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Activating Acids with Bases: Theory and Applications
An Homage to G. N. Lewis

Ischia Advanced School
of Organic Chemistry 2006
Ischia, Italy

19-23 September 2006

QuickTime™ and a
Photo - JPEG decompressor
are needed to see this picture.

G. N. Lewis (1875-1946)

(Asymmetric) Catalysis: The Chemical Evergreen

reagents

Periodic Table of the Elements

catalysts

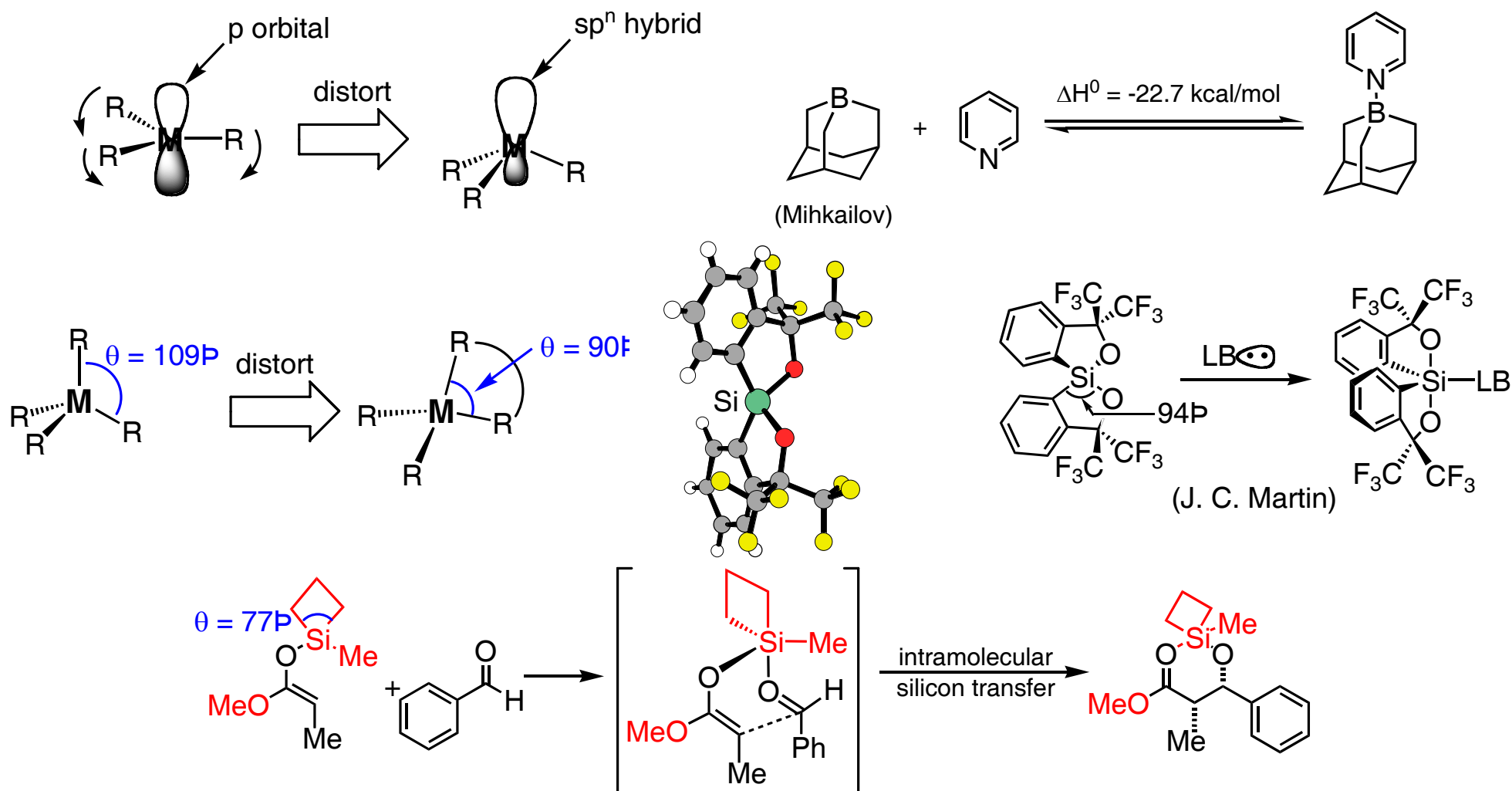
1A	2A	3B	4B	5B	6B	7B	8B	11B	12B	3A	4A	5A	6A	7A	8A																	
1 H hydrogen 1.008	4 Be beryllium 9.012	21 Sc scandium 44.96	22 Ti titanium 47.88	23 V vanadium 50.94	24 Cr chromium 52.00	25 Mn manganese 54.94	26 Fe iron 55.85	27 Co cobalt 58.93	28 Ni nickel 58.69	29 Cu copper 63.55	30 Zn zinc 65.39	31 Ga gallium 69.72	32 Ge germanium 72.58	33 As arsenic 74.92	34 Se selenium 78.96	35 Br bromine 79.90	36 Kr krypton 83.80															
3 Li lithium 6.941	11 Na sodium 22.99	19 K potassium 39.10	37 Rb rubidium 85.47	55 Cs cesium 132.9	87 Fr francium (223)	101 La* lanthanum 138.9	102 Ce cerium 140.1	103 Pr praseodymium 140.9	104 Nd neodymium 144.2	105 Pm promethium (147)	106 Sm samarium (150.4)	107 Eu europium 152.0	108 Gd gadolinium 157.3	109 Tb terbium 158.9	110 Dy dysprosium 162.5	111 Ho holmium 164.9	112 Er erbium 167.3	113 Tm thulium 168.9	114 Yb ytterbium 173.0	115 Lu lutetium 175.0												
