewis basic solvent can promote aldehyde allylation (*Kobayashi and Nishio*)



Solvent	Yield
CH_2Cl_2	trace
Et_2O	trace
benzene	trace
THF	trace
DMF	90%
CH_2Cl_2 + 1 equiv DMF	68%

- Important discovery: Neutral Lewis bases such as DMF can activate trichlorosilanes!!

■ Strict correlation of the silane geometry with the product configuration also obtained



Solvent	Si NMR
$CDCl_3$	+8.0
CD_3CN	+8.6
C_6D_6	+7.9
THF-d_8	+8.5
DMF-d_7	**–170**
HMPA	**–22**

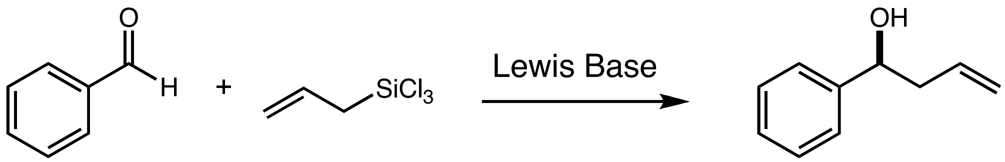
- High diastereoselectivity indicative of a rigid closed transition state
- Dual activation of both electrophile and nucleophile via a 6-membered closed TS.

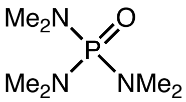
Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, *34*, 3453-3456.
Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620-6628.

Lewis Base Catalysis: n–σ Interactions*

Polyhalosilanes

🟥 Denmark

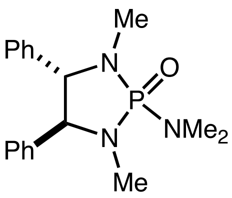




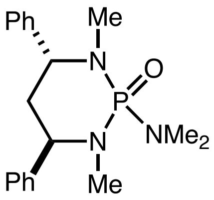
Hexamethyl phosphoramide
HMPA

1 equiv. HMPA, $CDCl_3$
86 % yield

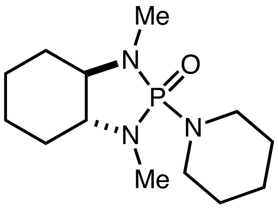
🟥 Can chiral HMPA derivatives be developed to catalyze the enantioselective variant?



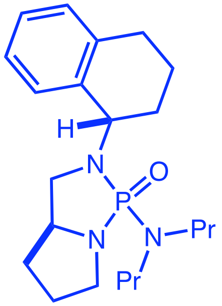
6h, –78 °C, CH_2Cl_2
1 equiv
e.r. 66.5:33.5



6h, –78 °C, CH_2Cl_2
1 equiv
e.r. 70.5:29.5



6h, –78 °C, CH_2Cl_2
0.1 equiv
40% yield
e.r. 76.5:23.5



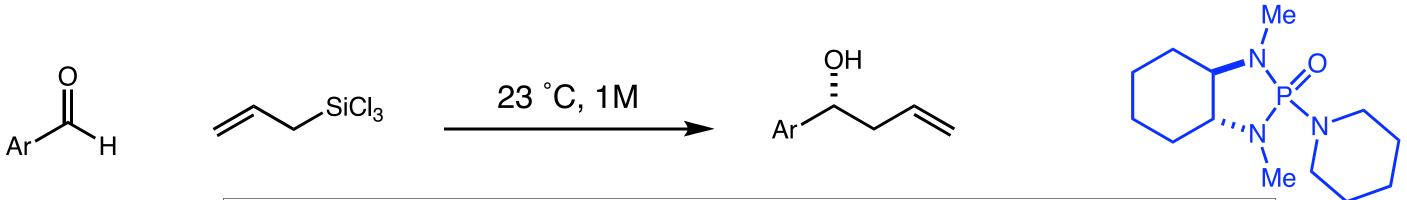
168h, –78 °C, THF
0.1 equiv
67 % yield
e.r. 92.5:7.5

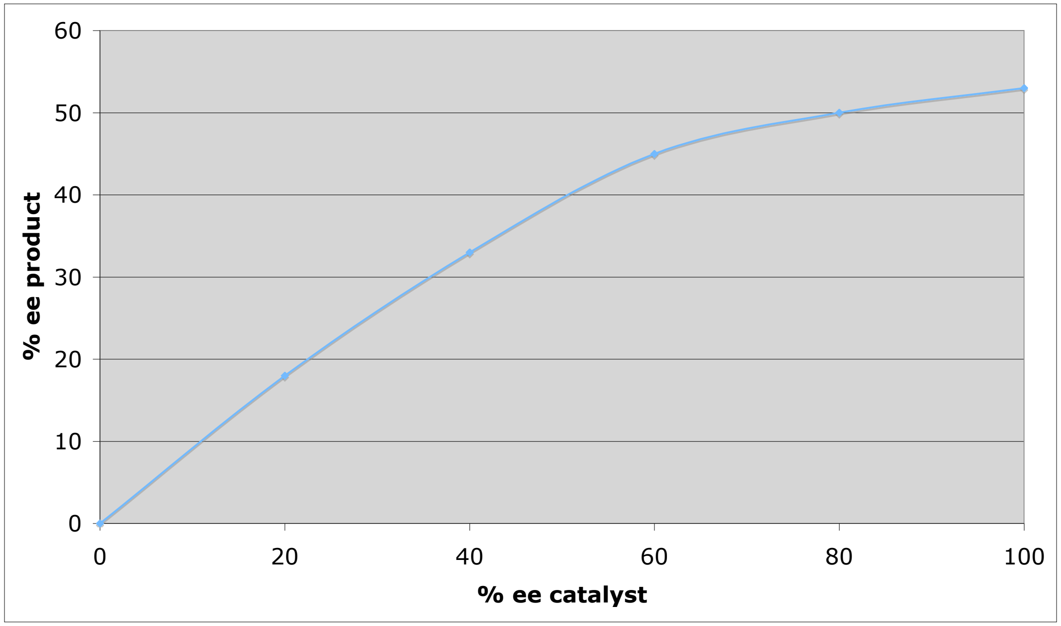
🟩 Weak loading dependence was observed in which lower loadings led to lower selectivities.

Denmark, S.E.; Su, X.; Nishigaishi, Y.; Coe, D.M.; Wong, K.-T.; Winter, S. B. D.; Choi, J.-Y, *J. Org. Chem.* **1999**, *64*, 1958

