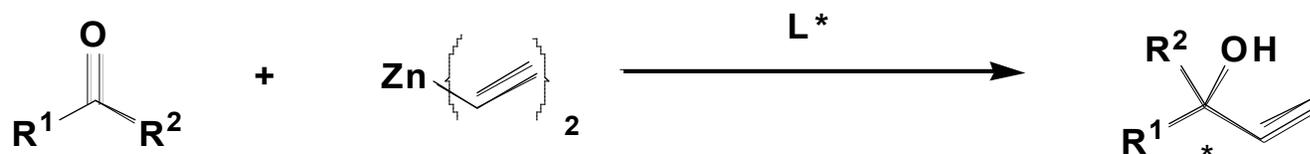


Enantioselective Vinylation of Aldehydes and Ketones

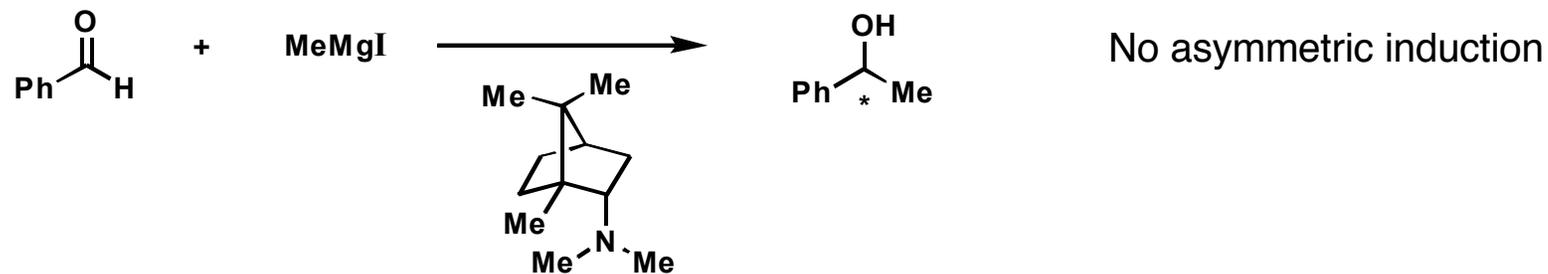


Group meeting

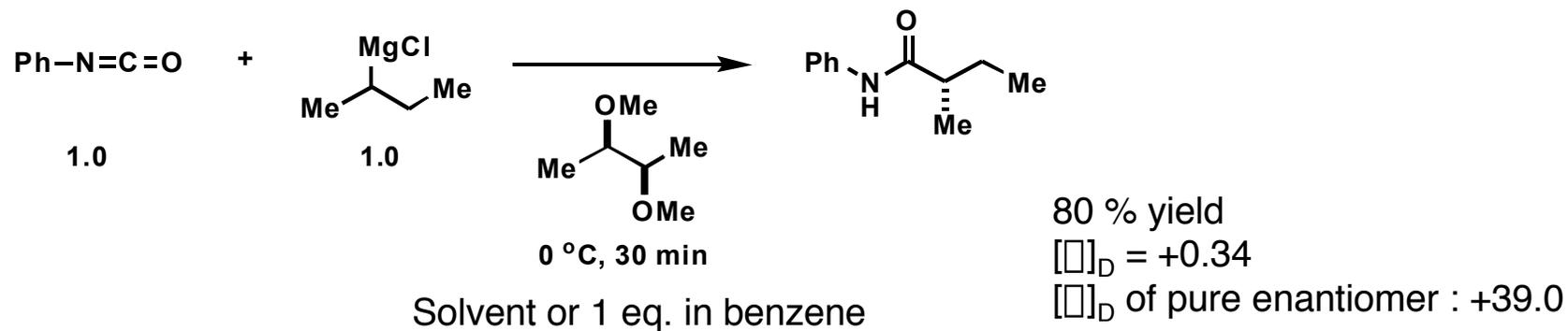
08/02/2005

Won-jin Chung

Early Attempts : Chiral Solvents

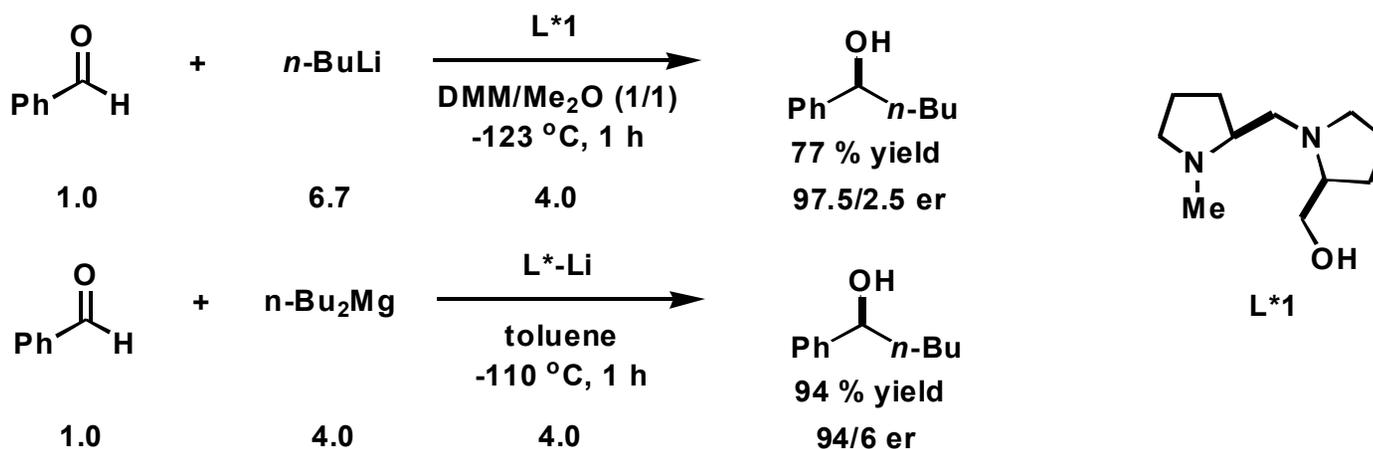


Tarbell, D. et al. *J. Am. Chem. Soc.* **1942**, *64*, 2842.

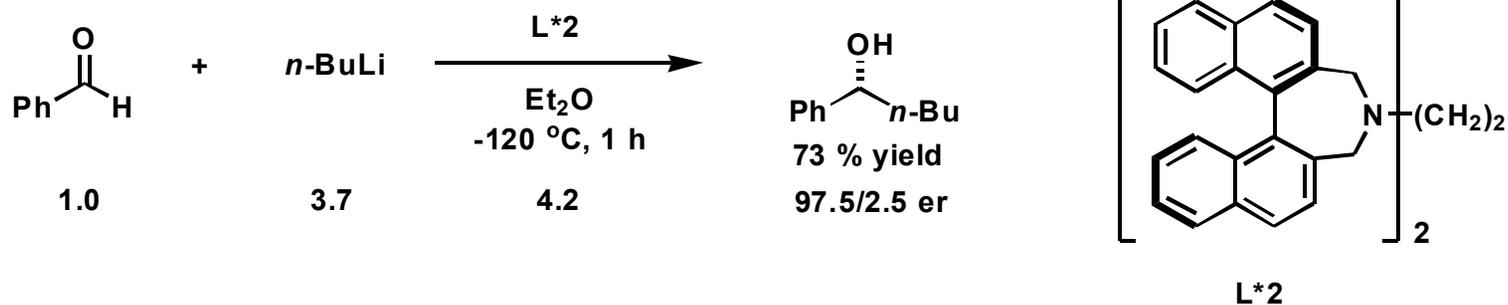


Cohen, H. et al. *J. Org. Chem.* **1953**, *18*, 432.

Early Attempts : Limited Success



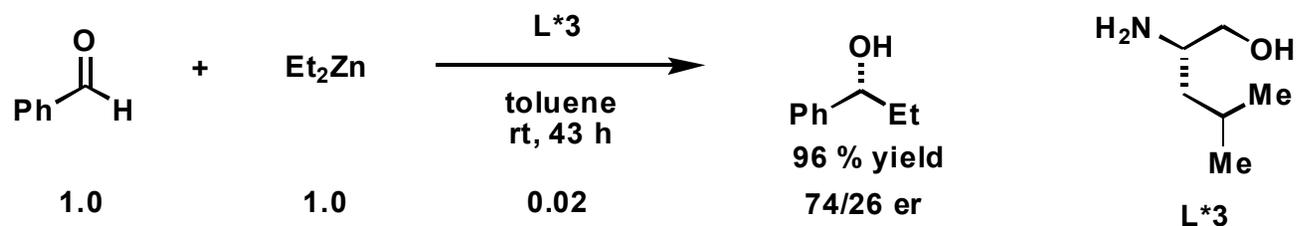
Mukaiyama, T. et al. *J. Am. Chem. Soc.* **1979**, *101*, 1455.



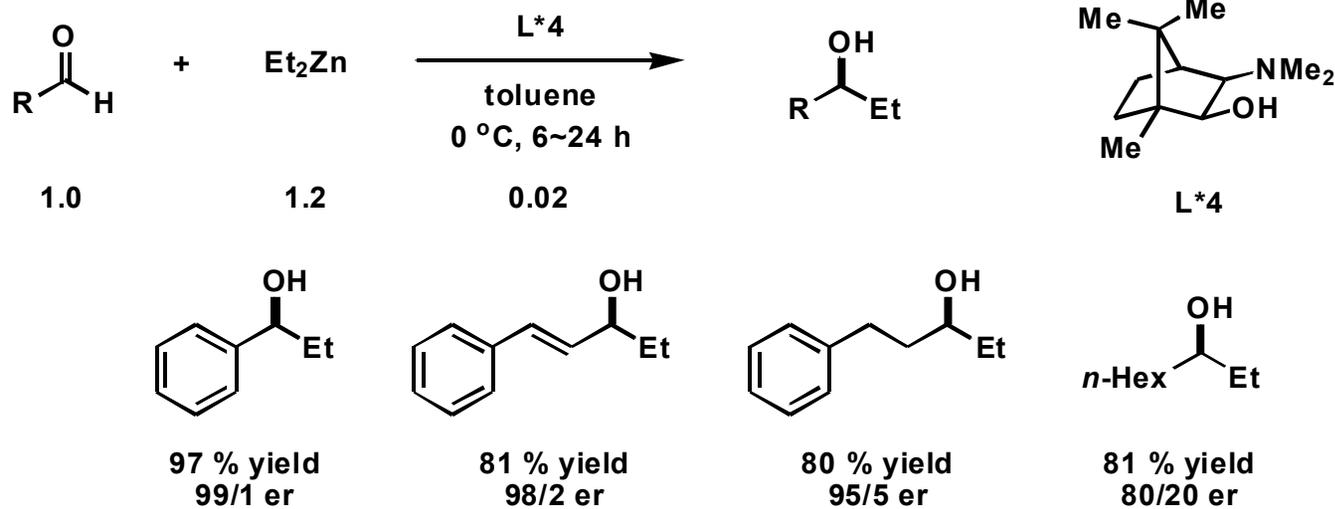
Cram, D. et al. *J. Am. Chem. Soc.* **1981**, *103*, 4585.