12 Mg magnesium 24.31	20 Ca calcium 40.08	38 Sr strontium 87.62	56 Ba barium 137.3	88 Ra radium (226)	104 Rf rutherfordium (261)	105 Db dubnium (260)	106 Sg seaborgium (263)	107 Bh bohrium (262)	108 Hs hassium (265)	109 Mt meitnerium (266)	110 Ds darmstadtium (271)	111 Uuu unnilium (272)	112 Uub ununium (277)	113 Uuq ununium (296)	114 Uuq ununium (296)	115 Uuq ununium (296)	116 Uun ununium (298)	117 Uun ununium (298)	118 Uuo ununium (?)													
		39 Y yttrium 88.91	40 Zr zirconium 91.22	41 Nb niobium 92.91	42 Mo molybdenum 95.94	43 Tc technetium (98)	44 Ru ruthenium 101.1	45 Rh rhodium 102.9	46 Pd palladium 106.4	47 Ag silver 107.9	48 Cd cadmium 112.4	49 In indium 114.8	50 Sn tin 118.7	51 Sb antimony 121.8	52 Te tellurium 127.6	53 I iodine 126.9	54 Xe xenon 131.3	89 Ac~ actinium (227)	90 Th thorium 232.0	91 Pa protactinium (231)	92 U uranium (238)	93 Np neptunium (237)	94 Pu plutonium (242)	95 Am americium (243)	96 Cm curium (247)	97 Bk berkelium (247)	98 Cf californium (249)	99 Es einsteinium (254)	100 Fm fermium (253)	101 Md mendelevium (256)	102 No nobelium (254)	103 Lr lawrencium (257)