Lewis Base Catalysis: n–σ Interactions*

- Loading dependence on the enantioselectivity





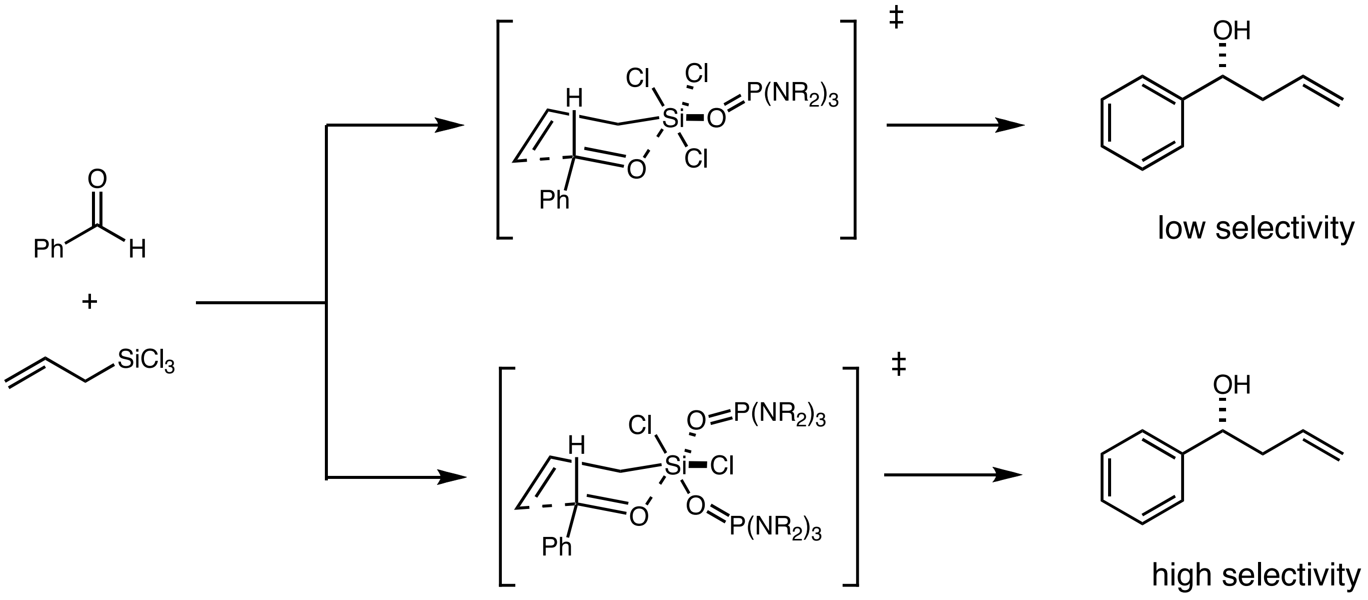
- These results represented the first suggestion that they were two distinct pathways involving the chiral phosphoramide with different levels of enantioselectivity

- Subsequent kinetic studies showed a non-integral order dependence of 1.77. This is due to competing mechanisms involving 1 or 2 prosphoramides on silicon

Lewis Base Catalysis: n–σ Interactions*

Polyhalosilanes

■ Divergent mechanistic pathways in reactions of allyltrichlorosilane



■ It is believed that that the monophosphoramide complex would be less enantioselective than a diphosphoramide pathway due to the diminished influence of the singular chiral promoter in the former

- In the transition state with only one phosphoramide, there is no experimental support for either a hexacoordinate octahedral neutral transition structure or a cationic, trigonal bipyramindal transition structure

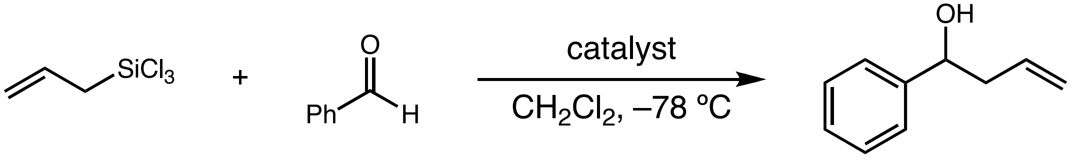
■ Would a bidentate phosphoramide avoid the problem of mono-coordination on allylations?

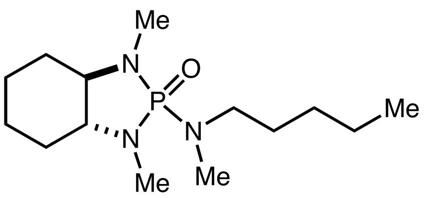
Denmark, S.E.; Fu, J.; Coe, D.M.; Su, X.; Pratt, N.M.; Griedel, B.D. *J. Org. Chem.* **2006**, *71*, 1513
Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2000,** *122*, 12021

Lewis Base Catalysis: n–σ Interactions*

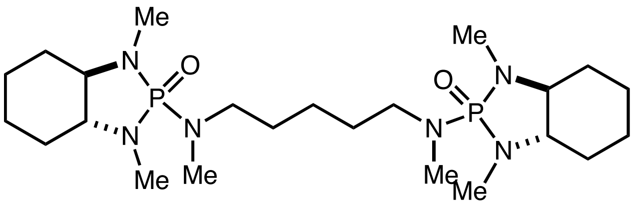
Dimeric phosphoramide

■ Dimeric phosphoramide catalyzed allylations.

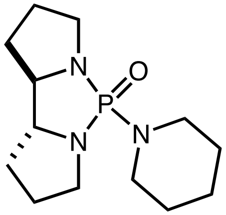




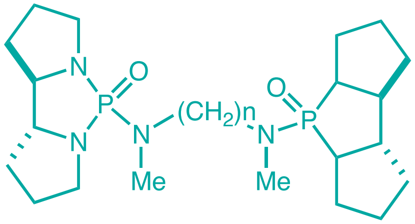
1 equiv.
73% yield; **51% ee**



0.1 equiv
54% yield; **72% ee**



0.05 equiv
56% yield; **56% ee**



n	equiv	yield	ee
4	0.05	54%	18%
5	0.05	85%	87%
6	0.05	58%	67%

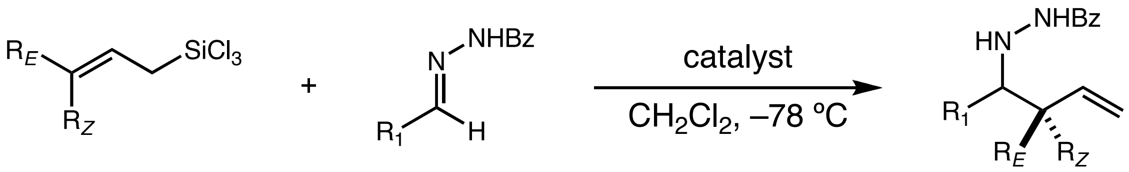
■ Advantages of dimeric phosphoramides

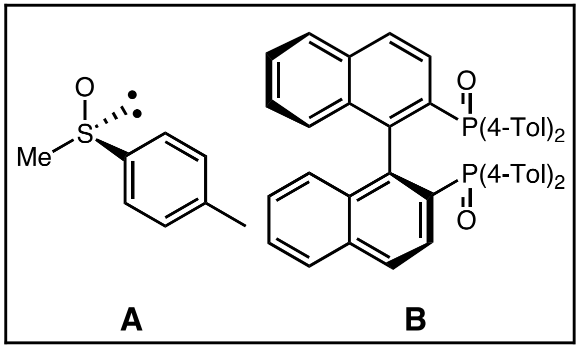
- Disfavors the less selective one-phosphoramide pathway
- Help overcoming the entropic disadvantage for the formation of the structure containing two Lewis bases.

Lewis Base Catalysis: n–σ Interactions*

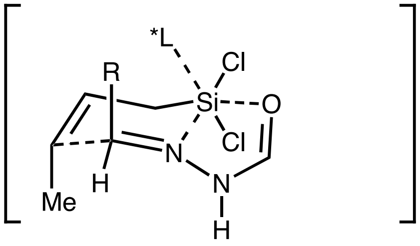
Addition to hydrazones

■ Allylation and crotylation of benzoylhydrazones - Kobayashi

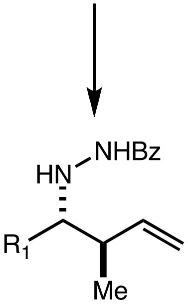




R_1	R_E	R_Z	Catalyst (equiv)	Yield [%]	d.r. *(syn/anti)*	ee [%]
$PhCH_2CH_2$	H	H	**A** (3.0)	73	–	93
*i*Pr	H	H	**A** (3.0)	80	–	98
$PhCH_2CH_2$	H	Me	**A** (3.0)	60	< 1:99	91
$PhCH_2CH_2$	Me	H	**A** (3.0)	58	> 99:1	89
EtO_2C	H	H	**B** (2.0)	91	–	98
EtO_2C	H	Me	**B** (2.0)	92	98:2	99
EtO_2C	Me	H	**B** (2.0)	96	< 1:99	96



