

Good reference:

Titanium and Zirconium in Organic Synthesis Ilan Marek Ed., 2002.

Electronegativity: Ti(1.54); Zr(1.33); Hf(1.3)

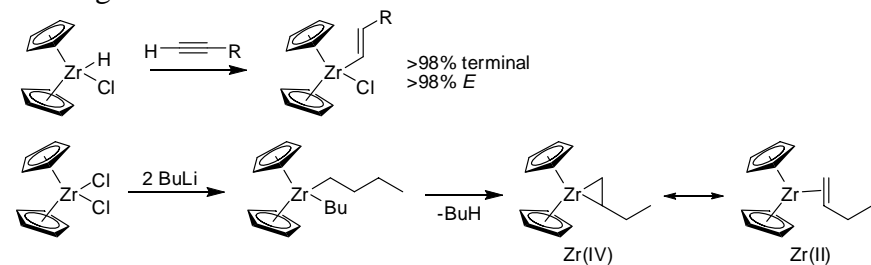
Much of the chemistry is dominated by the oxophilicity of these metals. There are many, many reactions that are catalyzed by Ti and Zr via Lewis acid activation of polar functional groups. Since these mechanisms are not terribly unique, our focus will not be on these reactions.

Since the oxidation state chemistry is dominated by the +4 oxidation state, oxidative addition is not possible and most reactions have to proceed by σ -bond metathesis.

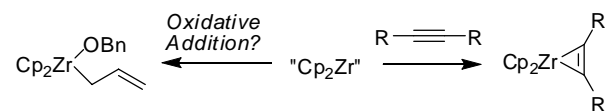
Oxidation State: +4 >> +2 > +3

+2 oxidation state is easiest to achieve for Ti (electronegativity)

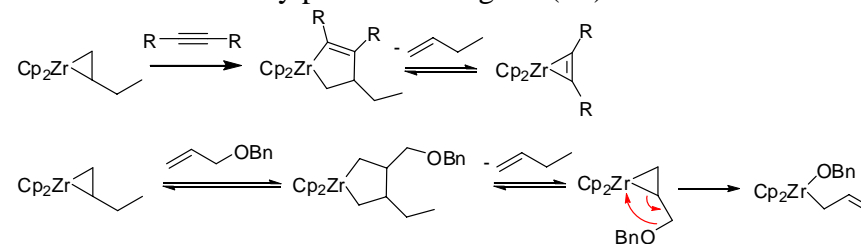
Making Zr—C bonds



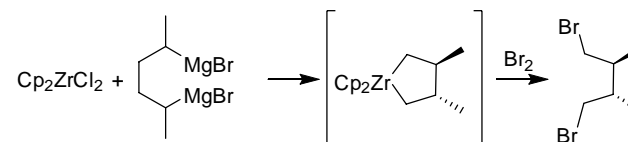
The zirconocene butene complex reacts as one would expect for Zr(II). Many similar reagents exist that are referred to as “Cp₂Zr”



These reactions really proceed through Zr(IV) intermediates.



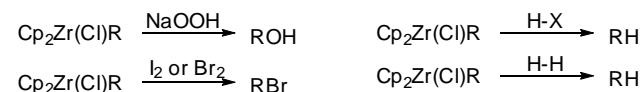
Note: Alkene insertion (carbozirconation) to form zirconacyclopentanes is reversible. Negishi, E. *JCS Chem Comm* **1990** 182.



Productive use of alkyl zirconocenes.

Insertion of polar π -electrophiles is common.

Can't reductively eliminate, so zirconium alkyls must be cleaved from the metal by A) β -hydride elimination, B) external reagents, C) transmetalation. Several common reactions are shown below.

