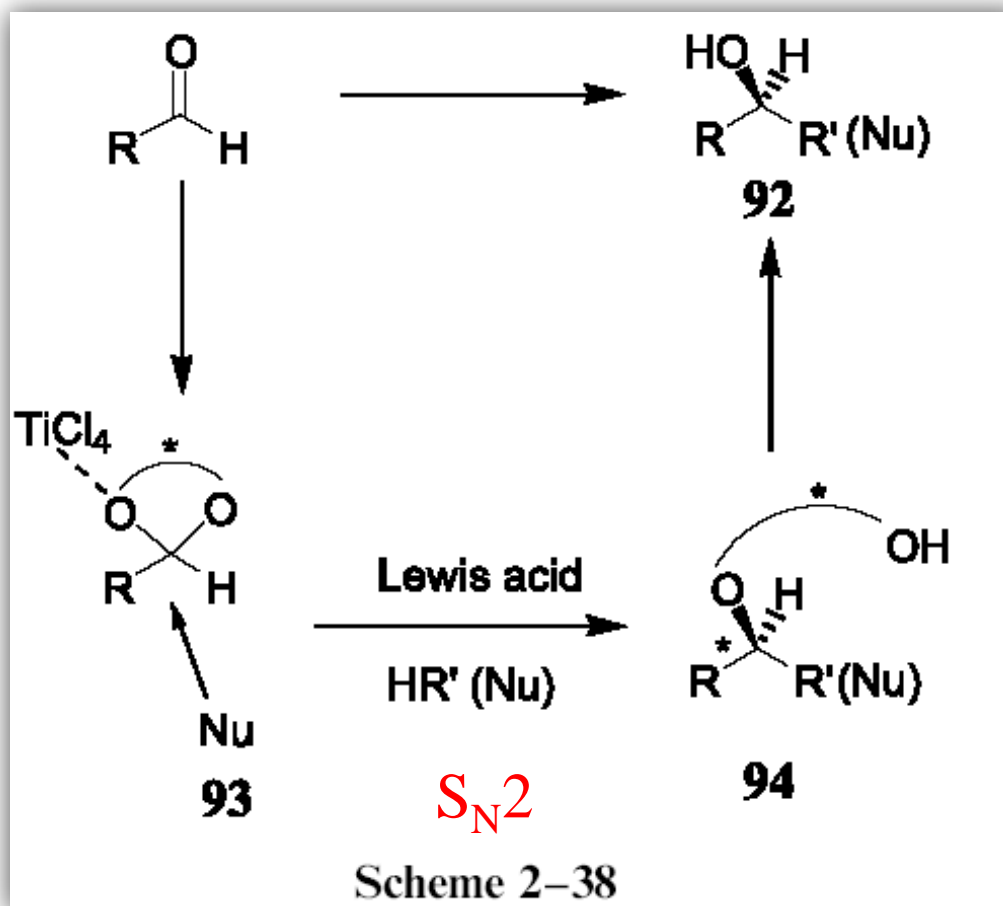


3. 羰基化合物(亚胺)的立体选择性亲核加成反应

第5次课

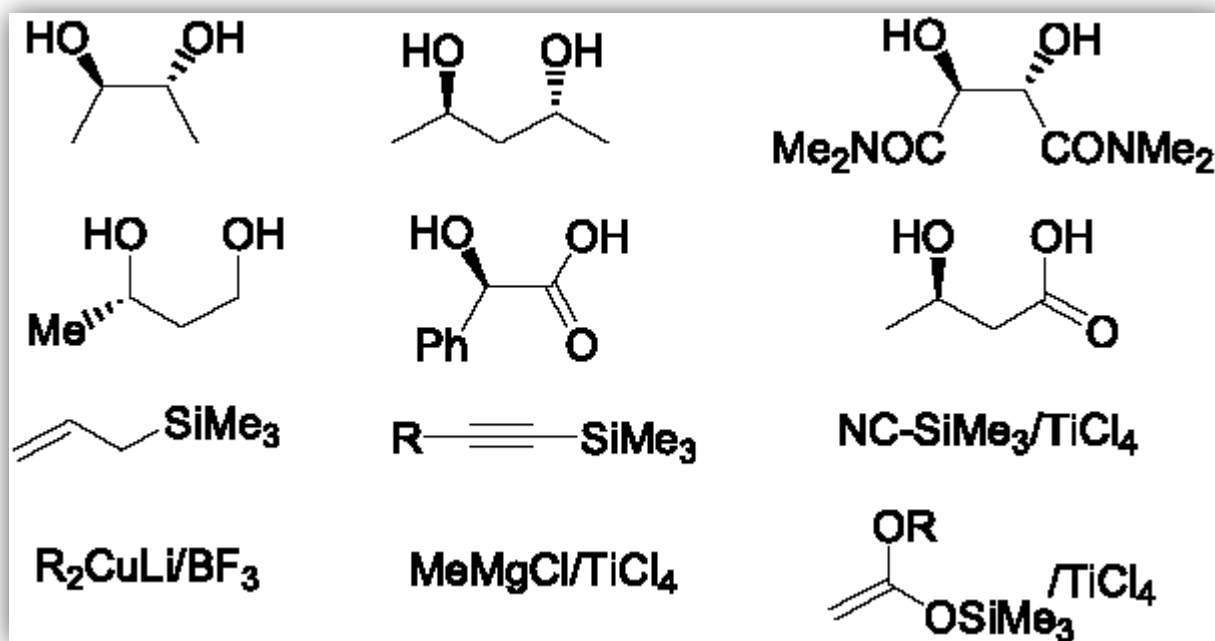
2016-03-16

3.1 NUCLEOPHILIC SUBSTITUTION OF CHIRAL ACETAL

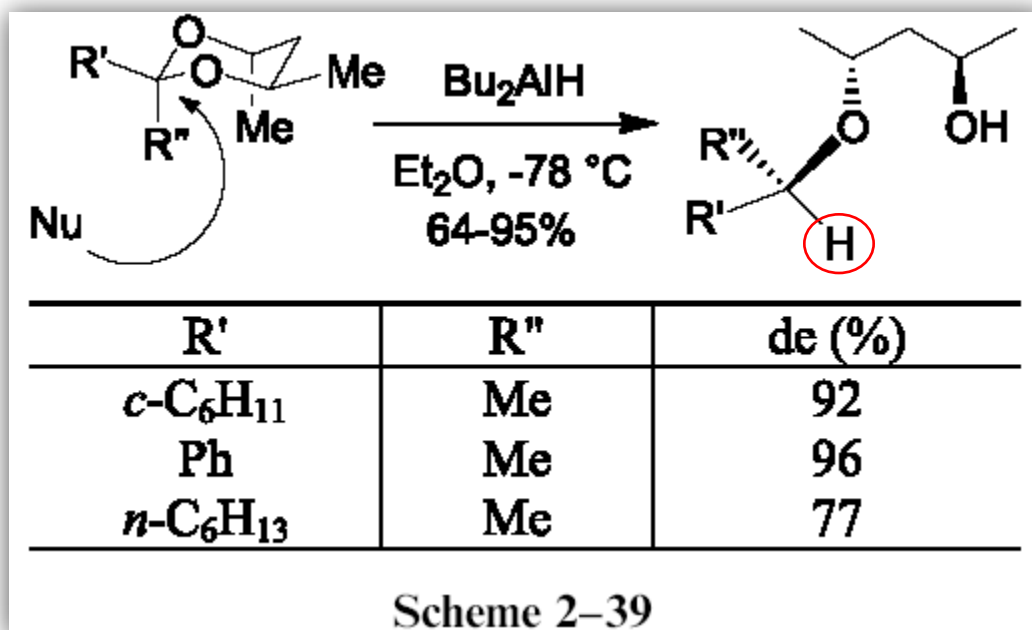


3.1 NUCLEOPHILIC SUBSTITUTION OF CHIRAL ACETAL

Mostly used chiral diols

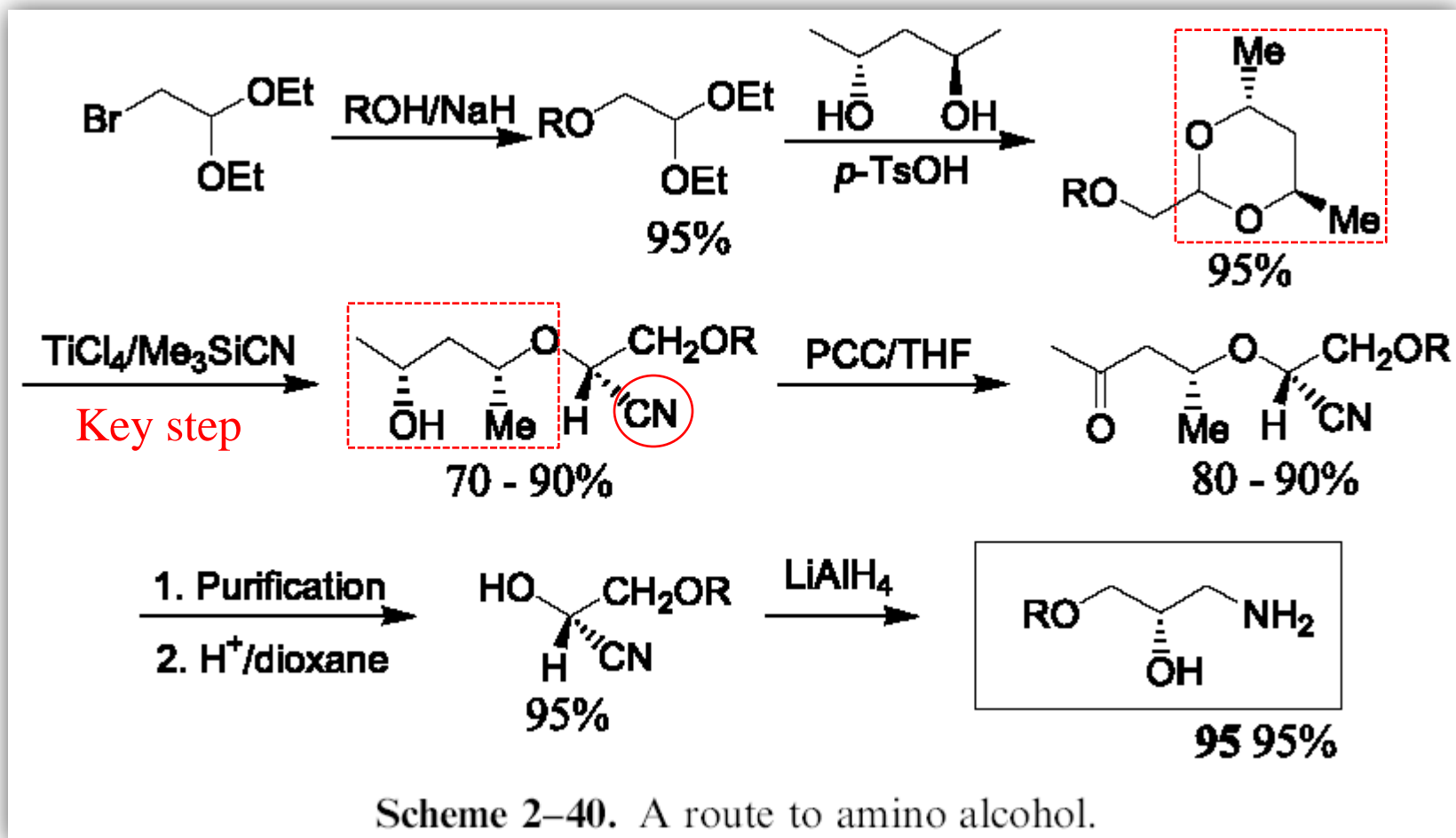


3.1 NUCLEOPHILIC SUBSTITUTION OF CHIRAL ACETAL



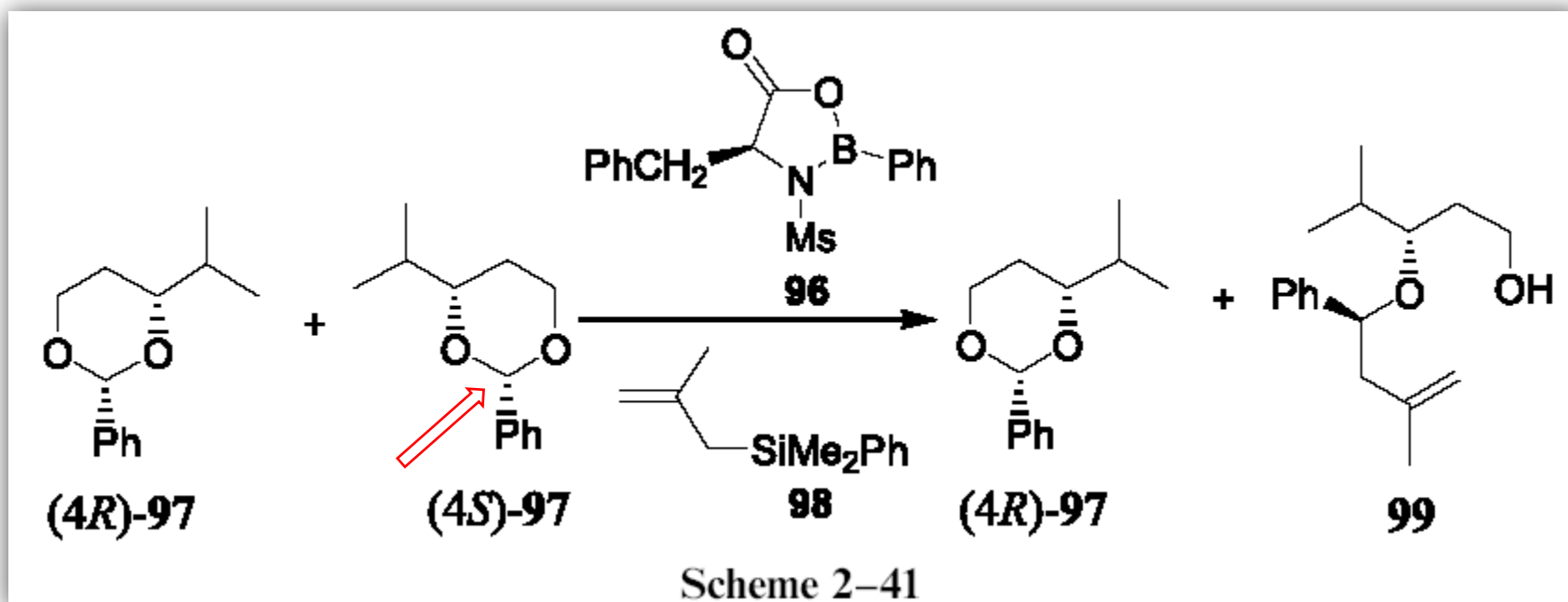
3.1 NUCLEOPHILIC SUBSTITUTION OF CHIRAL ACETAL