Opportunities for Catalysis in the Main Group?

- Lewis Acidity:
 - B(+3), Al(+3), Ga(+3), In(+3)
 - Si(+4), Sn(+2, +4), Pb(+4)
 - P(+5), Sb(+3, +5), Bi(+3, +5)
 - O(+2), S(+2, +4, +6), Se(+2, +4, +6), Te(+2, +4, +6)
 - F(+1), Cl(+1, +3, +5, +7), Br(+1, +3, +5, +7), I(+1, +3, +5, +7)
- Catalyzed Chemical Processes
 - Carbonyl addition reactions (aldol, allylation, ene)
 - Acetal addition reactions
 - Friedel-Crafts reactions
 - Conjugate addition reactions
 - Azomethine addition reactions
 - Epoxide opening reactions
 - Cycloadditions ([4+2], hetero [4+2], [3+2]), Electrocyclic reactions
 - Sigmatropic (and other) rearrangements

Strategies for Modulating Lewis Acidity: **Structural**

structural perturbations (“strain-release Lewis acidity”)



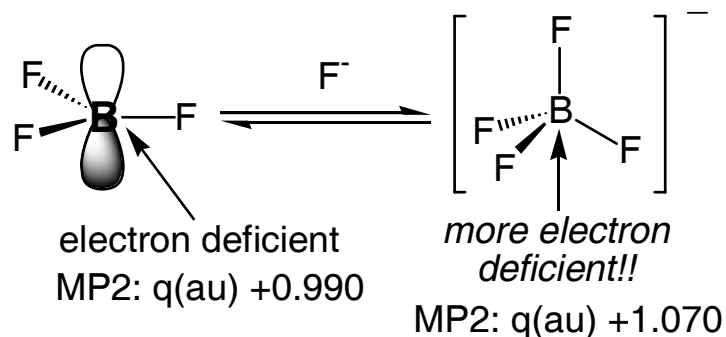
Strategies for Modulating Lewis Acidity: *Electronic*

electronic perturbations (electrophilic)



Binding equilibrium becomes more favorable as electron deficiency at **M** increases: $X = \text{NR}_2 < \text{OR} < \text{halide} < \text{TfO} \sim \text{Tf}_2\text{N}$

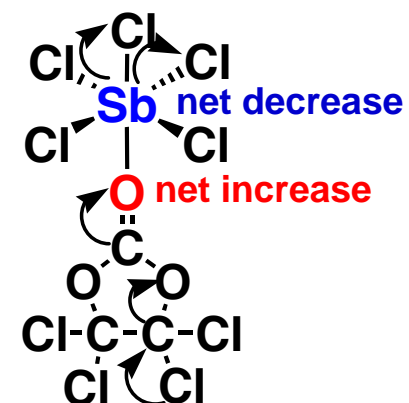
electronic perturbations (nucleophilic?)



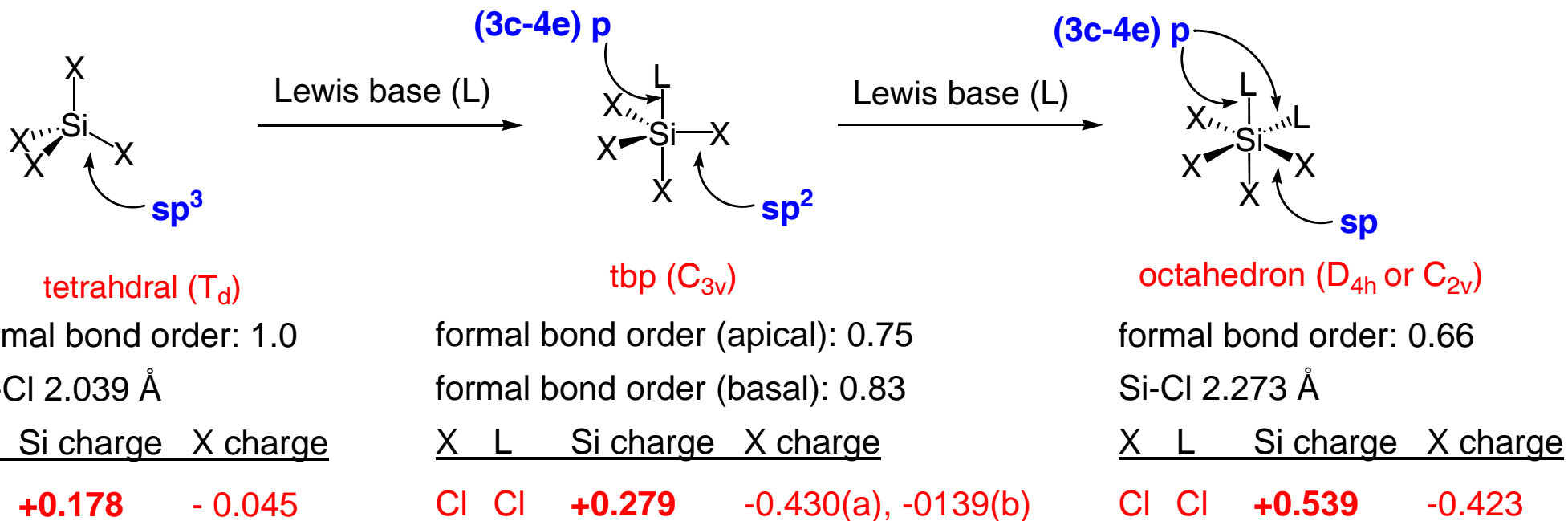
C. Cramer, private communication

Gutmann's Fourth Rule "spillover effect"

"...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** of electron density at the donor atom of the donor species and to a net **decrease** of electron density at the acceptor atom of the acceptor species."

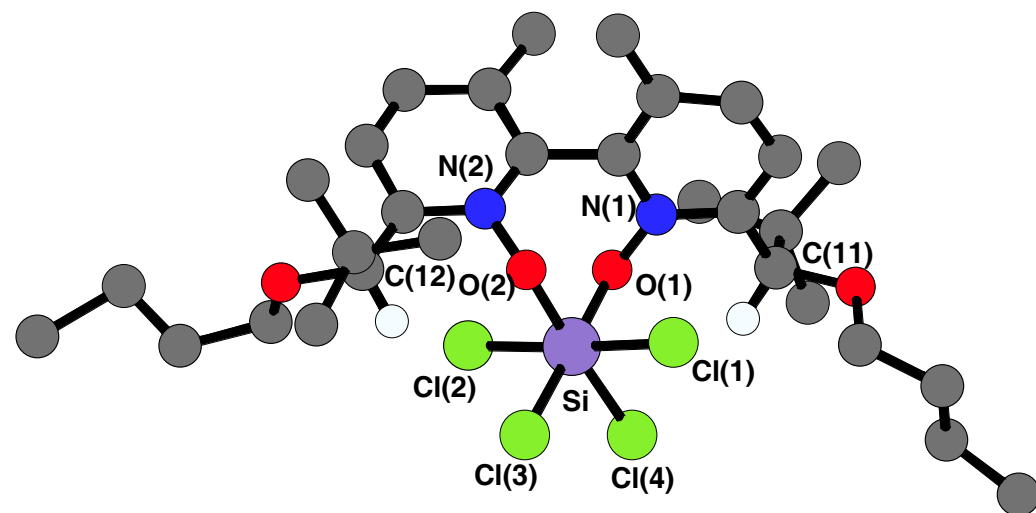
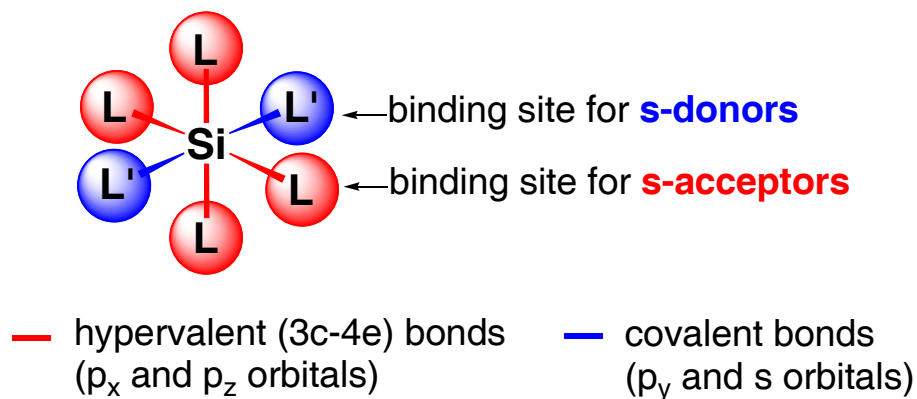
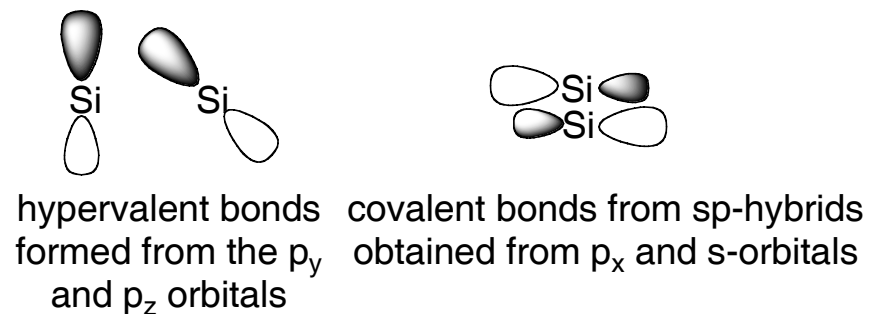
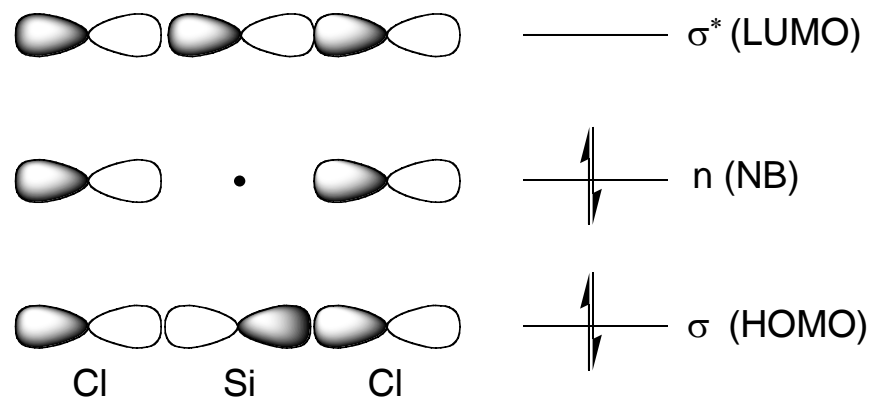