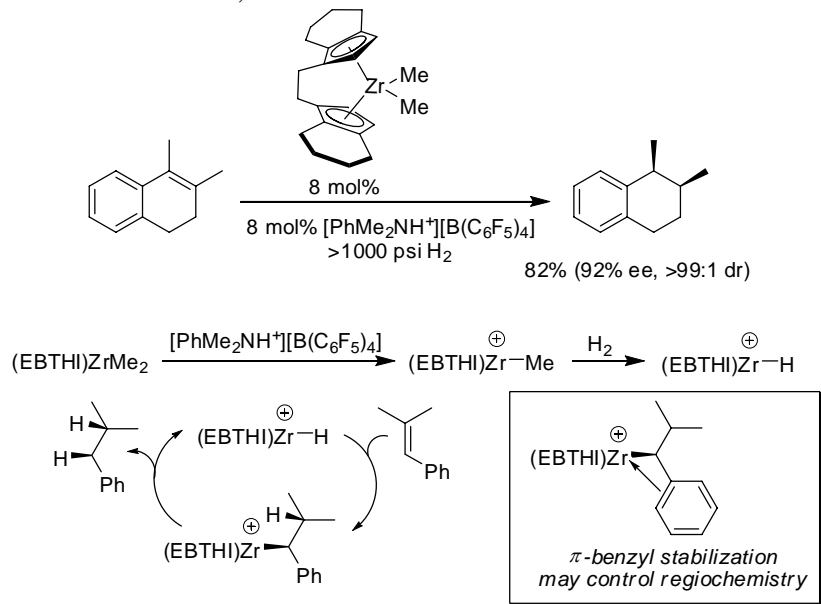


These reactions are often incompatible with catalytic reactions, so they are most often utilized stoichiometrically.

Transmetalation of vinyl zirconocenes is important in catalytic C—C bond forming reactions. Transmetalation from Zr to: Li, Mg, B, Al, Ni, Pd, Cu, and Zn are all possible.

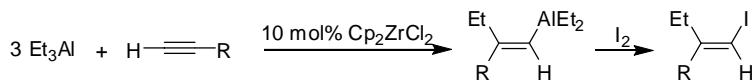
Hydrogenation

Asymmetric hydrogenation of olefins is often associated with late transition-metal Rh, Ir, Ru, and Pd catalysts, however Zr-catalysts are particularly useful for hydrogenation of tetrasubstituted alkenes. Buchwald, S. L. *JACS* **1999** 4916.

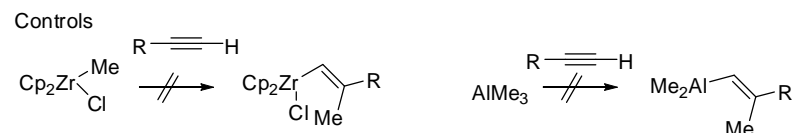


Olefin can't be monosubstituted because "small" alkenes are polymerized rapidly by cationic Zr complexes in a process known as **Ziegler-Natta olefin polymerization**.

Carboalumination

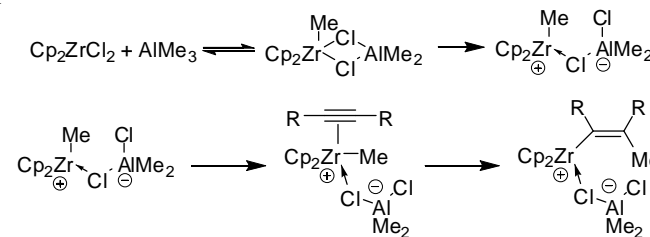


Mechanism of methylalumination: Negishi, E. *JACS* **1978** 2252; *JACS* **1985** 6639.

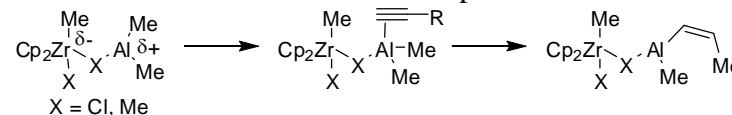


Metals must cooperate. How?

Dynamic polarization. Aluminum can act to make Zr more electrophilic...

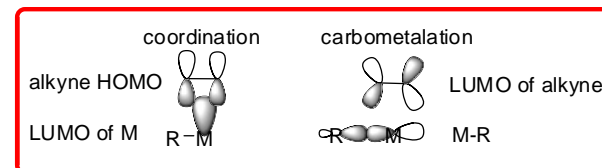


...or Zr can act to make Al more electrophilic.

