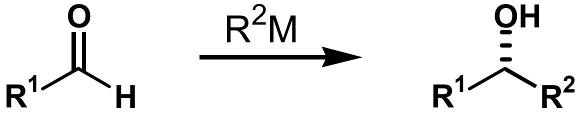
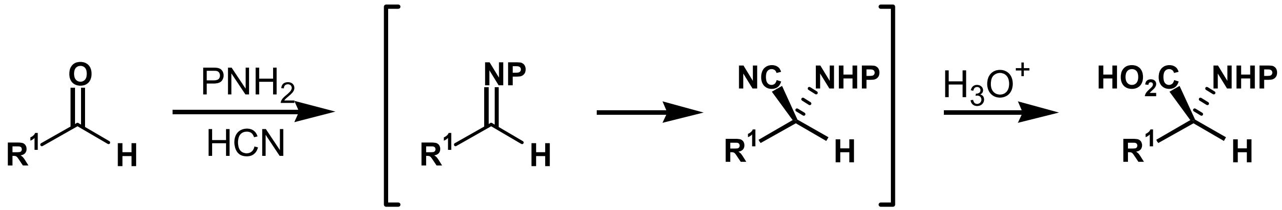
Lecture 5: Asymmetric Addition of Carbon Nucleophiles to Aldehydes, Imines and Enones

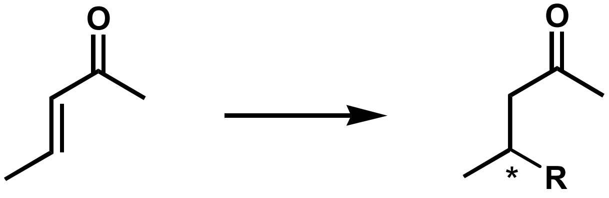
(a) Asymmetric addition to aldehydes



(b) Asymmetric addition to imines: the Strecker reaction



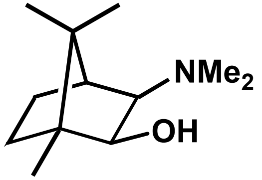
(c) Asymmetric conjugate addition



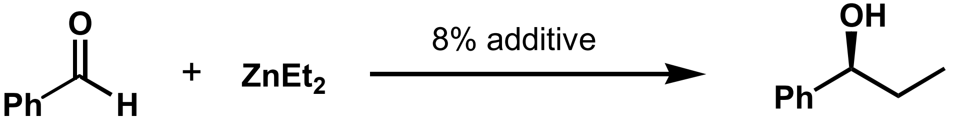
Catalytic asymmetric addition of organozincs to aldehydes

- Noyori was among the first to demonstrate the catalytic asymmetric addition of organometallics to aldehydes; requires the use of organozinc reagents which are unreactive towards aldehydes normally, but are activated in the presence of amino alcohols:

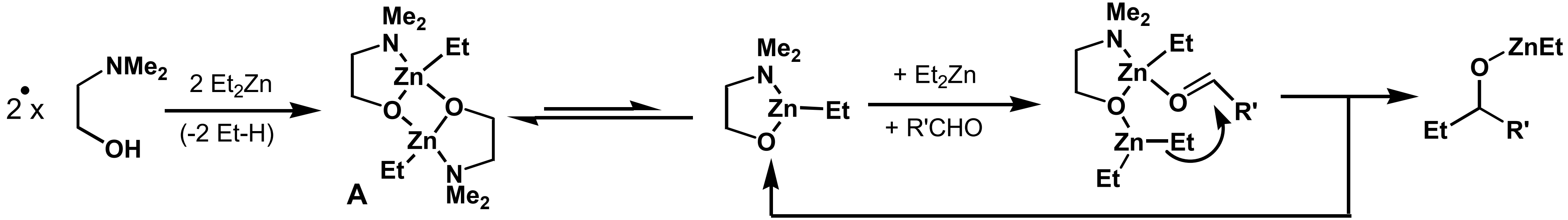
additive:



(-)-DAIB
(3-*exo*-(dimethylamino)isoborneol)



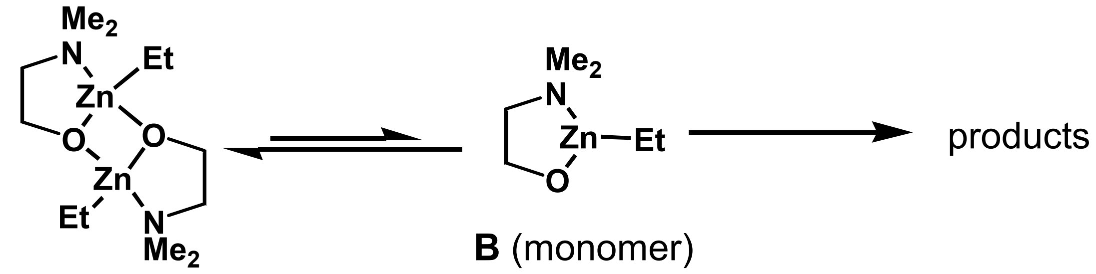
97%, 98% *ee*



Noyori, *J. Am. Chem. Soc.*, **1989**, *111*, 4028; theoretical study of mechanism: *J. Am. Chem. Soc.*, **1995**, *117*, 6327;
Review of asymmetric organozinc additions to aldehydes: *Chem. Rev.*, **1992**, *92*, 833

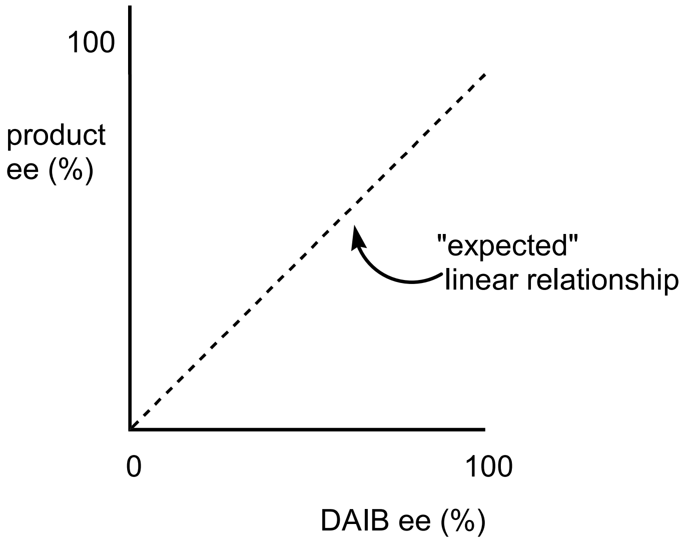
Non-linear effects in reaction of Et_2Zn with aldehydes

Noyori discovered an extraordinary non-linear effect: using additive of just 15% ee, he obtained product of 95% ee: almost as good as with enantiomerically pure additive!



