

Ligand Accelerated Catalysis (LAC)

Chris Borths
MacMillan Group Meeting
October 3, 2001

- I. Definition
- II. Oxidations
- III. Reductions
- IV. Alkylations
- V. Lewis base catalysis

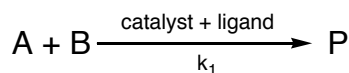
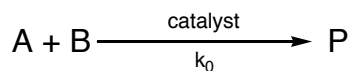
Reviews:

LAC: Berrisford, D.J.; Bolm, C.; Sharpless, K.B. *Ang. Chem. Int. Ed. Engl.* **1995**, *34*, 1059.

Non-Linear Effects: Girard, C.; Kagan, H.B. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2922. Blackmond, D.G. *J. Am. Chem. Soc.* **1997**, *119*, 12934.

Asymmetric Activation: Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; Ueki, M.; Angelaud, R. *Angew. Chem. Int. Ed. Engl.* **2000**, *112*, 3532.

A Definition of LAC



■ Ligand accelerated catalysis can be most simply defined as any reaction where $\frac{v_{ML}}{v_M} > 1$

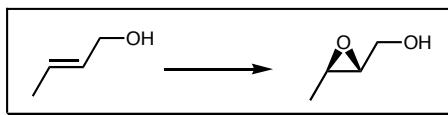
■ Ligand acceleration effect (LAE) is defined by $\frac{k_1 K_{eq}[\text{ligand}]}{k_0}$

■ Useful levels of selectivity can be achieved when the LAE is 20 or higher.

■ If ligand exchange occurs faster than or on the same time scale as the transformation, asymmetric catalysis becomes viable at high levels of LAE.

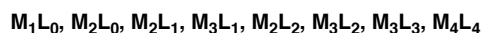
Berrisford, D.J.; Bolm, C.; Sharpless, K.B. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059.

Titanium-Catalyzed Asymmetric Epoxidation



■ Titanium exhibits complex metal ligand association in solution.

Metal-ligand species detected in solution: $Ti(OiPr)_4$ (M) and diisopropyl tartrate (L)



(evidence for existence based on NMR, MS, or XRD)

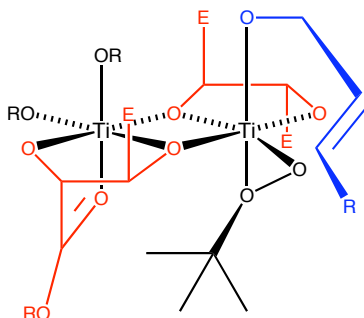
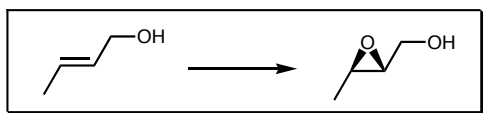
■ Multiple metal-ligand species are active epoxidation catalysts

	M_1L_0	M_2L_1	M_2L_2
solution fraction (1:1 M:L)	~ 10%	~ 10%	~ 80%
relative epoxidation rate	1.4	1.0	3.6
enantioselectivity	none	low	high

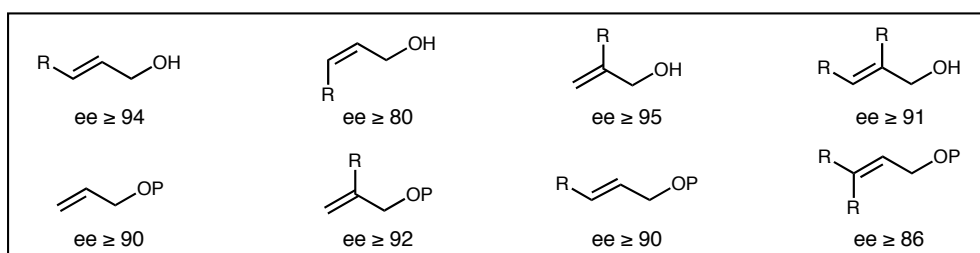
■ The standard SAE recipe calls for a 20% excess of tartrate, practically removing the unwanted epoxidation catalysts from solution.

Berrisford, D.J.; Bolm, C.; Sharpless, K.B. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059.

Titanium-Catalyzed Asymmetric Epoxidation

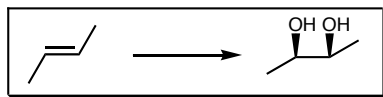


■ Sharpless system shows excellent enantioselectivity. (Ligand DET or DIPT)



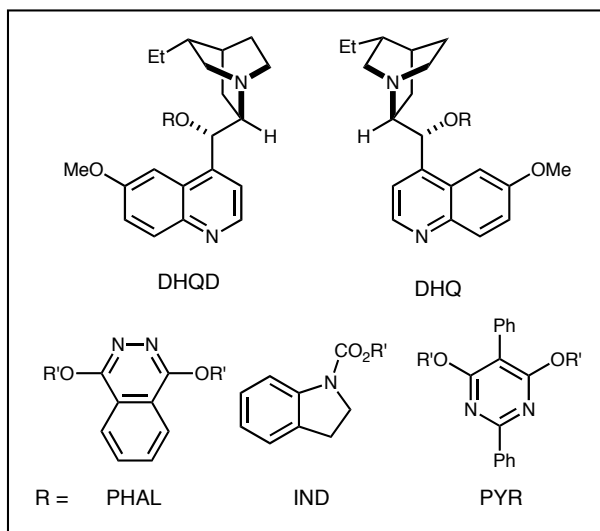
Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
McKee, B.H.; Kalantar, T.H.; Sharpless, K.B. *J. Org. Chem.* **1991**, *56*, 6966.

Osmium-Catalyzed Dihydroxylation

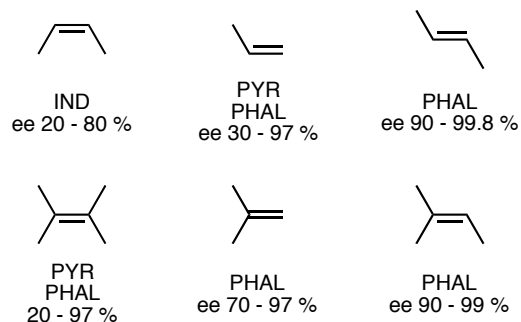
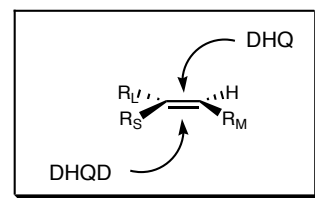


■ This is the first reaction to show ligand acceleration by chinchona alkaloids.

■ The ligand acceleration effect has been demonstrated to be greater than 15 and as high as 100 for stilbene at 0 °C.



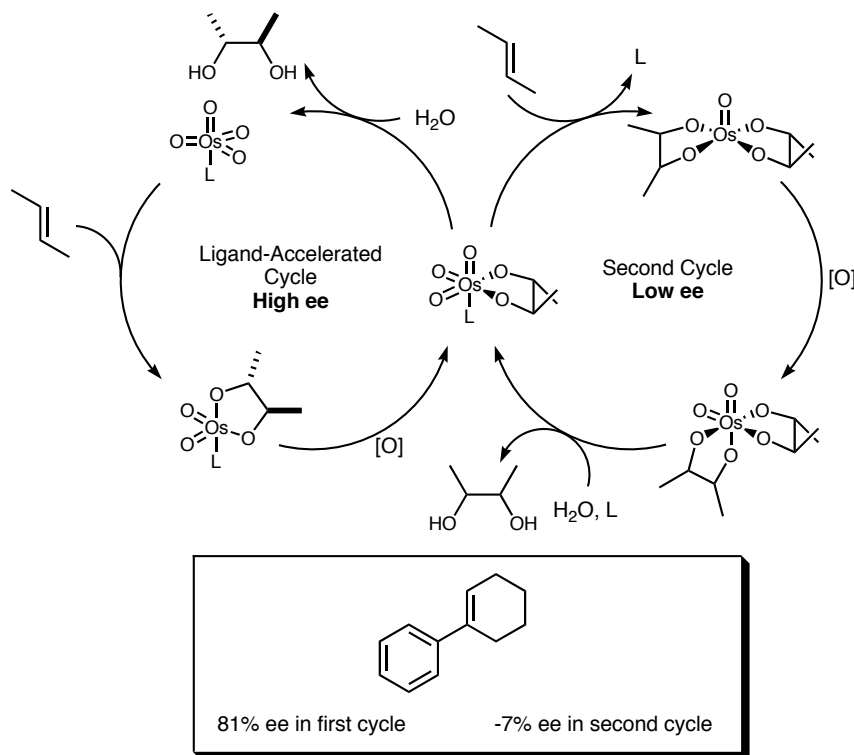
THE CATALYSTS



Jacobsen, E.N.; Markó, I.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
Jacobsen, E.N.; Markó, I.; France, M.B.; Svendsen, J.S.; Sharpless, K.B. *J. Am. Chem. Soc.* **1989**, *111*, 737.
Sharpless, K.B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585.
Kolb, H.C.; Van Nieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* **1994**, *94*, 2483.