Application



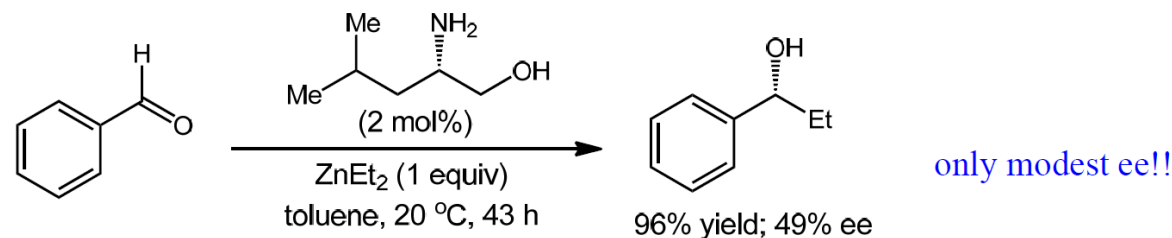
3.1 NUCLEOPHILIC SUBSTITUTION OF CHIRAL ACETAL

Herada, kinetic resolution

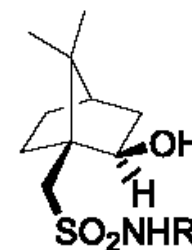
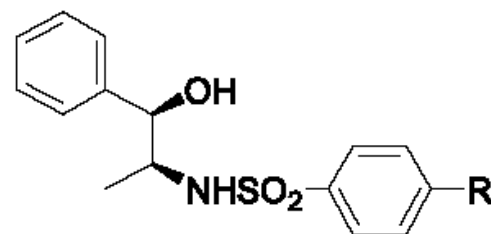
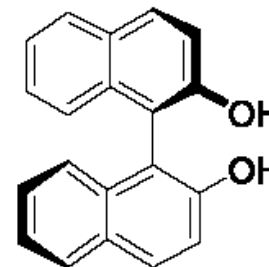
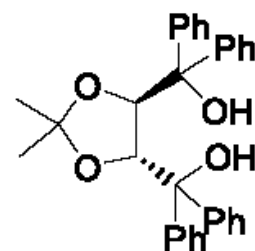
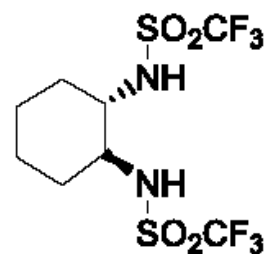


3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION

The first catalytic example by Oguni:



TL 1984, 25, 2823.



3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION

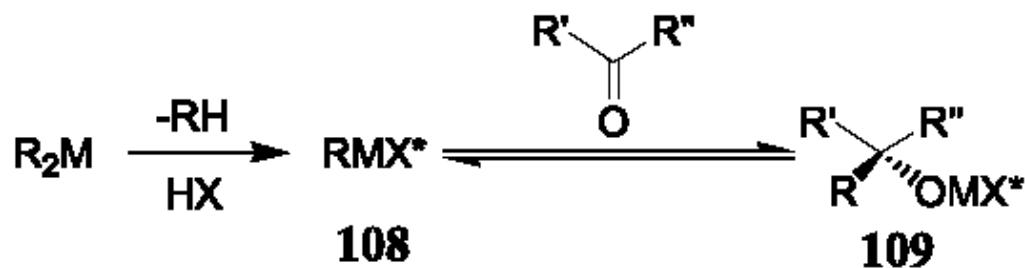


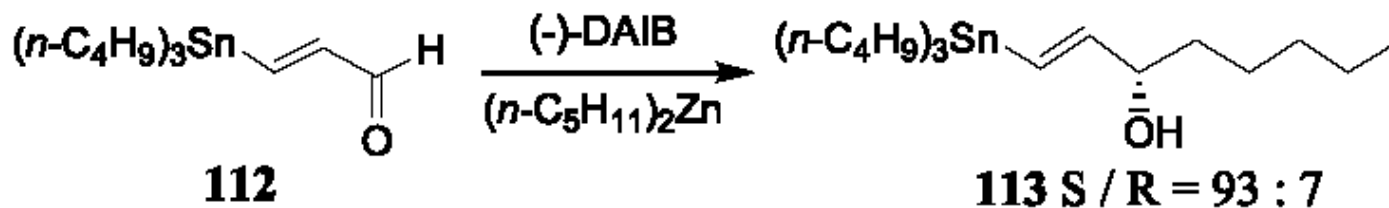
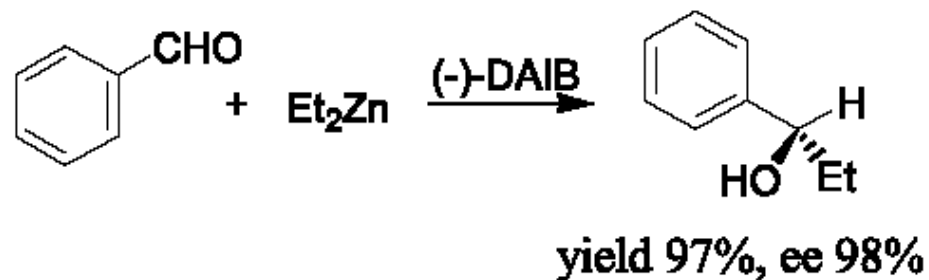
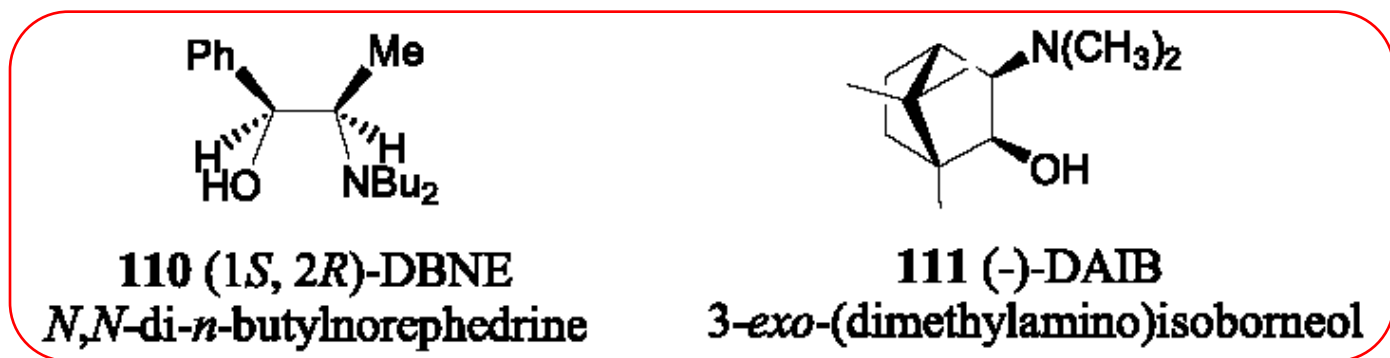
Figure 2–5. Enantioselective alkylation catalyzed by protonic auxiliary HX^* . M = Metallic species; X^* = chiral heteroatom ligand.

To get high enantioselectivity:

- 1) Control the competitive pathway**
- 2) Release the chiral auxiliary for the next catalytic cycle**

3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION

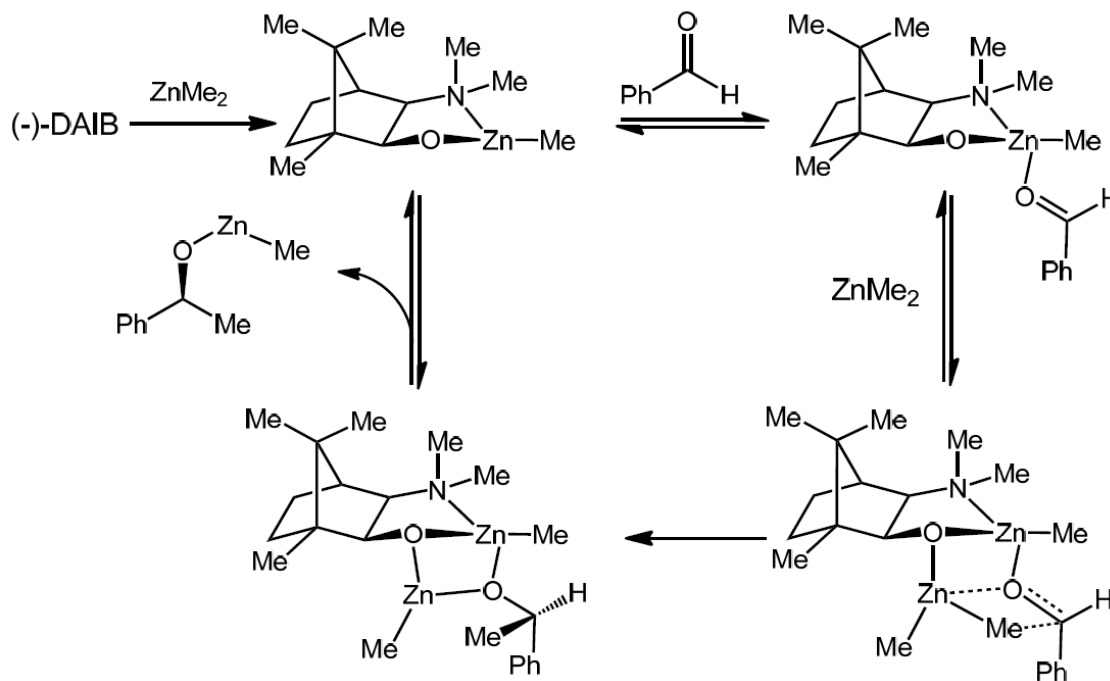
Noyori, 1986



Scheme 2-43

2.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION

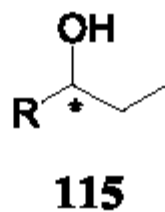
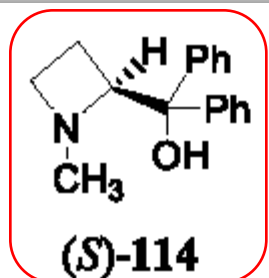
Mechanism



- 配体中通常有酸性氢和锌试剂反应形成锌络合物
- 手性放大、自催化

Noyori, R.; Kitamura, M. *ACIE* **1991**, *30*, 49.

3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION

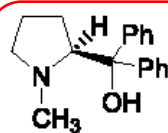
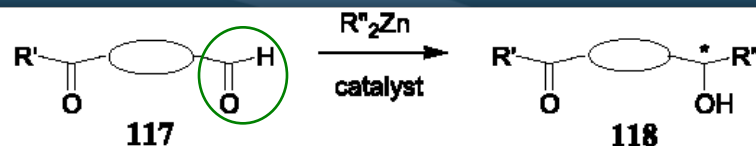


R	Ph	4-Cl-Ph	2-MeO-Ph	4-MeO-Ph	4-Me-Ph	(<i>E</i>)-PhCH=CH
ee (%)	98%	100%	94%	100%	99%	80%
config.	<i>S</i>	<i>S</i>	<i>S</i>	<i>S</i>	<i>S</i>	<i>S</i>

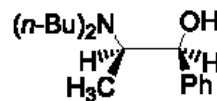
Scheme 2-44

3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION

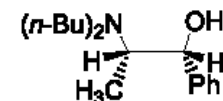
chemoselectivity



(S) -(+)-119



$(1S, 2R)$ -(-)-120

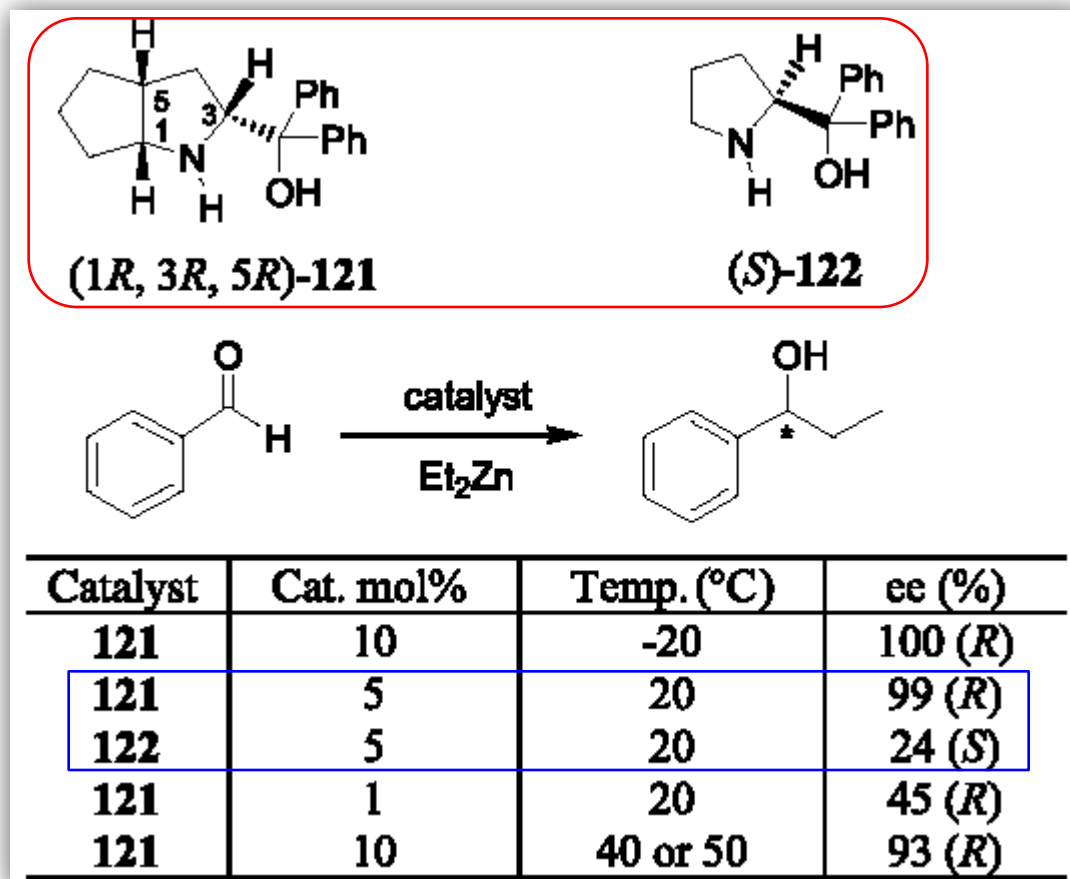


$(1R, 2S)$ -(+)-120

Entry	R_2Zn	Substrate	Catalyst	ee (%)
1	Et_2Zn		(S) -119	93
2	Et_2Zn		$(1S, 2R)$ -120	91
3	$(n-Bu)_2Zn$		(S) -119	92
4	Et_2Zn		$(1S, 2R)$ -120	87
5	Et_2Zn		$(1R, 2S)$ -120	85
6	Et_2Zn		$(1S, 2R)$ -120	81
7	Et_2Zn		(S) -119	88

Scheme 2-46. Chemo- and enantioselective alkylation of ketoaldehydes.