Z-Crotyltrichlorosilane



anti-Adducts

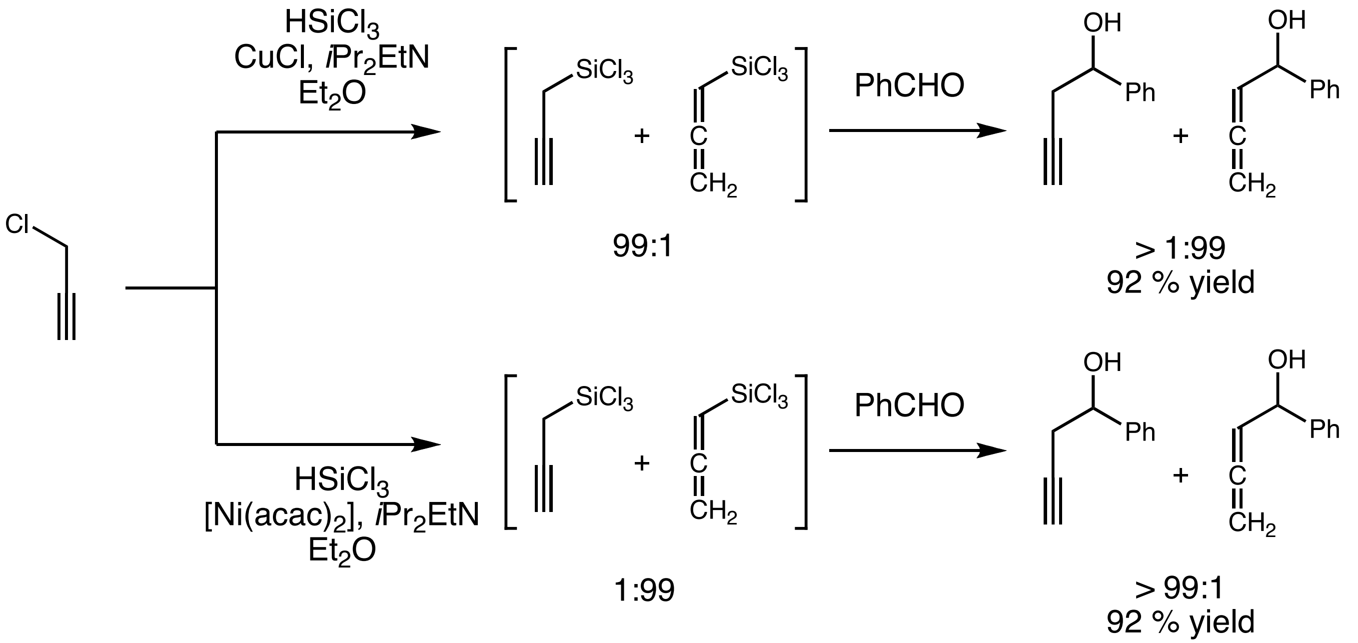
- The *E*-geometry of hydrazone put the R group at an axial direction; consequently, *syn*- and *anti*- homoallylic hydrazines are stereospecifically obtained from (*E*)- and (*Z*)-crotyltrichlorosilanes, respectively

Hirabayashi, R.; Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 9493
Ogawa, C.; Sugiura, M.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 6491

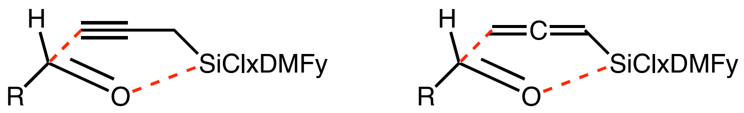
Lewis Base Catalysis: n–σ Interactions*

Propargylation and Allenylation

■ Lewis base catalyzed allenylation and propargylation - Kobayashi



■ Assumed transition state:

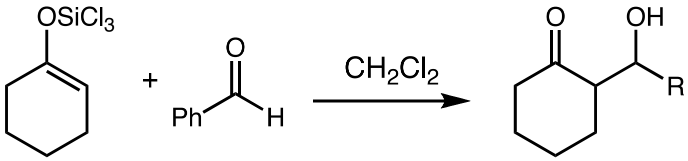


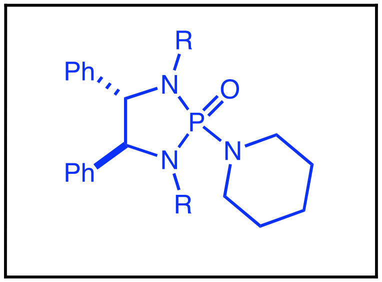
Schneider, U.; Sugiura, M.; Kobayashi, S. *Tetrahedron.* **2006**, *62*, 496
Schneider, U.; Sugiura, M.; Kobayashi, S. *Adv. Synth. Catal.* **2006**, *348*, 323

Lewis Base Catalysis: n–σ^* Interactions

Enoxytrichlorosilane

■ Phosphoramide-catalyzed asymmetric aldol reactions of trichlorosilyl enol ethers





Catalyst	Temp [ºC]	d.r.	% ee
none	0	98:2	–
R = Me	–78	< 1:99	93
R = Ph	–78	99:1	53

■ In analogy to catalyzed reactions with allylic trichlorosilanes a rate enhancement is observed using a Lewis base. This support the formation of a cationic hypervalent siliconium ion as reactive intermediate.

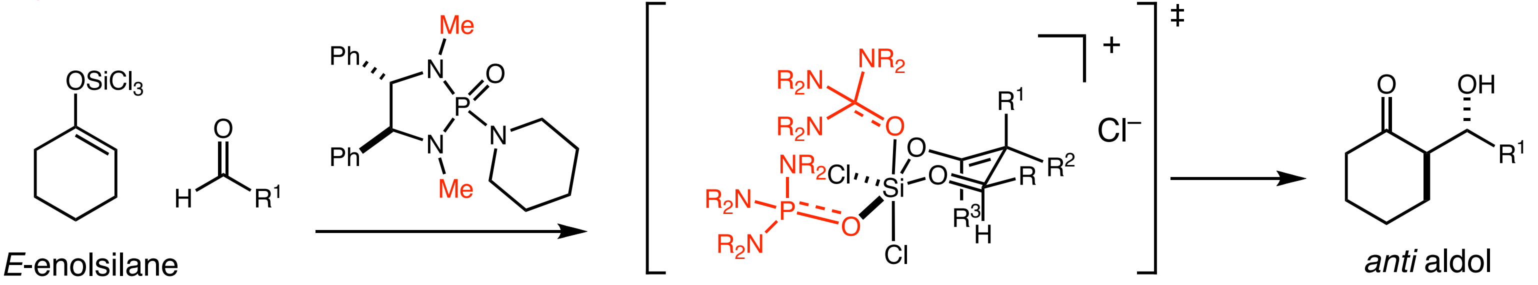
■ Dramatic difference between the observed diastereoselectivities indicates that the two catalysts must participate in different manners

Denmark, S. E.; Su, X.; Nishigaishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12990

Lewis Base Catalysis: n–σ Interactions*

Enoxytrichlorosilane

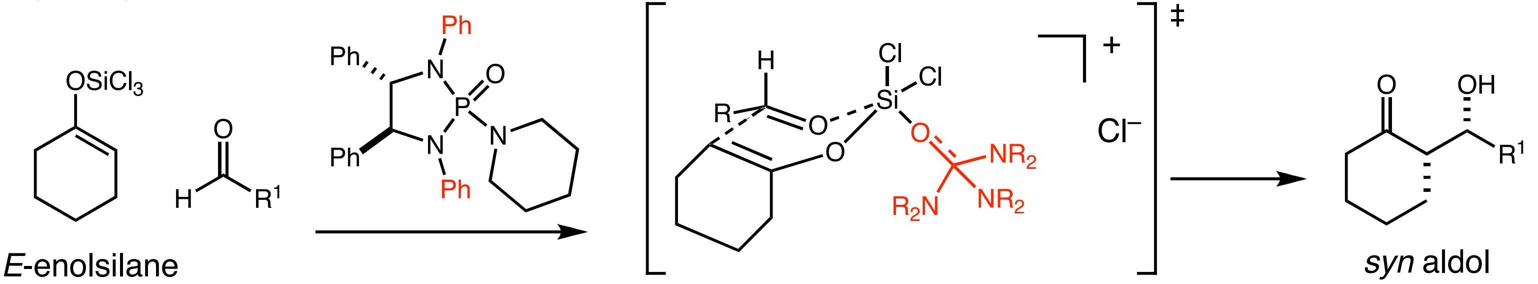
■ Pathway to anti aldol - double coordination



anti aldol
(92% ee)