Limitations: Low Temperature, Excess chiral ligand, and Narrow substrate scope

Organozinc reagent : Mild nucleophile

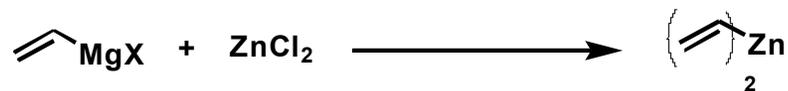
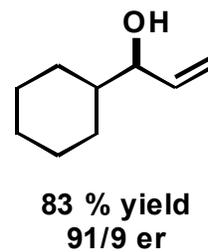
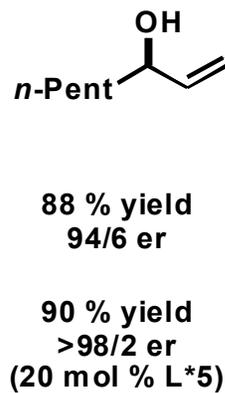
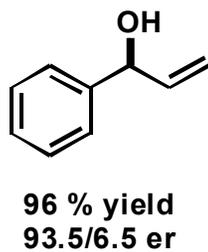
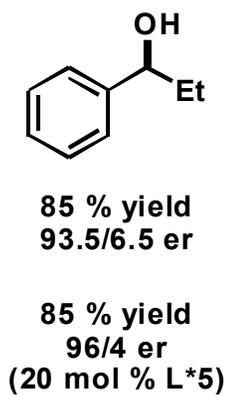
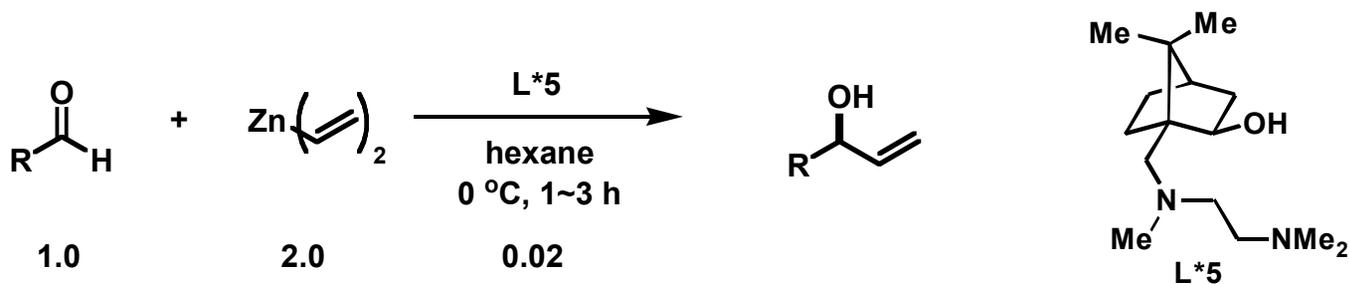


Oguni, N. et al. *Tetrahedron Lett.* **1984**, 25, 2823.

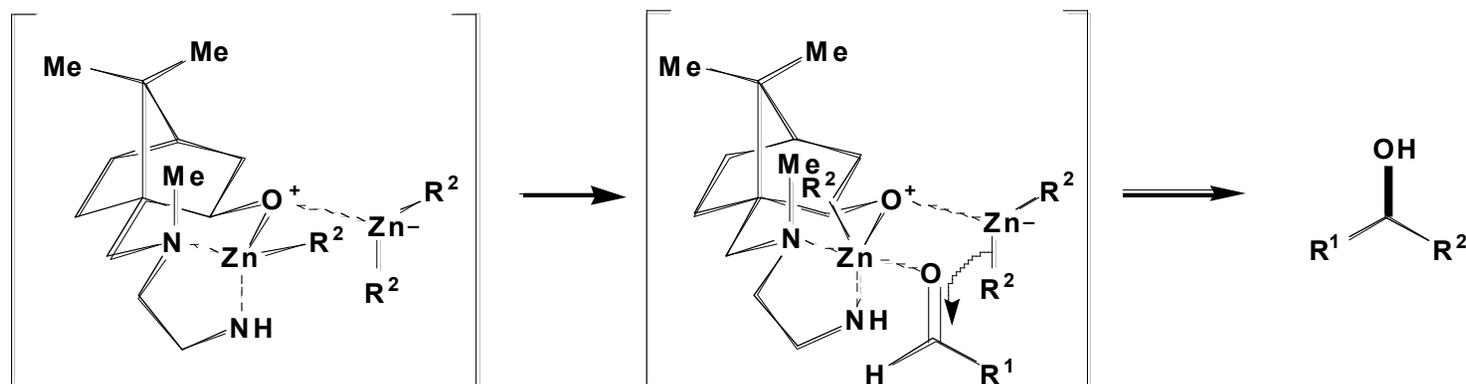
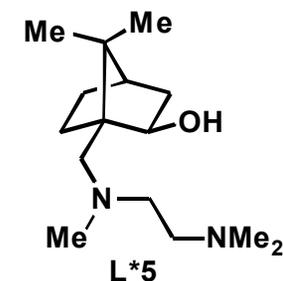
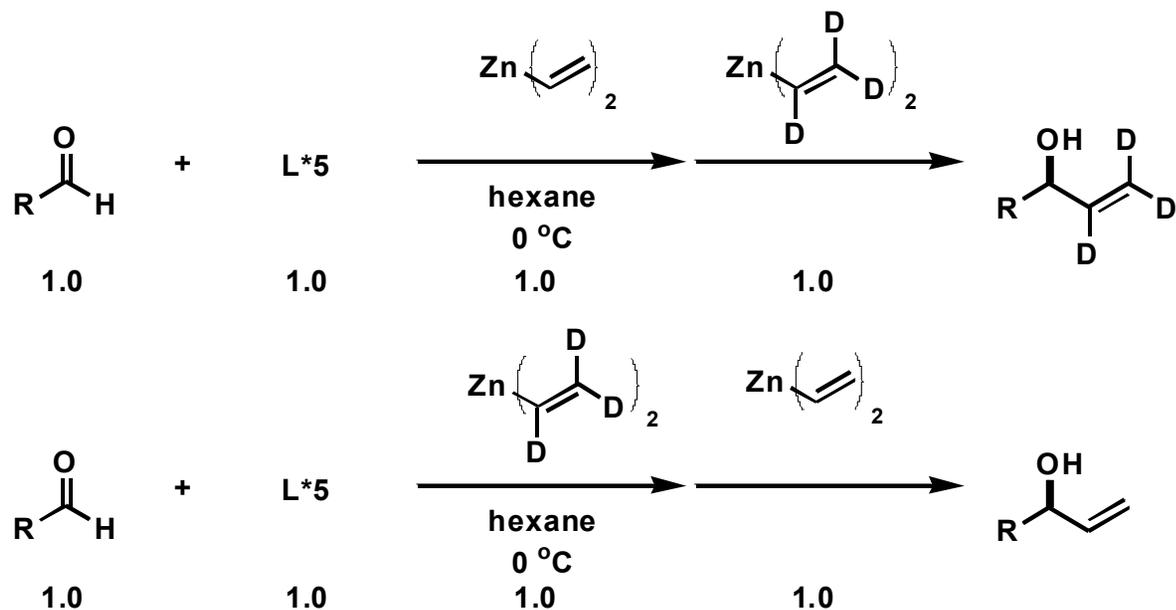


Noyori, R. et al. *J. Am. Chem. Soc.* **1986**, 108, 6071.

Vinylzinc

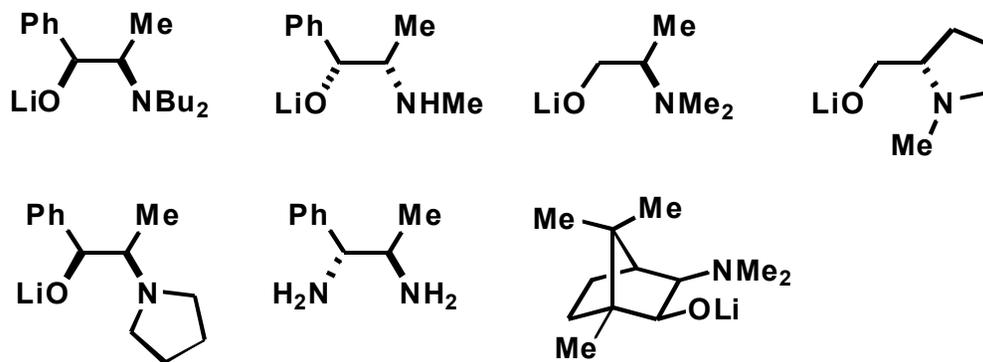
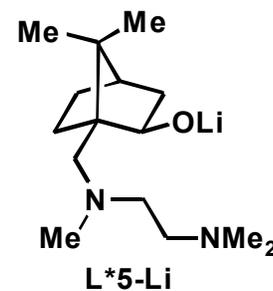
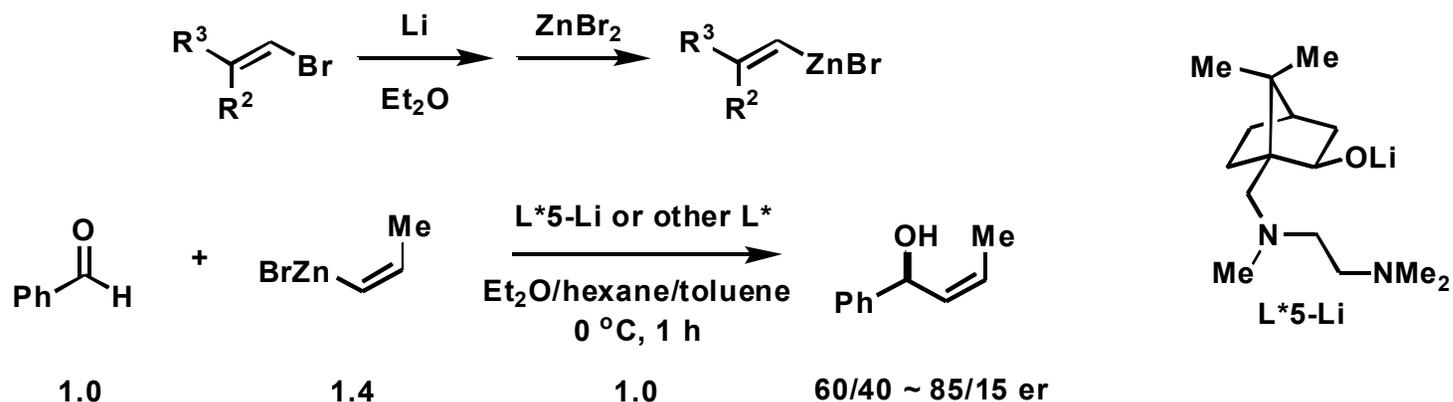


Vinylzinc : Mechanistic Study



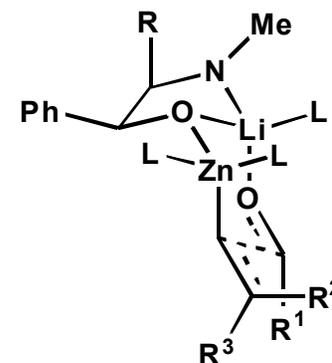
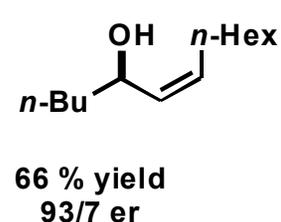
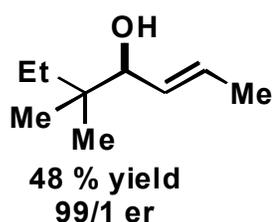
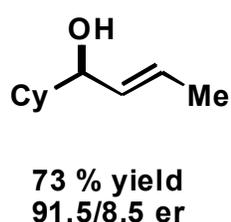
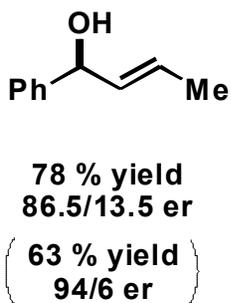
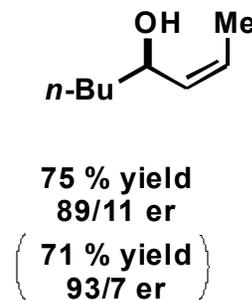
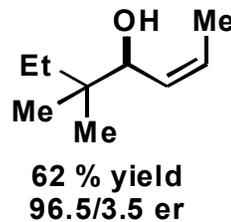
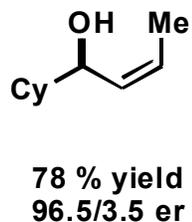
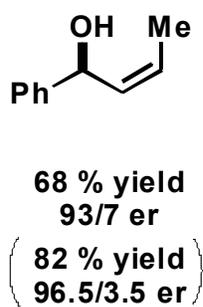
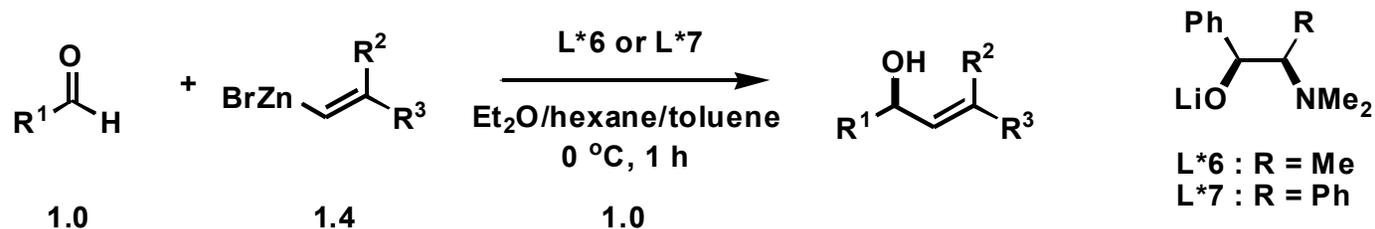
Two zinc species are involved in the addition process.