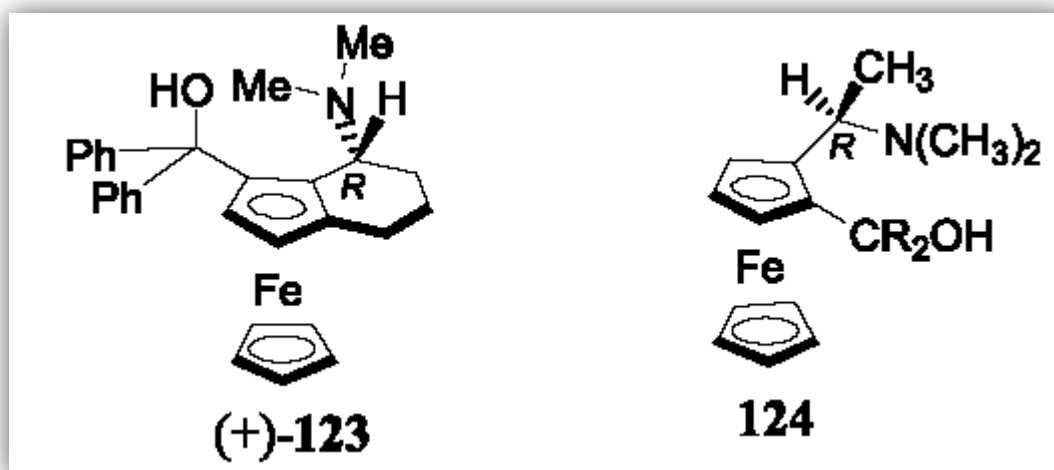
3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION



Scheme 2-47. Application of a new bicyclic catalyst.

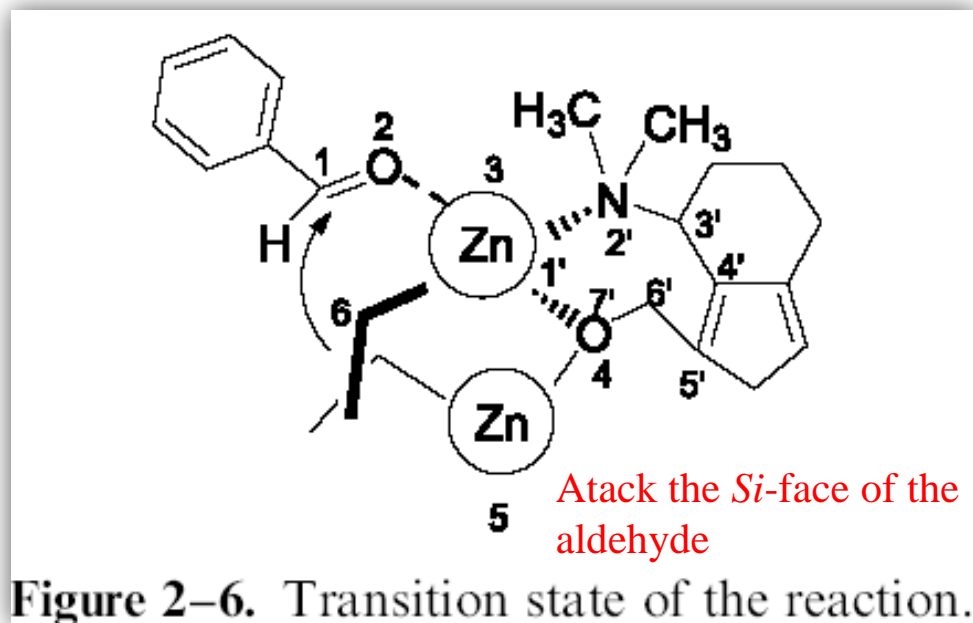
3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION

Schlögl



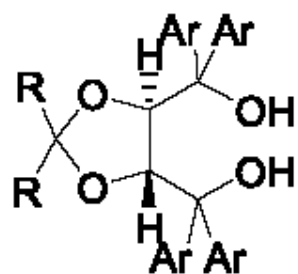
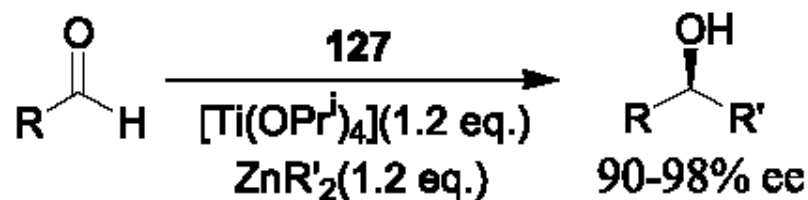
3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION

Noyori & Butsugan, 双中心催化体系或双金属催化剂



3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION

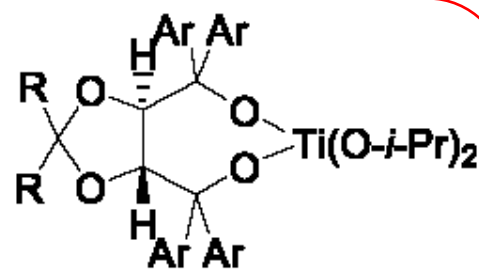
Seebach



TADDOL

104: R = Me, Ar = Ph,

126: R = Me, Ar = 2-naphthyl



127

Scheme 2-49. TADDOL and its analogs as titanium ligands in enantioselective addition of diethylzinc reagents to benzaldehyde.

3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION

Seebach

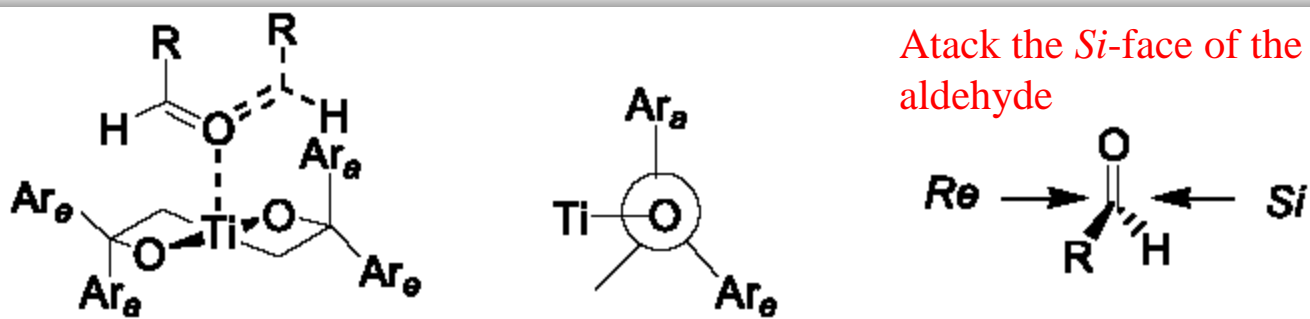
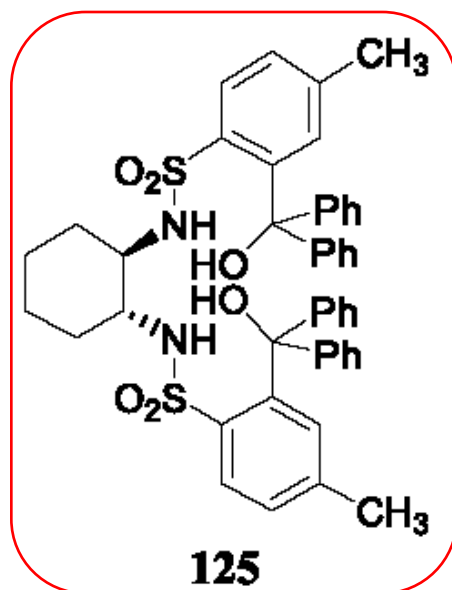
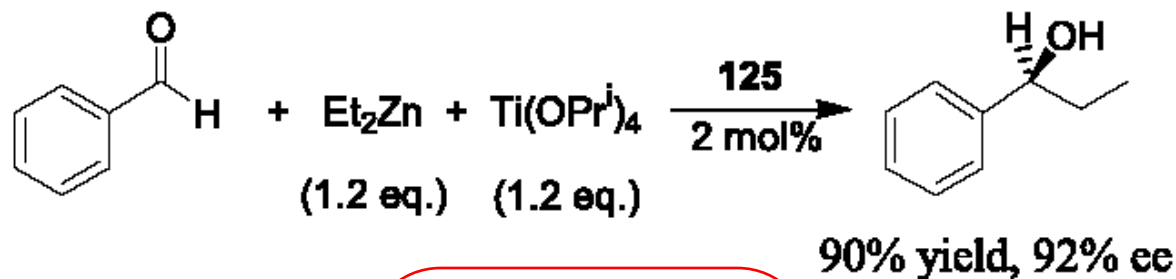


Figure 2–7. The role of $[Ti(OR^i)_4]$ in dialkylzinc addition reactions. The dioxolane in the rear is deleted for clarity.

3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION

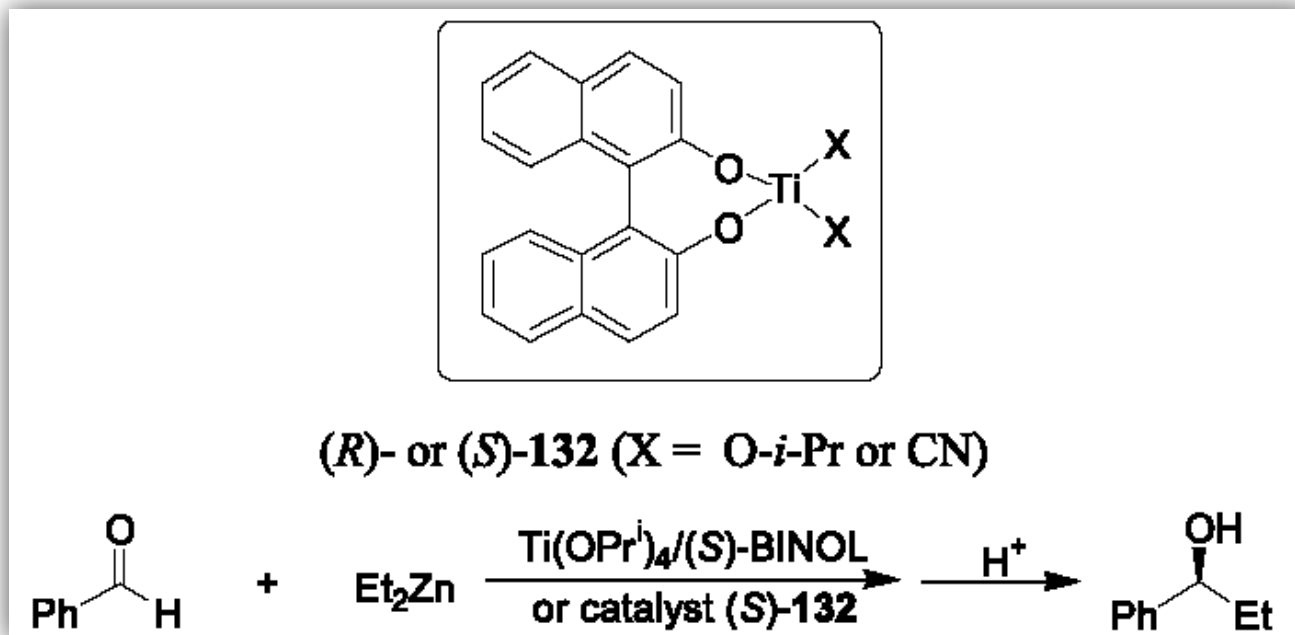
Walsh



Scheme 2-48

3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION

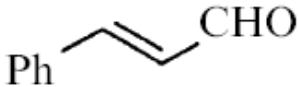
Chan & Nakai



3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION

Chan & Nakai

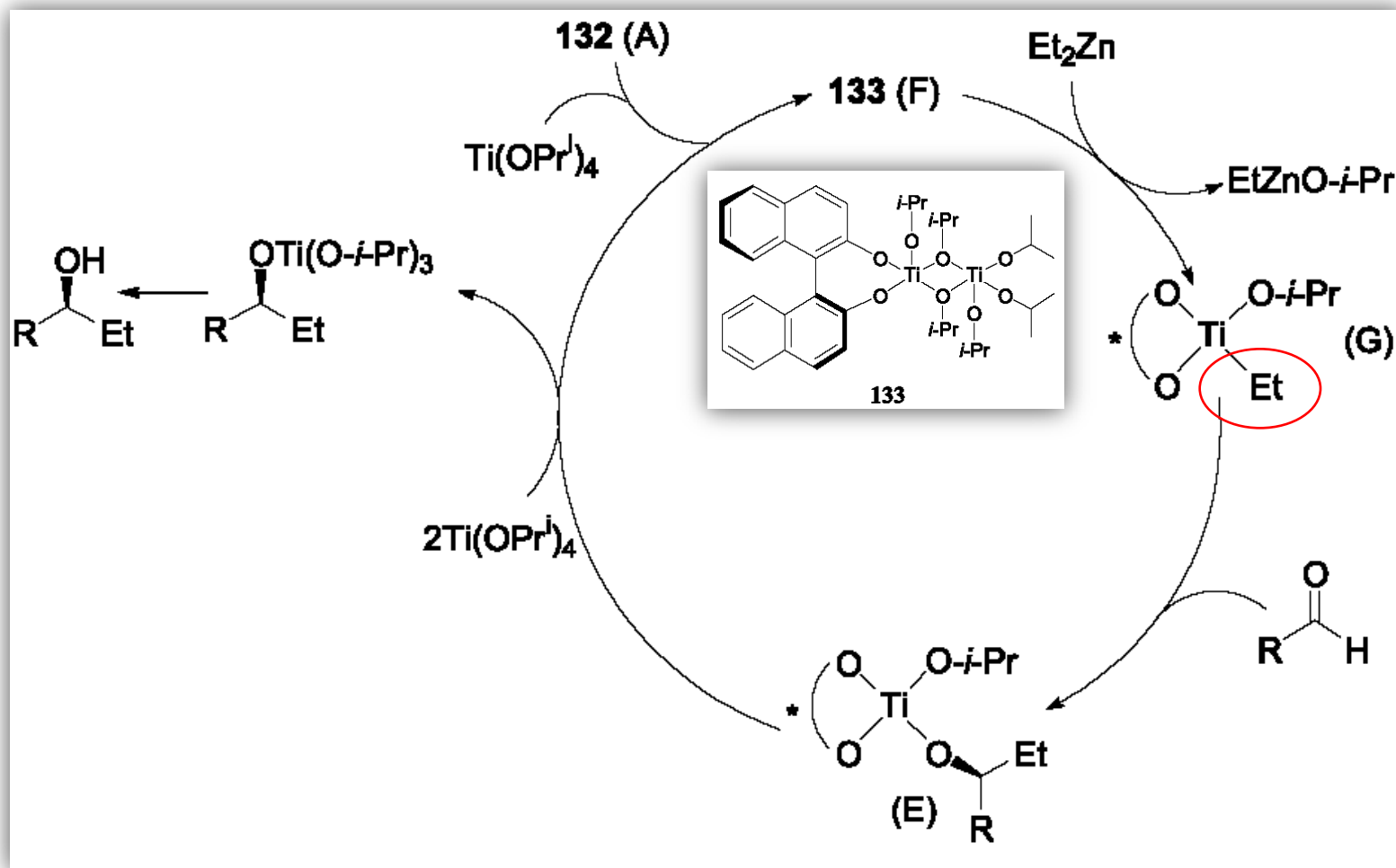
TABLE 2–14. Asymmetric Alkylation of Aromatic and Aliphatic Aldehydes