A (dimer)
catalytically inactive

B (monomer)
catalytically active



- If DAIB is not enantiomerically pure, three possible dimers: (+)-DAIB/((+)-DAIB; (-)/(-); (+)/(-)
- (+)/(-)-dimer is the most stable, and shows little tendency to dissociate
- Minor catalyst enantiomer is “tied up” as stable, unreactive heterochiral dimer

(-)-DAIB + (+)-DAIB

(75%) (25%)

$\downarrow Et_2Zn$

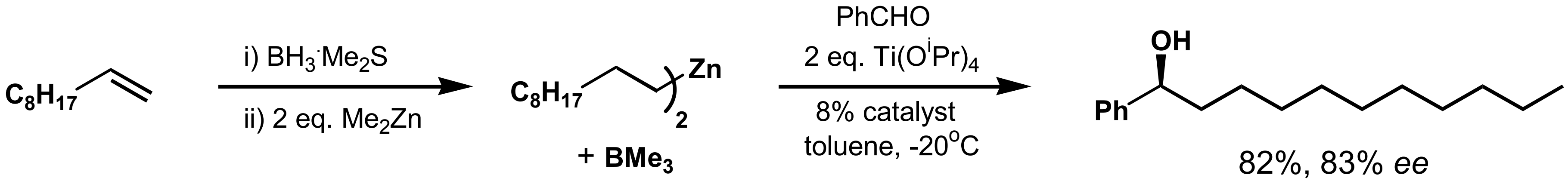
(-)-DAIB/(-)-DAIB dimer + (+)-DAIB/(+)-DAIB dimer + (-)-DAIB/(+)-DAIB heterochiral dimer

(50%) (50%)

Catalytic asymmetric addition of organozincs to aldehydes via titanium

- there are other protocols for asymmetric addition of organozincs, mostly centering on transmetallation. One good system is Knochel's titanium diamide, which gives excellent *ee*'s.

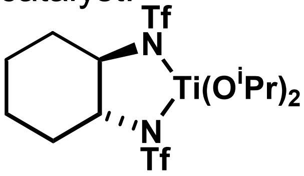
- the limiting factor in this reaction is still the availability of the organozinc, and Knochel has developed two methods for the synthesis of functionalised organozincs:

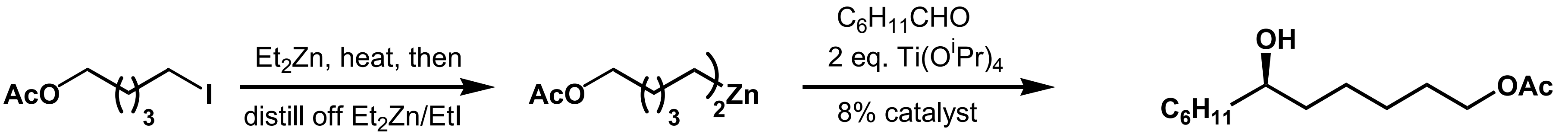


82%, 83% *ee*

Tetrahedron Lett., **1993**, *34*, 5261

catalyst:





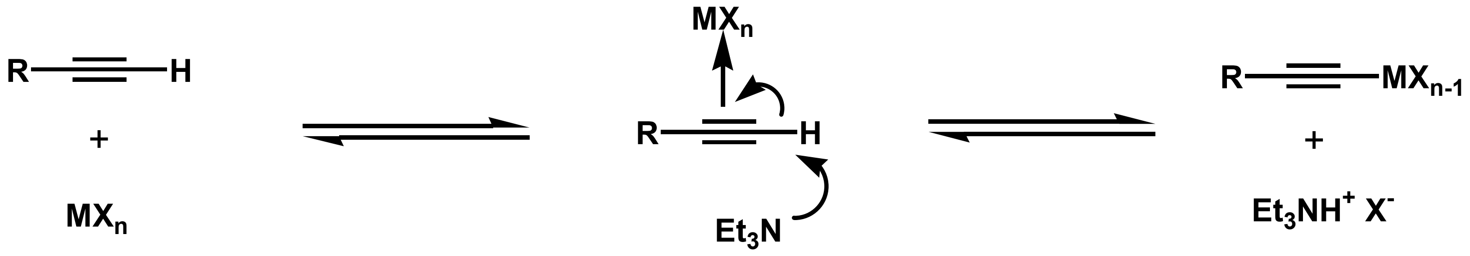
83%, 97% *ee*

J. Org. Chem., **1992**,*57*, 1956

Review of functionalised organozinc additions to aldehydes: *Chem. Rev.*, **1993**, *93*, 2117

In situ generation of nucleophilic organometallic species

- asymmetric addition of organometallics to aldehydes is a useful method in asymmetric synthesis but is hampered by the need for stoichiometric organometallics. A much more attractive option would be to generate the organometallic in situ, but this approach is unlikely to be successful in the presence of electrophiles (*eg* aldehydes). One exception are terminal alkynes, which are known to undergo metal assisted deprotonation by Et_3N:

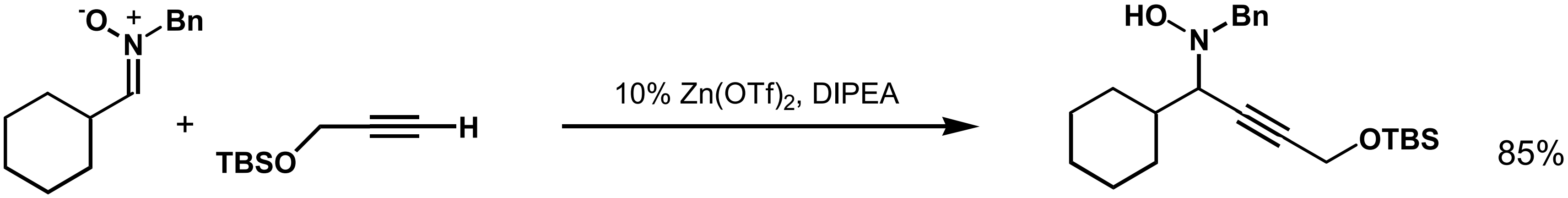


M = Cu^{2+}, Ag^+, Zn^{2+}

Sonagashira

zinc acetylides
add to carbonyls!