Vinylzinc Halide



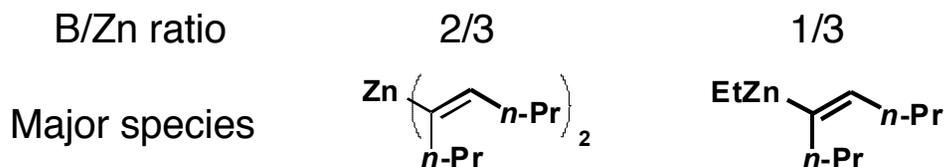
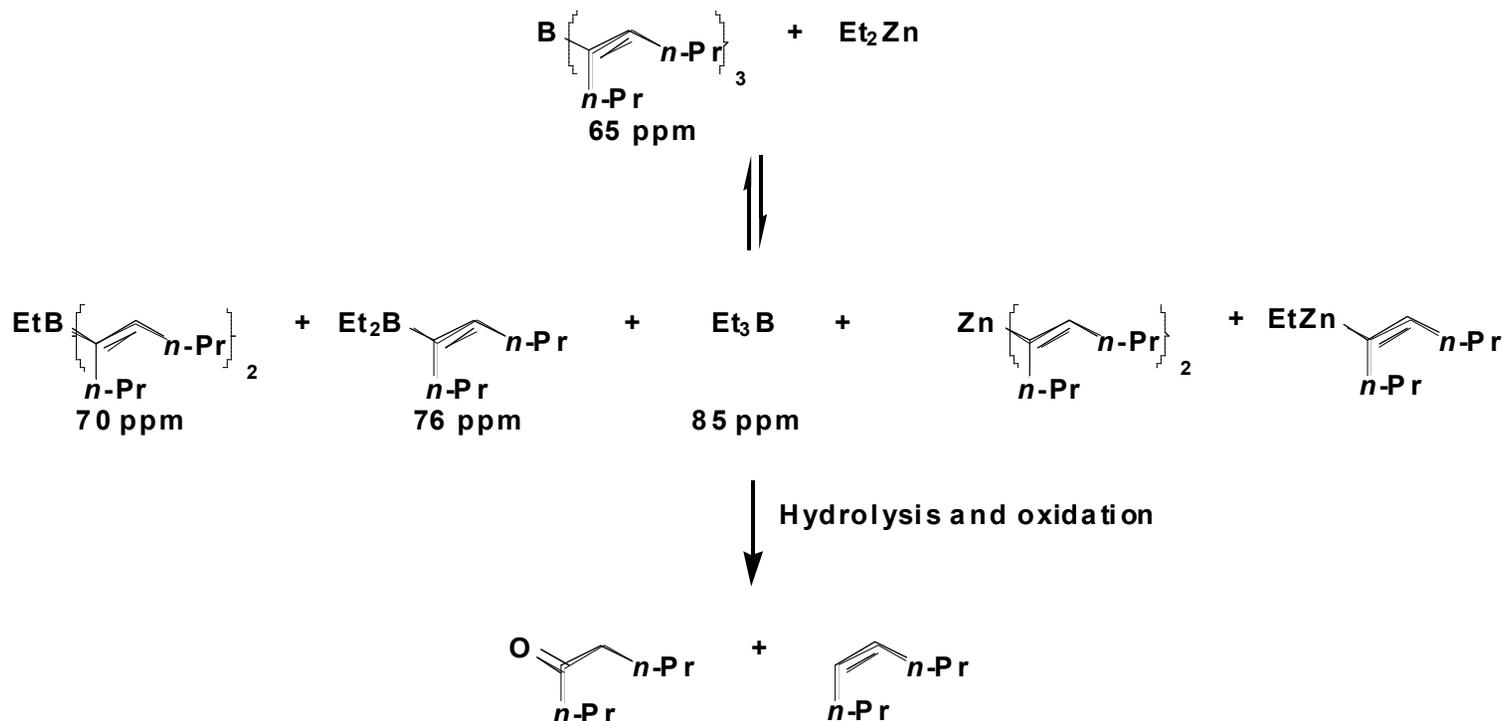
All the lithiated aminols or diamines exerted only modest induction.

Vinylzinc Halide



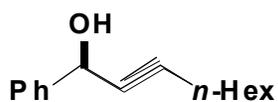
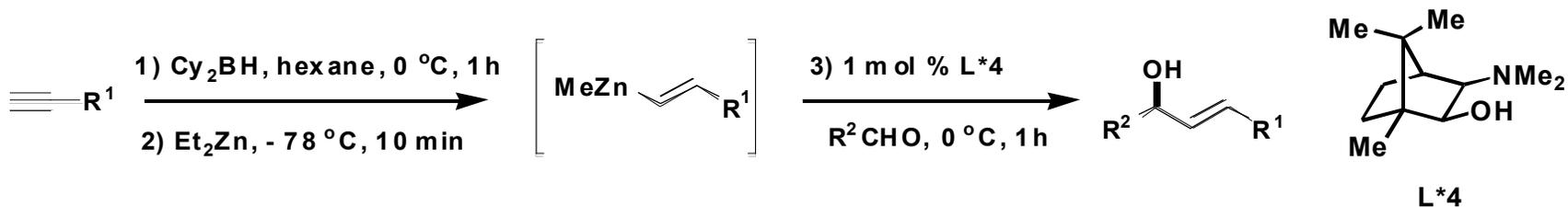
- The enantioselectivity increases with growing steric demand of substrates.
- The double bond geometry is retained.

Alkyl Vinylzinc by Transmetalation

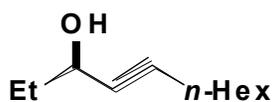


Equilibration : rapid in hexane, 24 h in THF, 7 h in Et₂O

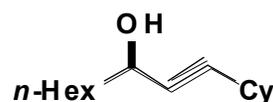
Alkyl Vinylzinc



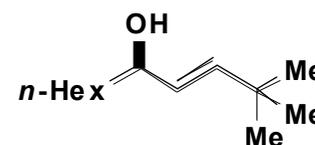
87 % yield
98/2 er



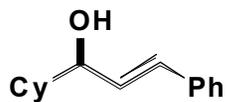
91 % yield
92/8 er



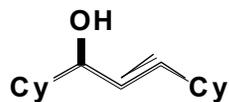
70 % yield
95.5/4.5 er



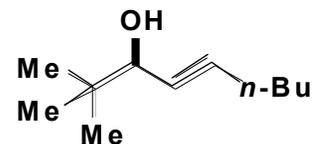
28 % yield
86.5/13.5 er



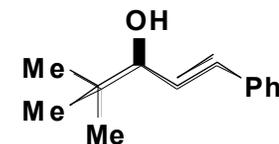
67 % yield
90/10 er



67 % yield
90/10 er

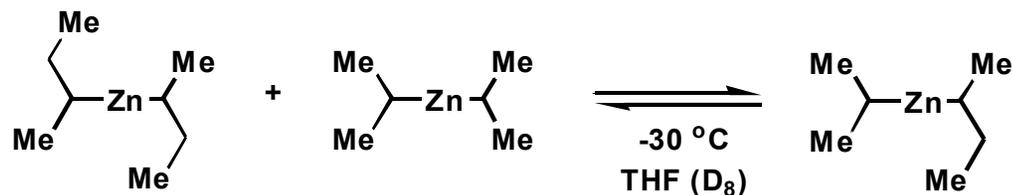


94 % yield
89.5/10.5 er



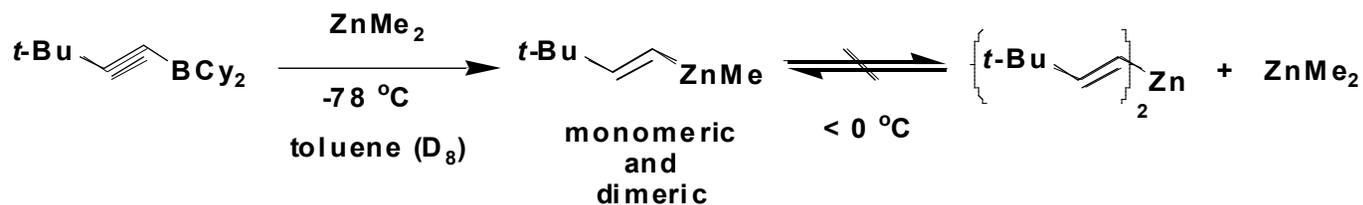
90 % yield
99/1 er

Equilibrium of Alkyl- and Alkenylzinc Species



¹³C NMR study

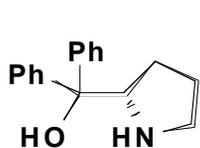
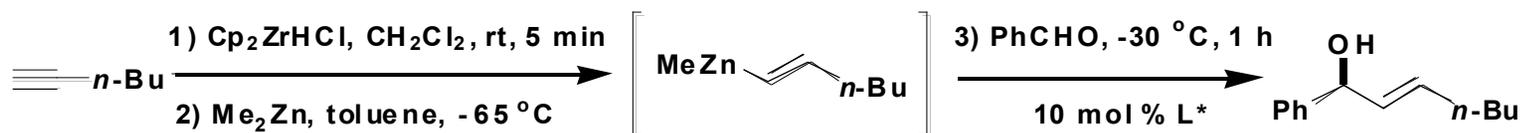
Mynott, R. et al. *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 335.



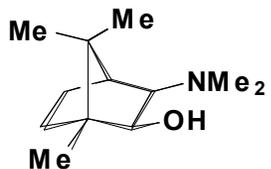
Ratio of two species didn't change after evaporation.

Oppolzer, W. et al. *Helv. Chim. Acta.* **1992**, 75, 170.

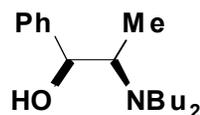
Alkyl Vinylzinc by Hydrozirconation



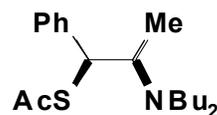
88 % yield
90.5/9.5 er



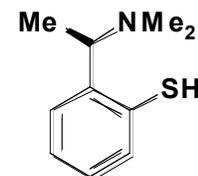
77 % yield
51.5/48.5 er



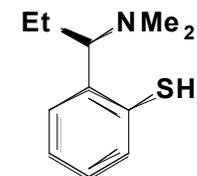
85 % yield
50.5/49.5 er



80 % yield
85/15 er



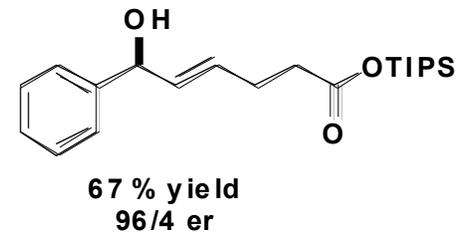
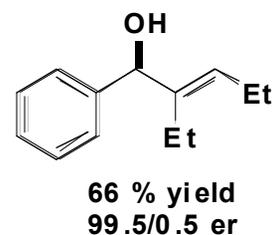
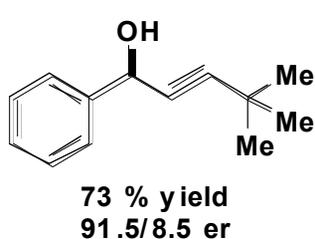
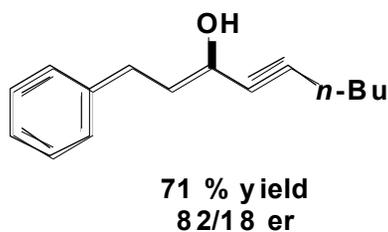
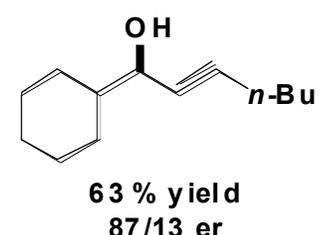
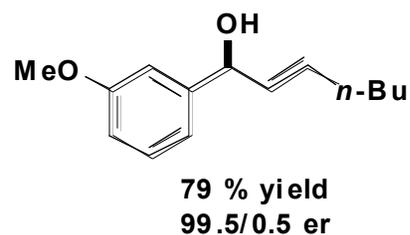
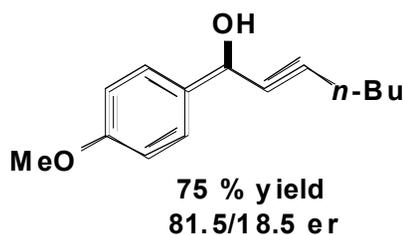
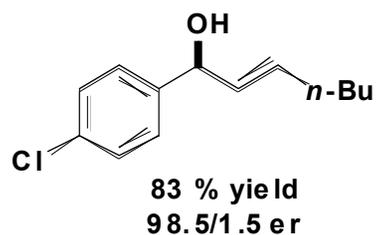
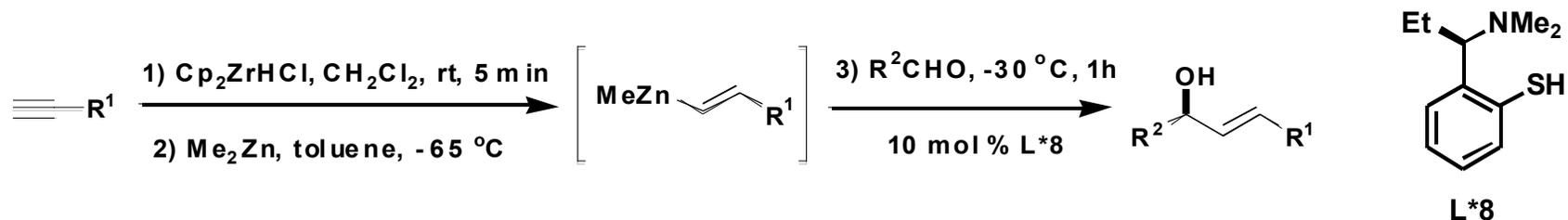
76 % yield
94.5/5.5 er



80 % yield
97.5/2.5 er

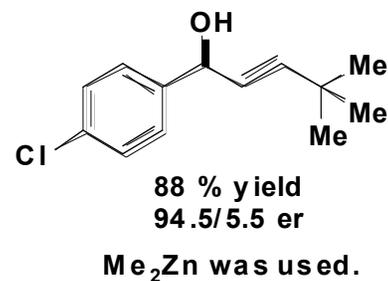
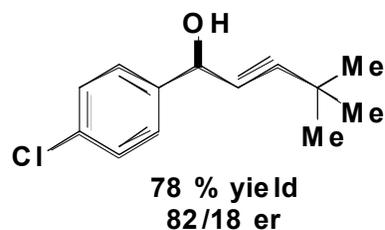
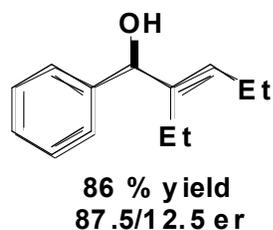
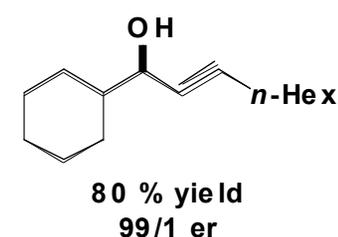
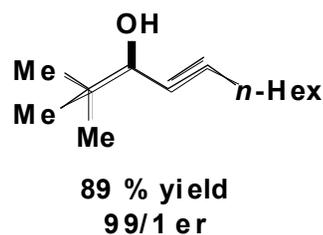
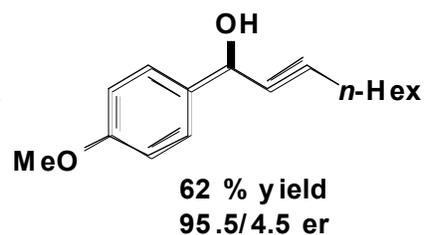
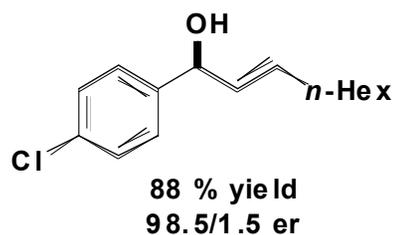
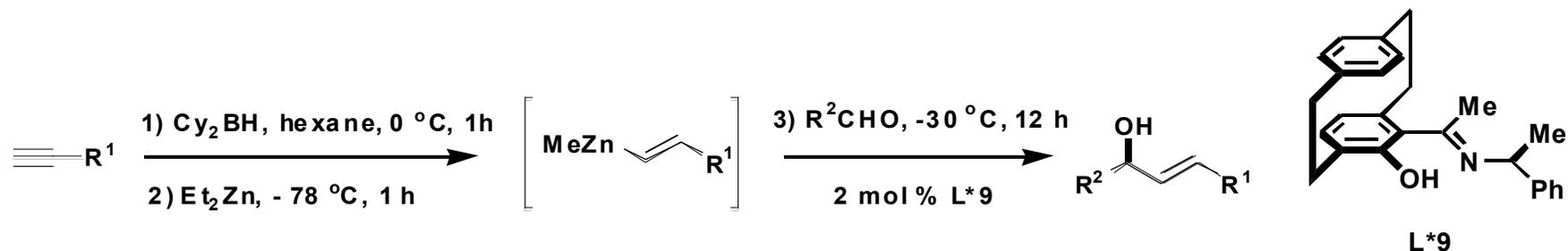
- The byproduct, Cp_2ZrMeCl was efficient promoter.
- Amino thiol ligand was superior to amino alcohol ligands.
- High temperature or low loading of catalyst resulted in attenuated selectivity.

Alkyl Vinylzinc by Hydrozirconation



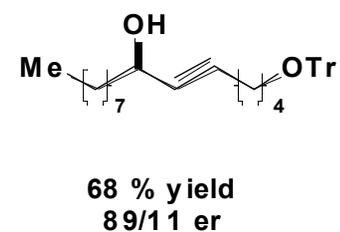
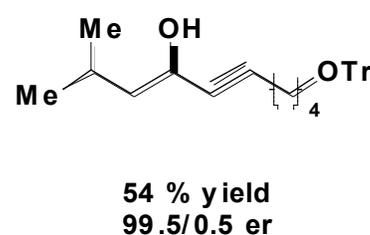
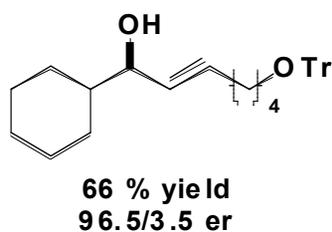
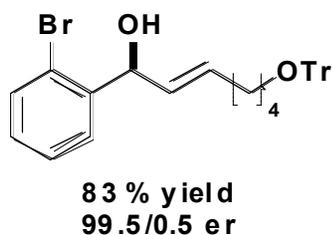
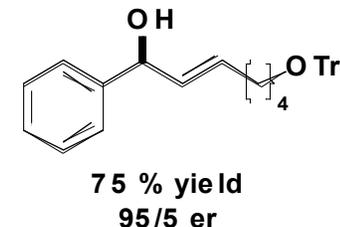
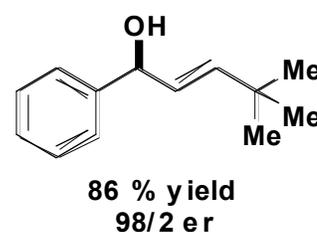
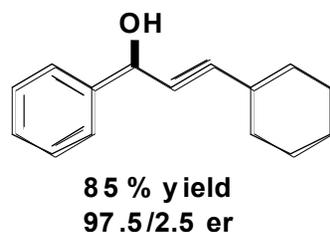
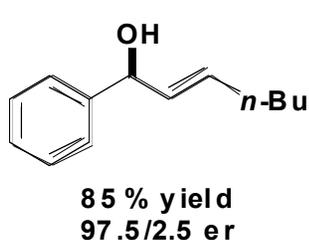
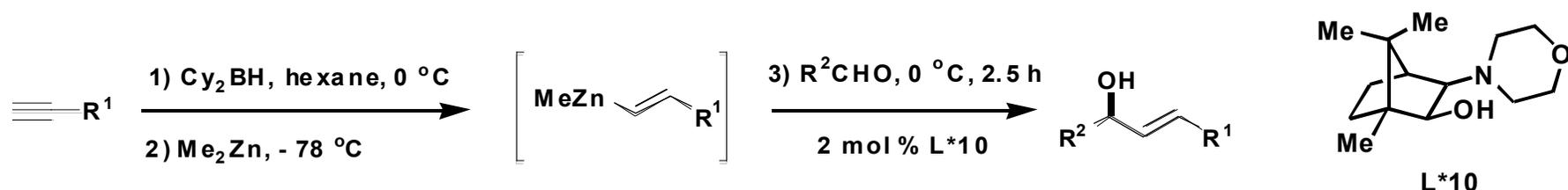
Alternative preparation of alkyl vinyl zinc species was provided.

Alkyl Vinylzinc Addition by Paracyclophanes



High enantioselectivities were obtained for the bulky aliphatic aldehydes.

Modified Oppolzer's Method

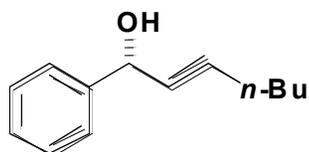
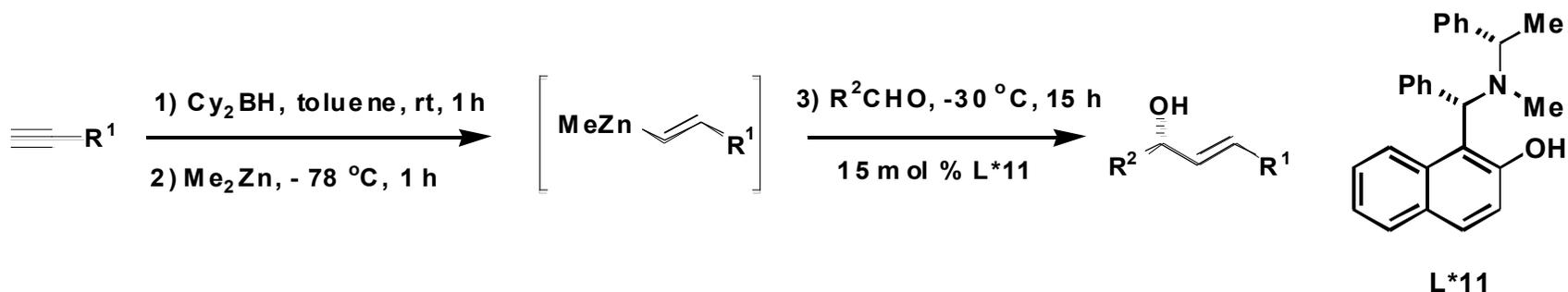


Enantioselectivity was improved by modifying Oppolzer's method.

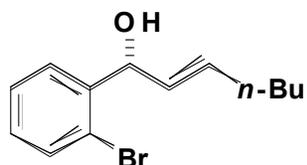
Walsh, P. et al. *J. Am. Chem. Soc.* **2002**, *124*, 12225.

Walsh, P. et al. *J. Am. Chem. Soc.* **2003**, *125*, 10677.

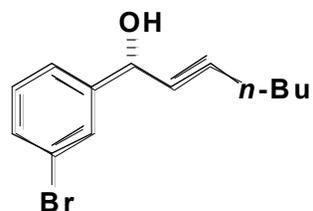
Alkyl Vinylzinc Addition by Aminonaphthol



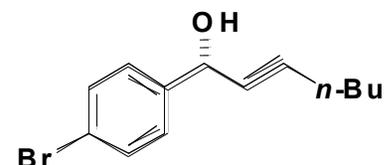
90 % yield
98.5/1.5 er



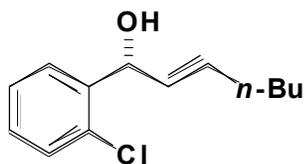
87 % yield
99/1 er



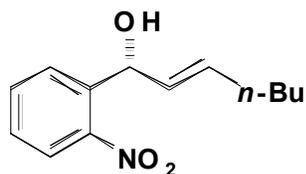
92 % yield
97/3 er



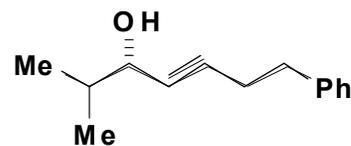
89 % yield
97/3 er



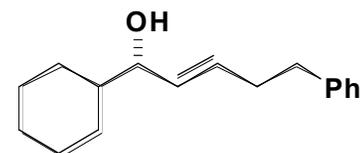
90 % yield
99.5/0.5 er



77 %
99.5/0.5 er



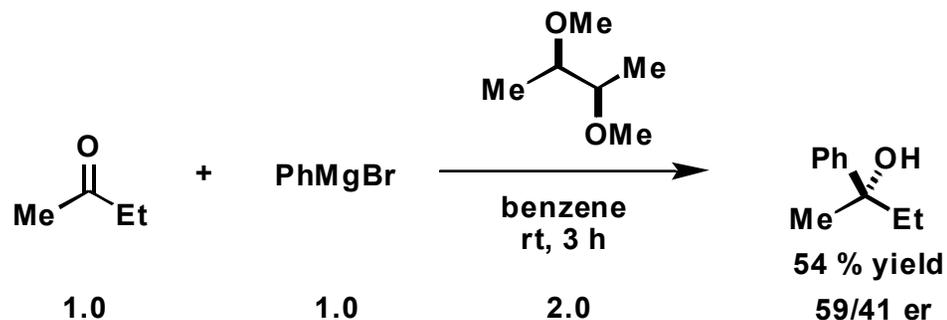
94 % yield
97/3 er



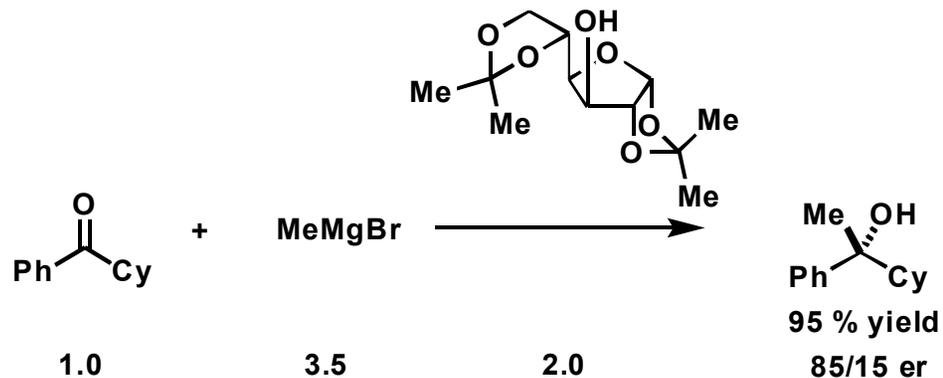
93 % yield
97.5/2.5 er

High enantioselectivities were obtained for *o*-substituted aromatic aldehydes.

Early Attempts : Chiral Additives

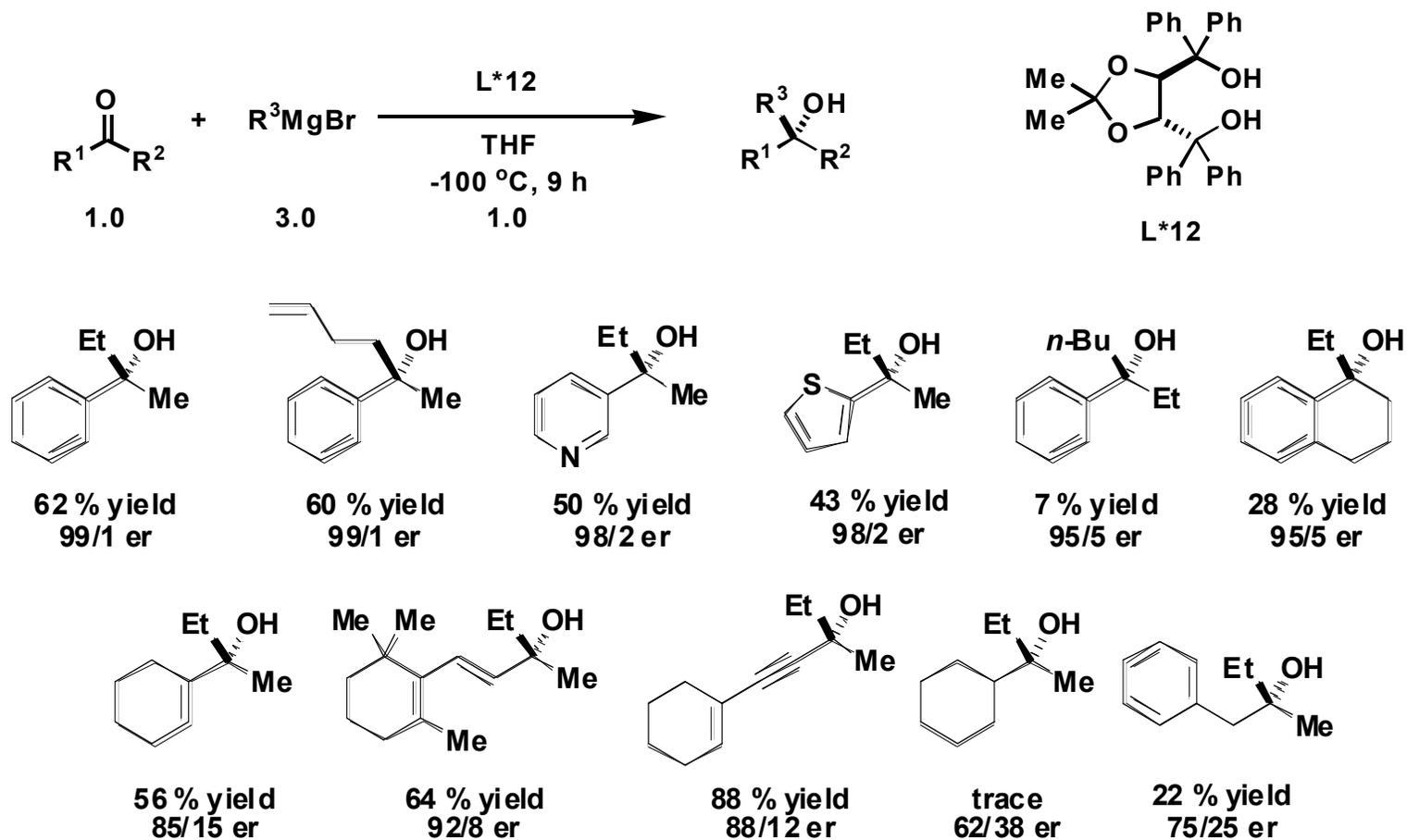


Wright, G. et al. *J. Org. Chem.* **1957**, *22*, 1.



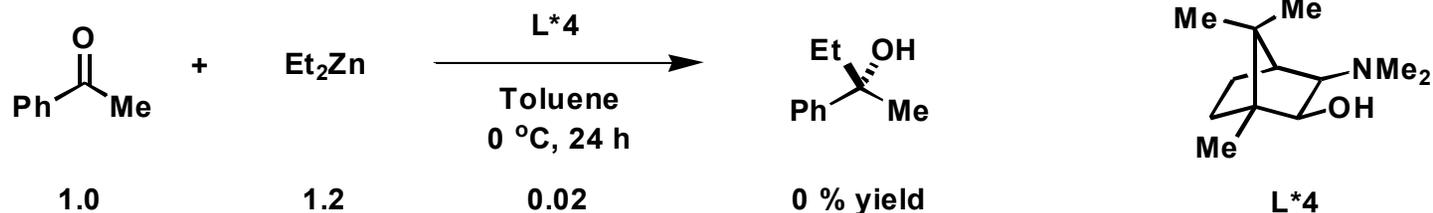
Inch, T. et al. *Tetrahedron Lett.* **1969**, *41*, 3657.

TADDOL-Assisted Additions to Ketones

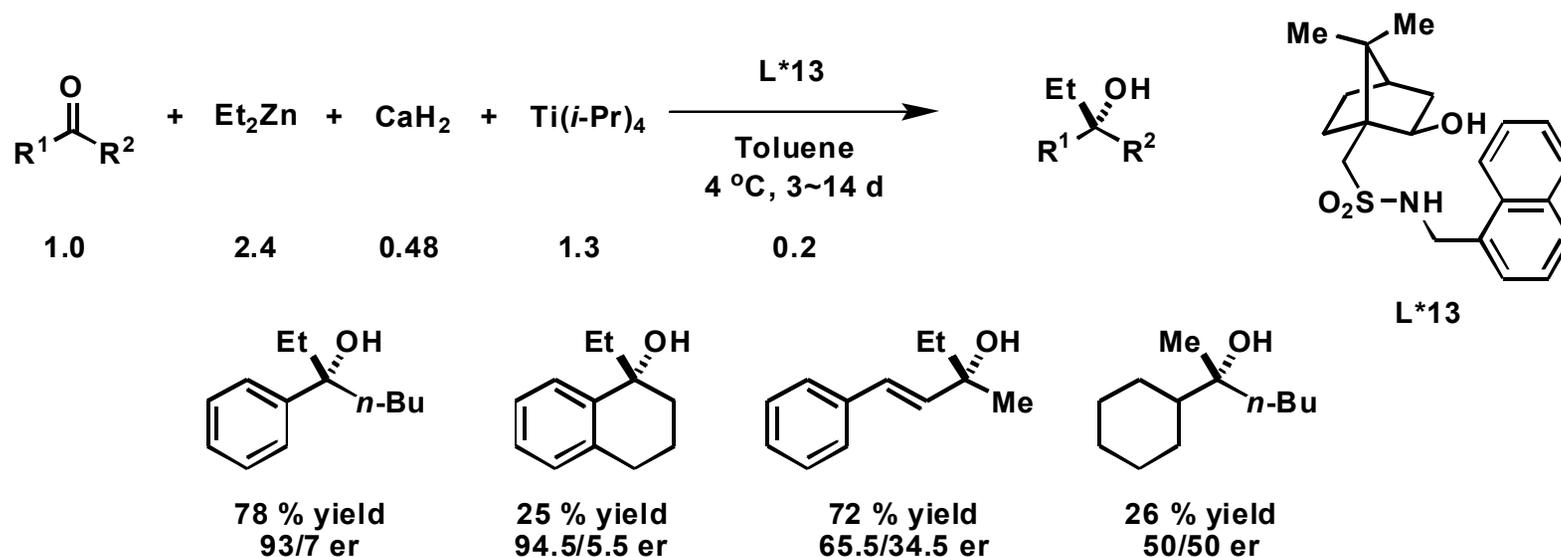


Limitations: Low Temperature, Excess chiral ligand, and Narrow substrate scope

Addition of Dialkylzinc to Ketones



Noyori, R. et al. *J. Organomet. Chem.* **1990**, 382, 19.

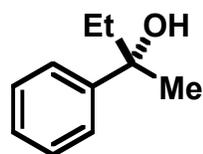
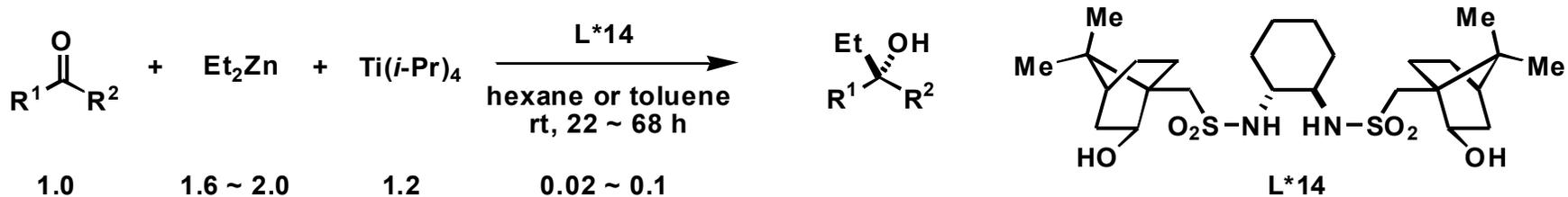


Due to the low reactivity of organozinc reagents toward ketones, Ti based Lewis acid was necessary.

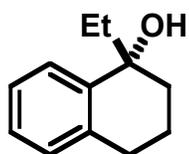
Yus, M. et al. *Tetrahedron Lett.* **1998**, 39, 1239.

Yus, M. et al. *Tetrahedron* **1998**, 54, 5651.

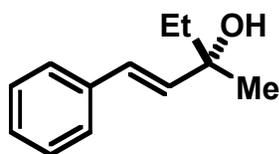
Addition of Dialkylzinc to Ketones: Ti Lewis acid



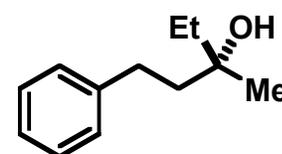
71 % yield
98/2 er



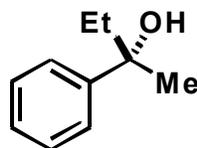
35 % yield
99.5/0.5 er



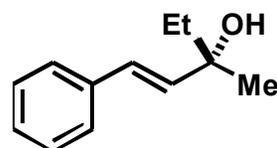
80 % yield
95/5 er



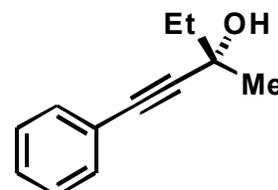
68 % yield
85/15 er



80 % yield
99/1 er



90 % yield
99.5/0.5 er

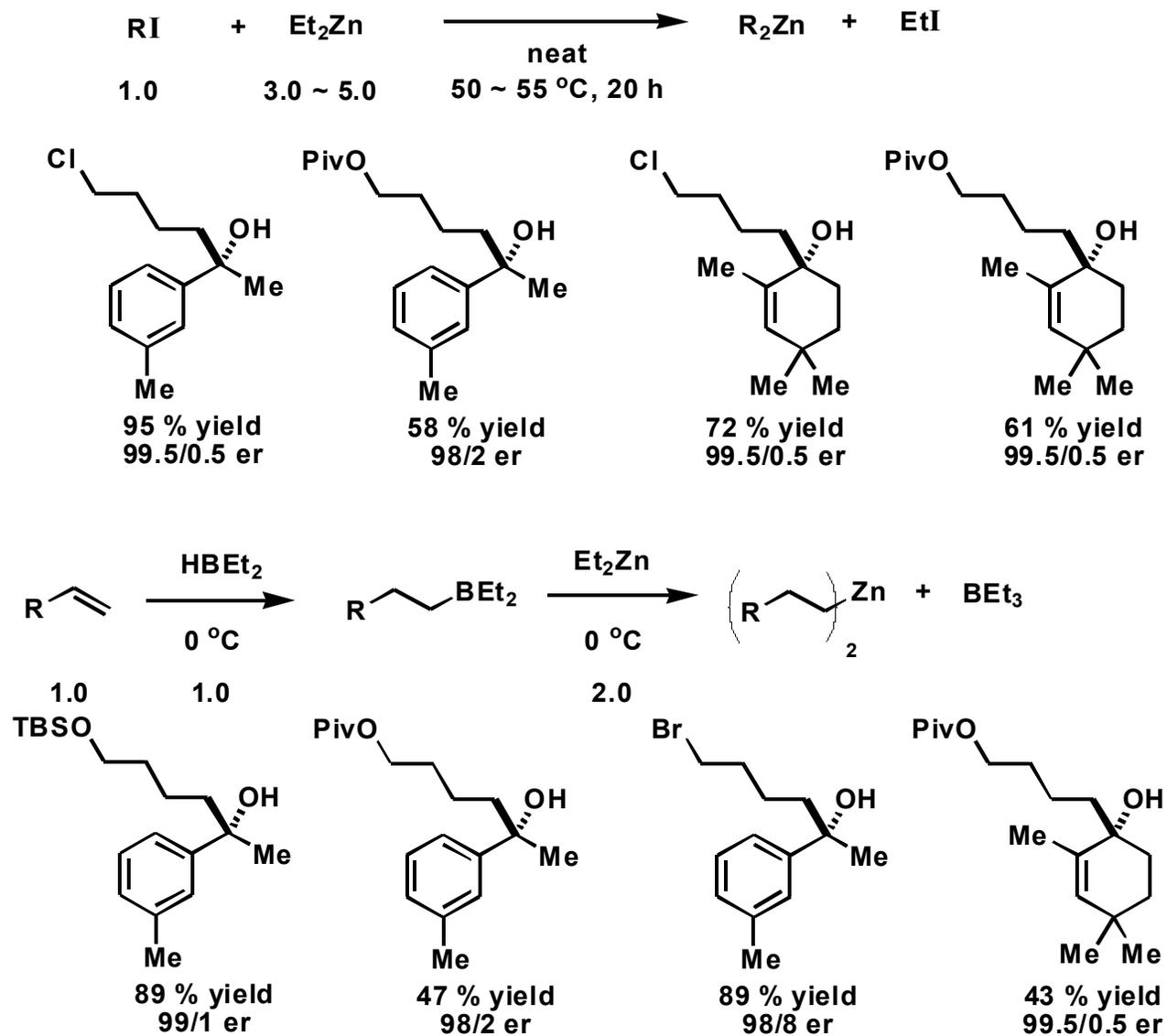


95 % yield
99.5/0.5 er

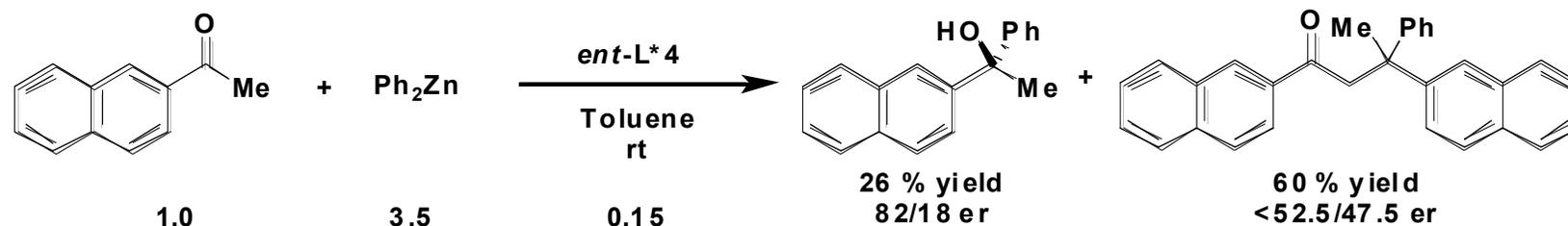
Walsh, P. et al. *J. Am. Chem. Soc.* **2002**, *124*, 10970.

Yus, M. et al. *Tetrahedron: Asym.* **2002**, *13*, 2291.

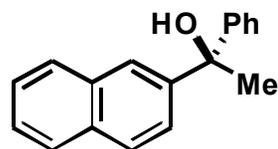
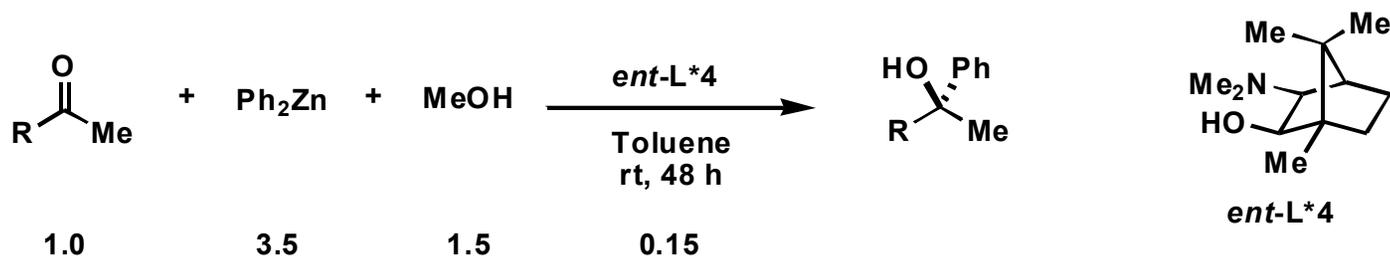
Addition of Functionalized Dialkylzinc



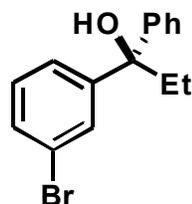
Addition of Diphenylzinc to Ketones



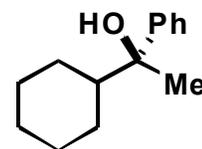
via aldol-dehydration-conjugate addition