Multiple Catalytic Cycles Operate in the Osmium Dihydroxylation

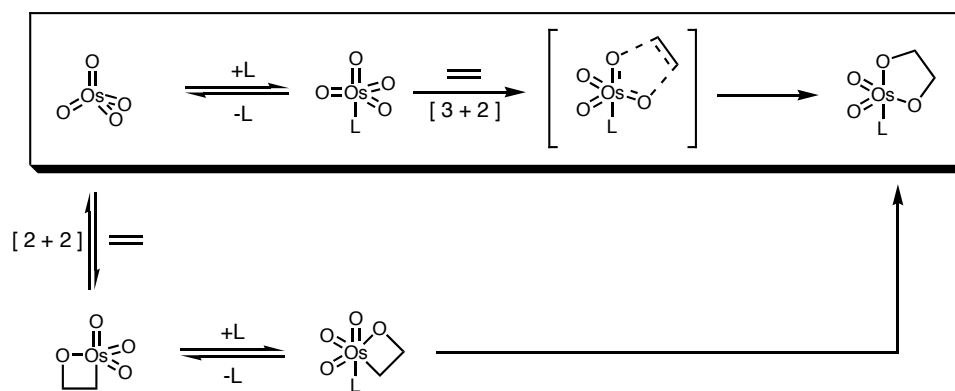
- Slow addition of olefin substrate in presence of acetate can select against the second catalytic cycle.
- Use of $K_3Fe(CN)_6$ as the oxidant can eliminate the second catalytic cycle.



Wai, J.S.M.; Markó, I.; Svendsen, J.S.; Finn, M.G.; Jacobsen, E.N.; Sharpless, K.B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.
 Kwong, H.L.; Sarato, C.; Ogino, Y.; Chen, H.; Sharpless, K.B. *Tetrahedron Letters* **1990**, *31*, 2999.

Mechanism of Osmium Dihydroxylation

A concerted [3 + 2] mechanism is believed to be correct

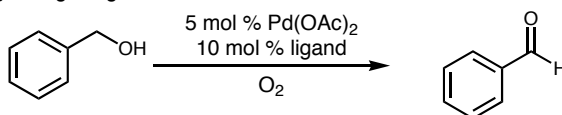


- Hammett studies favor the existence of a concerted mechanism
- Frontier molecular orbital calculations favor a concerted [3 + 2] mechanism.
- Transition state models with chiral chelating dinitrogen ligands are inconclusive.
- Kinetic isotope effects match the predicted [3 + 2] calculations and do not match the predicted [2 + 2] calculations.
- Quantum mechanical modelling based on the [3 + 2] mechanism (using MM3* calculations) can predict the experimental enantioselectivities to within a few percentage points.

Norrby, P.O.; Becker, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1996**, *118*, 35.
 Nelson, D.W.; Gypser, A.; Ho, P.T.; Kolb, H.C.; Kondo, T.; Kwong, H.L.; McGrath, D.V.; Rubin, A.E.; Norrby, P.O.; Gable, K.P.; Sharpless, K.B. *J. Am. Chem. Soc.* **1997**, *119*, 1840.
 DelMonte, A.J.; Haller, J.; Houk, K.N.; Sharpless, K.B.; Singleton, D.A.; Strassner, T.; Thomas, A.A. *J. Am. Chem. Soc.* **1997**, *119*, 9907.
 Norrby P.O.; Rasmussen, T.; Haller, J.; Strassner, T.; Houk, K.N. *J. Am. Chem. Soc.* **1999**, *121*, 10186.

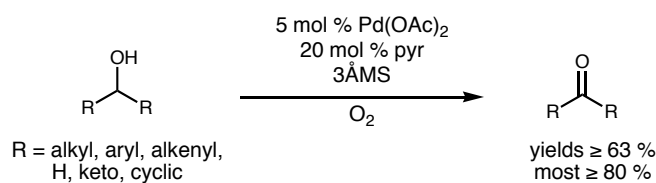
Palladium-Catalyzed Oxidations

- Reaction rate accelerated by nitrogen ligands



Ligand	Conversion (2h)
none	5 %
pyridine	86 %
2,6-lutidine	82 %
triethylamine	78 %
2,2'-bipyridine	5 %
pyridine with 3ÅMS	quantitative

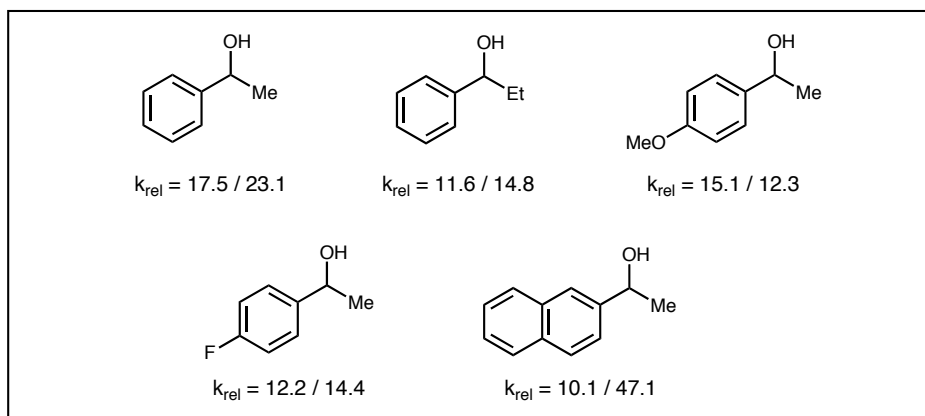
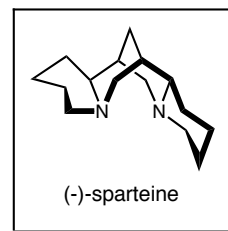
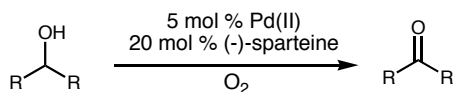
- Reaction rate shows a marked dependence on ligand concentration; efficient oxidations at 4 eq ligand / Pd



Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *Tetrahedron Letters* **1998**, *39*, 6011.
Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750.

Palladium-Catalyzed Oxidations: Kinetic Resolution

- (-)-Sparteine is most selective ligand.

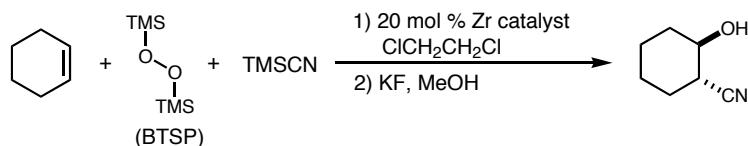


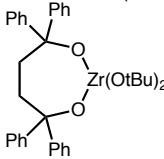
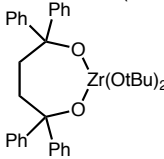
(Note: first k_{rel} is from Sigman paper, second k_{rel} is from Stoltz paper)

Jensen, D.R.; Pugsley, J.S.; Sigman, M.S. *J. Am. Chem. Soc.* **2001**, *123*, 7475.
Ferreira, E.M.; Stoltz, B.M. *J. Am. Chem. Soc.* **2001**, *123*, 7725.

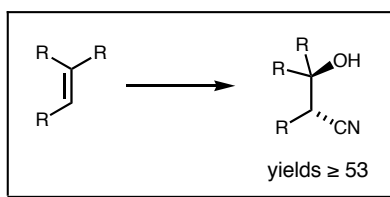
Zirconium-Catalyzed β -Cyanohydrin Synthesis

■ Reaction shows significant ligand acceleration.



Zr catalyst	time	yield (%)
$\text{Zr}(\text{OnBu})_4$	84 h	62
$\text{Zr}(\text{OiPr})_4$	63 h	63
$\text{Zr}(\text{OtBu})_4$	38 h	63
 alone	15 h	68
 + Ph_3PO	1.5 h	94

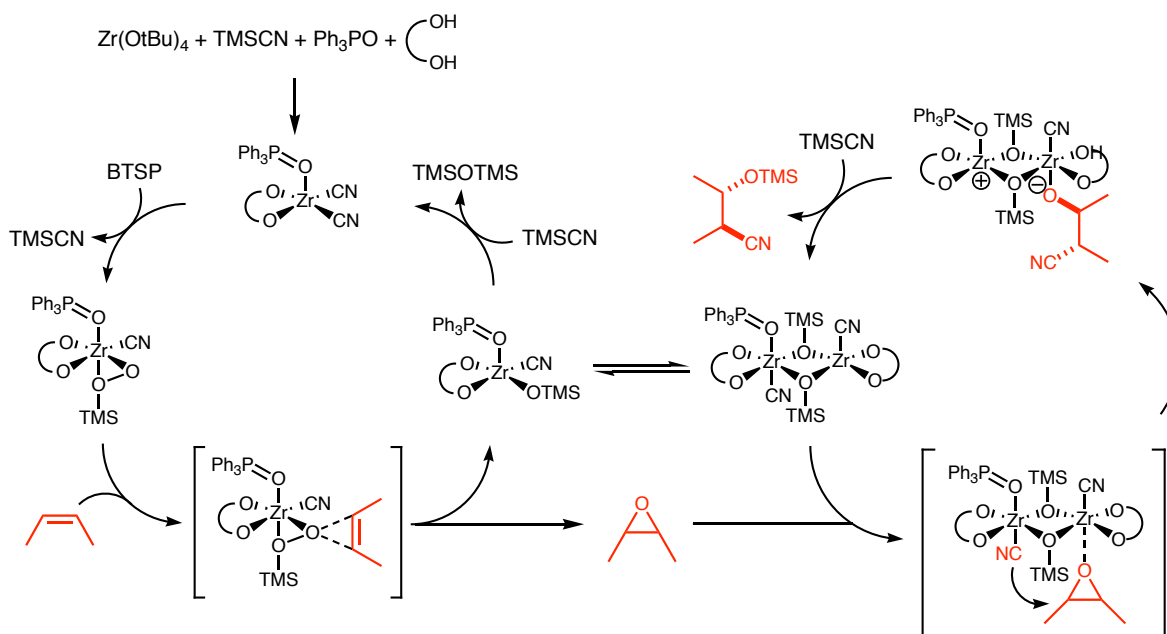
■ Mono-, di-, and tri-substituted olefins are good substrates for this reaction.



Yamasaki, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 1256.

Zirconium-Catalyzed β -Cyanohydrin Mechanism

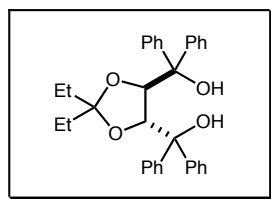
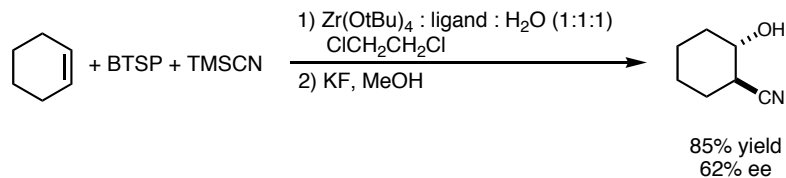
■ Mechanism proposal based on Ti-catalyzed epoxidation and Yb-catalyzed epoxide opening



Yamasaki, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 1256.

Enantioselective Zr-Catalyzed β -Cyanohydrin Synthesis

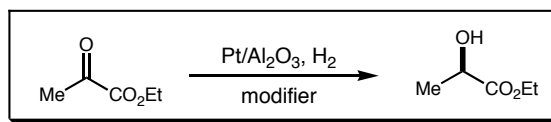
- An enantioselective variant has been proposed and is under development.



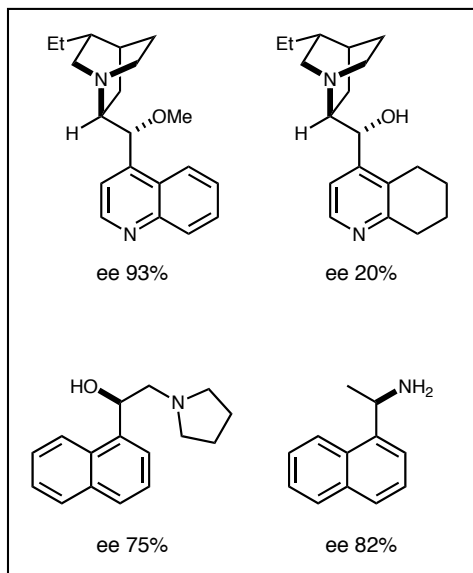
LIGAND

Yamasaki, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 1256.

Platinum-Catalyzed Hydrogenation of Ethyl Pyruvate

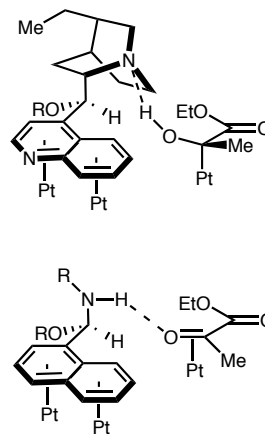


- Chincona alkaloids have been shown to adsorb to Pt surfaces in an ordered pattern with uniformly shaped pores.
- Relative reaction rates from kinetic data suggest a ligand acceleration effect of ≥ 13 .



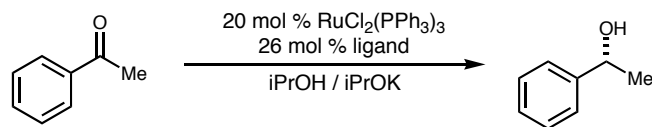
Pt Surface Modifiers

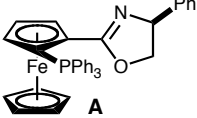
- Author's rendition of proposed transition states



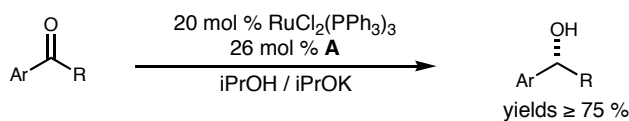
Blaser, H.U.; Jalett, H.P.; Lottenbach, W.; Studer, M. *J. Am. Chem. Soc.* **2000**, *122*, 12675.
Thomas, J.M. *Angew. Chem. Int. Ed. Engl. Adv. Mater.* **1989**, *28*, 1079.
Garland, M.; Blaser, H.U. *J. Am. Chem. Soc.* **1990**, *112*, 7048.

Ruthenium-Catalyzed Transfer Hydrogenation



Ligand	time	conversion
none	20 h	5 %
	6 h	93 % (94% ee)

■ Only aryl ketones are reduced enantioselectively.

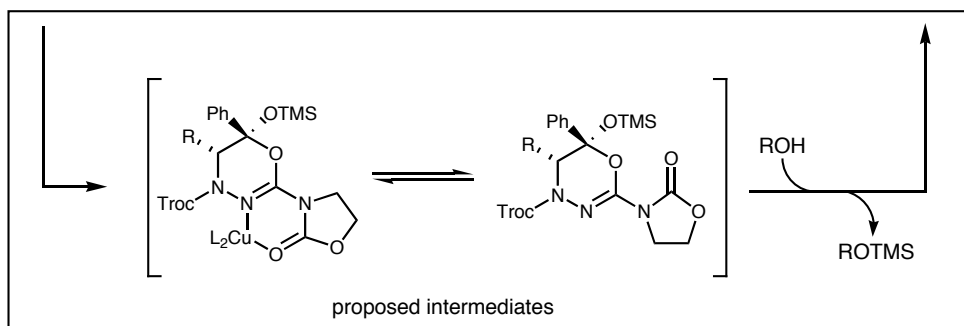
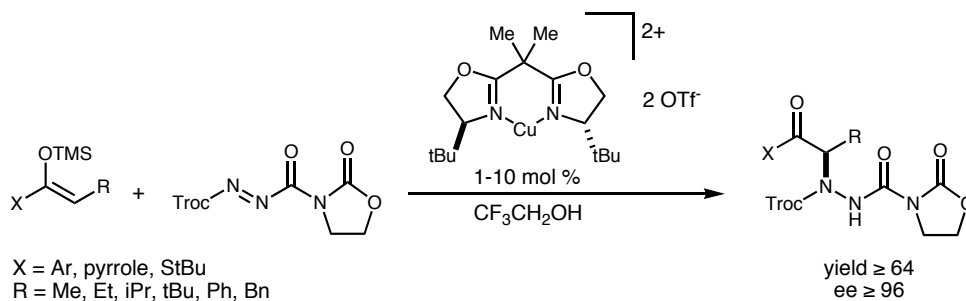


R	ee (%)
Me	≥ 84
Et	96 (Ar = Ph)
iPr	88 (Ar = Ph)

Sammakia, T.; Strangeland, E.L. *J. Org. Chem.* **1997**, *62*, 6104.

Copper-Catalyzed Enolsilane Amination

■ Evidence for LAC: Use of excess $\text{Cu}(\text{OTf})_2$ (50 mol %) relative to ligand (2 & 10 mol %) shows no significant decrease in enantioselectivity (99 % vs. 96 % ee).

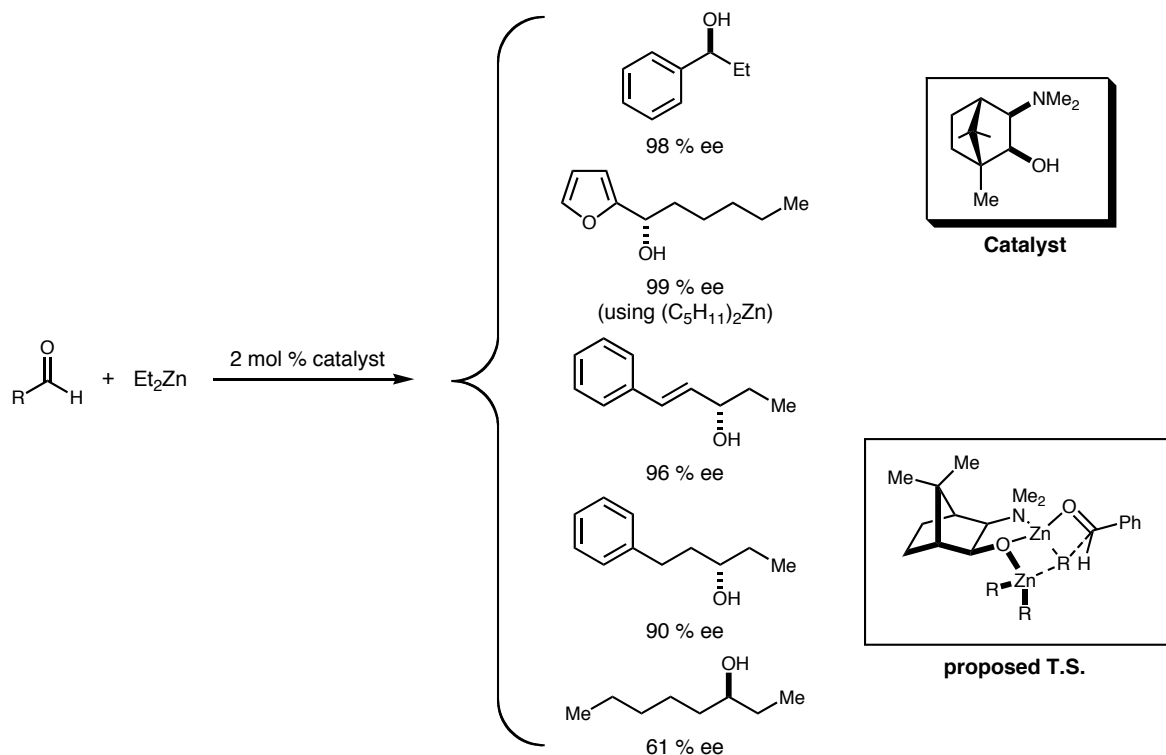


■ Amination reaction allows access to chiral building blocks: protected chiral hydrazines, hydrazino alcohols, and oxazolidones.

Evans, D.A.; Johnson, D.S. *Org. Lett.* **1999**, *1*, 595.

Conjugate Additions of Dialkylzinc Reagents

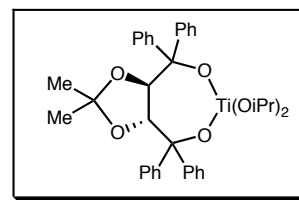
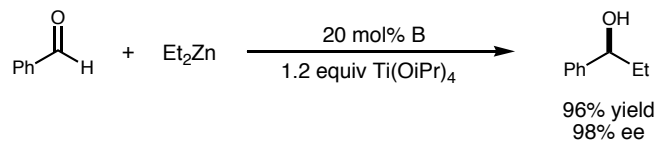
- Diamines and amino-alcohols accelerate the reaction of dialkylzinc reagents with aldehydes.
- Without catalyst, no product is generated under reaction conditions.



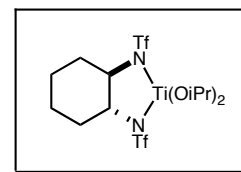
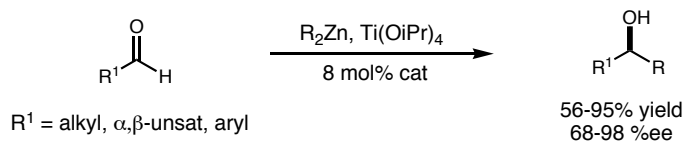
Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, 382, 19.
 Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons, Inc.: New York, 1994.

Titanium-Catalyzed Enantioselective Alkylation of Aldehydes

- Catalytic ligand loading can be used with stoichiometric titanium
- Taddol prevents titanium oligomerization.



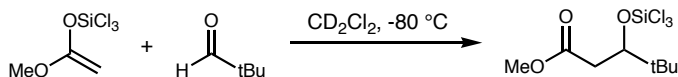
- Diamine ligand increases titanium's Lewis acidity.



Weber, B.; Seebach, D. *Tetrahedron* **1994**, 50, 7473.
 Rozema, M.J.; Sidduri, A.; Knochel, P.; *J. Org. Chem.*; **1992**; 57; 1956.
 Rozema, M.J.; Eisenberg, C.; Lütjens, H.; Ostwald, R.; Belyk, K.; Knochel, P.; *Tet. Lett.*; **1993**; 34; 3115.

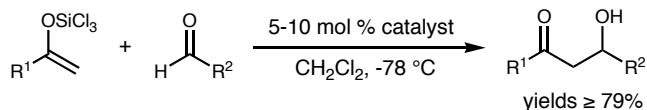
Lewis Base-Catalyzed Aldol Reactions

- Phosphoramidate ligands greatly increase the reactivity of silicon as a Lewis acid.

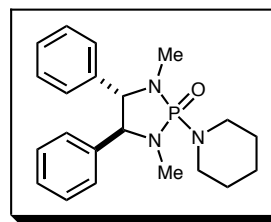


Additive	time	Conversion
none	2 h	50 %
10 mol % HMPA	<3 min	100 %

- Enantioselective methyl ketone aldol reactions:



R ¹	R ²	ee (%)
nBu	(E)-CH=CHPh	84
nBu	<i>c</i> -C ₆ H ₁₁	89
nBu	tBu	92
Me	Ph	87
tBu	Ph	52
Ph	Ph	49

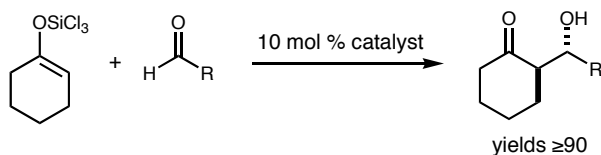


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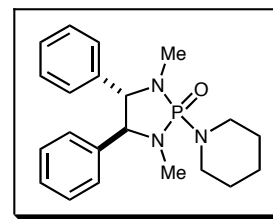
Denmark, S.E.; Stavenger, R.A. *Acc. Chem. Res.* **2000**, *33*, 432.

Lewis Base-Catalyzed Aldol Reactions

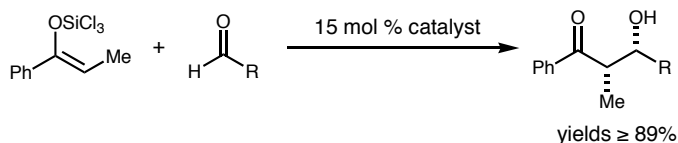
- Geometry of enolate controls stereochemical outcome of reaction.



R	syn/anti	ee (%)
aryl	1 / ≥61	≥93
CH=CHPh	<1 / 99	88
CMe=CHPh	<1 / 99	92
C=CPh	1 / 5.3	82



CATALYST



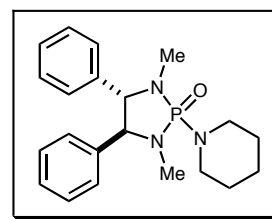
R	syn / anti	ee (%)
aryl	≥3 / 1	≥84
CH=CHPh	9.4 / 1	92
CH=CHMe	7.0 / 1	91
C=CPh	1 / 3.5	10*

* anti ee

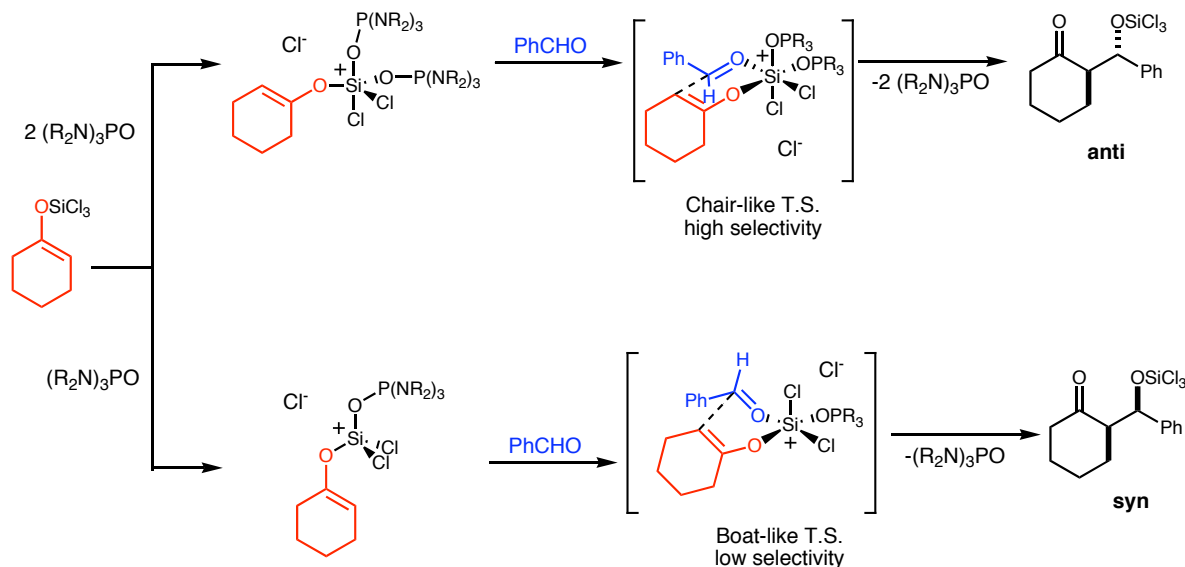
Denmark, S.E.; Stavenger, R.A.; Wong, K.T.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982.
Denmark, S.E.; Stavenger, R.A. *Acc. Chem. Res.* **2000**, *33*, 432.

Lewis Base-Catalyzed Aldol Mechanism

- Kinetics and a demonstrated non-linear relationship between catalyst ee and product ee suggest two phosphoramidate molecules involved in the transition state.
- Experimental evidence suggests chloride dissociation is involved in the reaction.
- Kinetics of a more sterically encumbered catalyst suggest an alternate mechanism involving only one phosphoramidate molecule.



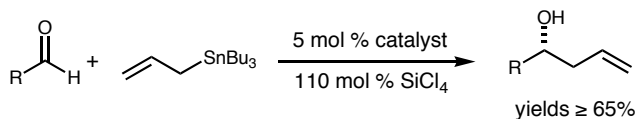
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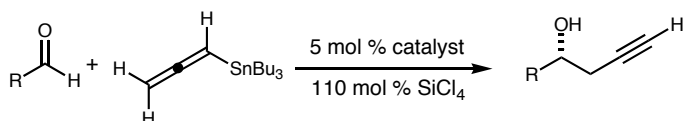
Denmark, S.E.; Stavenger, R.A. *Acc. Chem. Res.* **2000**, *33*, 432.

Silicon-Catalyzed Allylation and Propargylation of Aldehydes

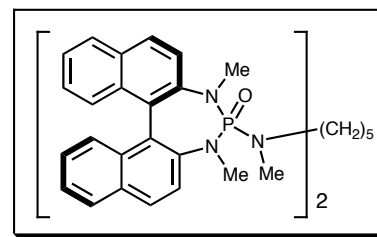
- Variation in catalyst linker length affects reaction efficiency and selectivity. This supports a mechanism involving 2 phosphoramidates in the transition state.



R	ee (%)
aryl	≥83
cinnamyl	65
C=CPh	22
furyl	62



R	ee (%)	yield (%)
Ph	97	81
cinnamyl	87	90
2-naphthyl	93	95



CATALYST

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

This is my Summary Slide

- Most ligand accelerated processes exhibit non-linear effects (rate and ee).
- LAC allows for highly selective transformations by selecting against an undesired pathway.
- LAC lends itself well to the development of asymmetric transformations.
- The discovery of more ligand-accelerated transformations will be a fruitful field in asymmetric catalysis.