- utility initially addressed in addition to benzyl nitrones:

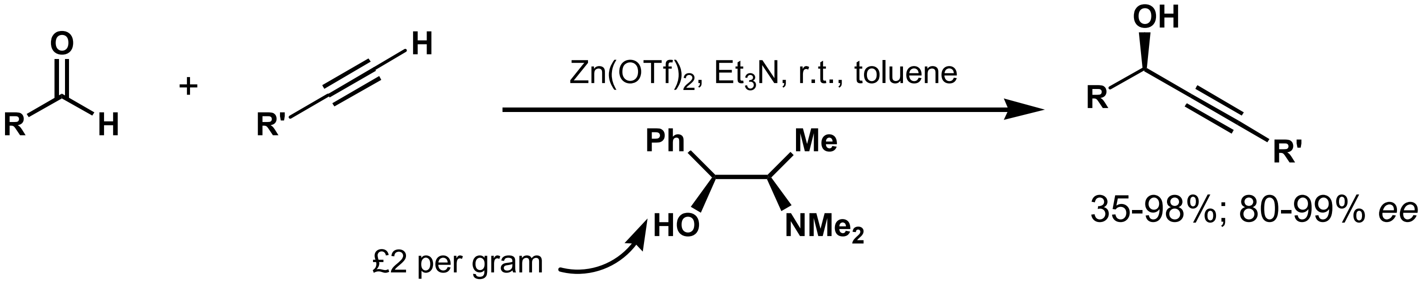


- preliminary results show that addition of chiral ligands gives asymmetric induction

Carreira, *J. Am. Chem. Soc.*, **1999**, *121*, 11245

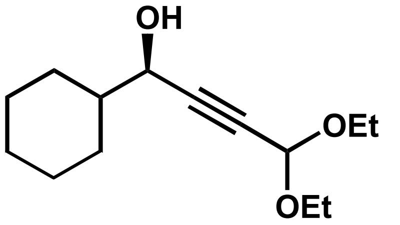
Catalytic asymmetric addition of terminal alkynes to carbonyls

- asymmetric addition of organometallics to aldehydes is a useful method in asymmetric synthesis but is hampered by the need for stoichiometric organometallics. A much more attractive option would be to generate the organometallic in situ, but this approach is unlikely to be successful in the presence of electrophiles (*eg* aldehydes). One exception are terminal alkynes, which are known to undergo metal assisted deprotonation by Et_3N:

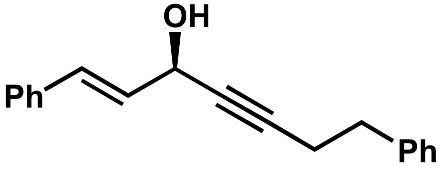


35-98%; 80-99% *ee*

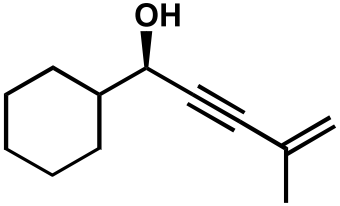
eg



90%, 98% *ee*



39%, 80% *ee*



94%, 98% *ee*

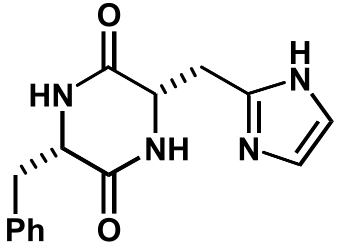
NB: reactions work in reagent grade toluene under an atmosphere of air!

Carreira, *Acc. Chem. Res.*, **2000,** *33*, 373.
J. Am. Chem. Soc., **2000**, *122*, 1806: stoichiometric in $Zn(OTf)_2$, amine and N-methylephedrine
J. Am. Chem. Soc., **2001,** *123,* 9687: can use sub-stoichiometric amounts (ca. 20 mol% $Zn(OTf)_2$ and N-methylephedrine, 50 mol% Et_3N) by carrying out the reaction at 60°C in toluene

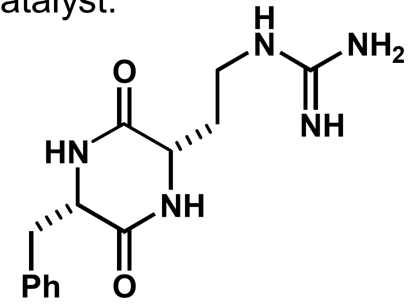
Asymmetric Strecker reactions - initial studies

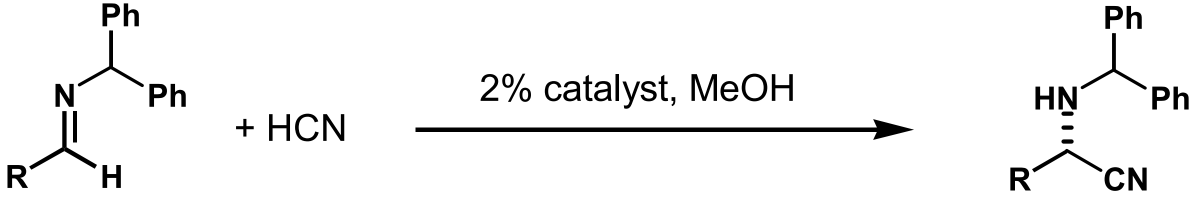
- Lipton expanded on previous results in asymmetric cyanohydrin formation using imidazole containing diketopiperazines; he found that the imidazole did not catalyse the Stecker reaction but that the use of more basic guanidine containing amino acids did the trick:

Inoue's cyanohydrin catalyst:



Strecker catalyst:





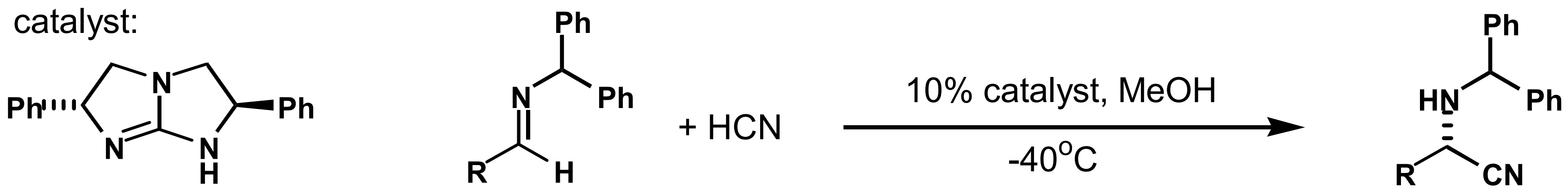
R	yield	ee
Ph	97	99
4-OMePh	96	96
3-NO_2Ph	71	<10
i-Pr	81	<10
tBu	80	17

- limited to electron rich aromatic aldehydes

Lipton, *J. Am. Chem. Soc.*, **1996**, *118*, 4910

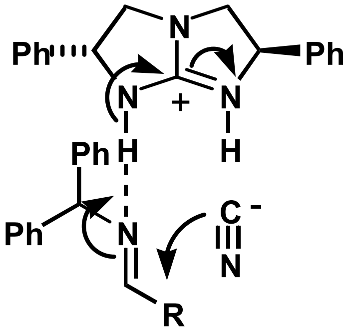
Asymmetric Strecker reactions - simple organic catalysts

- Recently, Corey has shown that a simple C_2-symmetric guanidine also catalyses the reaction. His proposed mechanism suggests a possible method by which the Lipton catalysts may be working.



R	yield	ee
Ph	96	86
4-OMe-Ph	99	84
4-F-Ph	97	86
1-naphthyl	90	76

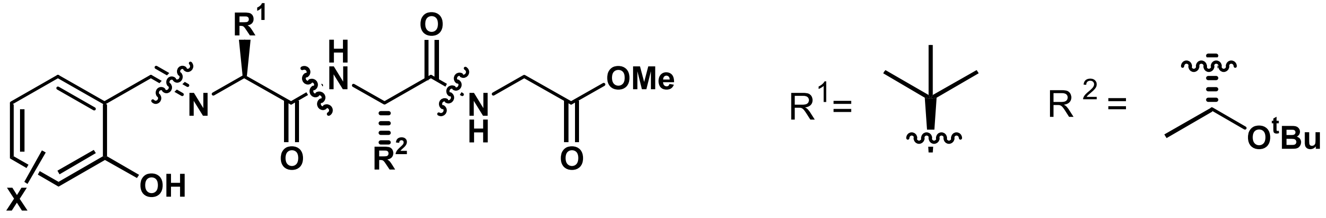
- only electron rich aromatic aldehydes reported - I wonder why........

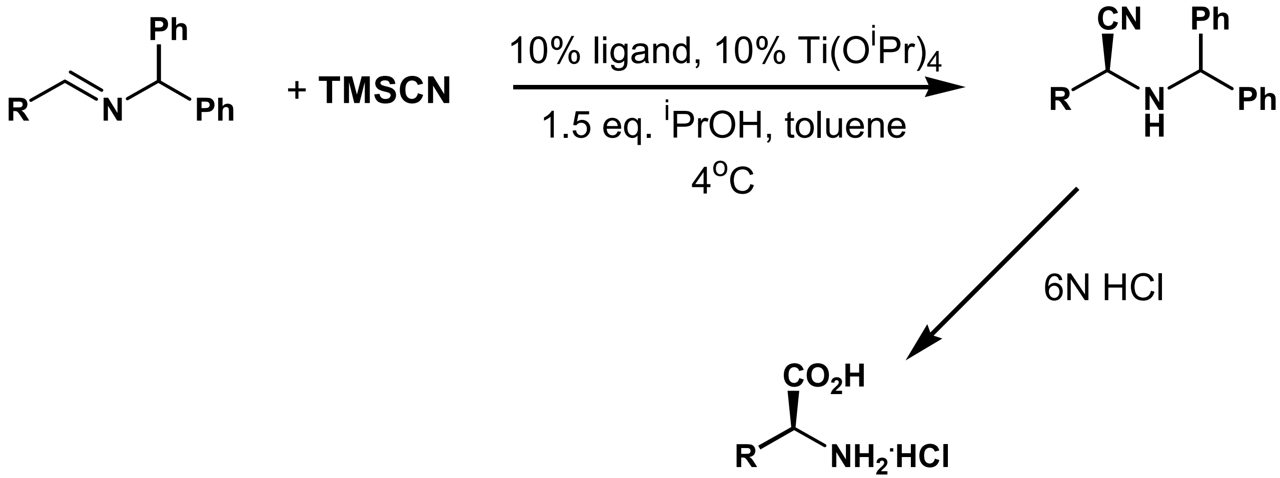


Corey, *Org. Lett.*, **1999**, *1*, 157

Asymmetric Strecker reactions - parallel catalyst discovery

- Snapper and Hoveyda had already used peptidyl substituted Schiff bases as ligands for Lewis acids in asymmetric epoxide opening reactions. As can be seen below, the modular design allows for variation of four components (five if the metal salt is included). A sample ligand was prepared and screened for catalysis of the Strecker reaction with TMSCN using a variety of metals. Ti(O^{i}Pr)$_4$ was the metal of choice; systematic variations then revealed the optimum structure to be that shown, with the X-group variable depending on the imine.