Entry	Aldehyde	BINOL	Condition	Yield (%)	ee (%)
1	PhCHO	0.2	0°C, 20 min	100 (conversion)	91.9 (<i>S</i>)
2	2-Naph-CHO	0.2	0°C, 20 min	100 (conversion)	93.6 (<i>S</i>)
3	<i>m</i> -MeOPhCHO	0.2	0°C, 20 min	100 (conversion)	94 (<i>S</i>)
4	<i>m</i> -ClPhCHO	0.2	0°C, 20 min	98.7 (conversion)	88.2 (<i>S</i>)
5	<i>n</i> -C ₈ H ₁₇ CHO	0.2	–30°C, 40 h	94	86 (<i>S</i>)
6	<i>n</i> -C ₆ H ₁₃ CHO	0.2	–30°C, 40 h	75	85 (<i>S</i>)
7		0.2	0°C, 1 h	97	82 (<i>S</i>)
8	TMS—≡—CHO	0.2	0°C, 1 h	>98	56 (<i>S</i>)
9	TBS—≡—CHO	0.2	0°C, 1 h	>98	79 (<i>S</i>)

ee = Enantiomeric excess.

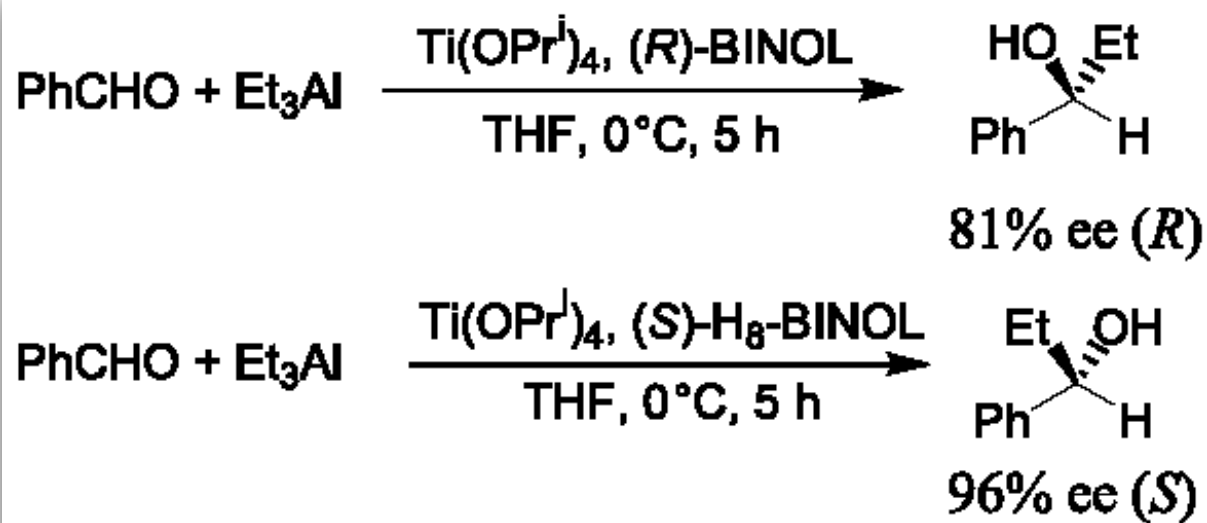
3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION

Nakai



Scheme 2-51

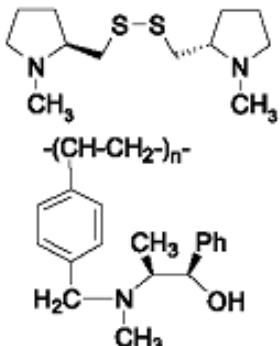
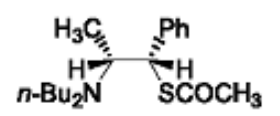
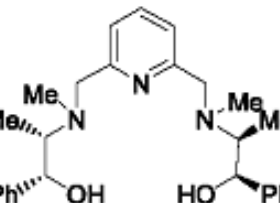
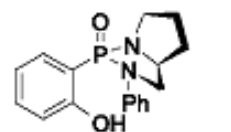
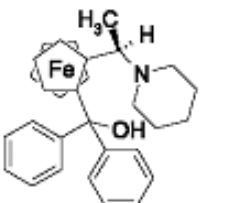
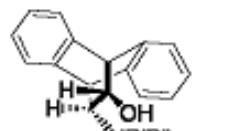
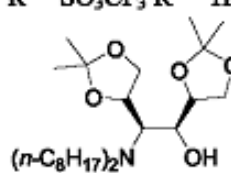
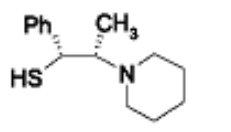
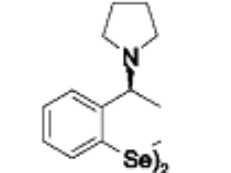
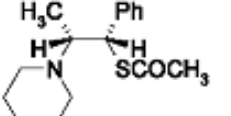
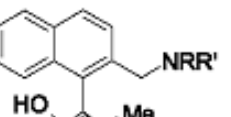
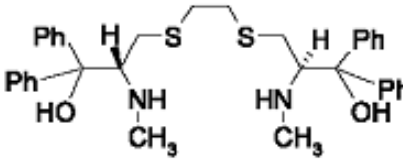
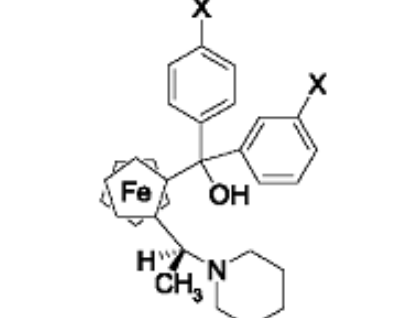
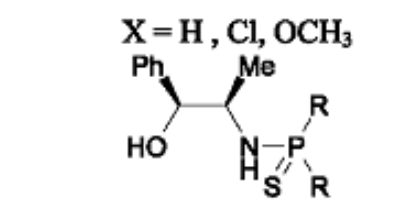
3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION



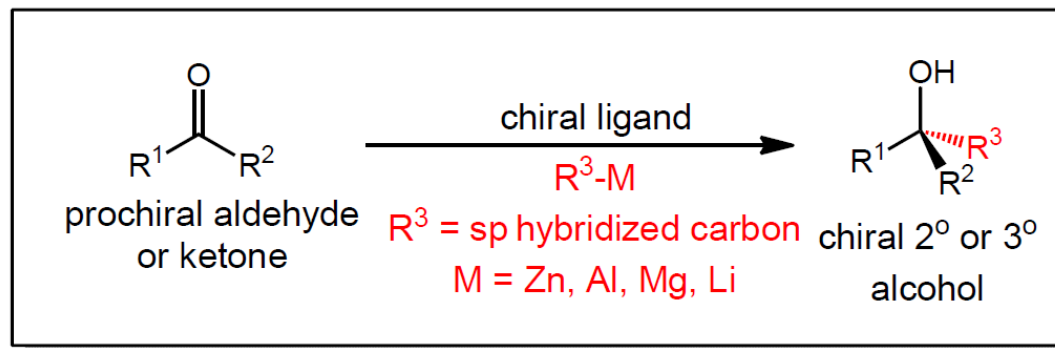
Scheme 2–52

3.2 CHIRAL CATALYST-INDUCED ALDEHYDE ALKYLATION: ASYMMETRIC NUCLEOPHILIC ADDITION

TABLE 2–15. Newly Developed Ligands for Alkylation Reactions

Chiral Auxiliary	Chiral Auxiliary	Chiral Auxiliary	Chiral Auxiliary
 $-(\text{CH}-\text{CH}_2)_n-$  	   $\text{R}' = \text{R}'' = \text{Me}$ $\text{R}' = \text{SO}_3\text{CF}_3$ $\text{R}'' = \text{H}$  $(n\text{-C}_8\text{H}_{17})_2\text{N}$	    $\text{R} = \text{H}, \text{R}' = \text{Me}$ $\text{R} = \text{R}' = \text{Me}$ $\text{R} = \text{R}' = n\text{-Bu}$	  $\text{X} = \text{H}, \text{Cl}, \text{OCH}_3$ 

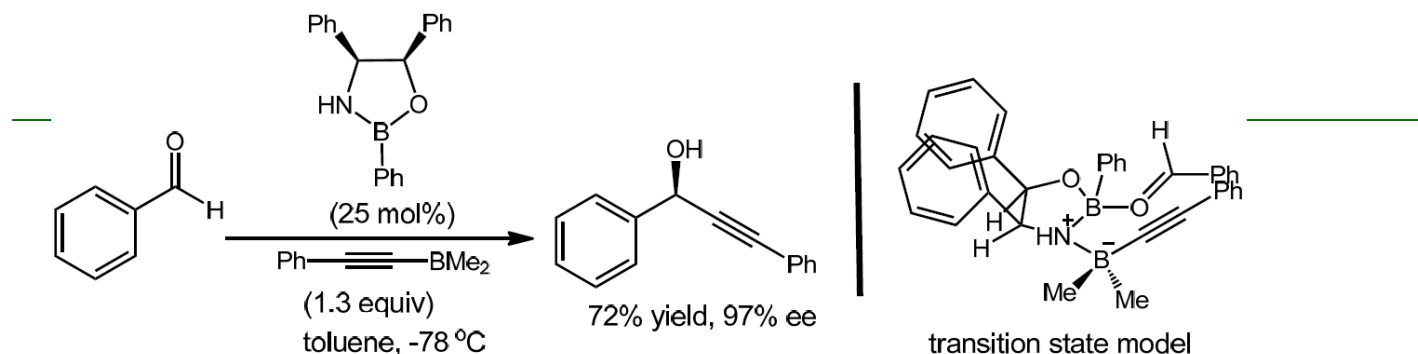
3.3 Addition of sp C-Nucleophiles to C=O



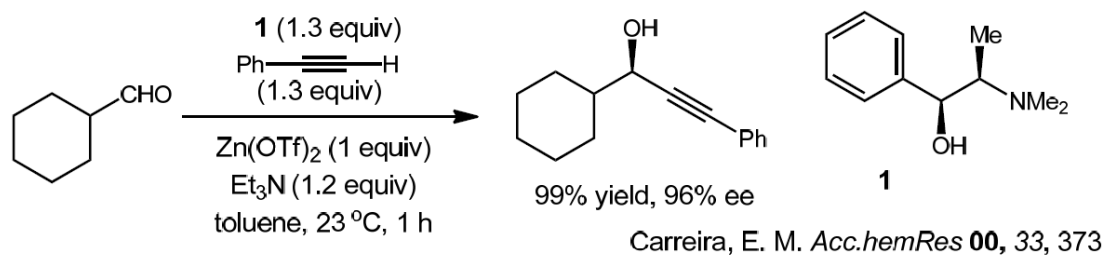
- 1、 Alkynylmetal reagents generally start with terminal alkynes which undergo metalation ($\text{pK}_a \sim 25$) with strong bases such as *n*-BuLi, EtMgBr, LHMDS, etc.
- 2、 The acidity of the C(sp)-H bond in terminal alkynes can be significantly increased in the presence of Cu(I) or Ag(I)
- 3、 Alkynylzinc reagents react only slowly with aldehydes and ketones in the absence of a Lewis base.

Reviews: (a) *Tetrahedron* **2003**, *59*, 9873. (b) *Chem. Rev.* **2008**, *108*, 2853. (c) *Adv. Synth. Catal.* **2009**, *351*, 963.

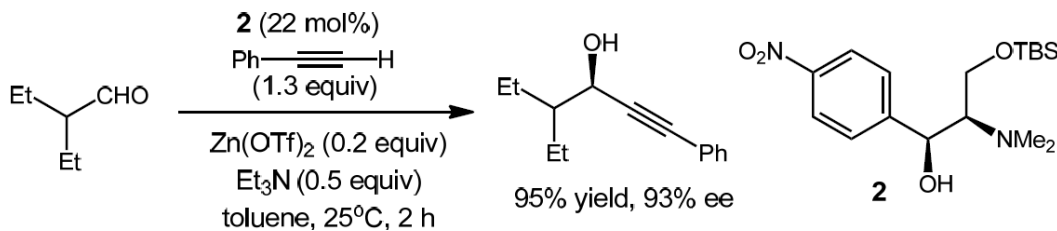
3.3 Addition of sp C-Nucleophiles to C=O



Corey *JACS* **94**, 116, 3151



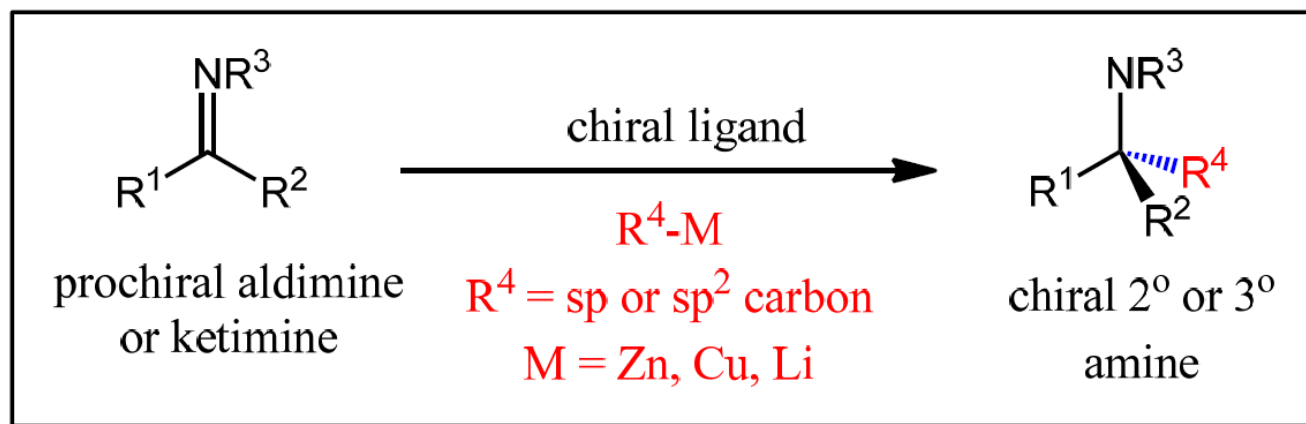
Carreira, E. M. *Acc.hemRes* **00**, 33, 373



Jiang, B. *CC* **02**, 1524 & 2098 ($\text{Zn}(\text{ODf})_2$)

Aromatic aldehydes are difficult substrates since they undergo the Cannizzaro reaction under base reaction conditions!