Hexacoordinate Si proposed
(Octahedral)
Good Enantioselectivity

■ Pathway to syn aldol – mono coordination



syn aldol
(50% ee)

Pentacoordinate Si proposed
(Trigonal bipyramidal)
Poor Enantioselectivity

■ Ligand binding forces $Cl^–$ dissociation. Experimental evidence:

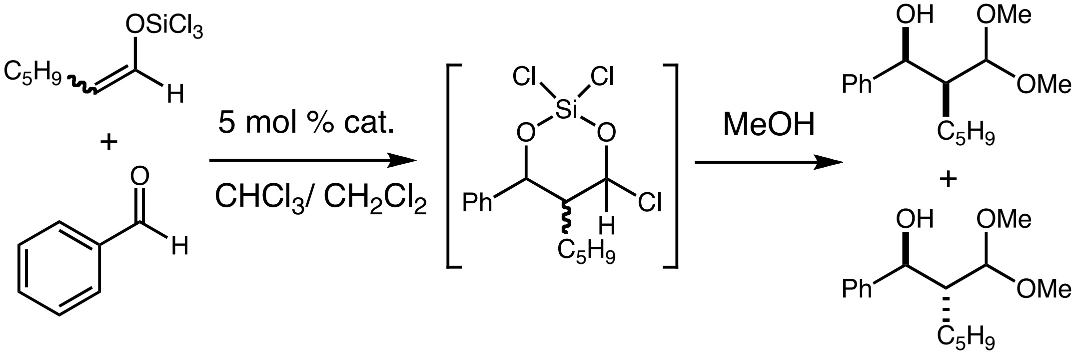
- Bu_4NCl retards the reaction rate - common ion effect
- Bu_4NOTf and Bu_4NI accelerate the rate by increasing ionic strength

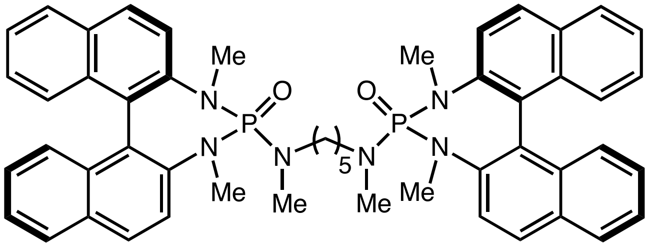
Denmark *J. Am. Chem. Soc.* **1998**, *120*, 12990.

Lewis Base Catalysis: n–σ Interactions*

Enoxytrichlorosilane

- Dimeric phosphoramide catalyzed asymmetric aldol reactions between aldehydes





bisphosphoramide catalyst

(*Z*) enolsilane 92 % yield ; *syn/anti* 99:1; 90% ee

(*E*) enolsilane 92 % yield ; *syn/anti* 3:97; 82% ee

- In situ formation of an inactive chlorohydrin prevents oligomerization

- The aldehyde is bound *trans* to one of the of the phosphoramides at the less sterically encumbered position

- The exposure of the *Re* face of the aldehyde is determined by two factors: Interaction with the *N*-methyl group and one of the naphtyl group

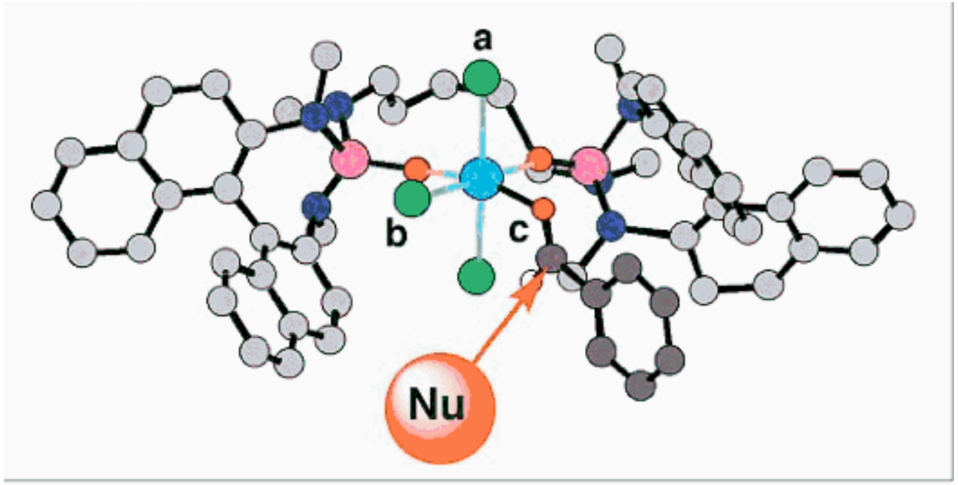


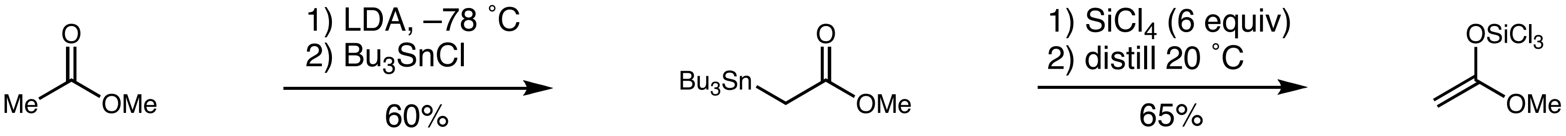
Fig. 5. Putative reactive complex between (*R*,*R*)-**1**, $SiCl_4$ and benzaldehyde

Denmark, S. E.; Ghosh, S. K. *Angew. Chem. Int. Ed.* **2001**, *40*, 4759

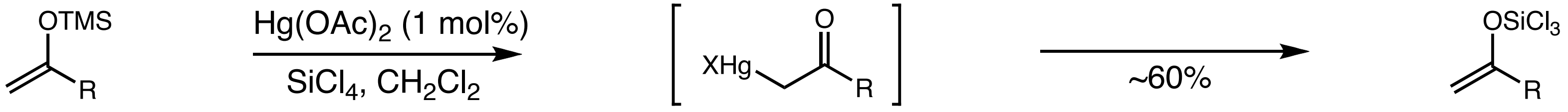
Lewis Base Catalysis: n–σ Interactions*

Limitations with trichlorosilanes

- Trichlorosilanes are difficult to prepare and handle



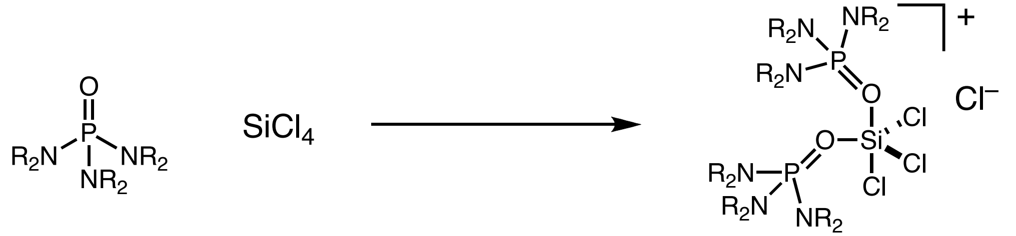
Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404-7405.



R = *i*Pr, *n*Bu, *i*Bu, *t*Bu, $TBSOCH_2$, Ph, CH_2CH

Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Org. Chem.* **1998**, *63*, 9517-9523.

- Possible solution to this problem?

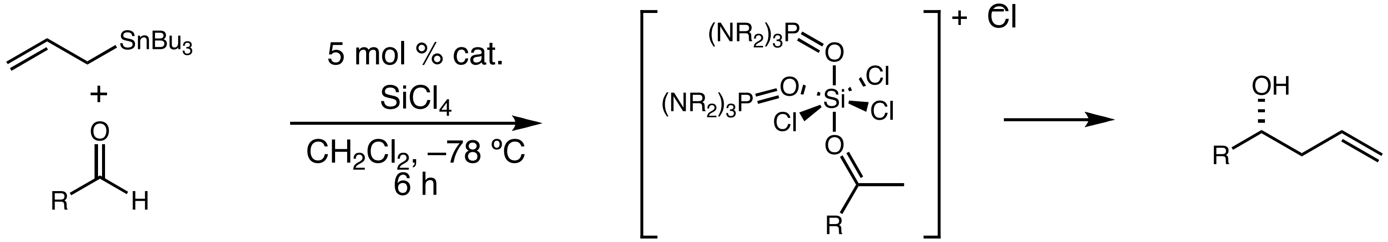


Lewis Base   Poor Lewis acid   Qu: Is this a useful Lewis Acid?

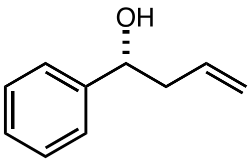
Lewis Base Catalysis: n–σ Interactions*

$SiCl_4$ mediated reactions

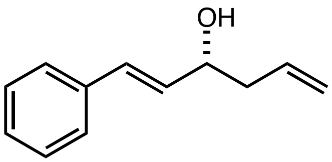
■ $SiCl_4$ mediated / phosphoramide-catalyzed allylatiions with stannanes



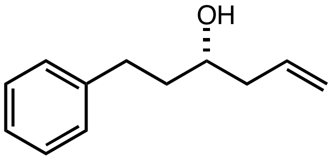
- Good yields and enantioselectivities obtained, but only aromatic and olefinic aldehydes were reactive



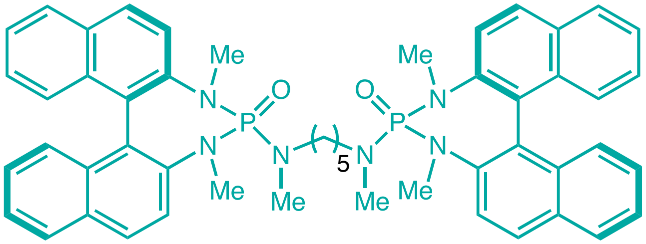
91 % yield
94 % ee



91 % yield
66 % ee



no reaction



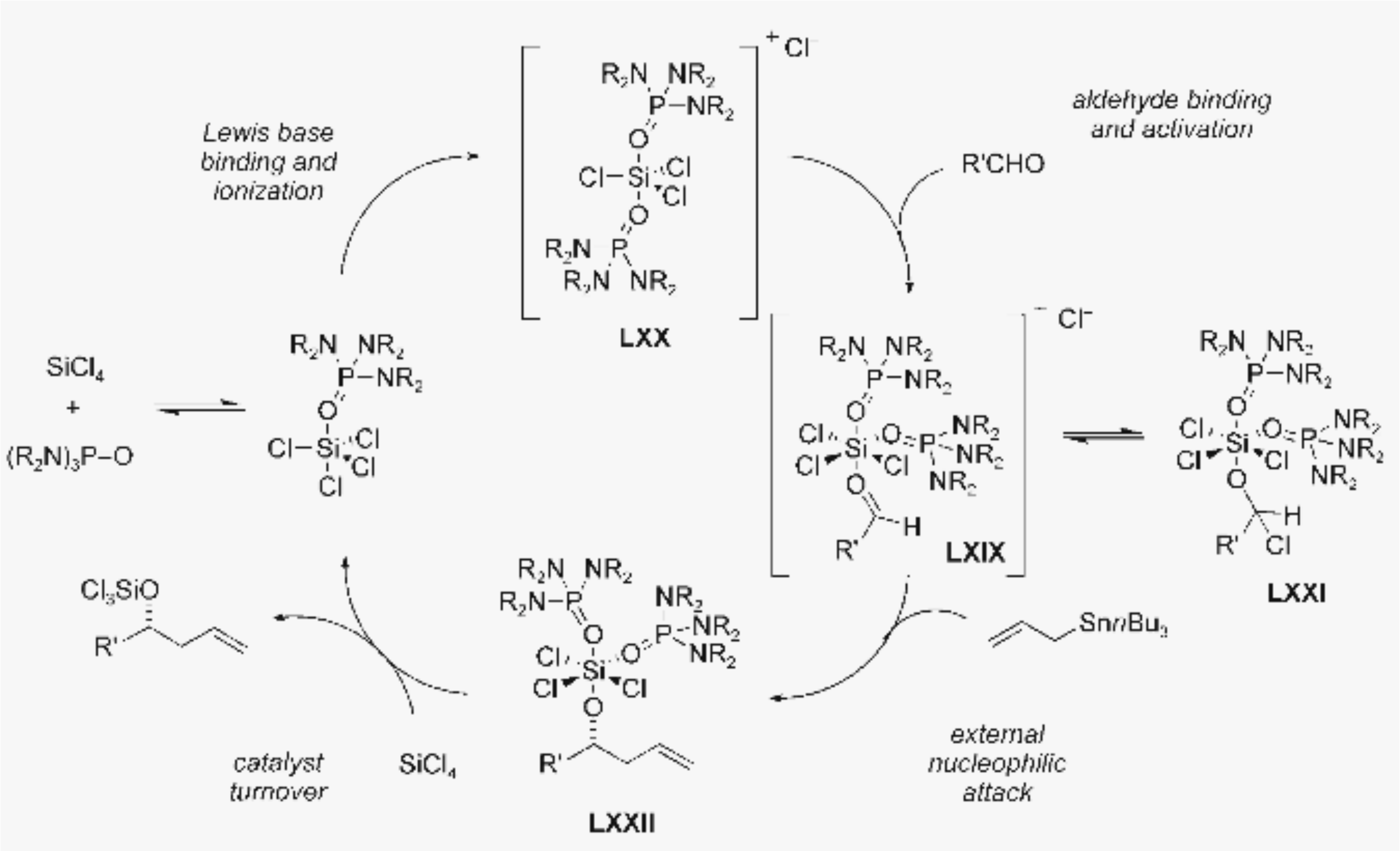
bisphosphoramide catalyst

Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199

Lewis Base Catalysis: n–σ^* Interactions

$SiCl_4$ mediated reactions

Catalytic cycle for $SiCl_4$-mediated / phosphoramide-catalyzed reactions



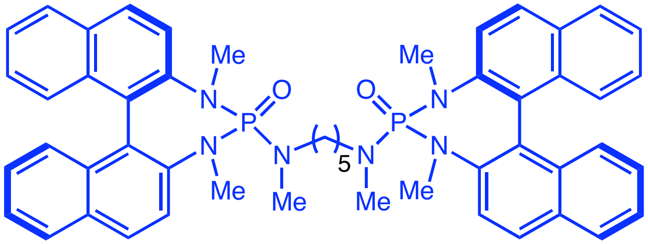
- The lack of reaction with aliphatic aldehydes is explained through the unproductive equilibrium between the hexacoordinated cationic intermediate and the unreactive chlorohydrin.

- Open transition state leads to the opposite sense of diastereoselection when compared to trichlorosilyl enol ethers, making this method complementary to the existing one. This allows access to both diastereomers starting from the same synthetic precursor.

Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199

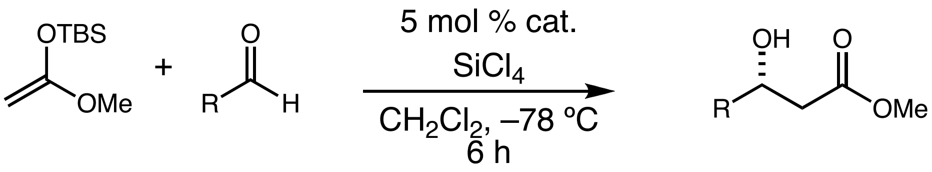
Lewis Base Catalysis: n–σ Interactions*

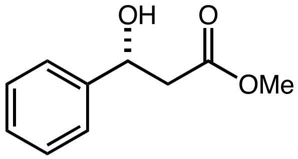
$SiCl_4$ mediated reactions



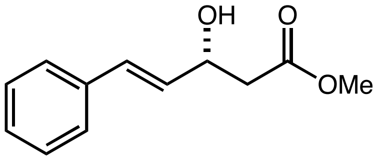
bisphosphoramide catalyst

Silyl ketene acetal

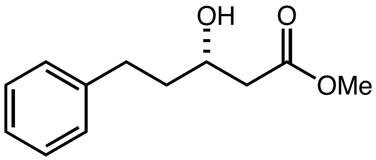




97 % yield
93 % ee

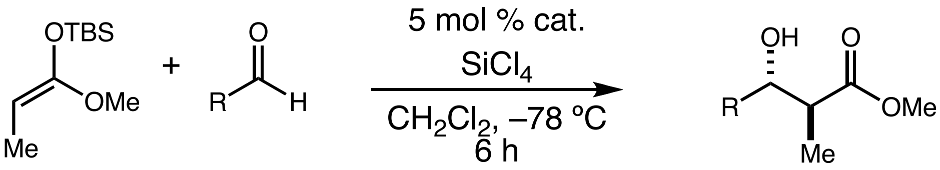


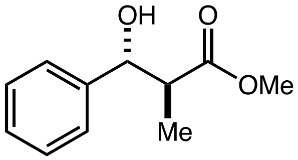
95 % yield
94 % ee



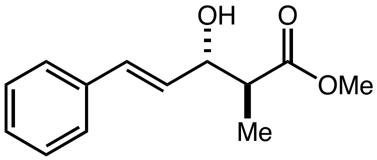
72 % yield
81 % ee

Propionate-derived silyl ketene acetal

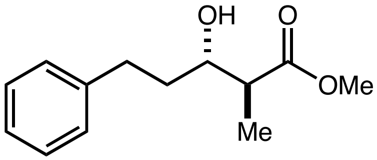




97 % yield
d.r. 99:1 ; 93 % ee



98 % yield
d.r. >99:1 ; 94 % ee

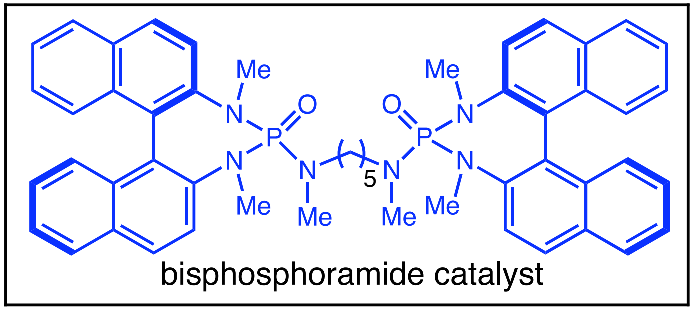


71 % yield
d.r. 91:9 ; 81 % ee

Denmark, S. E.; Wynn, T.; Beutner, G.L. *J. Am. Chem. Soc.* **2002**, *124*, 13405

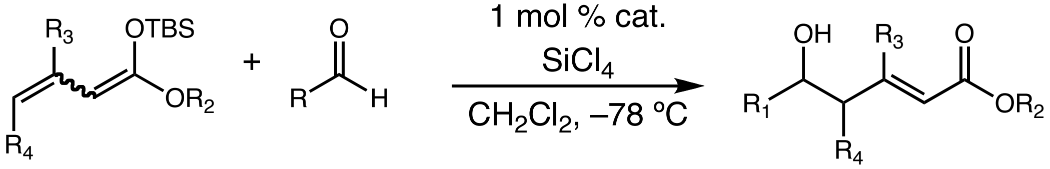
Lewis Base Catalysis: n–σ Interactions*

$SiCl_4$ mediated reactions

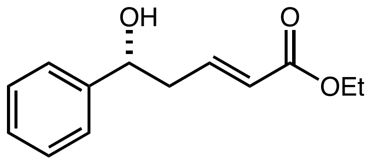


bisphosphoramide catalyst

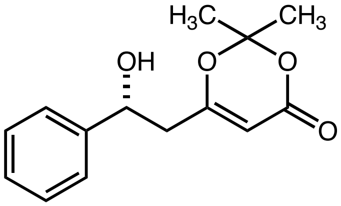
Addition of vinylogous enol ether



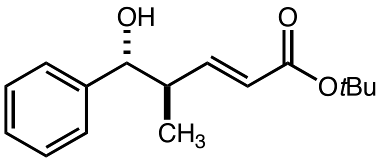
1 mol % cat.
$SiCl_4$
CH_2Cl_2, –78 °C



89 % yield
γ/α >99:1 ; 98 % ee



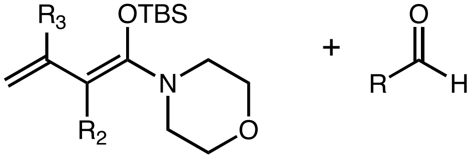
92 % yield
γ/α >99:1 ; 74 % ee



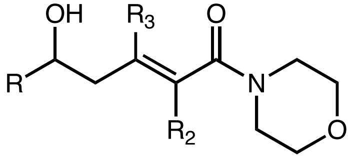
92 % yield
d.r. 99:1 ; 89 % ee

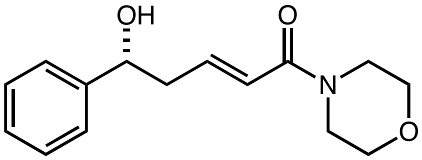
Denmark, S. E.; Beutner, G.L. *J. Am. Chem. Soc.* **2003**, *125*, 7800

Addition of *N-O*-ketene acetals

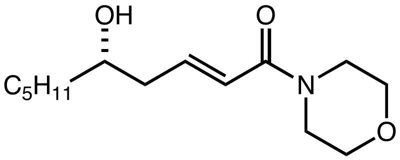


5 mol % cat.
$SiCl_4$
CH_2Cl_2, –78 °C
6 h

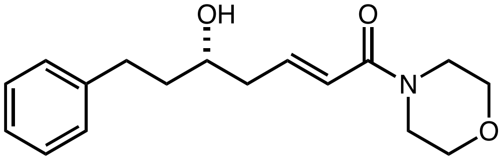




80 % yield
γ/α >99:1 ; 98 % ee



79 % yield
γ/α >99:1 ; 87 % ee



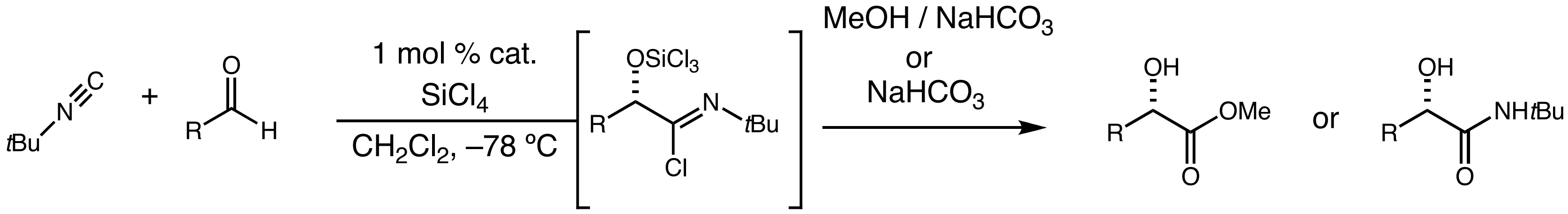
71 % yield
γ/α >99:1 ;94 % ee

Denmark, S. E.; Beutner, G.L.; Wynn, T.; Eastgate, M.D . *J. Am. Chem. Soc.* **2005**, *127*, 3774