58 % yield
86/14 er



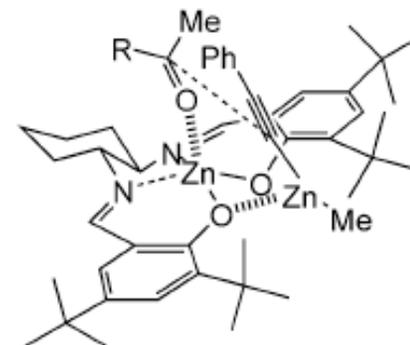
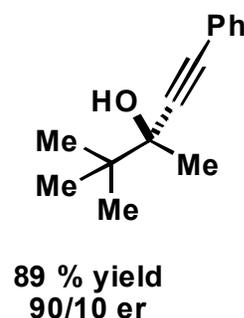
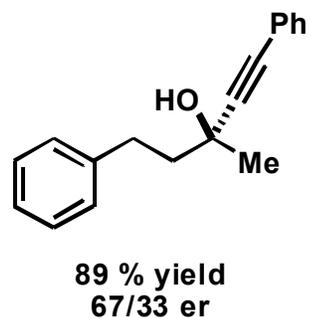
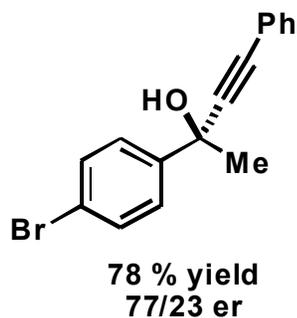
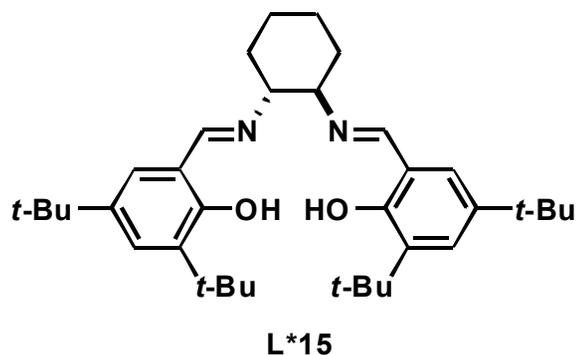
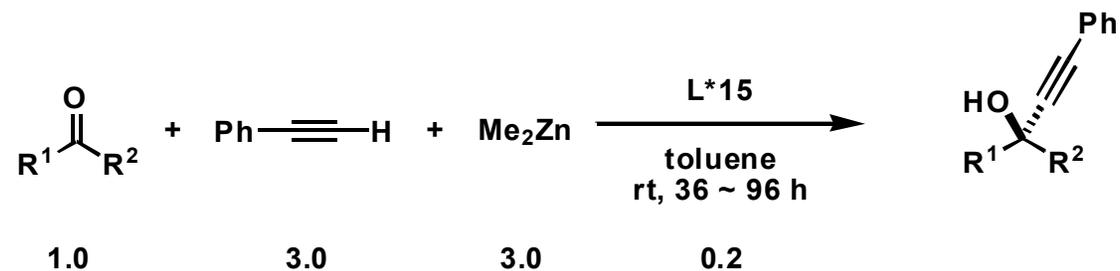
91 % yield
95.5/4.5 er



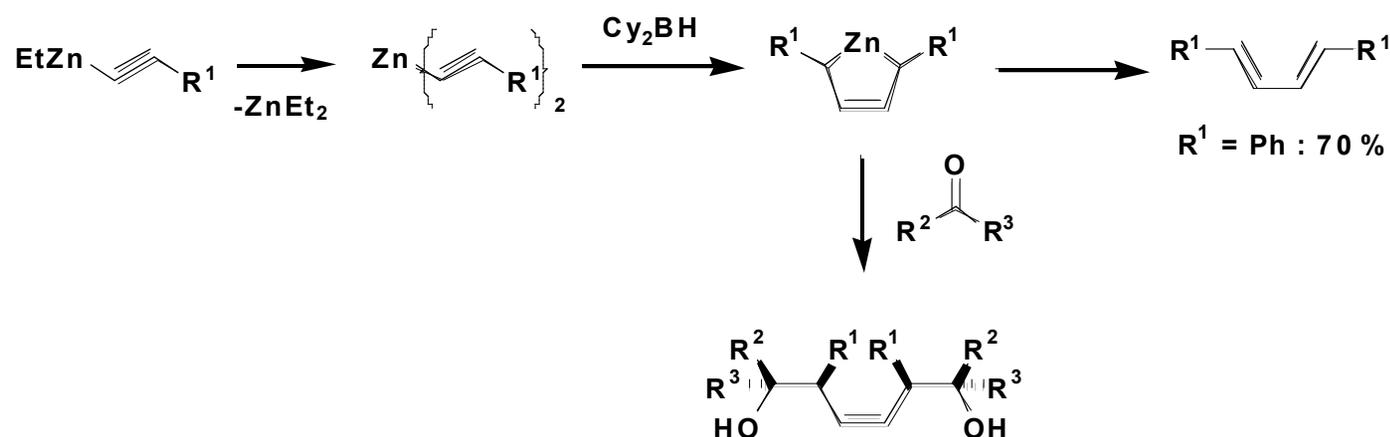
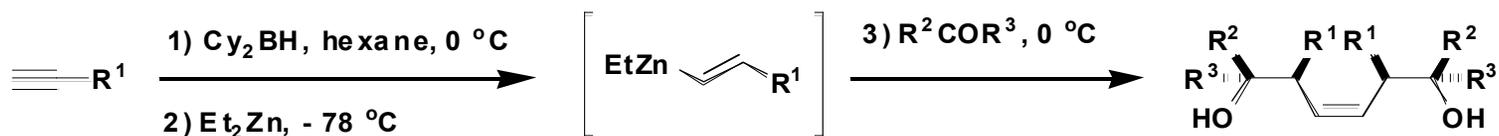
76 % yield
87.5/12.5 er

The side reaction was suppressed by the formation of reactive species, PhZnOMe.

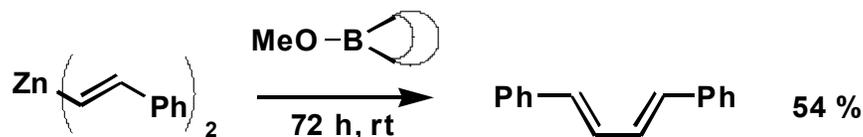
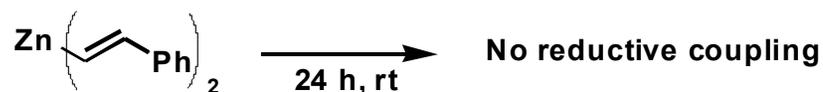
Addition of Alkynylzinc to Ketones



Addition of Vinylzinc to Ketones

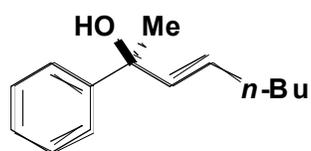
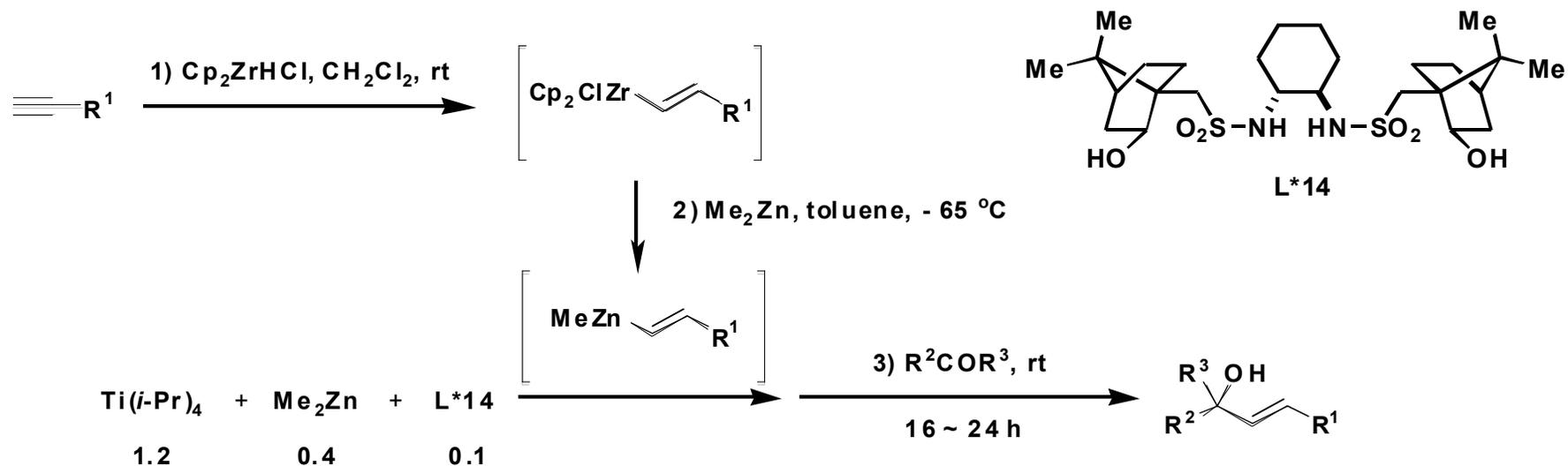


Walsh, P. et al. *J. Am. Chem. Soc.* **2003**, *125*, 3210.

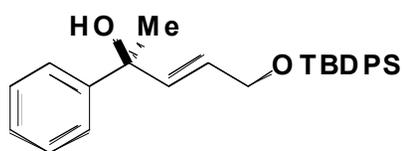


Molander, G. et al. *Organometallics* **1986**, *5*, 2161.

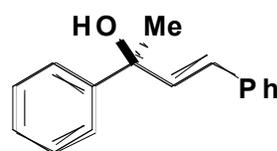
Addition of Vinylzinc to Ketones



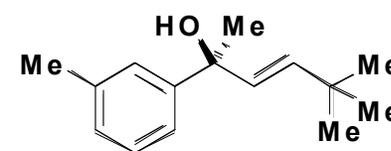
85 % yield
96.5/3.5 er



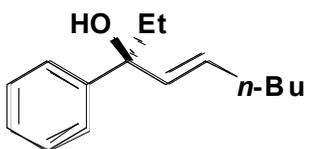
92 % yield
94.5/5.5 er



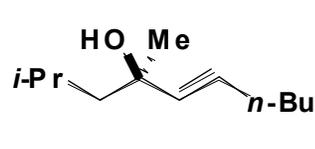
92 % yield
93.5/6.5 er



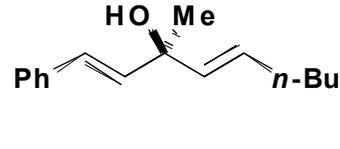
93 % yield
96/4 er



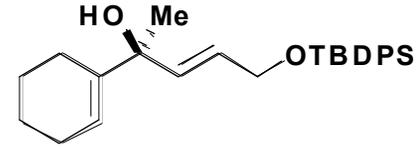
90 % yield
97/3 er



85 %
89.5/10.5 er

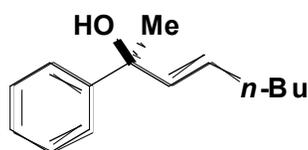
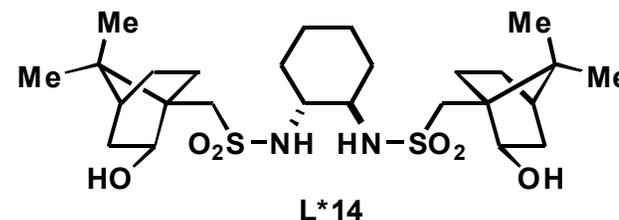
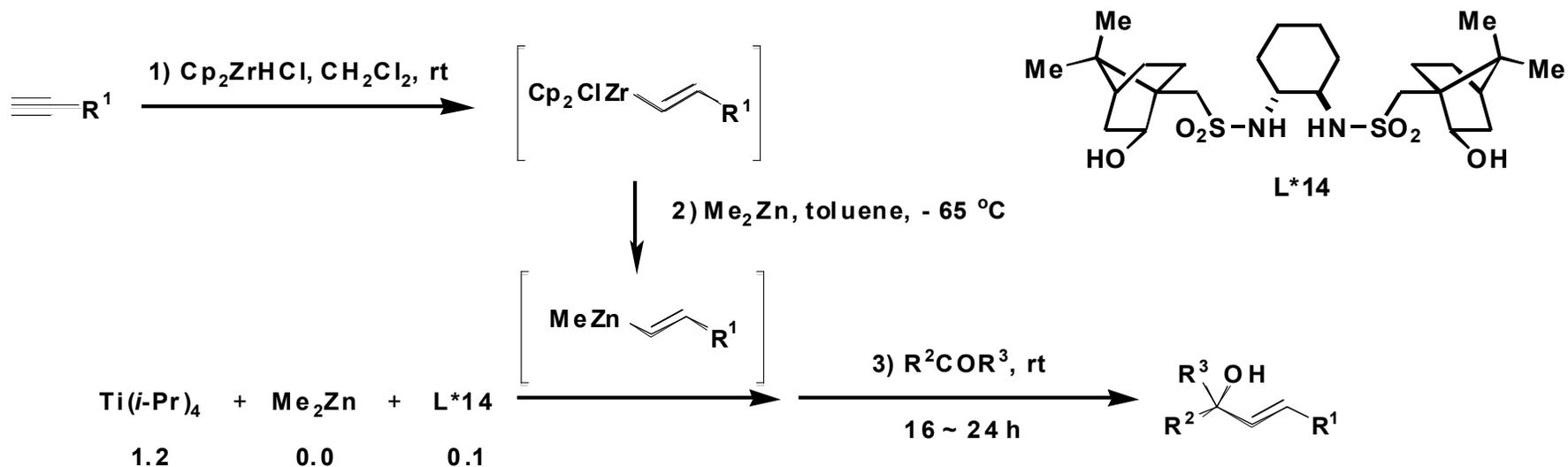


87 % yield
96/4 er

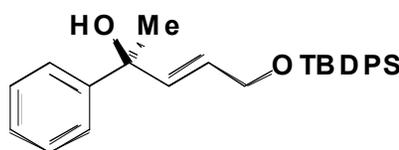


98 % yield
96/4 er

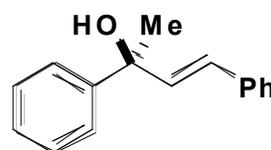
Addition of Vinylzinc to Ketones: Improvement



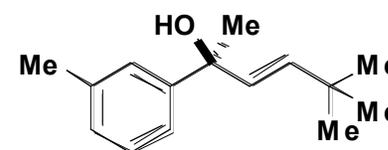
98 % yield
97.5/2.5 er



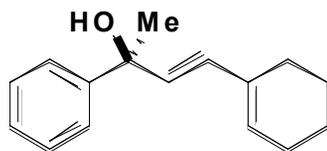
98 % yield
95.5/4.5 er



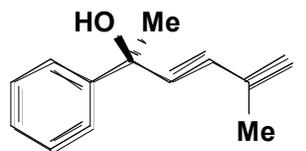
92 % yield
95/5 er



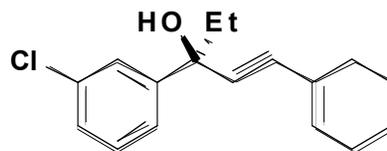
99 % yield
98.5/1.5 er



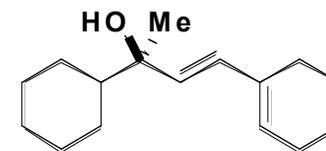
89 % yield
94.5/5.5 er



99 % yield
96.5/3.5 er



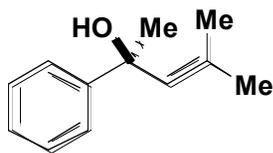
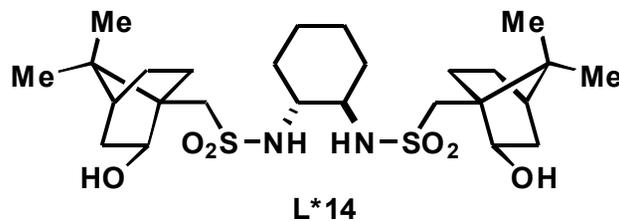
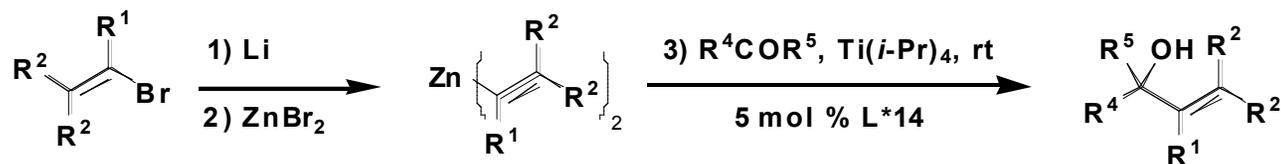
85 % yield
94.5/5.5 er



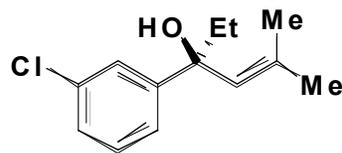
87 % yield
88.5/11.5 er



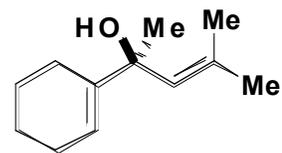
Addition of Divinylzinc to ketones



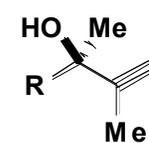
95 % yield
96.5/3.5 er



99 % yield
87.5/12.5 er

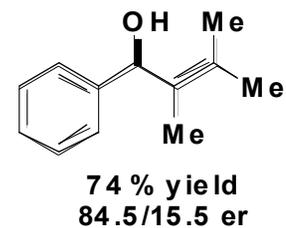
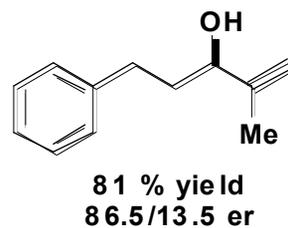
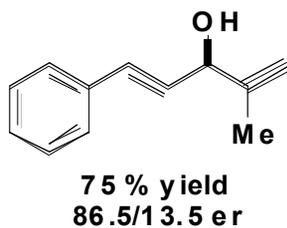
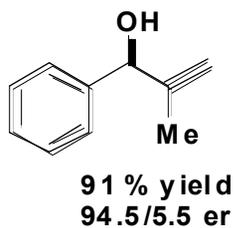
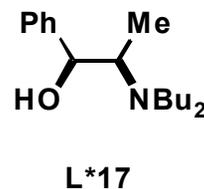
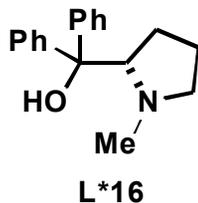


70 % yield
98/2 er



No reaction

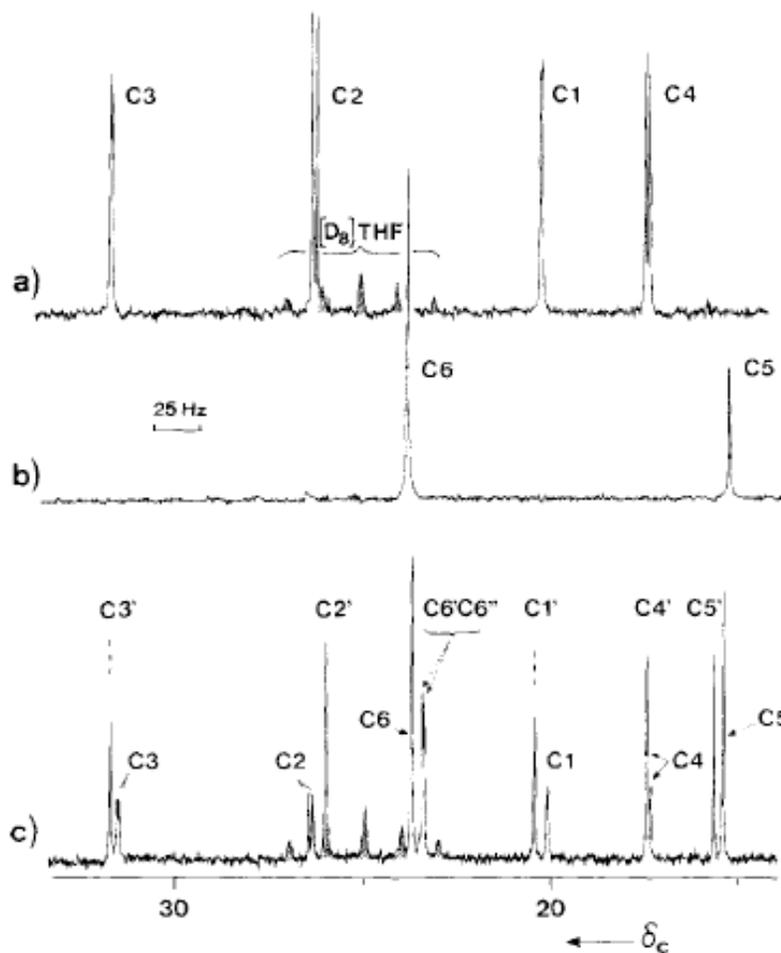
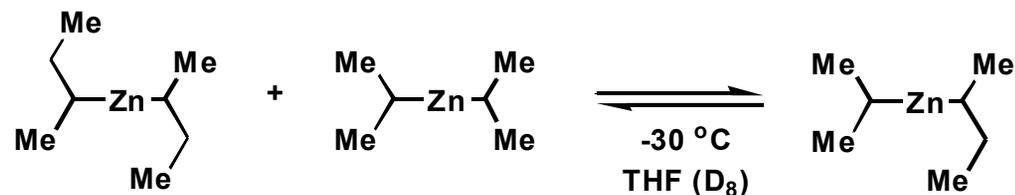
Addition of Diisopropenylzinc to Aldehydes



Summary

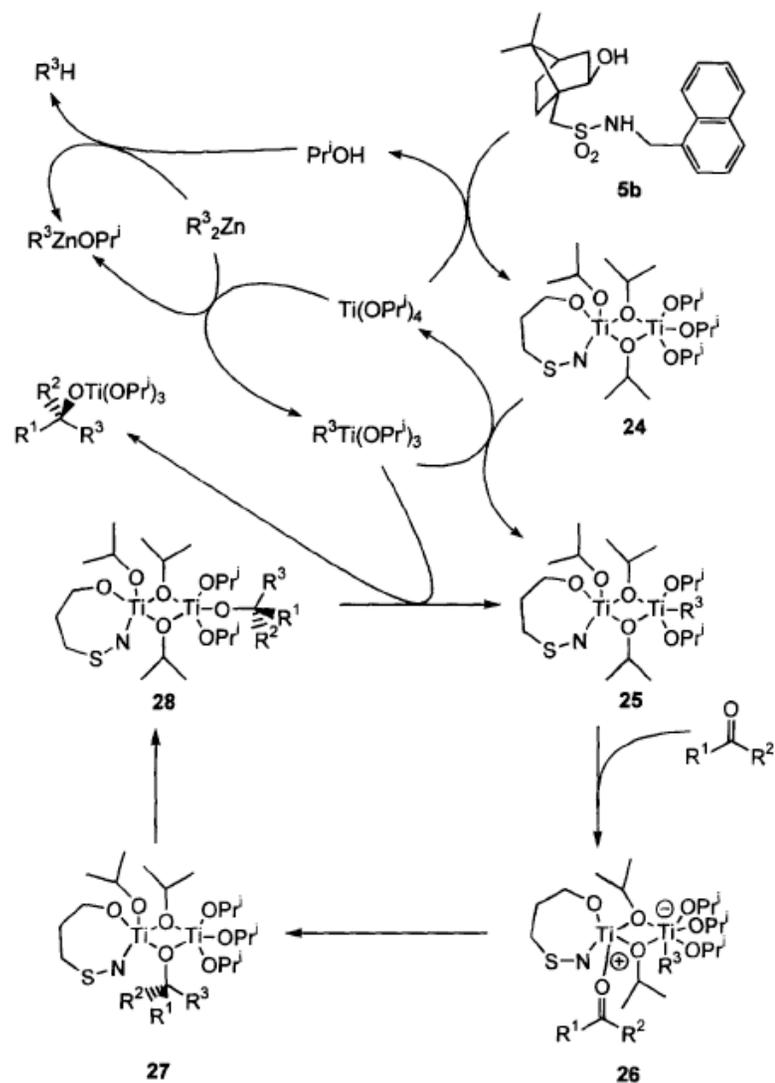
- Enantioselective vinylation of aldehydes was successfully catalyzed by various chiral bidentate ligand.
- Simple vinyl zinc reagents can be easily prepared by transmetalation.
- The preparation of highly substituted vinyl zinc reagents is still difficult.
- The low reactivity problem of ketones was overcome by Ti Lewis acid.
- The reactions of ketones still require very long reaction time.
- The addition of highly substituted vinyl zinc reagents is limited.

Equilibrium of Alkyl and Alkenyl Zinc Species



Mynott, R. et al. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 335.

Addition of dialkylzinc to ketones : Mechanism



Ti complex