Structure, Bonding and Charge Distribution in Hypercoordinate Silicon Compounds



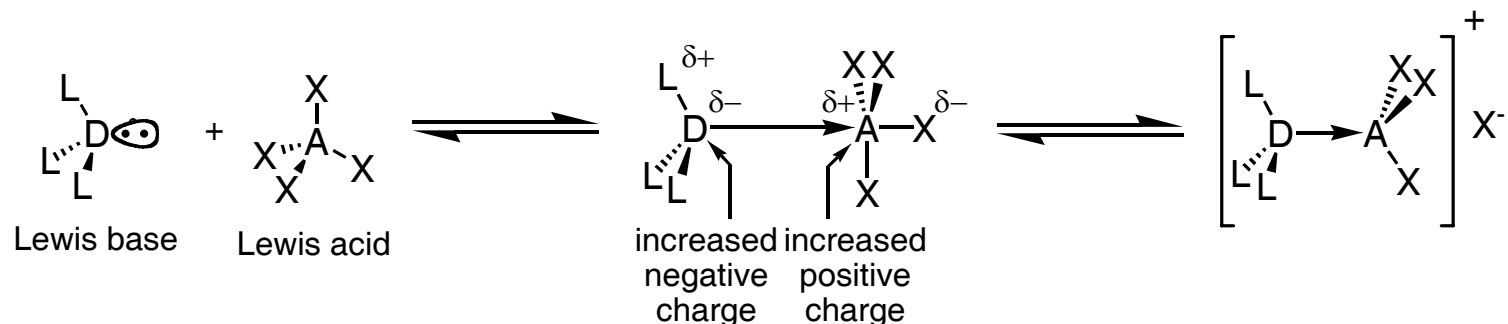
1. Coordination by both neutral and anionic ligands results in a **decrease** in the electron density at the central silicon atom and an **increase** in electron density on the ligands.
2. Hypervalent bonding is highly ionic in character and dissociation can be facile.
3. Hypervalent bonds favor electronegative ligands, sp bonds favor electropositive ligands