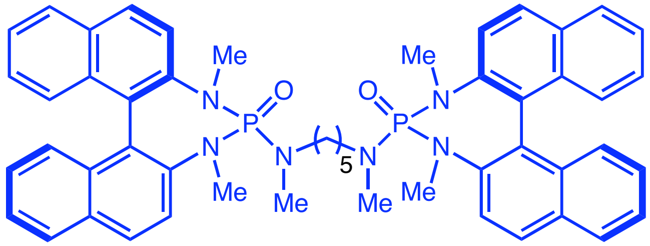
Lewis Base Catalysis: n–σ Interactions*

$SiCl_4$ mediated reactions

🟥 Addition of isocyanide



R	Quench	Yield [%]	ee [%]
Ph	$NaHCO_3$	96	> 98
Ph	MeOH	97	>98
(*E*)-PhCH=CH	$NaHCO_3$	81	96
(*E*)-PhCH=CH	MeOH	71	96
$PhCH_2CH_2$	$NaHCO_3$	92	64
$PhCH_2CH_2$	MeOH	88	64



bisphosphoramide catalyst

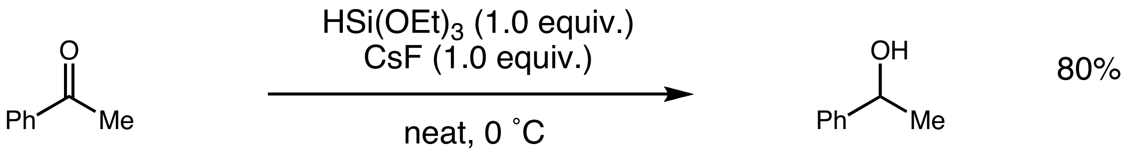
- 🟦 Under standard reaction conditions developed for the $SiCl_4$-mediated reactions, of enoxysilanes, an isocyanide can add to aromatic, olefinic, and aliphatic aldehydes in high yields and enantioselectivities
- 🟦 After hydrolysis either the amide or the ester product can be obtained selectively
- 🟦 After 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 a chloroimine and disfavoring the formation of inactive chlorohydrins

Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825

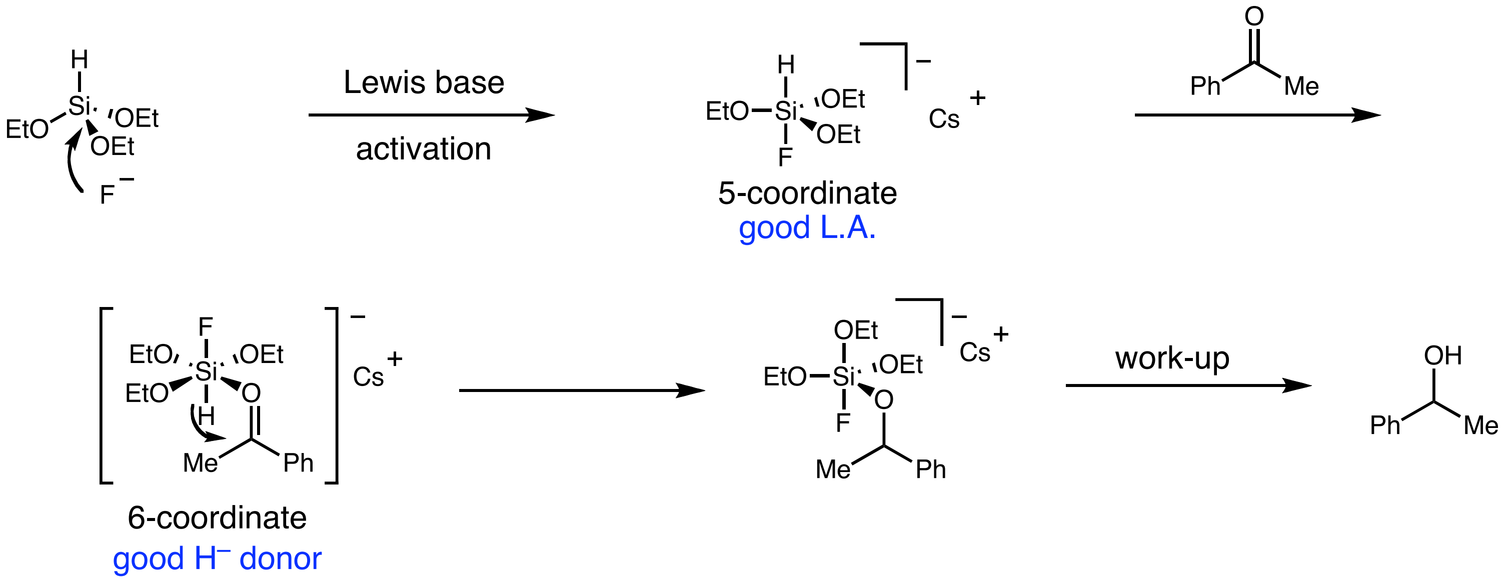
Lewis Base Catalysis: n–σ^* Interactions

Reduction of carbonyls and imines

■ Hydrosilation – Corriu (1981)



■ Probable mechanism

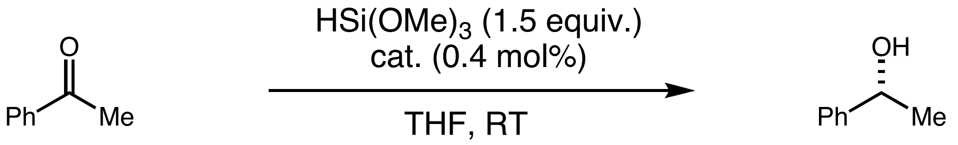


Boyer, J.; Corriu, R. J. P.; Perz, R.; Reye, C. *Tetrahedron*, **1981**, *37*, 2165.
Corriu, R. J. P.; Perz, R.; Reye, C. *Tetrahedron*, **1983**, *39*, 999.

Lewis Base Catalysis: n–σ Interactions*

Reduction of carbonyls and imines

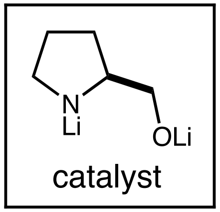
■ Hosomi (1988)



$HSi(OMe)_3$ (1.5 equiv.)
cat. (0.4 mol%)

THF, RT

89%
52% ee

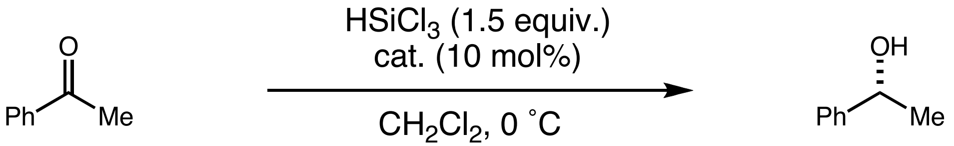


catalyst

Kohra, S; Hayashida, H.; Tominaga, Y.; Hosomi, A. *Tetrahedron Lett.*, **1988**, *29*, 89.

- Hosomi discovered that lithium alkoxides can act as reversible binding Lewis bases
- Development of highly catalytic processes (0.4 mol%)
- Problem: Product alkoxide can also act as a Lewis base catalyst – alternative low ee reaction

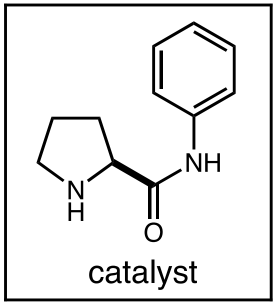
■ Iwasaki (1999)



$HSiCl_3$ (1.5 equiv.)
cat. (10 mol%)

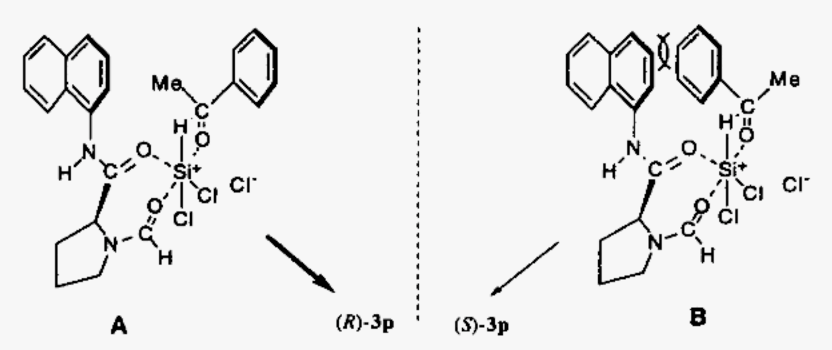
CH_2Cl_2, 0 °C

87%
29% ee



catalyst

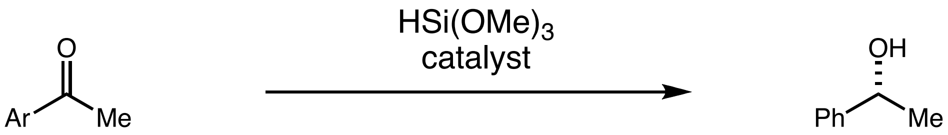
Iwasaka et al. *Tett. Lett.*, **1999**, *40*, 7507.



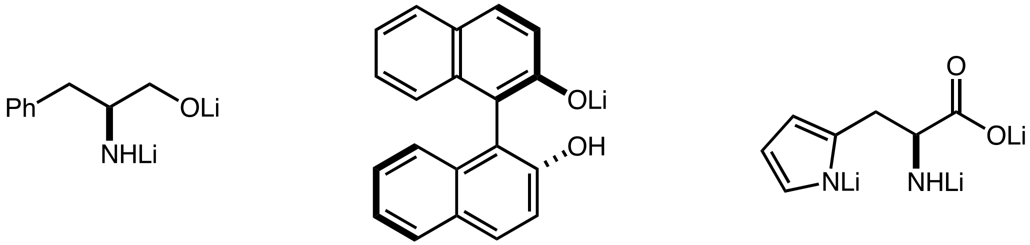
Lewis Base Catalysis: n–σ^* Interactions

Reduction of carbonyls and imines

■ Reduction of ketones with trimethylsiloxane



- Problem: Product alkoxide can also act as a Lewis base catalyst – alternative low ee reaction



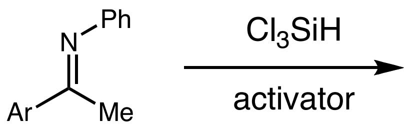
4 mol %	10 mol %	4 mol %
Ar = Ph	Ar = Ph	Ar = 4-anisyl
62 % yield	80 % yield	89 % yield
77 % ee	61 % ee	70 % ee

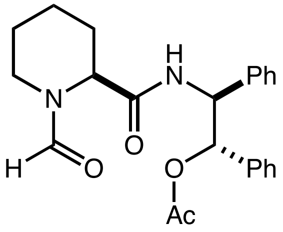
Schiffers, R.; Kagan, H. B. *Synett.*, **1997**, 1175.

Lewis Base Catalysis: n–σ Interactions*

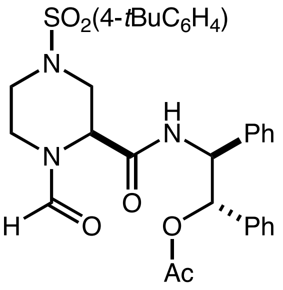
Reduction of carbonyls and imines

■ Reduction of imines with trichlorosilane

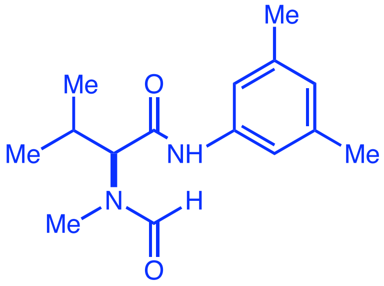




10 mol %
Ar = 4-anisyl
95 % yield
93 % ee

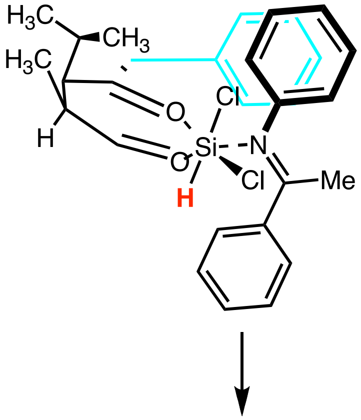


10 mol %
Ar = $4\text{-}NO_2C_6H_4$
99 % yield
90 %

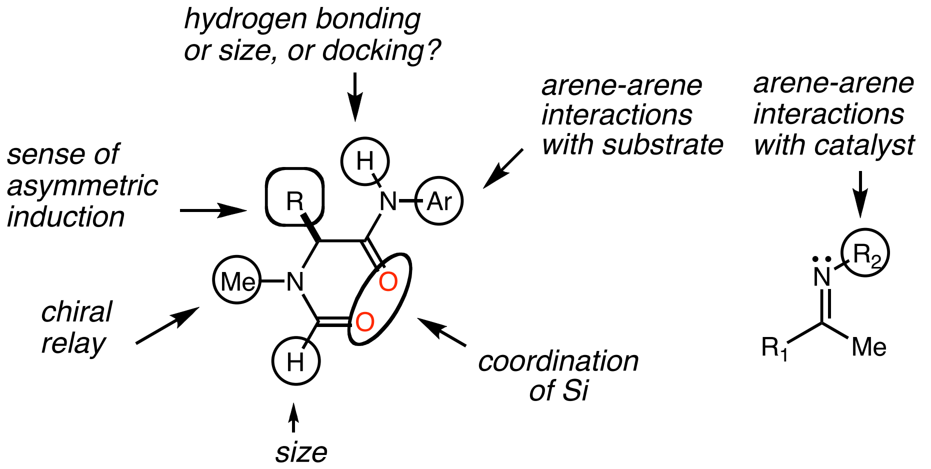


10 mol %
Ar = $4\text{-}NO_2C_6H_4$
99 % yield
90 % ee (*S*)

■ My proposed TS:



***(S)*-major**



hydrogen bonding or size, or docking?

arene-arene interactions with substrate

arene-arene interactions with catalyst

sense of asymmetric induction

chiral relay

coordination of Si

size

Malkov, A.V.; Stoncius, S.; MacDougall, K.N.; Mariani, A.; McGeoch, G.D.; Kocovski, P. *Tetrahedron*, **2006**, *62*, 264.
Wang, Z.; Ye, X.; Wei, S.; Wu, P.; Zhang, A.; Sun, J. *Org. Lett*, **2006**, *8*, 999.
Wang, Z.; Cheng, P.; Wei, S.; Wu, P.; Sun, J. *Org. Lett*, **2006**, *8*, 3045.

Conclusion

- Lewis base catalysis has seen tremendous growth over the past 10 years due in part to the efforts of Scott. E. Denmark

- Considering the different ways in which electron-pair donors can enhance chemical reactivity through various mechanis, the opportunities for invention are important.

- Problem: It is difficult to accurately assess the precise nature, coordination and conformation of the active catalyst and transition state orientation.