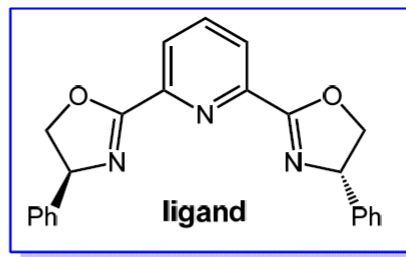
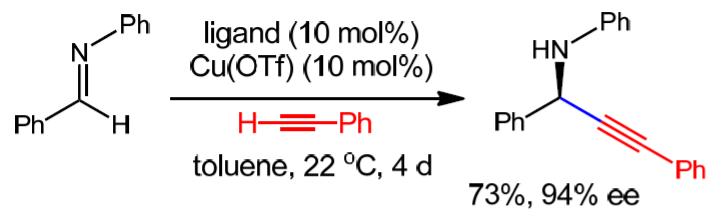
3.4 Addition of sp and sp^2 C-Nucleophiles to $C=N$



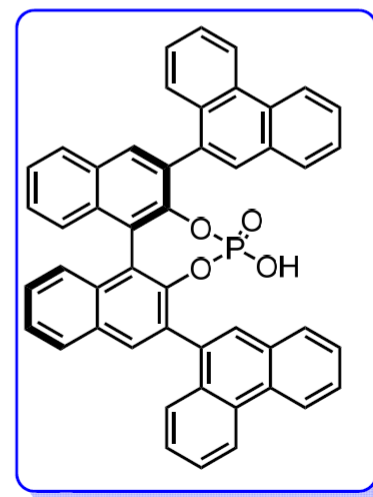
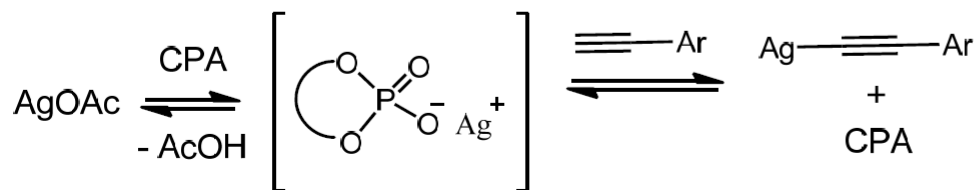
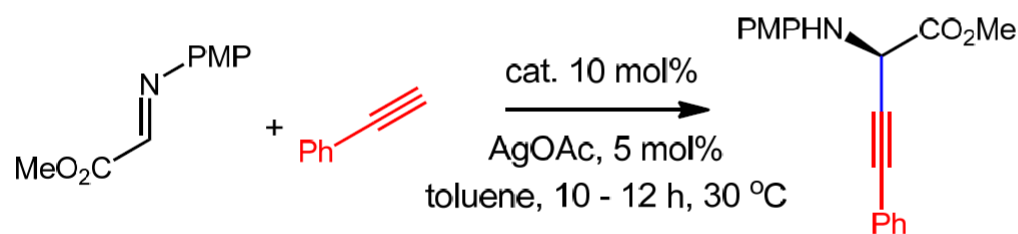
Reviews for imine alkynylation, alkenylation, arylation:

1. (a) *Eur. J. Org. Chem.* **2004**, 4095; (b) *Chem. Commun.* **2006**, 4263; (c) *Curr. Org. Chem.* **2009**, 13, 1498
2. (a) *Top. Curr. Chem.* **2007**, 279, 77; (b) *Acc. Chem. Res.* **2007**, 40, 1394.
3. (a) *Chem. Rev.* **2008**, 108, 2903; (b) *Chem. Soc. Rev.* **2009**, 38, 2190.

3.4 Addition of sp and sp^2 C-Nucleophiles to $C=N$



Li, C.-J. *JACS* **02**, 638.

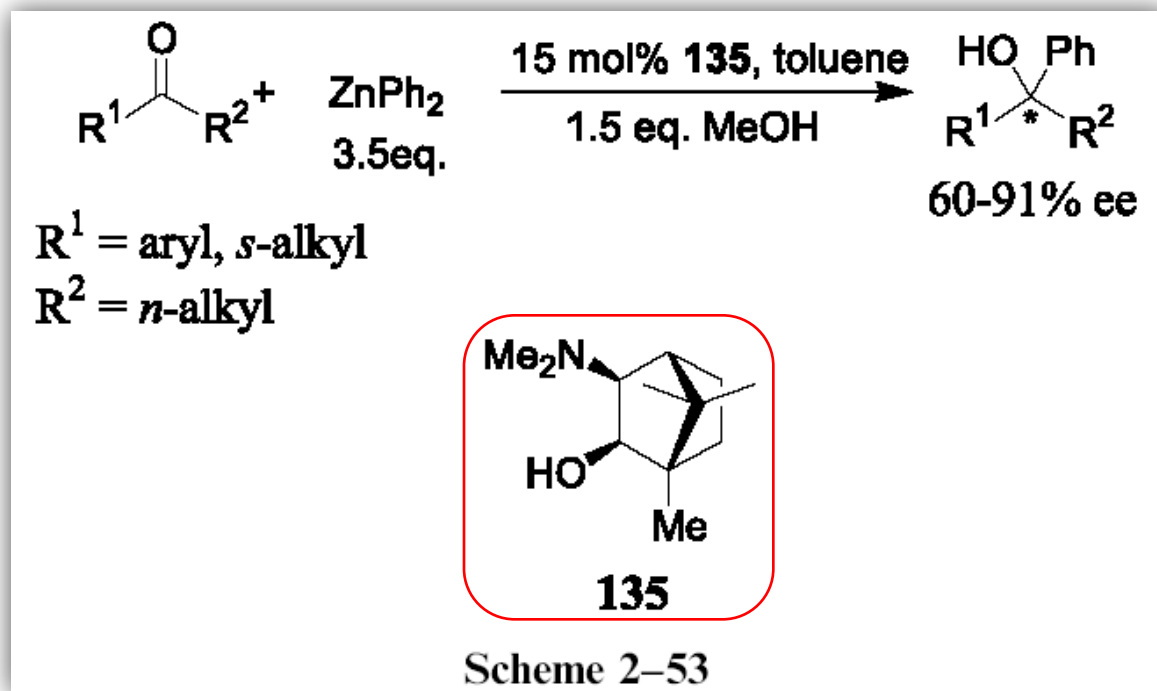


Rueping, M., *ACIE* **07**, 6903.

3.5 CATALYTIC ASYMMETRIC ADDITIONS OF DIALKYLZINC TO KETONES: ENANTIOSELECTIVE FORMATION OF TERTIARY ALCOHOLS

More challenging substrates: ketones

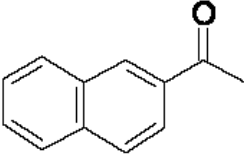
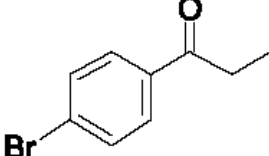
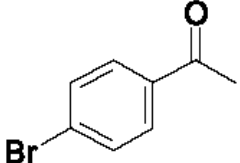
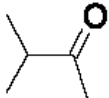
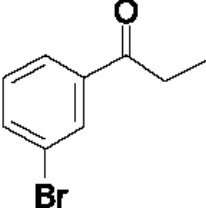
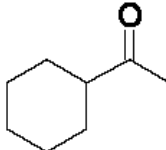
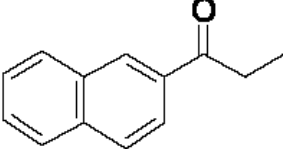
Fu, G. C.



3.5 CATALYTIC ASYMMETRIC ADDITIONS OF DIALKYLZINC TO KETONES: ENANTIOSELECTIVE FORMATION OF TERTIARY ALCOHOLS

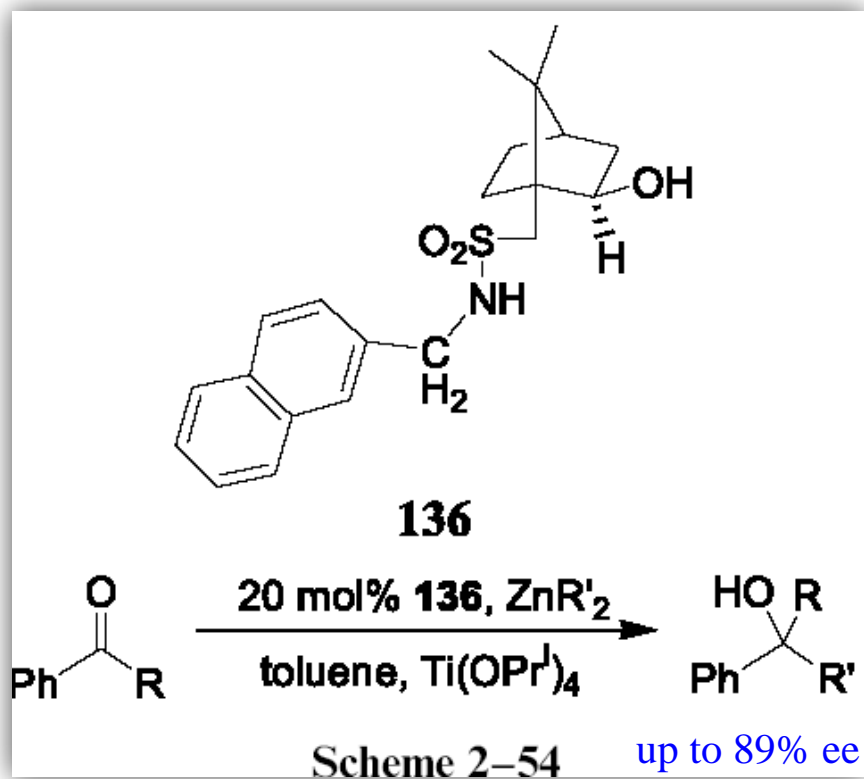
Fu, G. C.

TABLE 2-16. Enantioselective Alkylation of Ketones

Entry	Substrate	ee (%)	Yield (%)	Entry	Substrate	ee (%)	Yield (%)
1		72 (+)-(R)-	58	5		90 (-)-	83
2		80 (-)-	53	6		60 (+)-	63
3		91 (-)-	91	7		75 (+)-	76
4		86 (-)-(R)-	79				

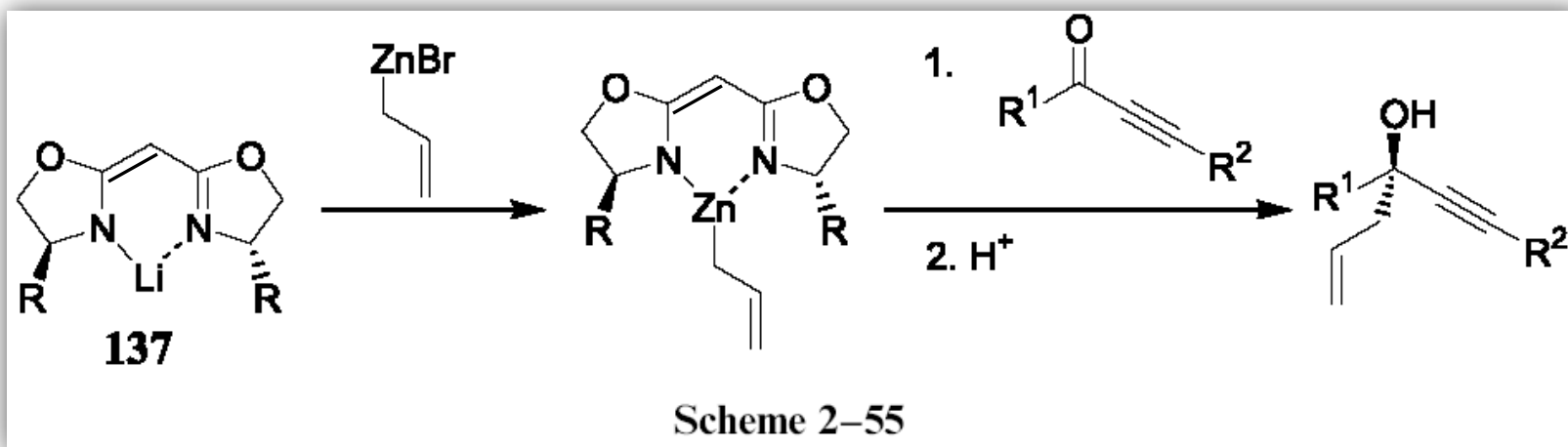
3.5 CATALYTIC ASYMMETRIC ADDITIONS OF DIALKYLZINC TO KETONES: ENANTIOSELECTIVE FORMATION OF TERTIARY ALCOHOLS

Ramón

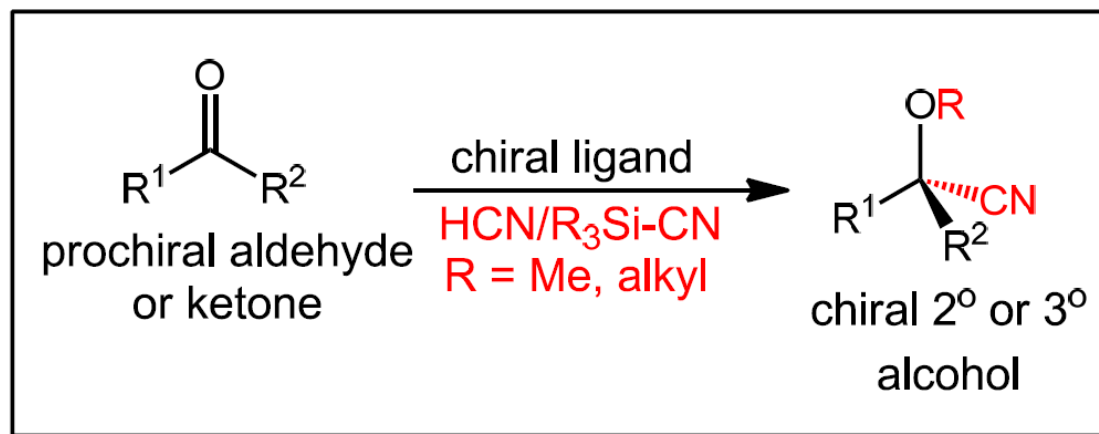


3.5 CATALYTIC ASYMMETRIC ADDITIONS OF DIALKYLZINC TO KETONES: ENANTIOSELECTIVE FORMATION OF TERTIARY ALCOHOLS

Nakamura



3.6 ASYMMETRIC CYANOHYDRINATION

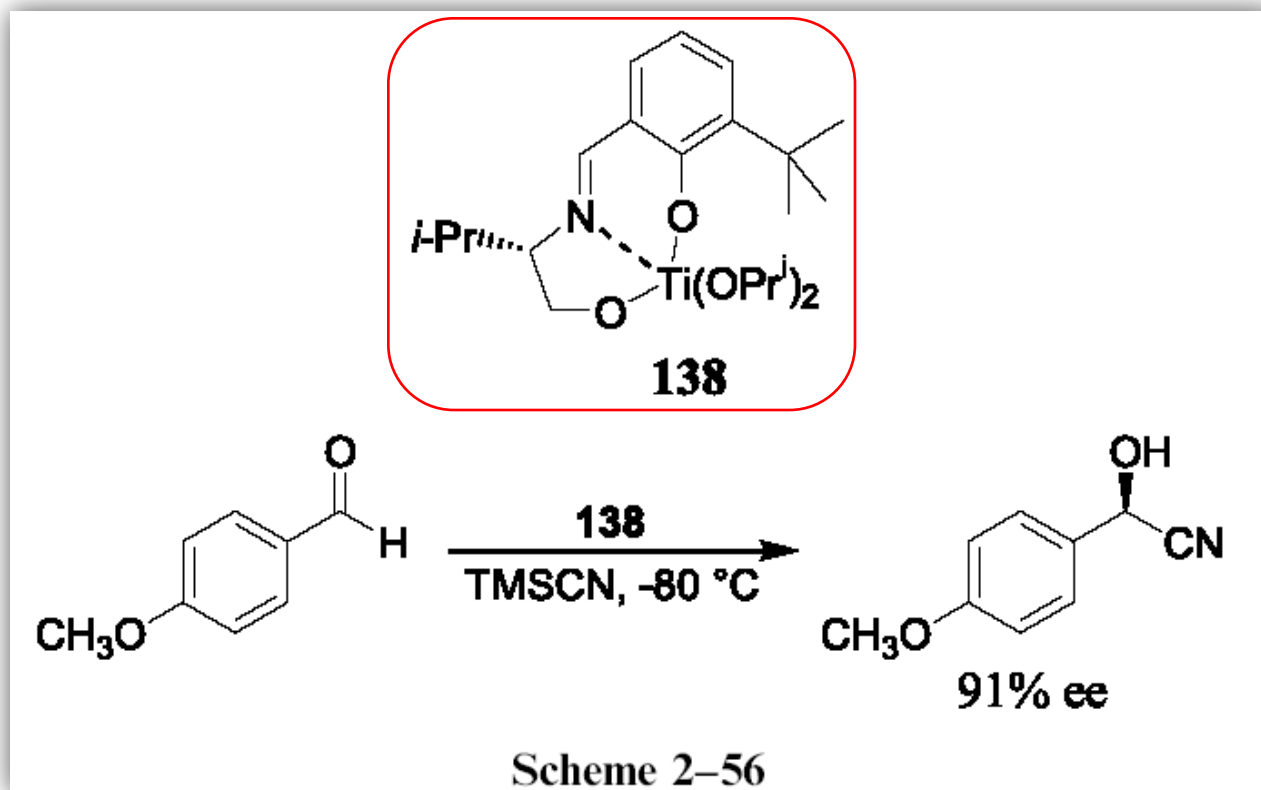


- 1、Cyanohydrin formation is readily reversible under basic conditions, it is essential to conduct enantioselective addition of HCN under irreversible conditions.
- 2、An impressive number of approaches have been described using a wide range of chiral catalysts including metal-containing and metal-free catalytic molecules.

North, M.; Usanov, D. L.; Young, C. *Chem. Rev.* 2008, 108, 5146.

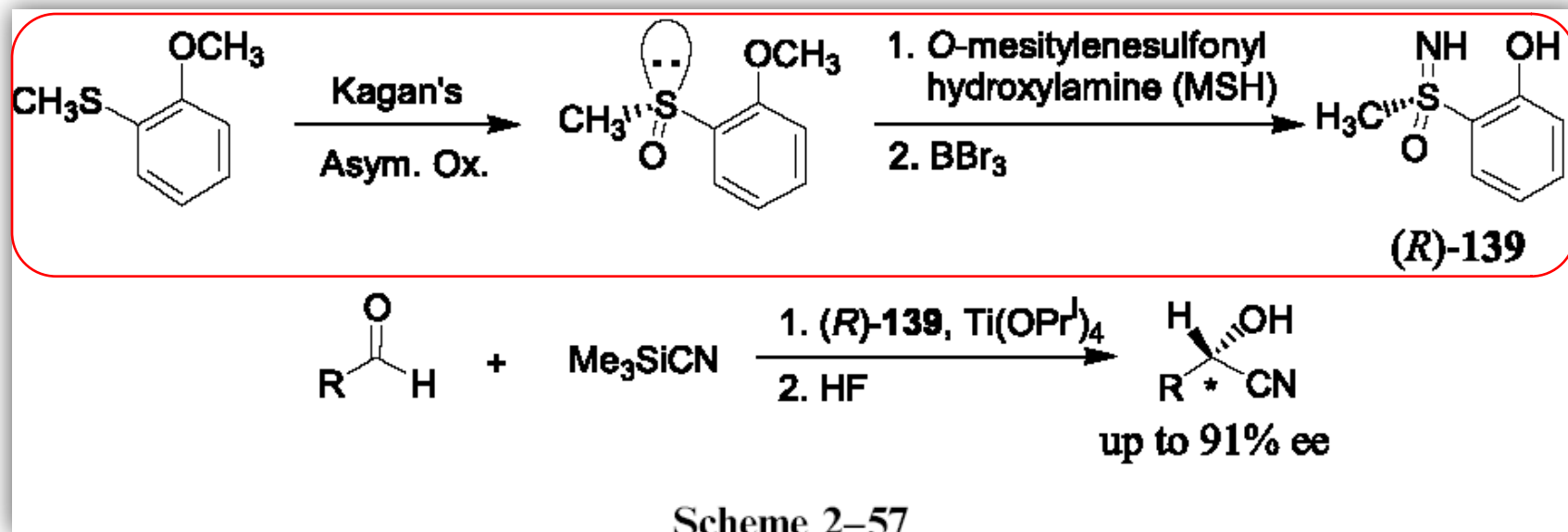
3.6 ASYMMETRIC CYANOHYDRINATION

Oguni



3.6 ASYMMETRIC CYANOHYDRINATION

Bolm



3.6 ASYMMETRIC CYANOHYDRINATION

Bolm

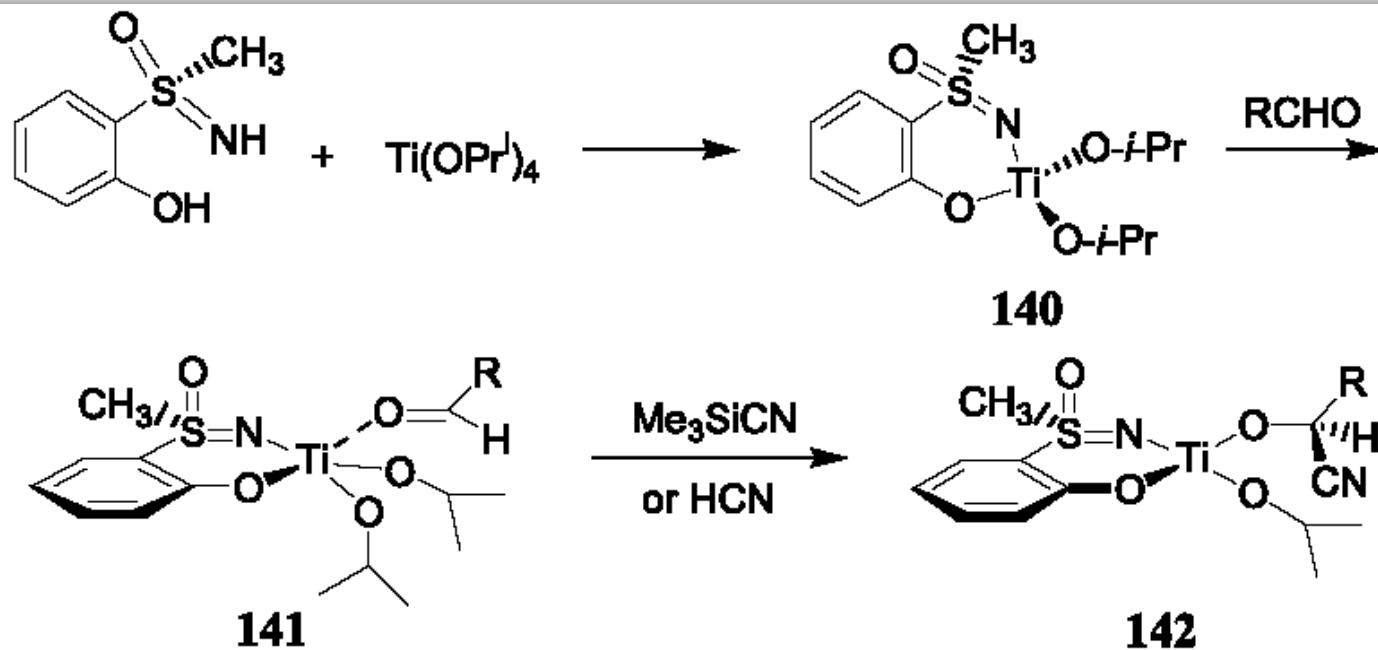
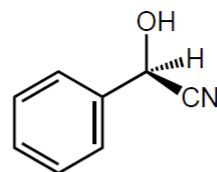
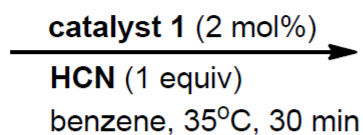
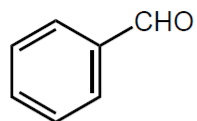


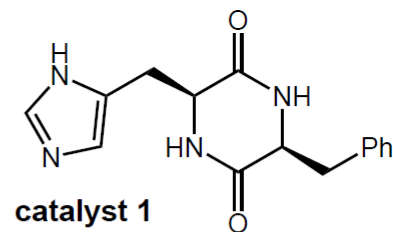
Figure 2–8. Proposed reaction mechanism for Ti(OPrⁱ)₄-mediated asymmetric silylcyanation.

3.6 ASYMMETRIC CYANOHYDRINATION

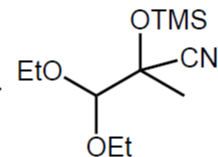
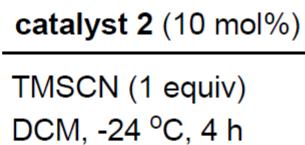
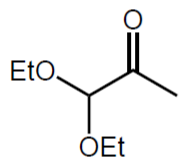
Utilizing Organocatalysts



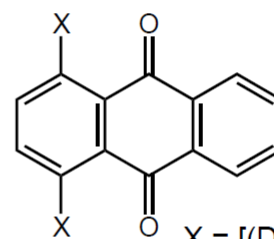
40% yield, 90% ee



JCS CC 81, 229

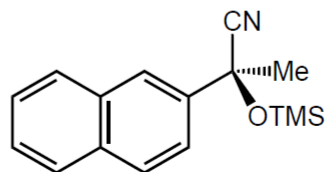
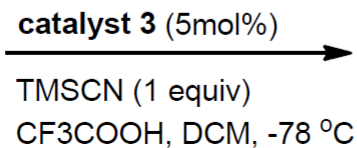
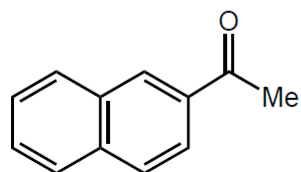


98% yield, 90% ee

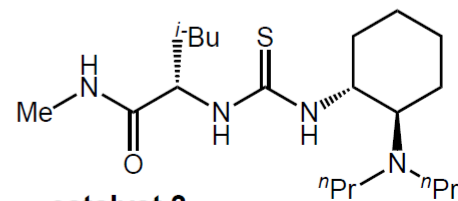


X = [(DHQ)₂-AQN]

JACS 03, 9900



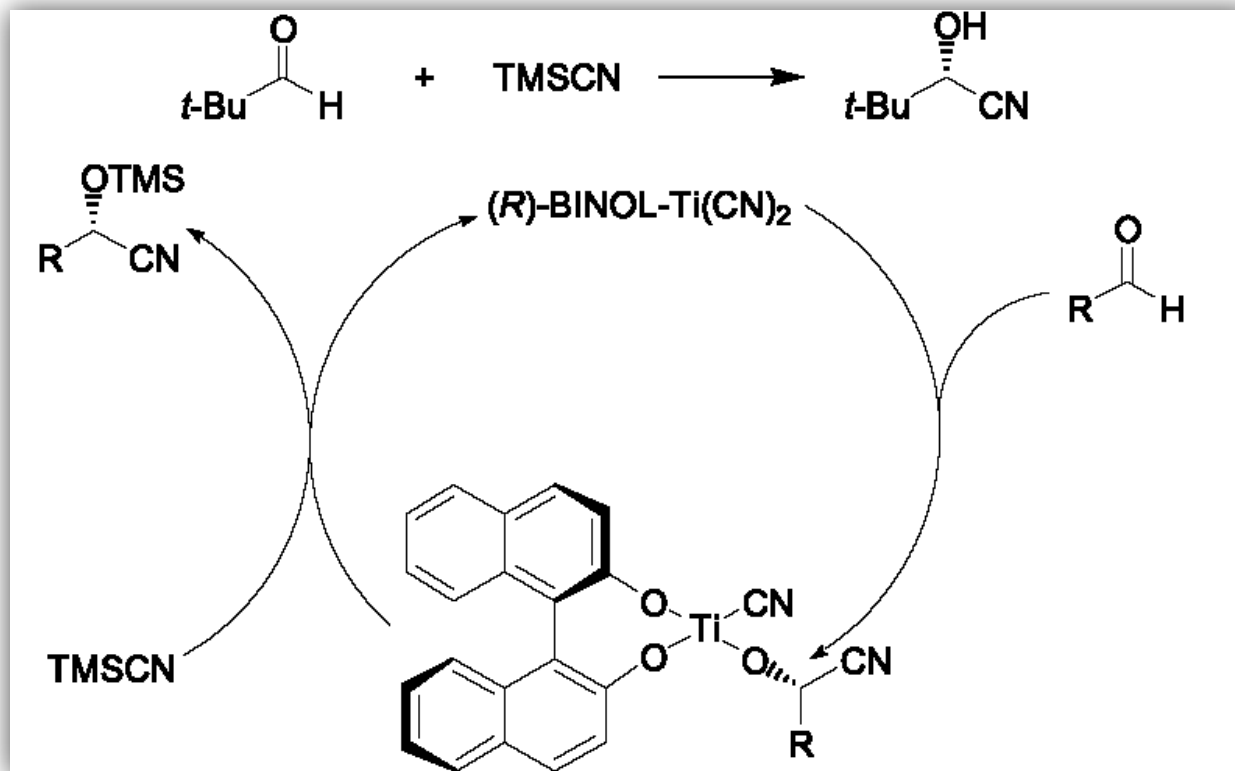
98% yield, 97% ee



JACS 05 8964

3.6 ASYMMETRIC CYANOHYDRINATION

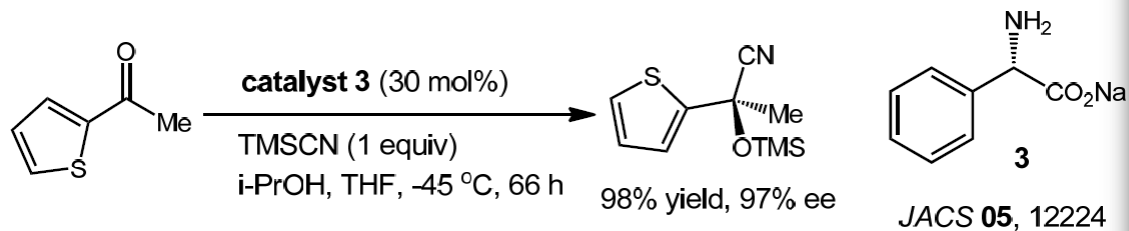
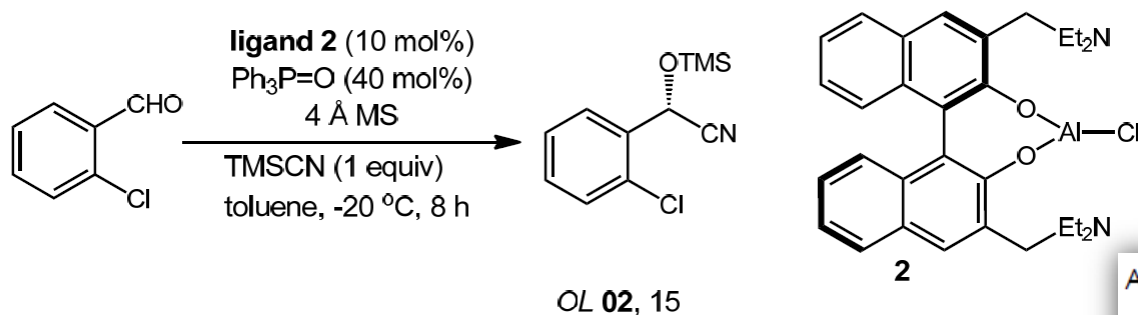
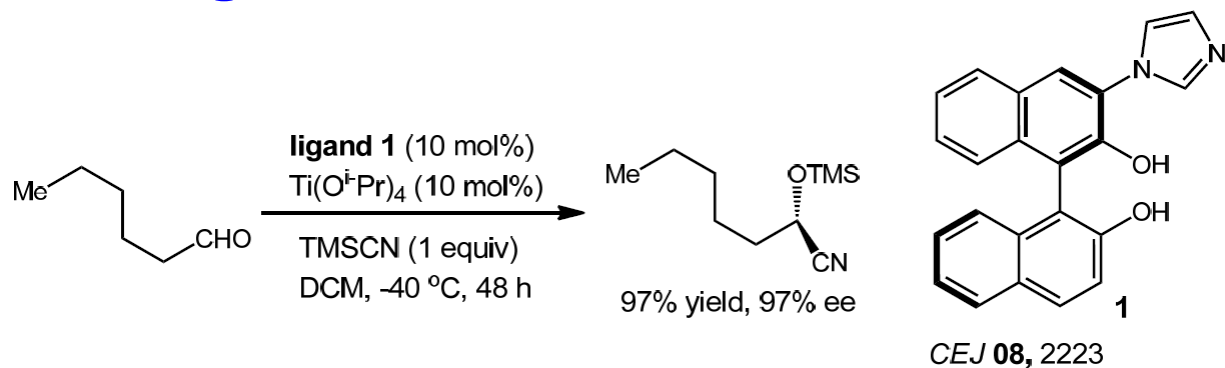
Nakai



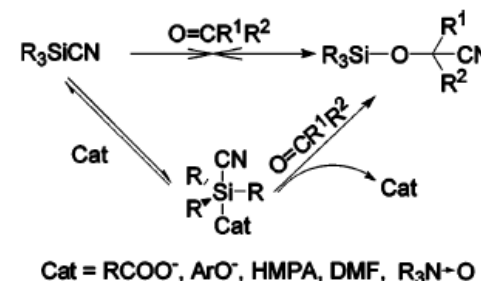
Scheme 2-58.

3.6 ASYMMETRIC CYANOHYDRINATION

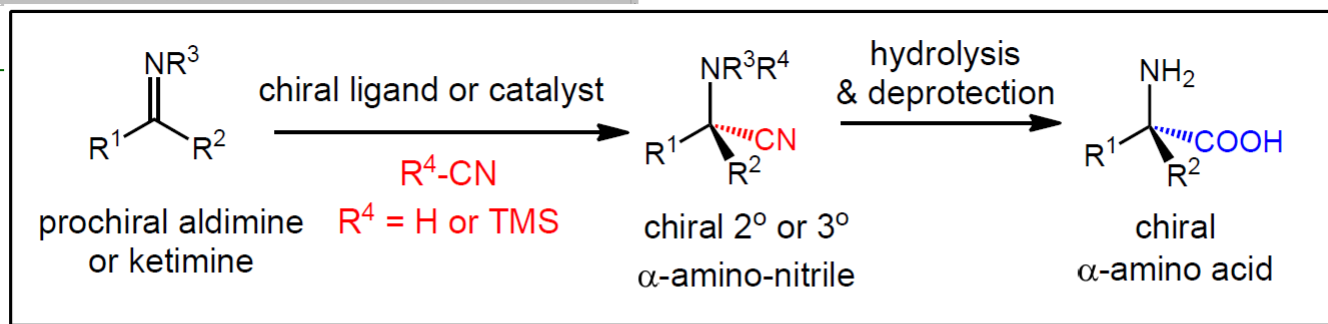
Utilizing metal-



Activation of Organosilicons by Nucleophilic Catalysts

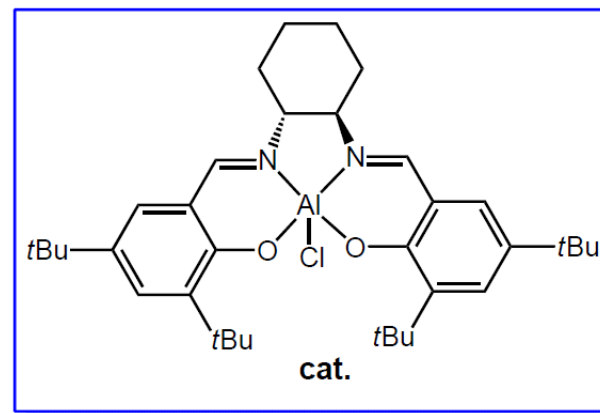
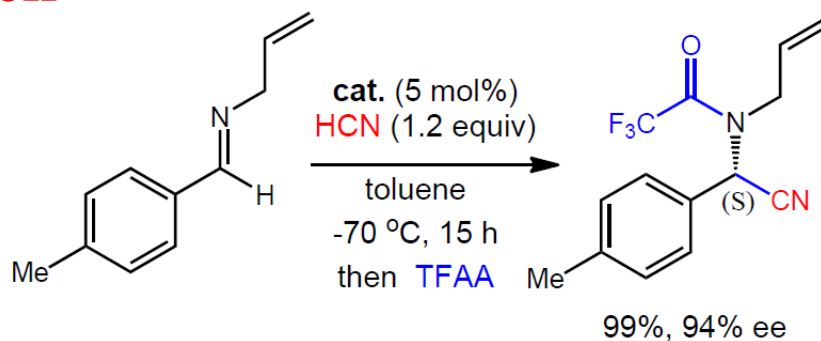


3.7 ASYMMETRIC CYANOHYDRINATION

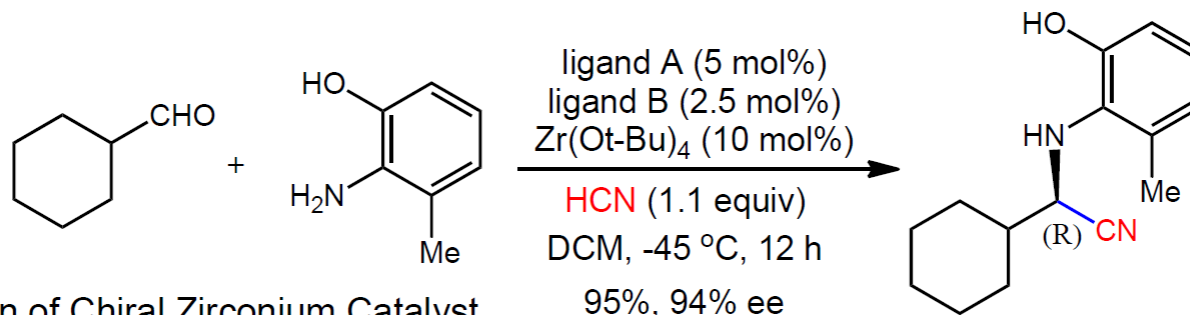


- The efficiency of cat. varies with substrates and steric properties of substituent on the imine N.
- Asymmetric Strecker rxn can be carried out as a three-component process.
- **Two types of cats:** chiral metal complexes or proton-donating chiral organic molecules

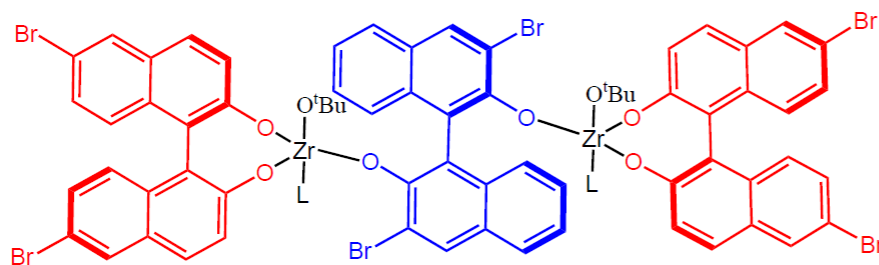
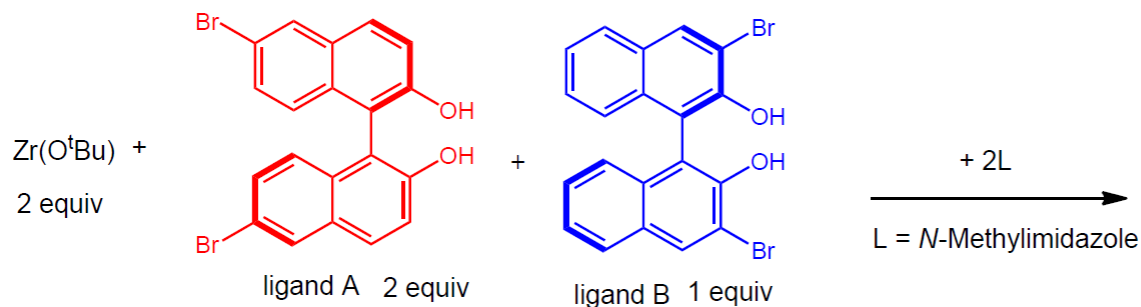
Jacobsen



3.7 ASYMMETRIC CYANOHYDRINATION



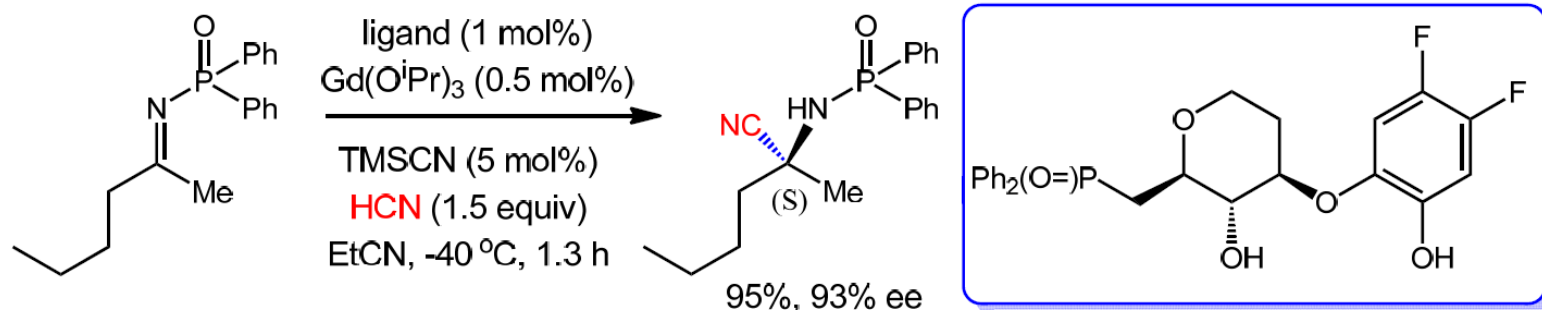
Preparation of Chiral Zirconium Catalyst



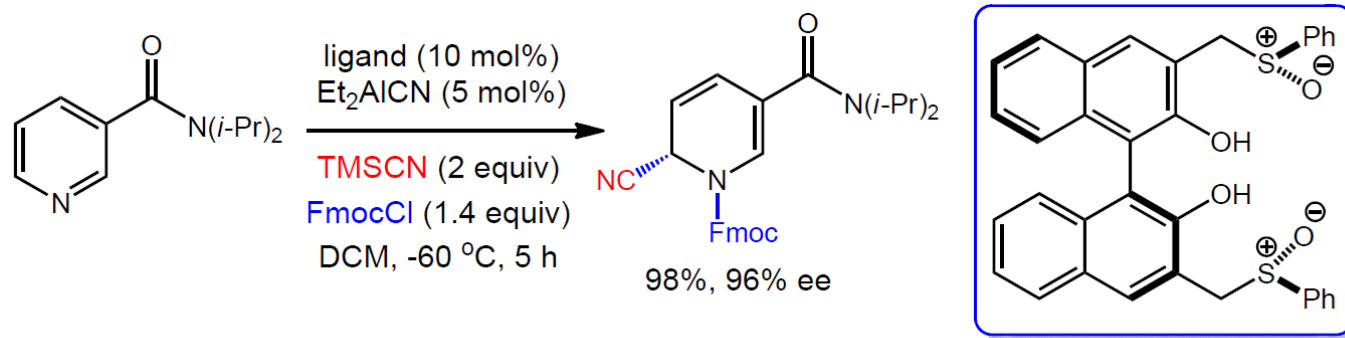
A key catalyst in
the three-component
reactions

Kabayashi, S. *JACS* **00**, 762.