The Hypervalent 3-Center/4 Electron Bond

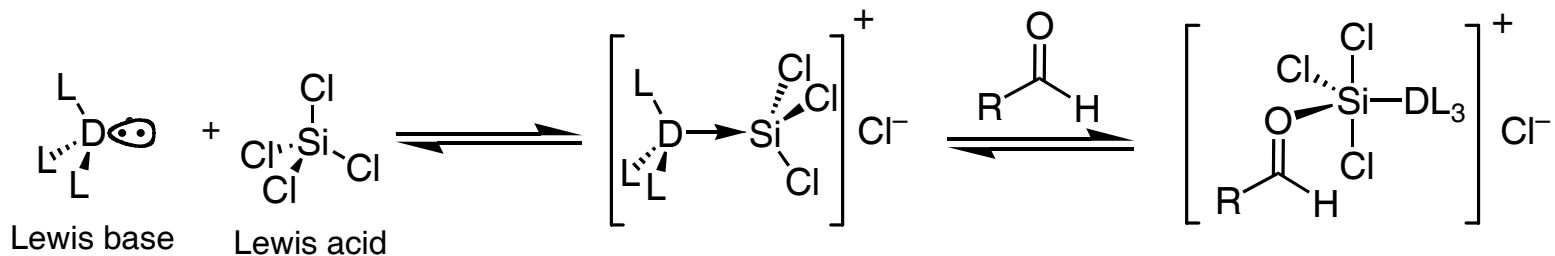


Si-Cl(1)/Cl(2): 2.180 Å
 Si-Cl(3)/Cl(4): 2.197 Å

Lewis Base Activation of Lewis Acids



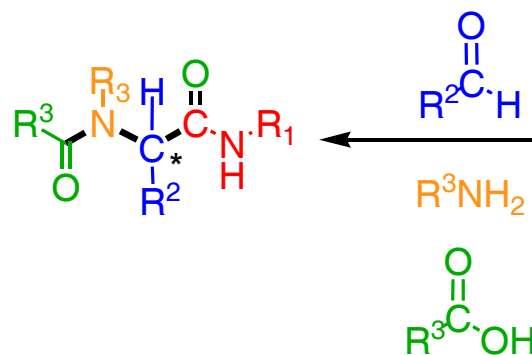
- The kinetically significant (strong) Lewis acid is generated only in the presence of the Lewis base thus negating the achiral background reaction.
- Reactions can be run with a stoichiometric amount of the weak Lewis acid
 - Increased rates
 - Product inhibition is minimized



Other electrophiles: enals, enones, azomethines, epoxides, nitrones, nitroalkenes
 Pro Nucleophiles: Nu-SiR₃ = allylsilanes (stannanes) enol silanes, silyl ketene acetals, etc.

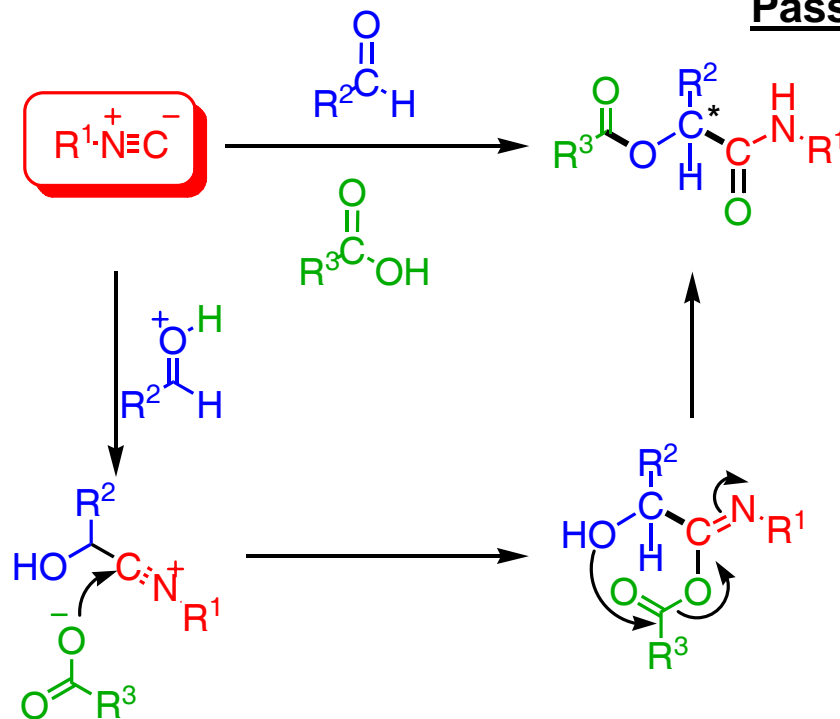
Catalytic Enantioselective Passerini Reaction