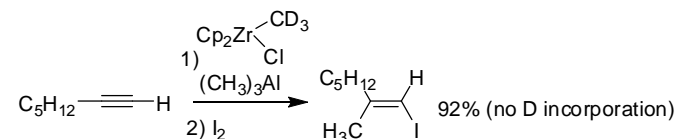


If the metal is more electrophilic (lower LUMO), then binding of alkyne is more favorable.

Binding of the alkyne to a more electrophilic metal polarizes it (i.e. lowers its LUMO) so metalation is facile.

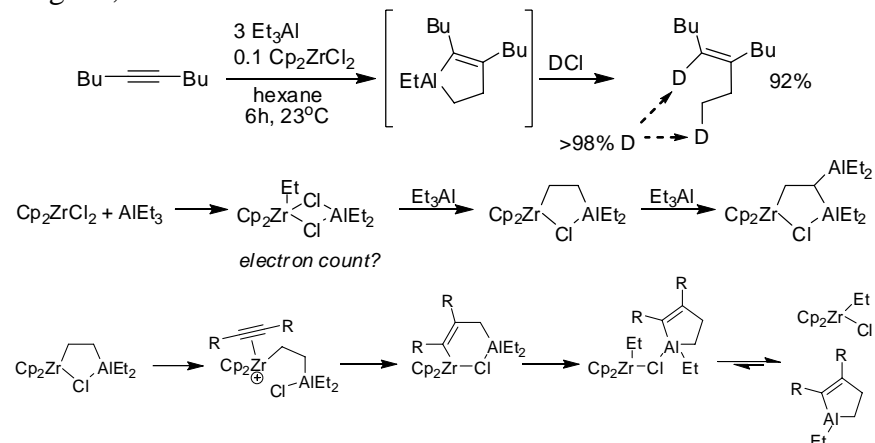


Which mechanism is it?



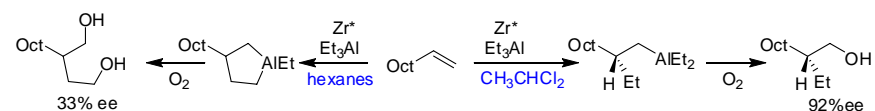
Note: It is important that the CH₃ and CD₃ do not exchange over the time of the experiment.

Mechanism of *ethylaluminum* in nonpolar solvents is different: Negishi, E. *JACS* **1996** 9577.

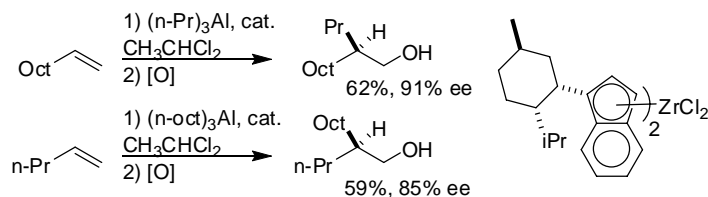


Mechanism is different for Et₂AlCl or *i*BuAl₃ are different still.

Solvent effect:

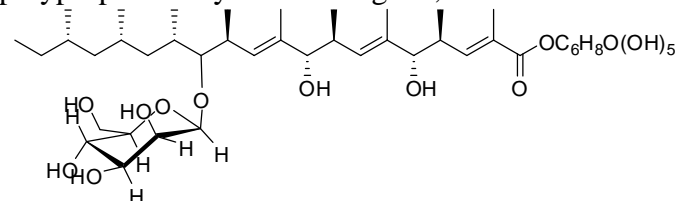


Asymmetric Carboalumination (ZACA) Negishi, E. *JACS* **1996** 1577.



Stereoselectivity for methylaluminum: ca. 75% ee

Uses: polypropionate synthesis. Negishi, E. *PNAS* **2004** 5782.



Iterate by repeating Swern-Wittig-ZACA.

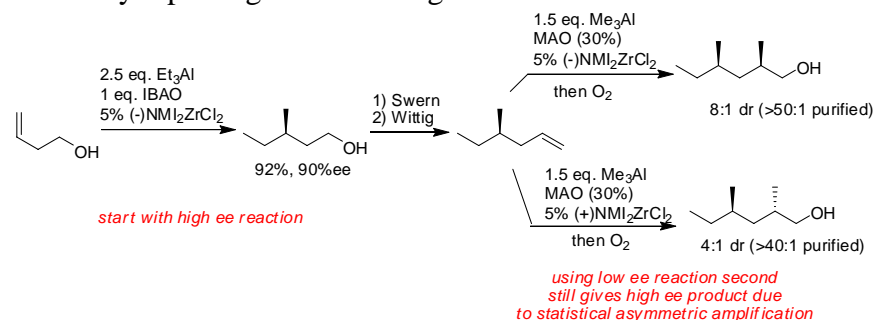
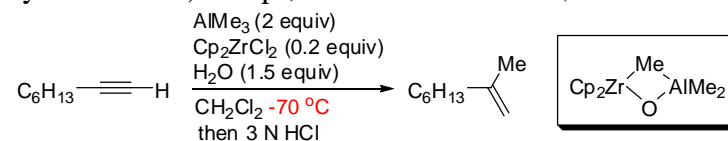


Table 1. Statistical asymmetric amplification

ee in step or species I	ee in step or species II	Max. yield of major stereoisomer	Overall ee
70	70	74.5	94.0
80	80	82.0	97.6
90	80	86.0	98.8
90	90	90.5	99.4
99	99	99.0	99.995

Values shown are percentages. Max., maximum.

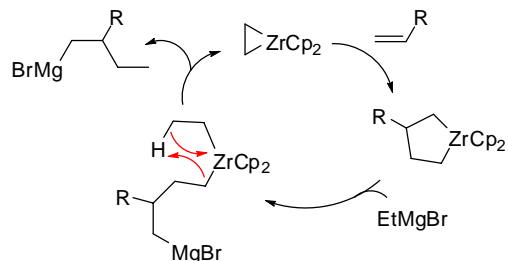
Carboalumination is accelerated by H₂O or MAO (methylalumoxane). Wipf, P. *ACIE* **1993** 1068.; *OL* **2000** 1713.



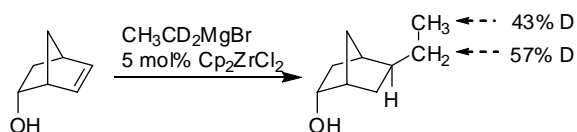
Carboalumination of Dienes: Waymouth, R. *JACS* **1995** 5873.

Titanium-catalyzed Carboalumination: Waymouth, R. M. *Organomet* **2000** 1870.

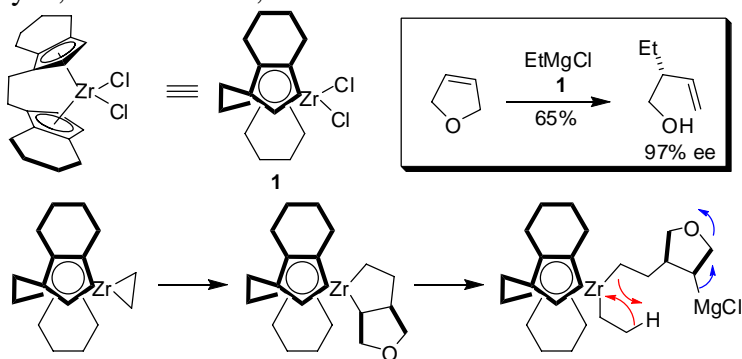
Carbomagnesiation: Ethylmagnesiation see: Dzhemilev, U. M. *Russ. Chem. Rev.* **2000** 121.



Mechanism of regioselective carbomagnesiation: Morkin, J. P.; Hoveyda, A. H. *JACS* **1992**, 6692.



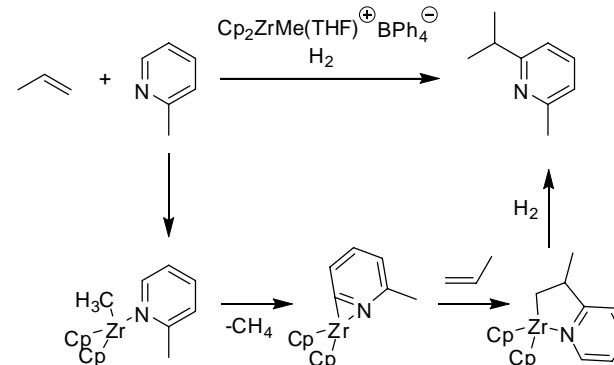
Asymmetric Carbomagnesiation-Elimination: Morkin, J.; Hoveyda, A. *JACS* **1993**, 6997.



For kinetic resolution of allylic alcohol derivatives using Zr-catalyzed carbomagnesiation see: Hoveyda, A. H. *JACS* **1995** 7097.

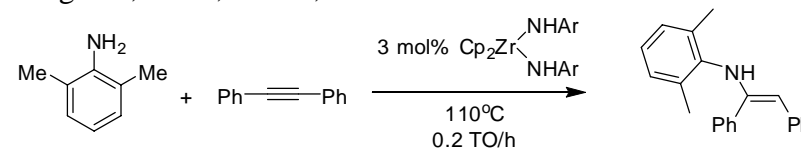
C-H alkylation: Jordan, R. F. *JACS* **1989** 778.

A unique reaction because catalysis takes place under H₂.

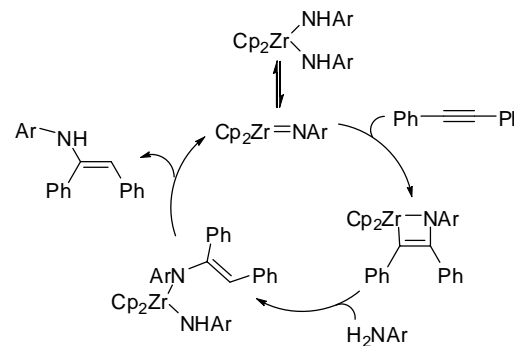


Hydroamination

Bergman, R. G.; Walsh, P. J. *JACS* **1992** 1708.

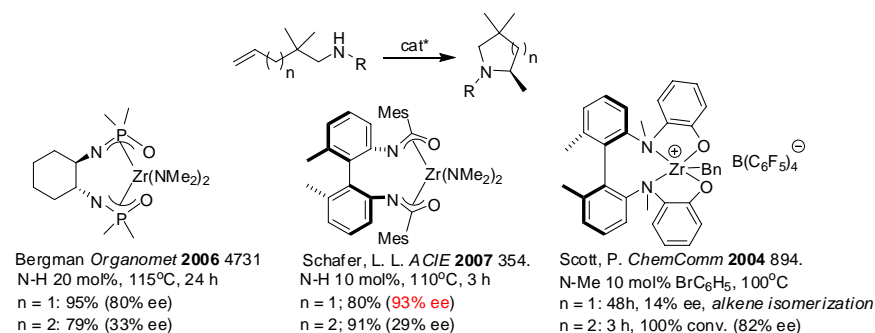


The mechanism of this reaction has been well worked out by Walsh and Bergman. All of the reaction intermediates have been isolated and are observed to undergo the individual stoichiometric reactions.



Rate = $k[\text{Zr}][\text{alkyne}][\text{amine}]^{-1}$ which step is rate-limiting?

Asymmetric hydroamination of alkenes.

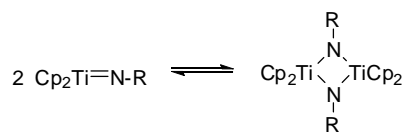


Titanium catalysts are generally faster than Zr catalysts at *alkyne* hydroamination. Lanthanide and Actinide catalysts are as well. See: Marks, T. J. *JACS* **2007** 6149.

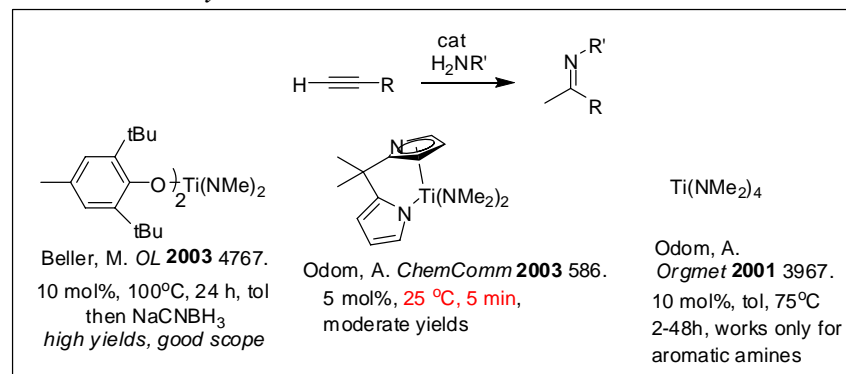
However, Ti catalysts have not been very successful at *alkene* hydroamination. Exceptions: Schaefer, L. L. *OL* **2005** 2959; Odom, A. *ACIE* **2005**, 5972; Ackermann, L. *OL* **2004** 2515.

Mechanism of Cp₂TiMe₂-catalyzed alkyne hydroamination. See: Doye, S. *ACIEE* **2001** 2305.

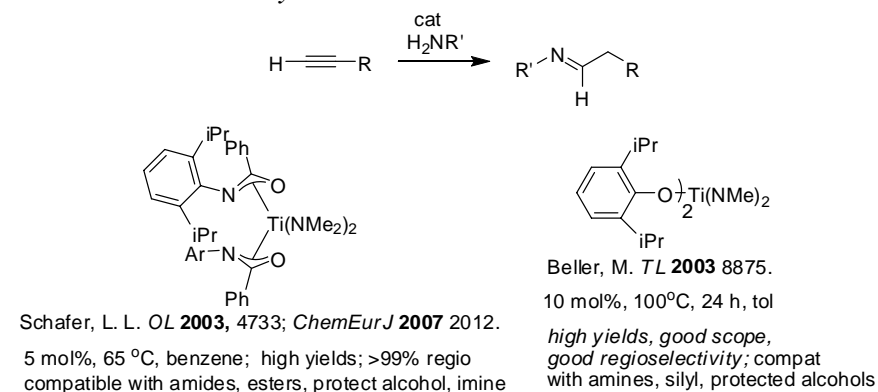
Note: "Small" amines do not work well due to dimerization:



Markovnikov Hydroamination

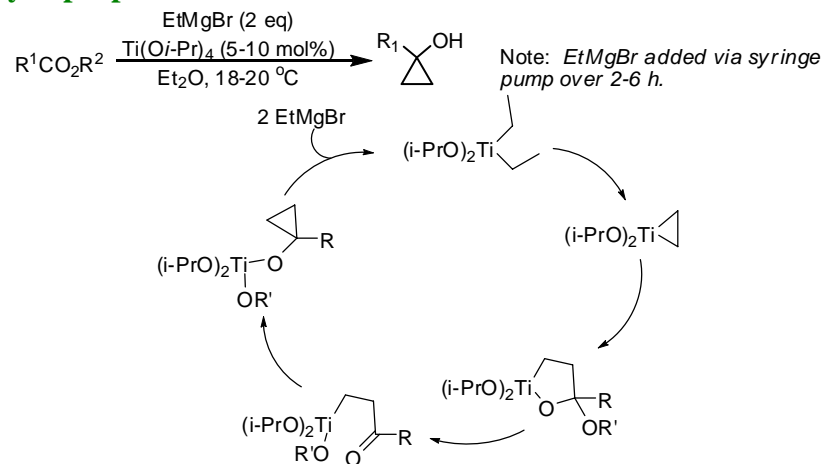


Anti-Markovnikov Hydroamination

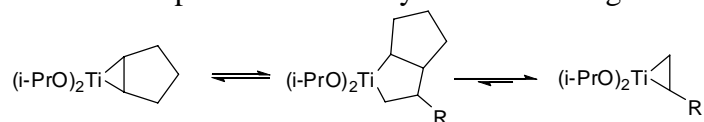


In general *catalysis with titanium is more facile* and thus a wider range of reactions are catalyzed by titanium. Furthermore, Ti(II) is much more prevalent than Zr(II), so redox catalysis through Ti(II)-Ti(IV) cycles is more common.

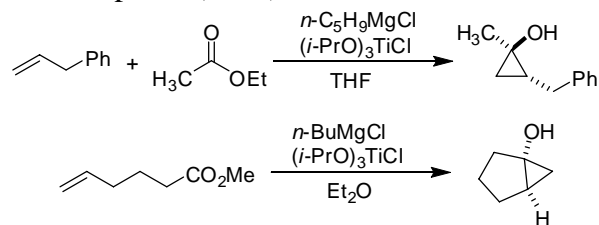
Cyclopropanation



Alkenes can be coupled with esters by alkene exchange.



Org. Syn. Vol. 80, p.111 (2003).

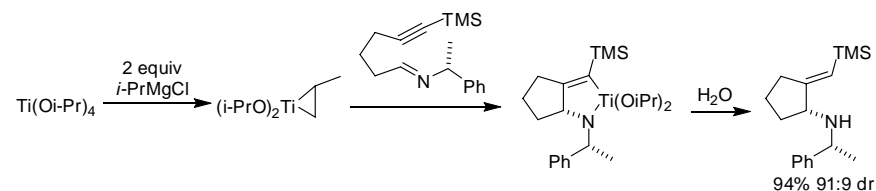


Asymmetric cyclopropanation: Corey, E. J. *JACS* **1994** 9345.

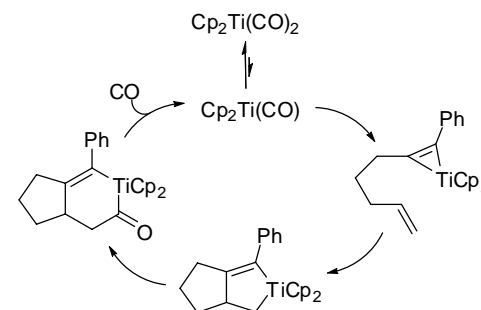
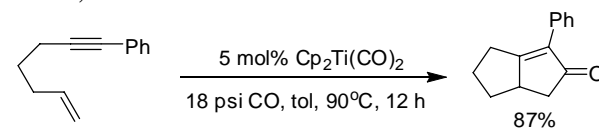
Reductive cyclization

Titanacyclopropanes are excellent reagents for reductive coupling. Most of the chemistry is stoichiometric in Ti because cleavage of the resulting metallacycle to regenerate a catalyst is difficult.

Example of stoichiometric reductive coupling. Sato, F. *ChemComm* **1996** 533.

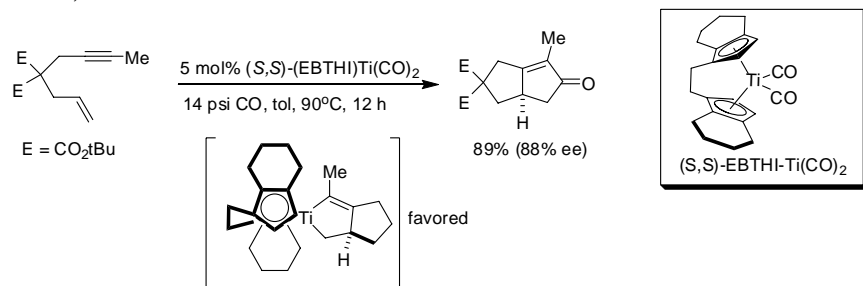


Catalytic Pauson-Khand: Buchwald, S. L. *JACS* **1996**, 9450; *JACS* **1999**, 5881.

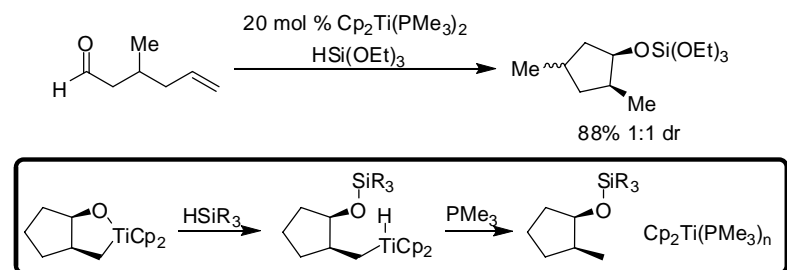


Isonitriles (i.e. TMSNC) can replace CO: Buchwald, S. L. *JOC* **1996**, 2713.

Asymmetric Ti-catalyzed Pauson-Khand: Buchwald, S. L. *JACS* **1999**, 7026.

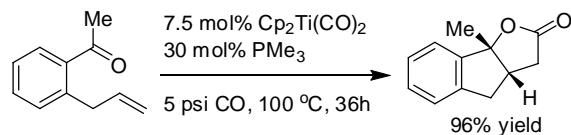


Catalytic reductive cyclizations of carbonyl compounds. Crowe, W. E. *JACS* **1995** 6787.



Silanes are good “oxophilic” reductants.

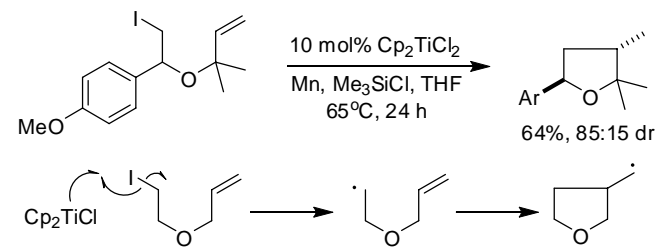
Buchwald, S. L. *JACS* **1997**, 4424.



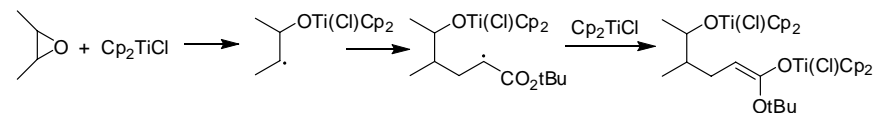
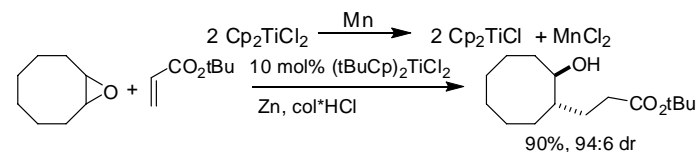
Ti(III) catalysis: Titanium(III) is much more prevalent than Zr(III).

Ti(III) catalysis usually takes place by atom-abstraction to generate Ti(IV) intermediates. A coreductant (Mn or Zn) is necessary to regenerate Ti(III).

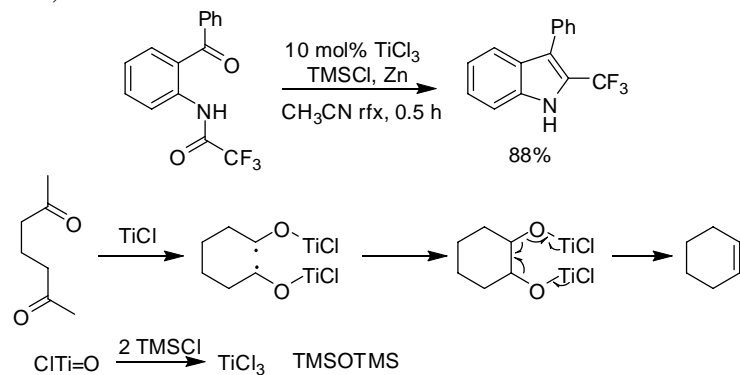
Hirao, T. *JOC* **2003** 1633.



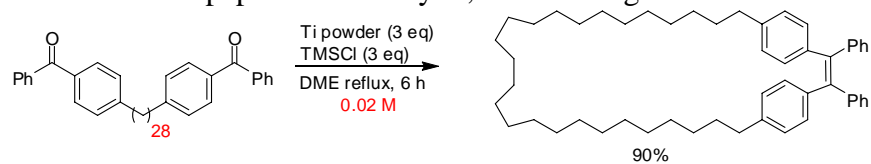
Epoxide opening : Stoichiometric: Nugent, W. A.; RajanBabu, T. V. *JACS* **1988** 8561; *JACS* **1994** 986. Catalytic: Gansauer, A. *JACS* **1999** 12849.



McMurry Coupling

Furstner, A. *JACS* **1995** 4468.

From the same paper – not catalytic, but amazing.

Nelson, S. *JOC* **1997** 4566. $(\text{THF})_3\text{TiCl}_3$ complex dramatically accelerated McMurry type pinacol coupling.