3.7 ASYMMETRIC CYANOHYDRINATION



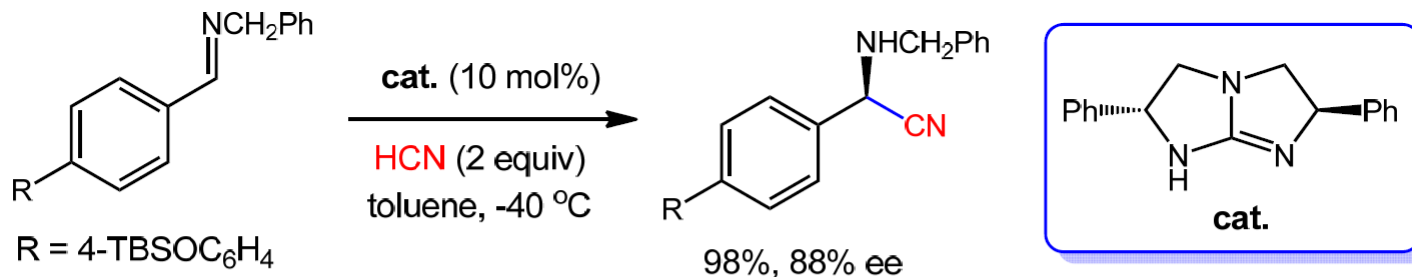
Shabasaki, M. *TL* **04**, 3147.



➤ **new Lewis acid-Lewis base asymmetric bifunctional catalysts.** Such bifunctional catalysts contain **additional chiralities on the sulfur atoms**, which might enhance the enantioselectivity if it is matched with the axial chirality of the BINOL core

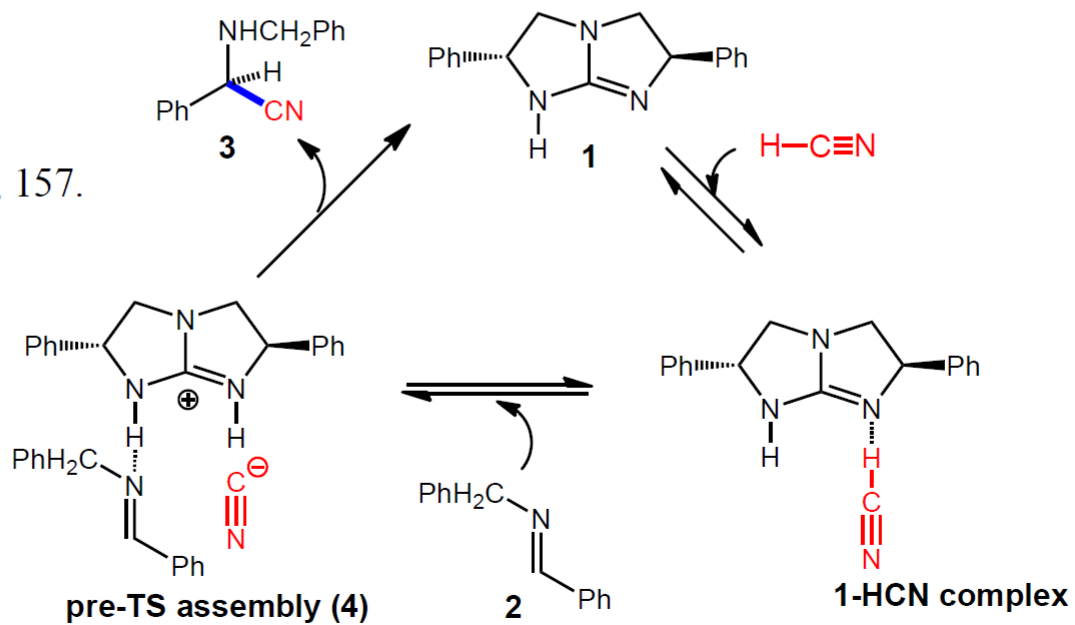
Shibasaki, M. *JACS* **04**, 11808.

3.7 ASYMMETRIC CYANOHYDRINATION

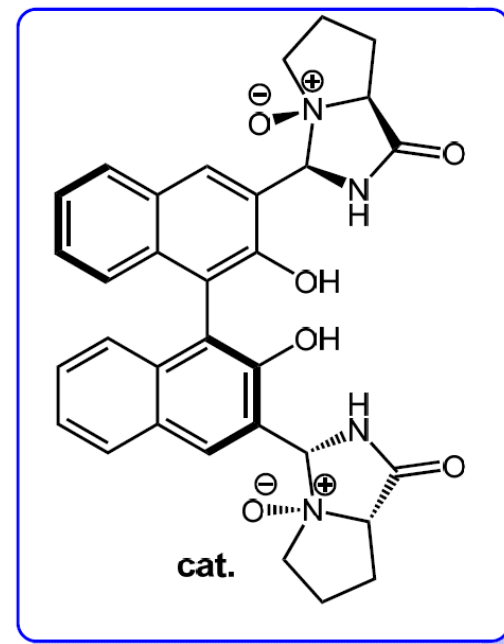
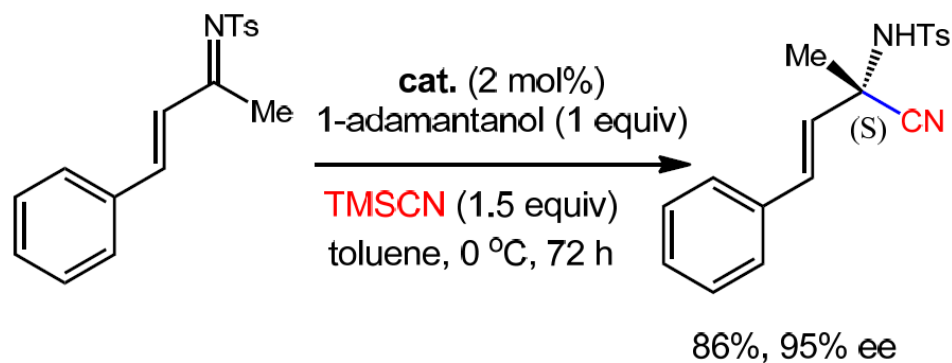


Mechanism

Corey, E. J. *OL* **99**, 157.

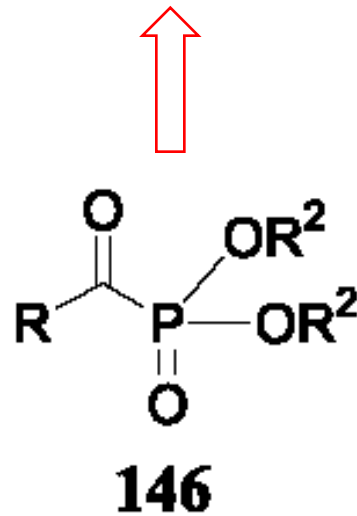


3.7 ASYMMETRIC CYANOHYDRINATION

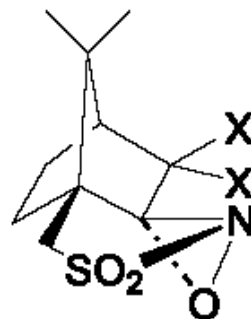
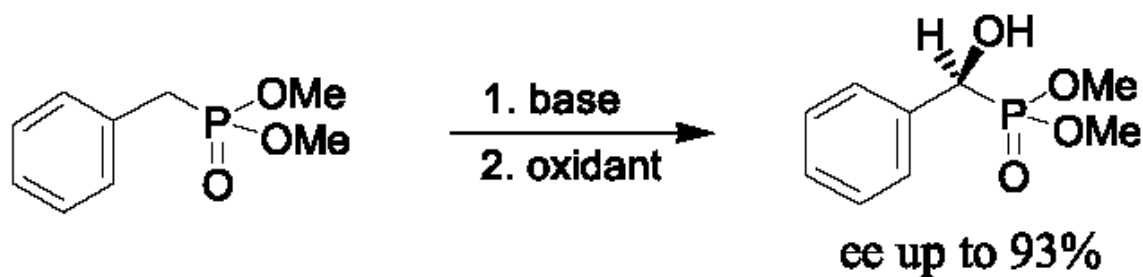


Feng, X. *CEJ* **08**, 4484.

3.8 ASYMMETRIC α -HYDROXYPHOSPHONYLATION



3.8 ASYMMETRIC α -HYDROXYPHOSPHONYLATION



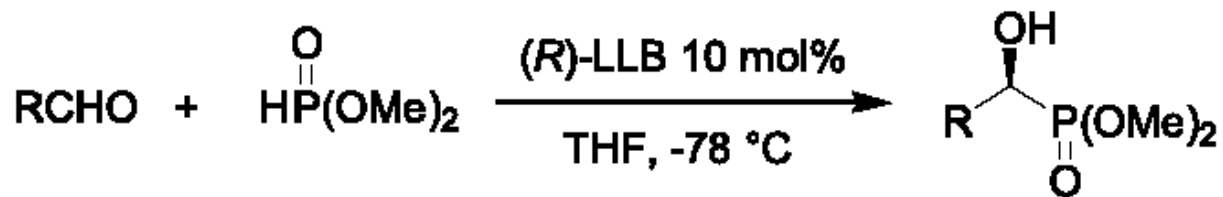
(+)-147a X = H

(+)-147b X = Cl

Scheme 2-60

3.8 ASYMMETRIC α -HYDROXYPHOSPHONYLATION

Shibasaki



Scheme 2-61

(R)-LLB: $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$ (1 eq), *(R)*-BINOL-Li (2.7 eq), NaO^tBu (0.3)

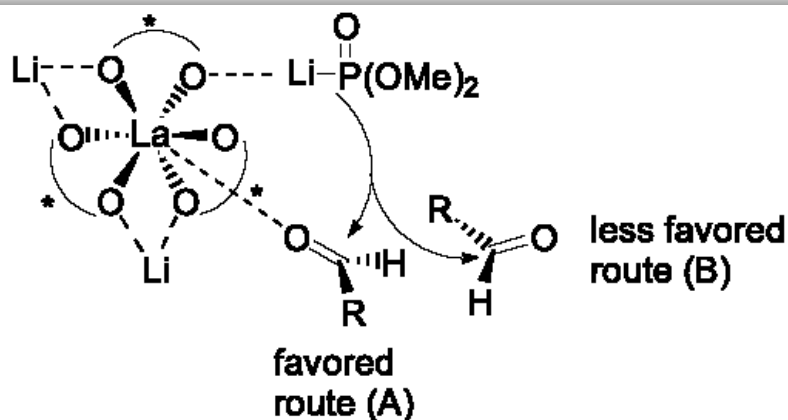
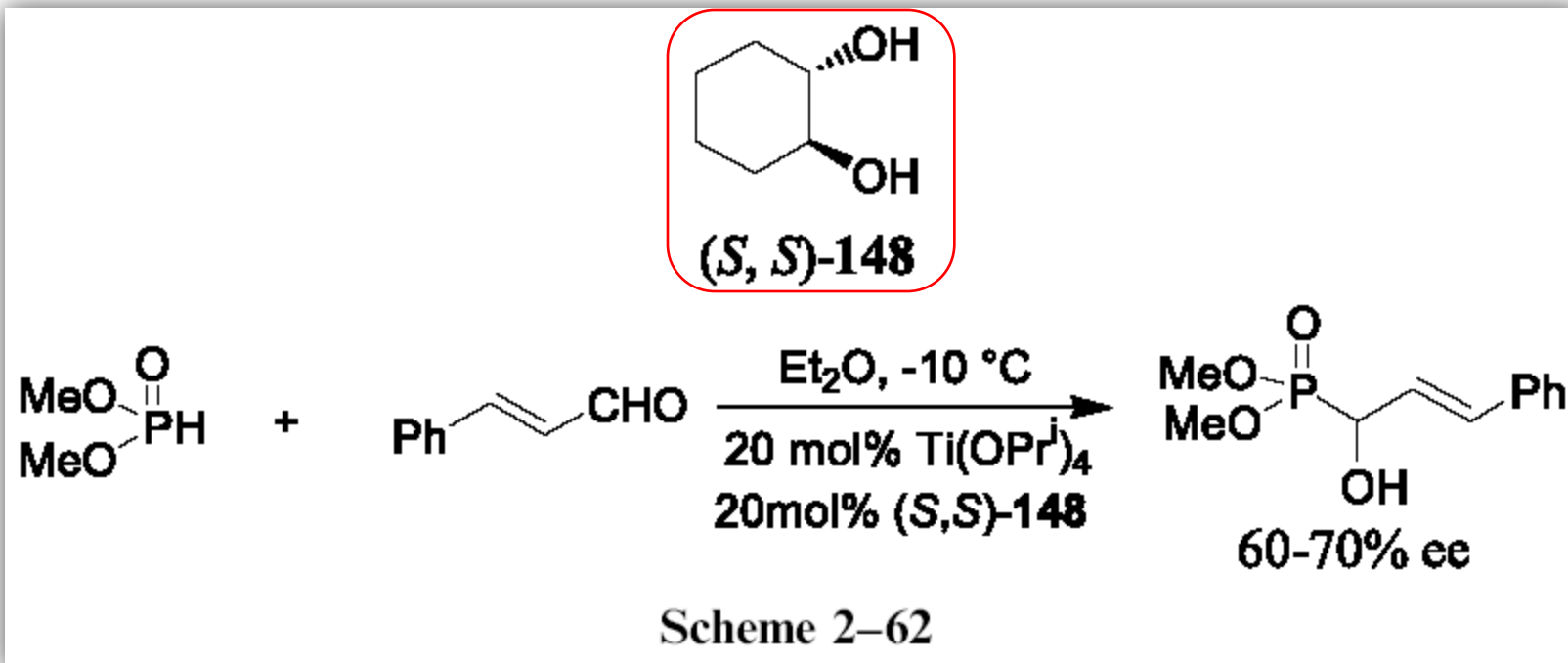


Figure 2-9. Proposed mechanism for the asymmetric hydroxyphosphonylation catalyzed by LLB.

3.8 ASYMMETRIC α -HYDROXYPHOSPHONYLATION



3.8 ASYMMETRIC α -HYDROXYPHOSPHONYLATION