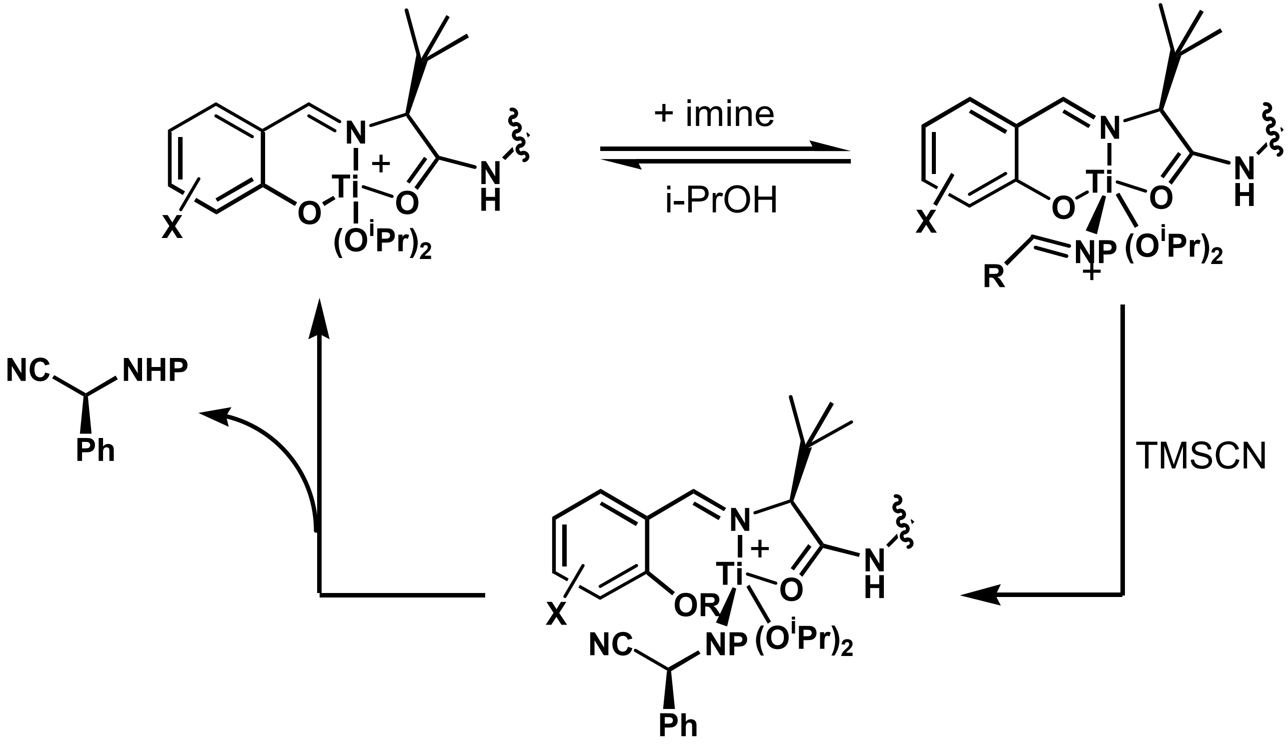
R =	X =	yield, ee
Ph	5-OMe	99, 97
o-Br-Ph	3,5-di-Cl	99, 94
p-MeO-Ph	3,5-di-Cl	100, 94
t-Bu	3,5-di-Br	100, 85

Snapper and Hoveyda, *J. Am. Chem. Soc.*, **1999**, *121*, 4284

- as yet, only for non-enolizable imines

Asymmetric Strecker reactions - parallel catalyst discovery

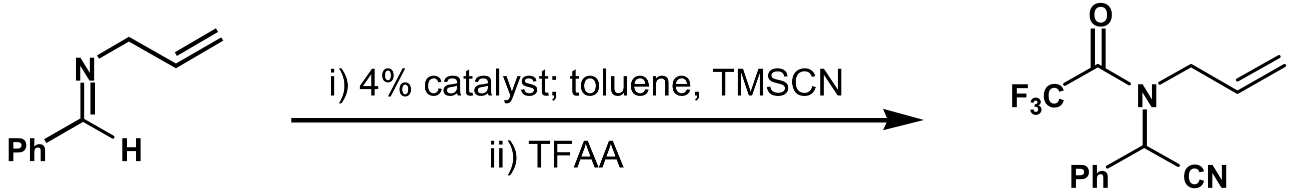
- proposed mechanism based upon the rate and selectivity enhancing ability of the isopropanol additive.



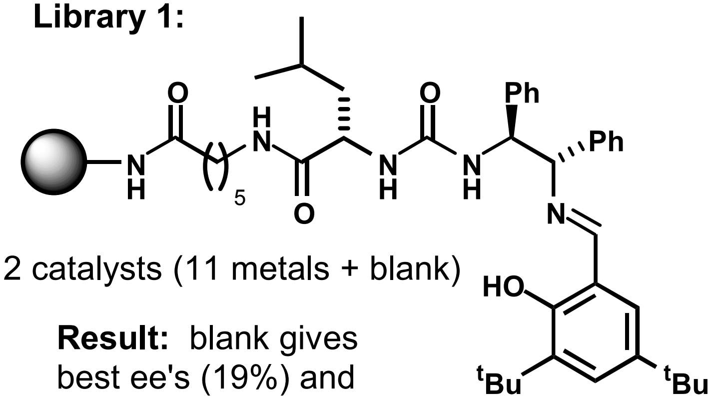
Snapper and Hoveyda, *J. Am. Chem. Soc.*, **1999**, *121*, 4284

Asymmetric Strecker reactions - parallel catalyst discovery

- Jacobsen tried the same approach, but on solid phase. This greatly simplifies the synthesis of the ligands and the screening; it also means that you have a ready made heterogeneous catalyst for use!



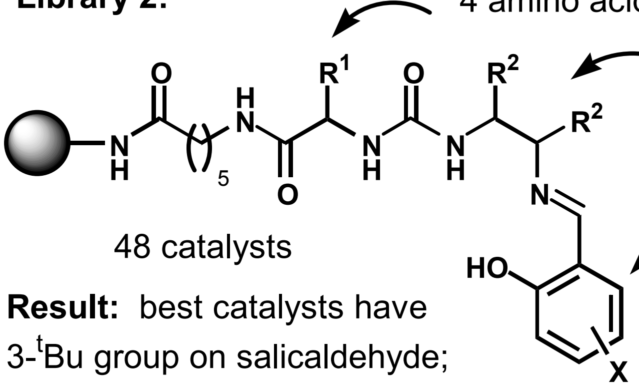
Library 1:



12 catalysts (11 metals + blank)

Result: blank gives best ee's (19%) and moderate conversion

Library 2:



4 amino acids

2 diamines

6 salicaldehydes

48 catalysts

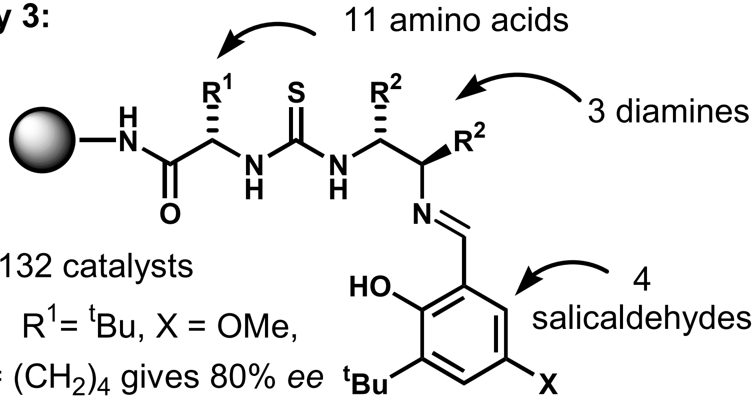
Result: best catalysts have 3-^{t}Bu group on salicaldehyde; non-polar L-amino acids with R,R-diamines ee's up to 32%

Jacobsen, *J. Am. Chem. Soc.*, **1998**, *120*, 4901

Asymmetric Strecker reactions - parallel catalyst discovery

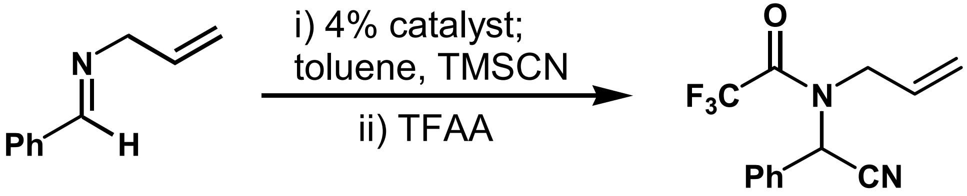
- in his final library, he had observed that the urea and caproic acid unit were giving problems, so these were replaced by thiourea and direct linkage to the resin support respectively.

Library 3:

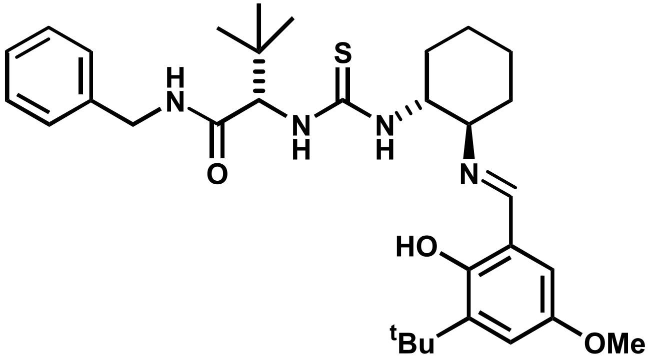


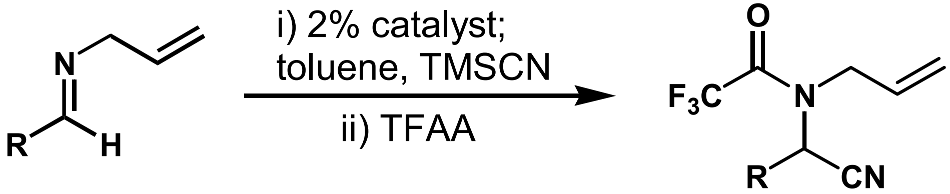
132 catalysts

Result: $R^1 = {}^tBu$, X = OMe, $R^2,R^2 = (CH_2)_4$ gives 80% *ee*



- gratifyingly, the solution phase analogue behaved even better and, despite being optimised for benzaldimines, the catalyst proved to be general: even aliphatic enolisable imines worked, the first time that they had been successfully used in a catalytic asymmetric Strecker.



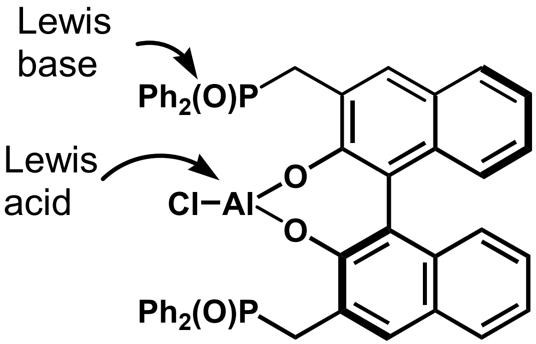


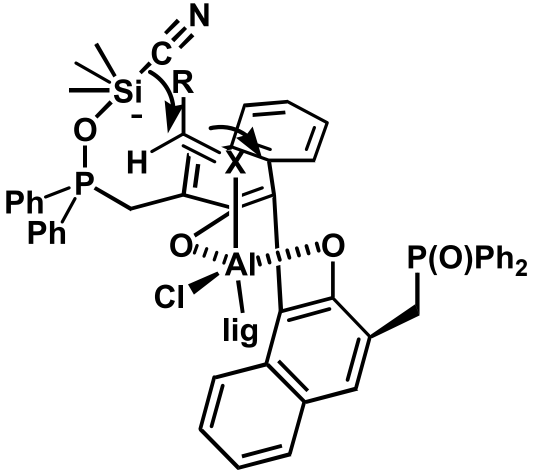
R	Ph	p-OMePh	p-Br-Ph	t-Bu	cyc
yield	78	92	65	70	77
ee	91	70	86	85	83

Jacobsen, *J. Am. Chem. Soc.*, **1998**, *120*, 4901

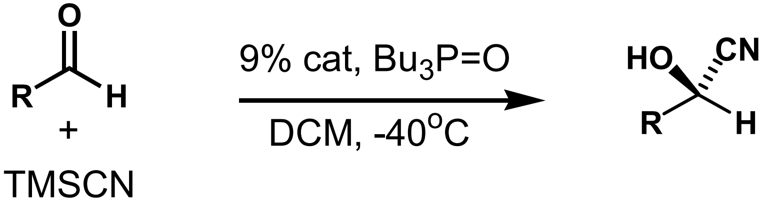
Asymmetric Strecker reactions - bifunctional asymmetric catalysis

- Shibasaki has developed many catalysts which work by dual catalysis, ie the same molecule has two different reactive functionalities which work together to promote the reaction. One example is the use of Lewis acid/ Lewis base promotion of the addition of TMSCN to aldehydes and imines:

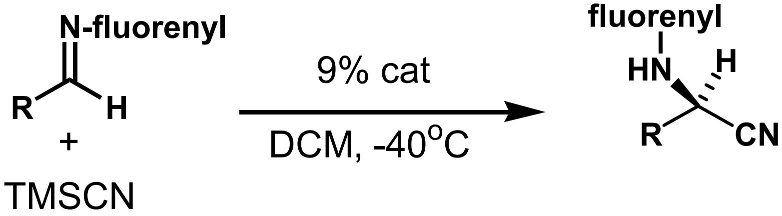




X = O, NR



R	yield	ee
$Ph(CH_2)_2$	97	97
i-Pr	96	90
PhCH=CH-	99	98
Ph	98	96
2-furyl	86	95

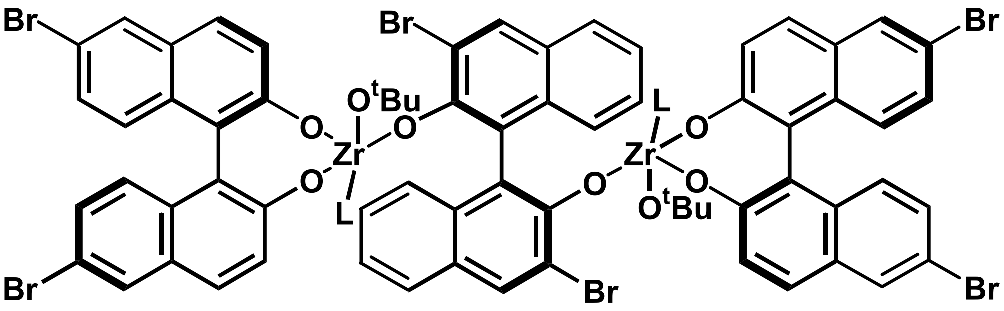


R	yield	ee
i-Pr	89	73
PhCH=CH-	80	96
Ph	92	95
2-furyl	93	79

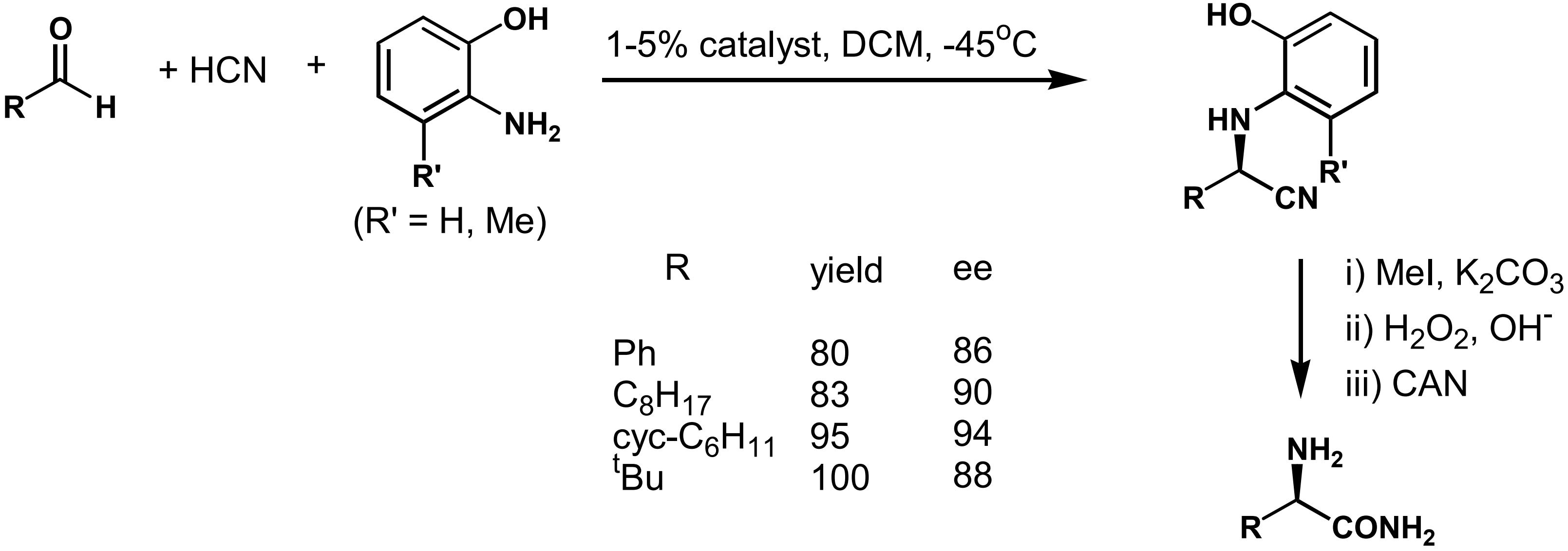
Shibasaki, *J. Am. Chem. Soc.*, **1999**, *121*, 2641; *Angew. Chem., Int. Ed. Engl.*, **2000**, *39*, 1651

Asymmetric Strecker reactions - one-pot synthesis

- all of the reactions so far have required pre-formed imines; it would of course be more convenient simply to mix cyanide, aldehyde and imine with the catalyst and go directly to the product. This has now been achieved by Kobayashi (*J. Am. Chem. Soc.*, **2000**, *122*, 762).



L =N-Me-imidazole

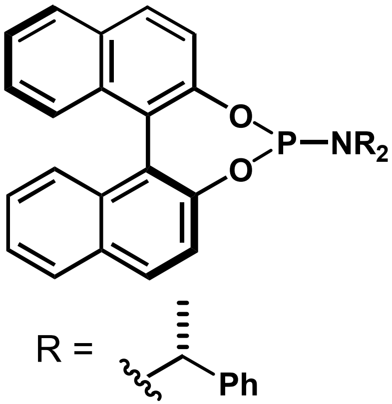


R	yield	ee
Ph	80	86
C_8H_{17}	83	90
cyc-C_6H_{11}	95	94
^{t}Bu	100	88

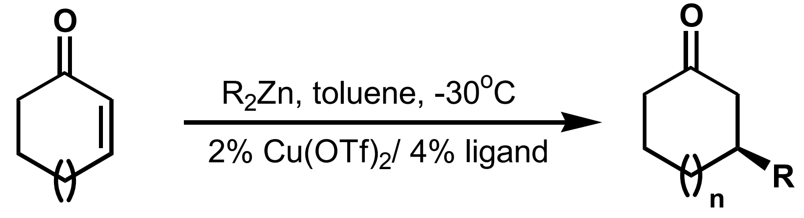
Catalytic asymmetric addition of organozincs to enones/enoates