Ugi



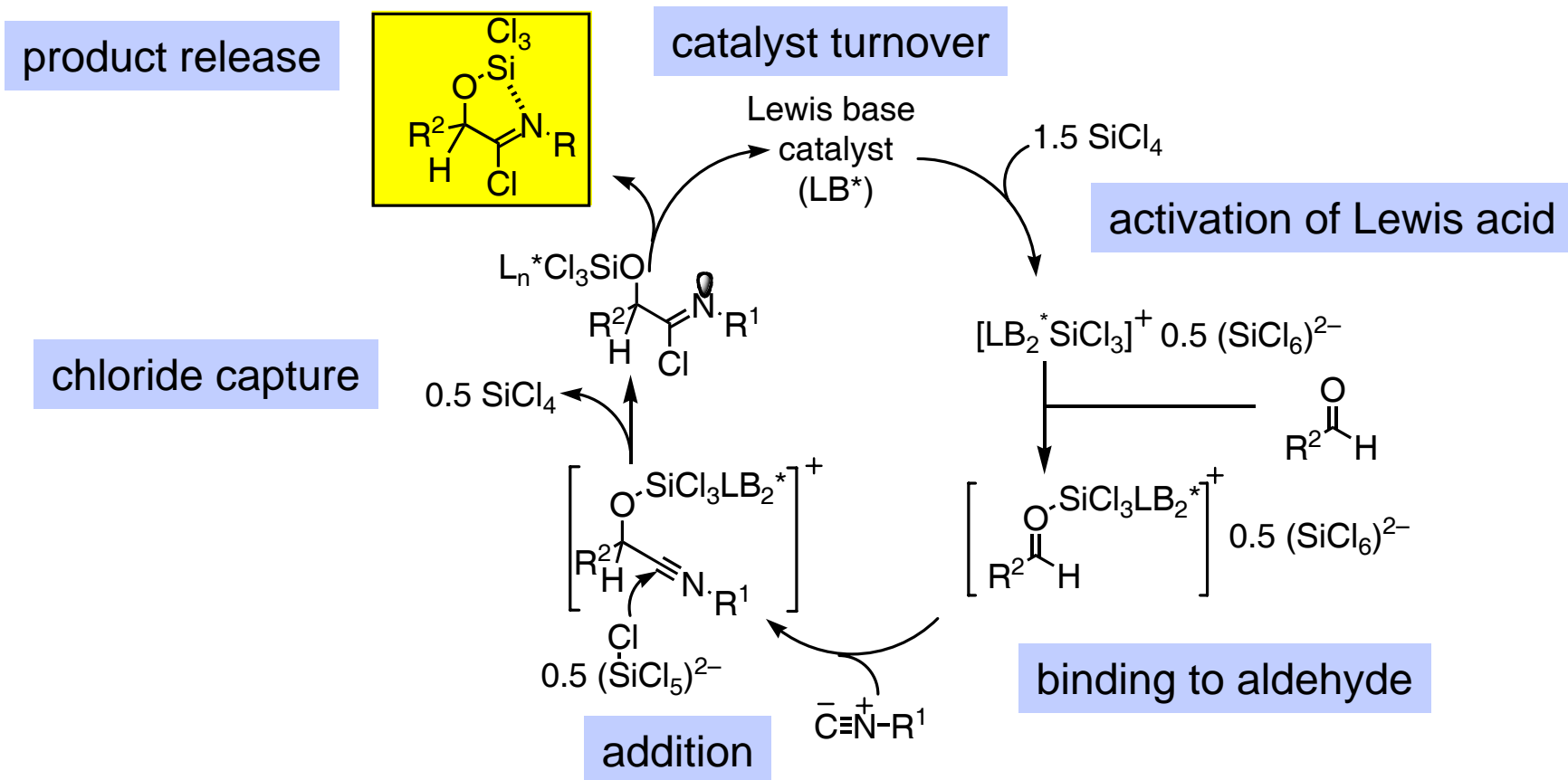
multicomponent reactions for
molecular diversity

Passerini



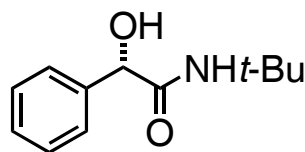
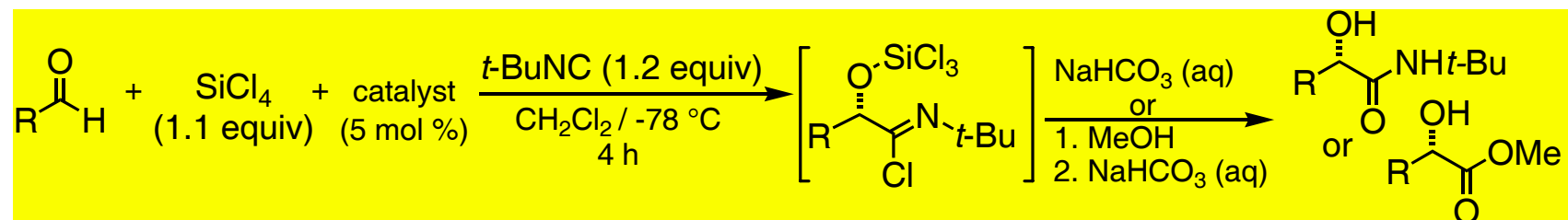
Isocyanide bears divalent carbon atom with electrophilic and nucleophilic properties
Up to four new bonds and one stereocenter created in very useful α -acyloxy amides
Auxiliary-based approaches but **no examples of catalytic enantioselective process!!**

Passerini Reaction: Lewis Base Activation of Lewis Acid

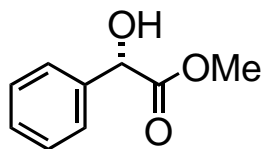


- activated silyl cation preferentially binds carbonyl substrate, instead of the isocyanide
- attenuated Lewis acidity of the silicon center in imidoyl chloride results facile turnover
- catalyst turnover becomes the release of the Lewis base, instead of the Lewis acid

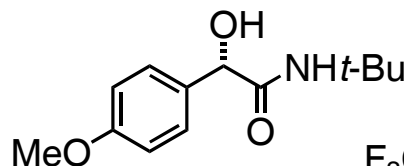
Catalytic Enantioselective Passerini Reaction: Aldehyde Survey



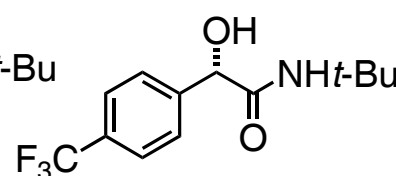
yield 96%
er: > 99/1



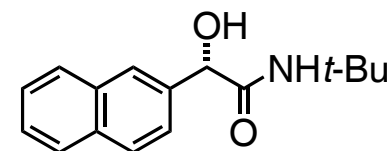
yield 95%
er: > 99/1



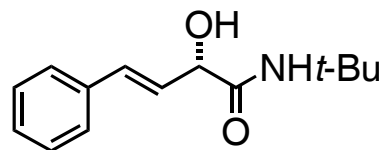
yield 89%
er: 98.3/1.7



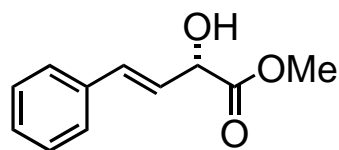
yield 89%
er: 96.5/3.5



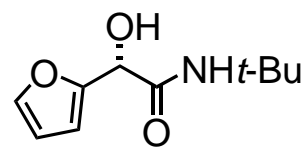
yield 93%
er: > 99/1



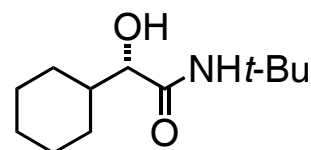
yield 81%
er: 97.8/2.2



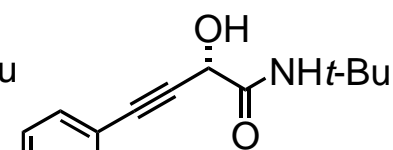
yield 71%
er: 97.9/2.1



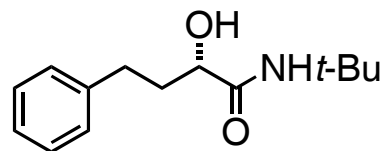
yield 83%
er: 95.9/4.1



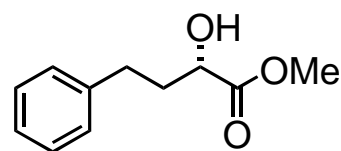
yield 53%
er: 87.1/12.9



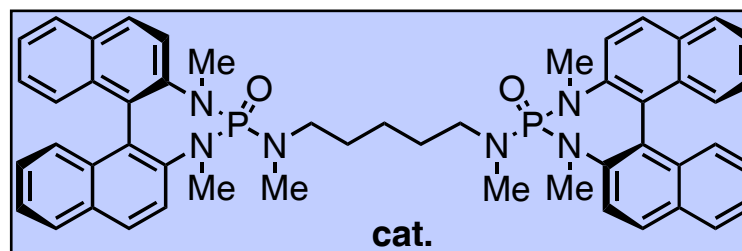
yield 76%
er: 77.0/23.0



yield 92%
er: 81.9/18.1



yield 88%
er: 81.8/18.2



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