- one of the best catalyst systems for conjugate addition of organozincs involves transmetallation to copper phosphoramidite complexes. The phosphoramidite ligands of Feringa are, in contrast to many compounds of this type, relatively stable to hydrolysis. $Cu(OTf)_2$ is the most convenient source of copper, and is apparently reduced to Cu(I) *in situ*.

ligand:



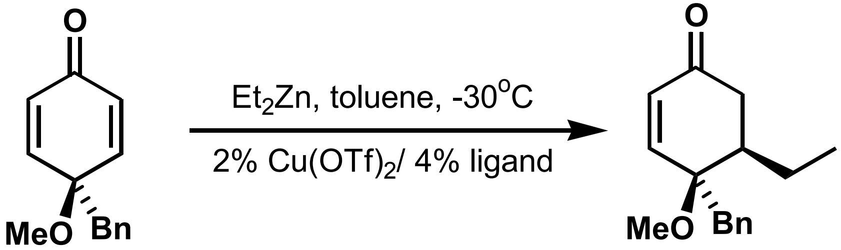
cyclic enones:



R = Et
n = 1 94%, >98% *ee*
n = 2 82%, 53% *ee*
R = ^{i}Pr
n = 1 95%, 94% *ee*

Feringa, *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 2620

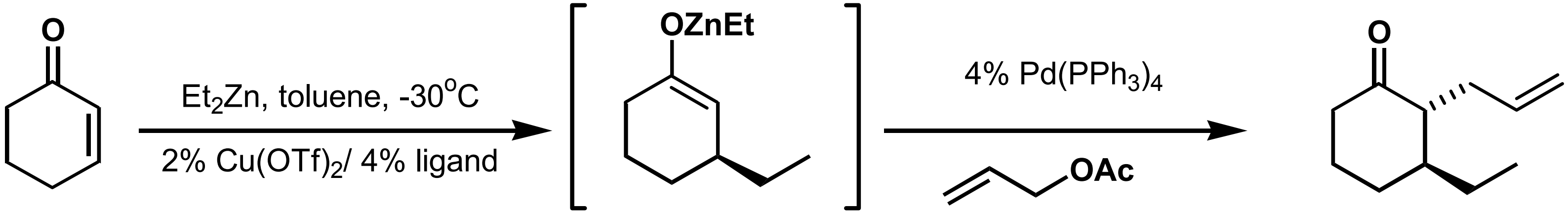
cyclohexadienones:



97 : 3 dr
93% *ee*

Feringa, *Org. Lett.*, **1999**, *1*, 623

tandem addition/coupling:



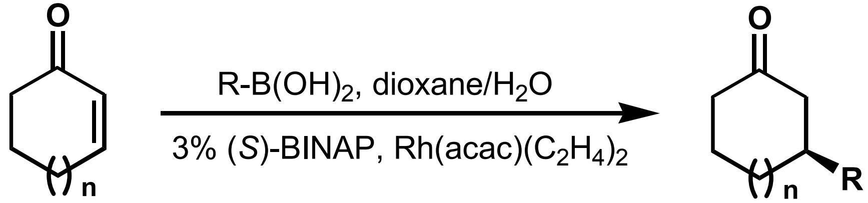
88%, 96% *ee*

Feringa, *J. Am. Chem. Soc.*, **1999**, *121*, 1104

Review of phosphoramidites in asymmetric synthesis: *Acc. Chem. Res.*, **2000**, *33*, 346

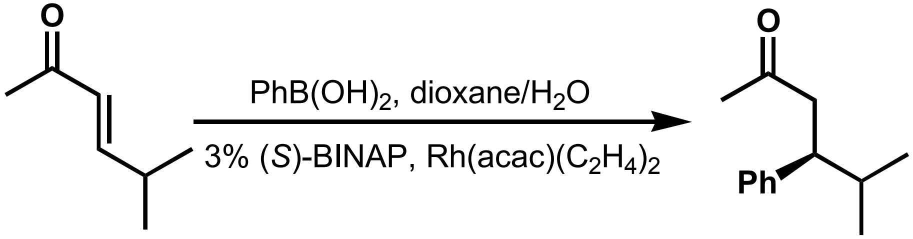
Catalytic asymmetric addition of carbon nucleophiles to enones/enoates

additions of organometallics to acyclic enones/enoates remains a challenging field, with no general solution as yet. One very promising approach, however, utilises boronic acids, a range of which are commercially available:



R = Ph
n = 0 (97% *ee*), 1 (97% *ee*), 2 (94% *ee*)

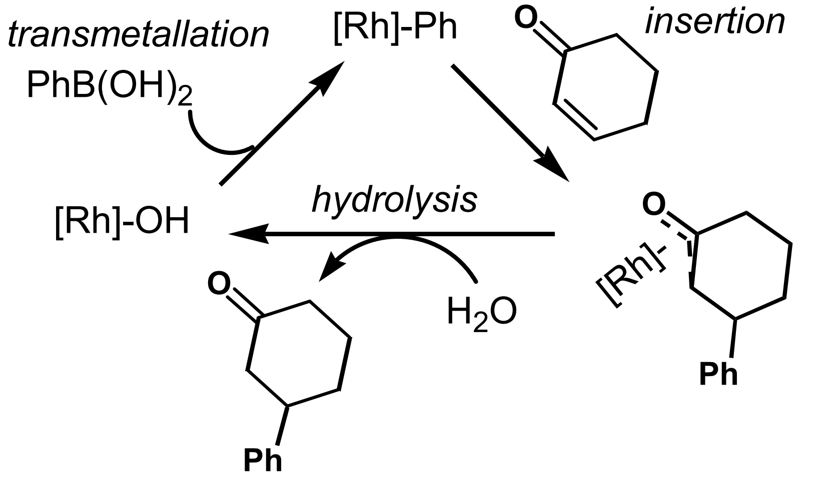
R = *E*-1-heptenyl
n = 1 (96% *ee*)



97% *ee*

Hayashi, Miyaura, *J. Am. Chem. Soc.*, **1998**, *120*, 5579
Synlett, **2001**, 879.

Mechanism (see *J. Am. Chem. Soc.*, **2002,** *124,* 5052):



(*S*)-BINAP: