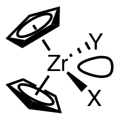
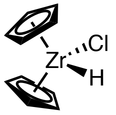
**Reviews:**

• *Metallocenes in regio- and stereoselective synthesis, Vol. 8*, Takahashi, T. Ed.; Springer: Berlin; New York, **2005**.
• Marek, I.; Chechik-Lankin, H.; *Functionalized Organozirconium and Titanium in Organic Synthesis*, in *Handbook of Functionalized Organometallics: Applications in Synthesis*, Knochel, P Ed.; Wiley-VCH: Weinheim, **2005**.

### General Reactivity of Zirconocene Compounds

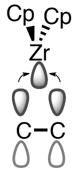


Generalized zirconocene

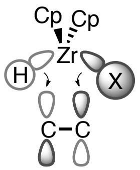


Zirconocene hydrochloride (Schwartz's reagent)

- Zirconocene complexes of the formula $Cp_2ZrXY$ are 16-electron $d^0$ Zr(IV) complexes with one empty valence shell orbital available for coordination. Consequently, many reactions of these compounds are initiated by the interaction of an electron donor such as the $\pi$-bond of an olefin with the empty Zr orbital.



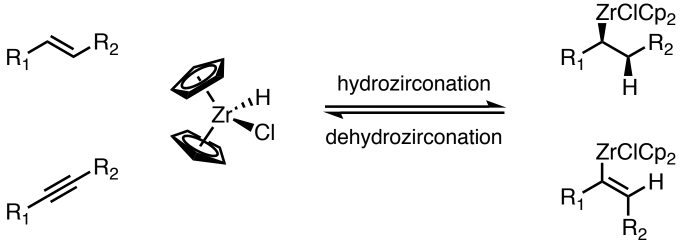
bonding



backbonding

### Hydrozirconation

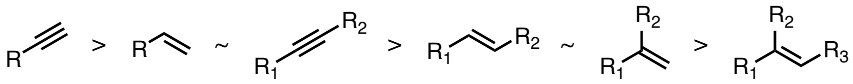
- Treatment of alkenes and alkynes with zirconocene hydrochloride gives rise to alkyl- and alkenylzirconium intermediates, respectively.



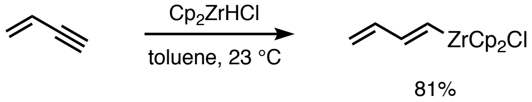
$R_1$=alkyl, aryl; $R_2$=alkyl, H

- Hydrozirconation proceeds by a stereospecific, concerted 4-centered process that typically places zirconium on the less-substituted carbon.

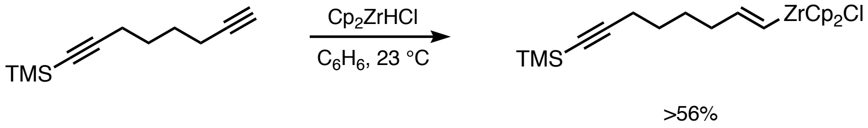
- The relative rates of hydrozirconation for different substrates are as follows:



- Selective hydrozirconations have been reported:

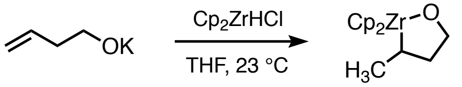


Fryzuk, M. D.; Bates, G. S.; Stone, C. *J. Org. Chem.* **1991**, *56*, 7201–7211.



Crombie, L.; Hobbs, A. J. W.; Horsham, M. A.; Blade, R. J. *Tetrahedron Lett.* **1987**, *28*, 4875–4878.

- Neighboring groups can influence the site of zirconation:



Takaya, H.; Yamakawa, M.; Mashima, K. *J. Chem. Soc., Chem. Commun.* **1983**, 1283–1284.

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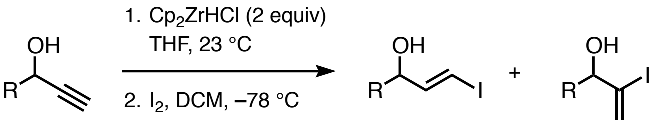
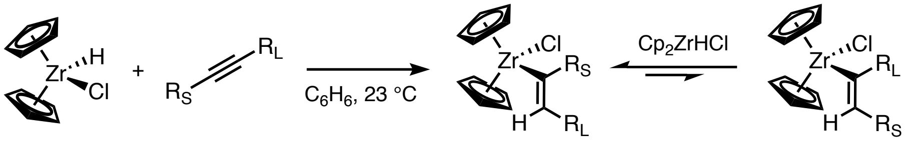
- $CH_3Li–ZnCl_2$ reverses the regioselectivity in hydrozirconation of propargylic alcohols. The authors propose that alkoxide generation with $CH_3Li$ promotes directed hydrometalation, while $ZnCl_2$ blocks isomerization to the thermodynamically favored linear vinylzirconium species.



| | *linear* | *branched* |
|---|---|---|
| without additive | > 50 | 1 |
| MeLi (1 equiv), $ZnCl_2$ (6 equiv) | 1 | > 50 |

Zhang, D.; Ready, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 12088–12089.

- If the thermodynamic product is desired, however, equilibration can be achieved by treatment with additional hydrozirconation reagent.

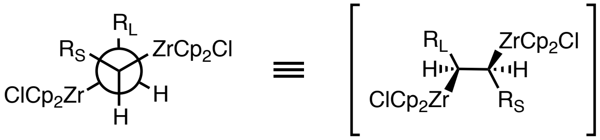


**1** **2**

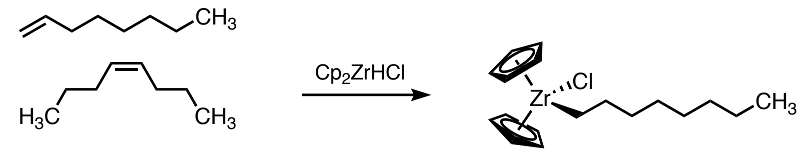
| | | Product ratio **1 : 2** | |
|---|---|---|---|
| $R_S$ | $R_L$ | Initially observed | after treatment with $Cp_2ZrHCl$ |
| H | *n*-Bu | > 98 : 2 | ND |
| $CH_3$ | Et | 55 : 45 | 89 : 11 |
| $CH_3$ | *n*-Pr | 69 : 31 | 91 : 9 |
| $CH_3$ | *i*-Bu | 55 : 45 | > 95 : 5 |
| $CH_3$ | *i*-Pr | 84 : 16 | > 98 : 2 |
| $CH_3$ | *t*-Bu | > 98 : 2 | ND |

Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679–680.

- Isomerization presumably occurs via a dimetalated species:



- Similarly, internal alkenes undergo rapid isomerization at room temperature to terminal alkenes via β-H-elimination of the initially formed alkyl zirconium intermediate, followed by re-addition. By contrast, considerably higher temperatures are required for alkene isomerization in hydroalumination and hydroboration reactions.



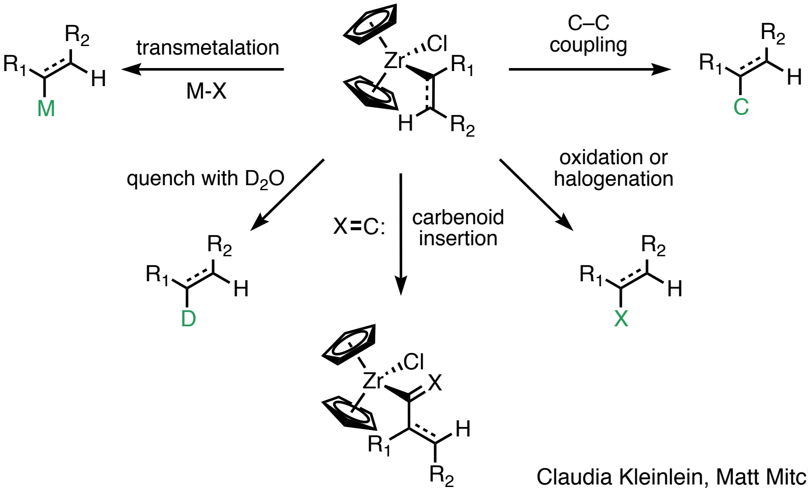
quantitative

Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115–8116.

### Reactions of organozirconocene compounds

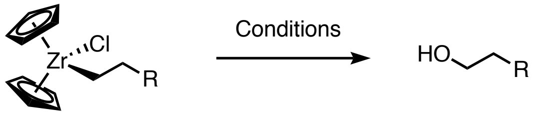
Review: Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853–12910.

- Due to steric crowding around zirconium, only small electrophiles react with organozirconocenes.



### Oxidation

- A number of reagents are capable of oxidizing alkylzirconocenes to the corresponding linear alcohols. These methods do not apply to alkenylzirconocenes.
- In the following table, *n*-octylzirconocene chloride (R = *n*-Hex) was obtained by hydrozirconation–isomerization of a mixture of linear octenes (*vide supra*).

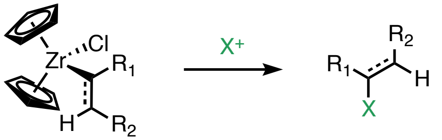


| R | Conditions | Yield |
|---|---|---|
| *t*-Bu | $O_2$; $H_2O$ | 91% |
| isopropenyl | $O_2$; $H_2O$ | 77% |
| *n*-Hex | $H_2O_2$, NaOH | 69% |
| *n*-Hex | *t*-BuOOH | 72% |
| *n*-Hex | *m*-CPBA | 45% |
| *n*-Hex | $CrO_2Cl_2$ | 52% |

Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115–8116.

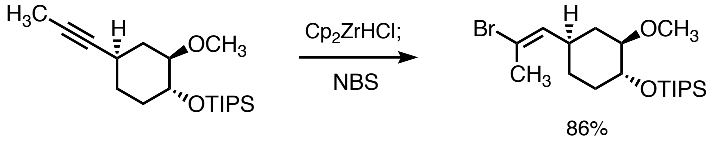
### Halogenation

- Electrophilic halogenation of alkyl- and alkenylzirconocenes is commonly employed for the synthesis of vinyl halides.



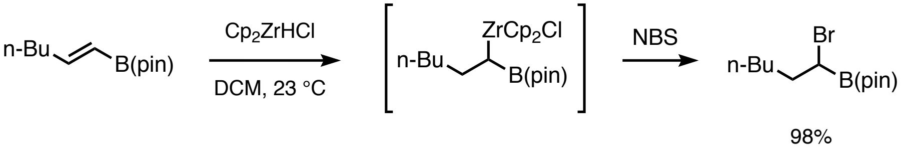
$X^+$ = $I_2$, $Br_2$, $PhICl_2$, NBS, NCS

- The reaction proceeds with retention of configuration at carbon and affords *E*-vinyl halides from alkynes.



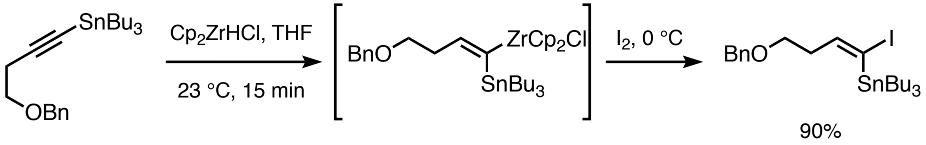
Ragan, J. A.; Nakatsuka, M.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 4267–4268.

- 1,1-Bimetallic reagents of zirconium and boron can be prepared *in situ* and converted into valuable building blocks. In the example shown, $\alpha$-zirconation occured exclusively.



Zheng, B.; Srebnik, M. *Tetrahedron Lett.* **1994**, *35,* 1145–1148.

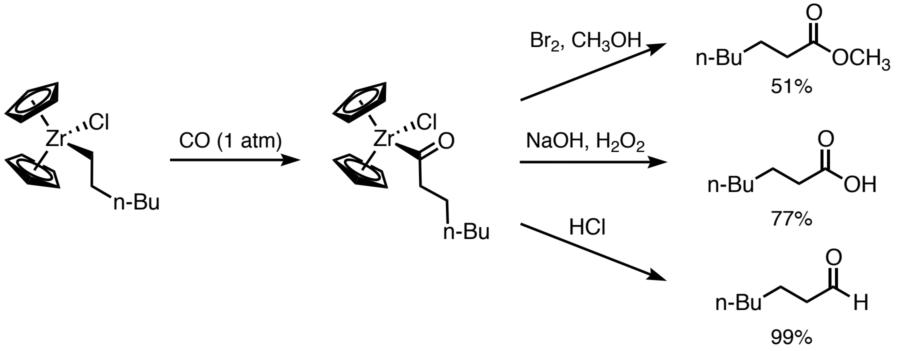
- High regioselectivity is observed in the hydrozirconation of alkynyl stannanes as well:



Lipshutz, B. H.; Keil, R.; Barton, J. C. *Tetrahedron Lett.* **1992**, *33*, 5861–5864.

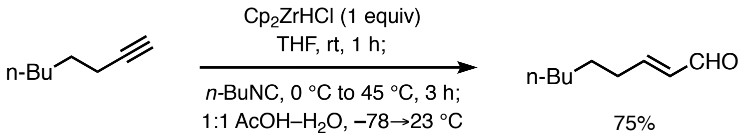
### Carbenoid insertion

- Acylzirconocenes are formed by insertion of carbon monoxide.
- These acyl zirconium complexes can be converted into the corresponding aldehydes, carboxylic acids and esters by the methods shown:



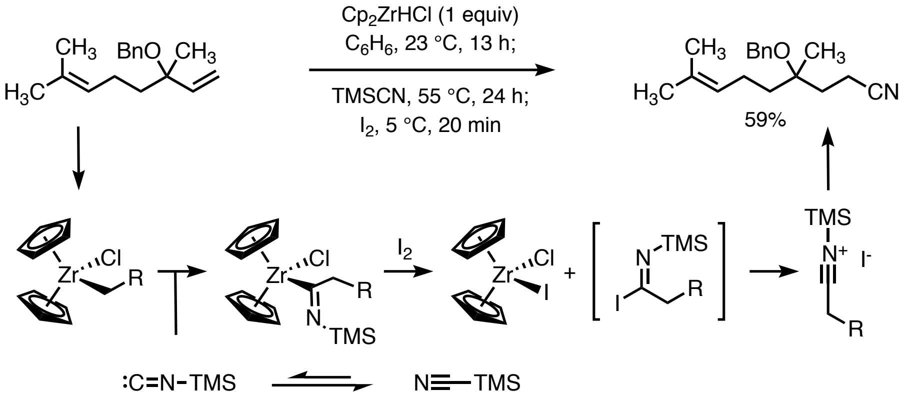
Bertelo, C. A.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 228–230.

- Homologated aldehydes are obtained by protonation–hydrolysis of isonitrile insertion products.



Negishi, E.-i.; Swanson, D. R.; Miller, S. R. *Tetrahedron Lett.* **1988**, *29*, 1631–1634.

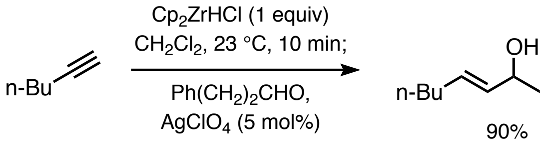
- Similarly, Buchwald and LaMaire report the preparation of homologated nitriles by treatment of an organozirconocene with cyanotrimethylsilane and iodine.



Buchwald, S. L.; LaMaire, S. J. *Tetrahedron Lett.* **1987**, *28*, 295–298.

### Silver-catalyzed Addition to Aldehydes and Epoxides

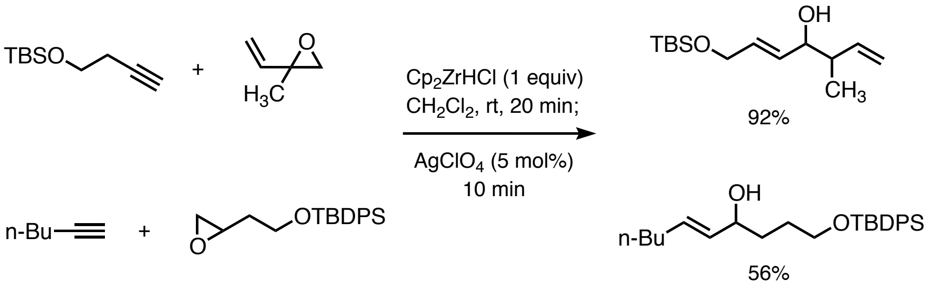
- Silver-promoted chloride abstraction from organozirconocenes relieves steric congestion and forms a Lewis-acidic cationic complex that activates aldehydes for 1,2-addition.



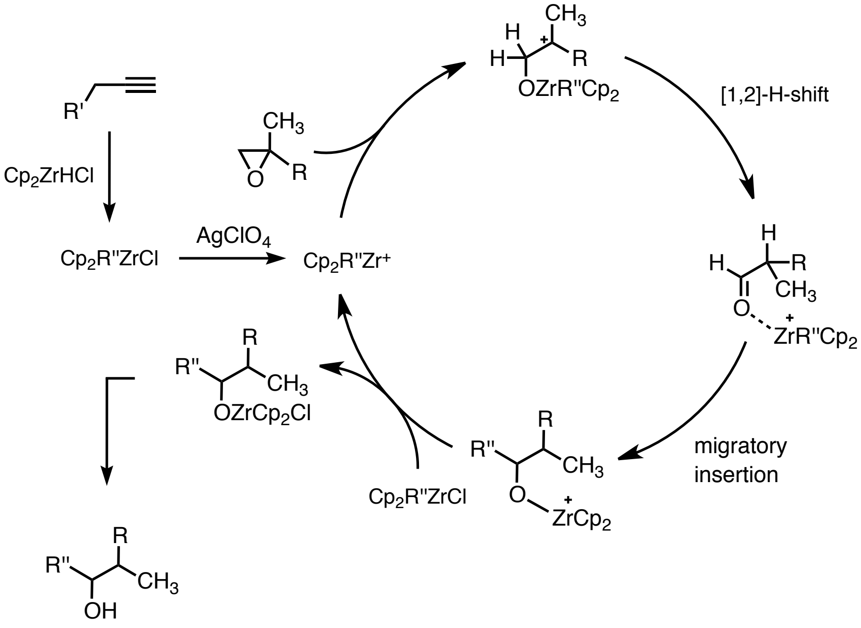
| $AgClO_4$ | time | yield [%] |
|---|---|---|
| none | 2 h | 17 |
| 5 mol% | 10 min | 90 |

Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett.* **1992**, *33*, 5965–5968.

- Halide abstraction can initiate a tandem epoxide rearrangement–carbonyl addition sequence to give allylic alcohols:



- The reaction with epoxides is proposed to be initiated by $[Zr]^+$-induced epoxide opening, followed by [1,2]-hydride shift and nucleophilic attack on the resulting aldehyde.



Wipf, P.; Xu, W. *J. Org. Chem.* **1993**, *58*, 825–826.

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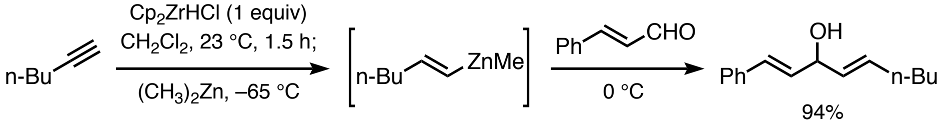
### Transmetalation

- While steric bulk limits the scope of electrophiles that organozirconocenes may engage directly, transmetalation enables a broad variety of transformations involving organometallic intermediates.
- Transmetalations of organozirconocenes to aluminum, boron, copper, mercury, nickel, palladium, tin, and zinc have been reported.

### Transmetalation to Zinc

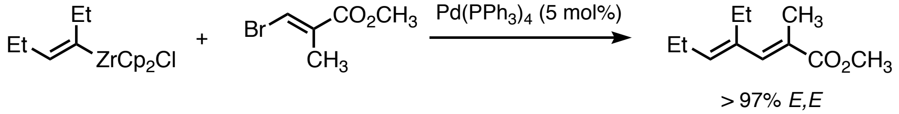
Review: Wipf, P.; Kendall, C. *Chem. Eur. J.* **2002**, *8*, 1778–1784.

- Transmetalation to zinc combines the facile formation of organozirconium compounds with the broad synthetic utility of organozincs.



Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197–5200.

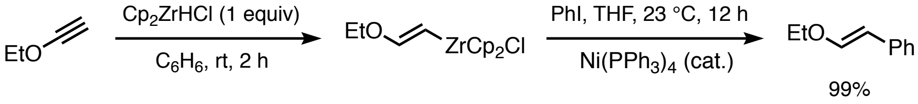
- Addition of substoichiometric zinc chloride dramatically enhances the rate of palladium-catalyzed cross-coupling of organozirconocenes. It is believed that direct Zr→Pd transmetalation is prohibitively slow due the steric demands of the zirconocene.



| | |
|---|---|
| 0.5 equiv $ZnCl_2$, 1 h | 82% |
| 0.2 equiv $ZnCl_2$, 2 h | 72% |
| no $ZnCl_2$, 6 h | < 2% |

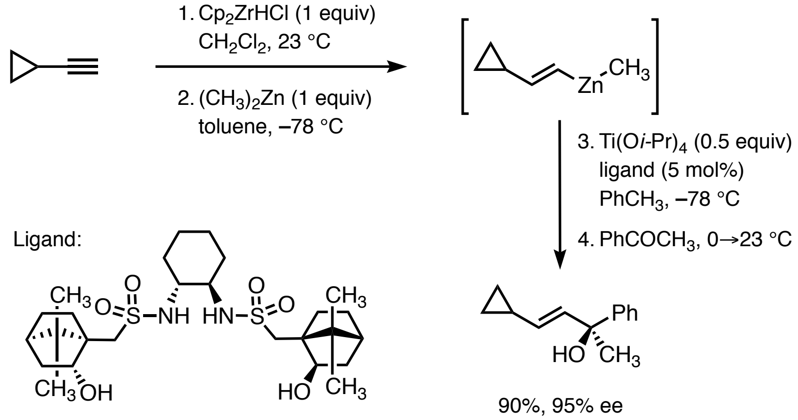
Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254–2256.

- However, less bulky, electron-rich organozirconocenes undergo transmetalation to Pd or Ni rapidly enough such that no organozinc intermediate is necessary.



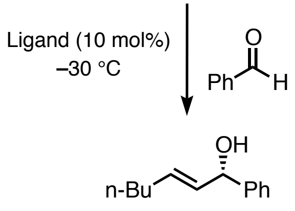
Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393–2401.

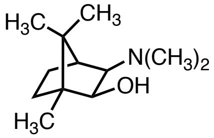
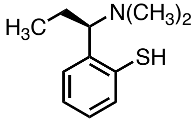
- Special procedures have been developed to enable asymmetric vinyl additions.



Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 8355–8361.

- A drawback of *in situ* organozinc generation is that residual zirconocene complexes can complicate further reactions. For example, zirconocene complexes can catalyze racemic carbonyl additions, resulting in low enantioselectivities for otherwise robust asymmetric organozinc additions.



| Ligand | yield | ee |
|---|---|---|
|  | 77% | 3% |
|  | 80% | 95% |

Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454–6455.

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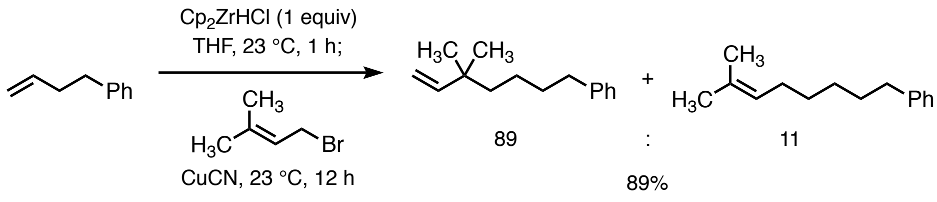
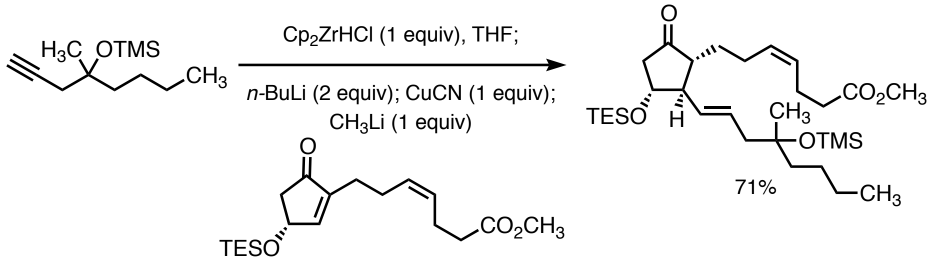
### Transmetalation to Copper

- Commonly used copper sources for transmetalation include $CuBr{\cdot}S(CH_3)_2$ and CuCN.
- Reaction of the resulting organocopper intermediate with allyl halides leads to C–C bond formation by $S_N2'$ addition.



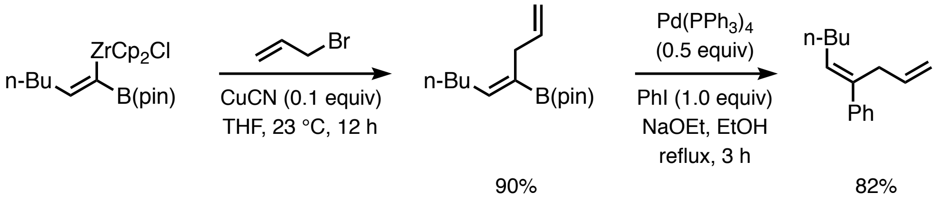
Venanzi, L. M.; Lehmann, R.; Keil, R.; Lipshutz, B. H. *Tetrahedron Lett.* **1992**, *33*, 5857–5860.

- Addition of an organolithium reagent often accelerates transmetalation to copper. In the following example, *n*-BuLi is added to promote organocuprate formation in a hydrozirconation–transmetalation–conjugate addition sequence *en route* to a prostaglandin.



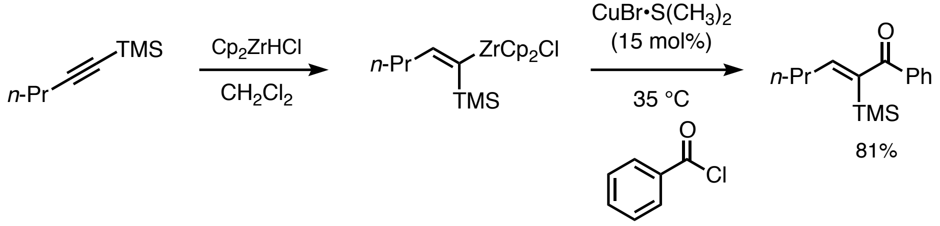
Babiak, K. A.; Behling, J. R.; Dygos, J. H.; McLaughlin, K. T.; Ng, J. S.; Kalish, V. J.; Kramer, S. W.; Shone, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 7441–7442.

- Hydrozirconation of readily available alkynyldioxaborolanes gives access to 1,1-bimetalloalkenes, which can be used to synthesize trisubstituted alkenes.



Deloux, L.; Skrzypczak-Jankun, E.; Cheesman, B. V.; Srebnik, M.; Sabat, M. *J. Am. Chem. Soc.* **1994**, *116*, 10302–10303.

- Ketones can be synthesized from acid halides and alkenes or alkynes:



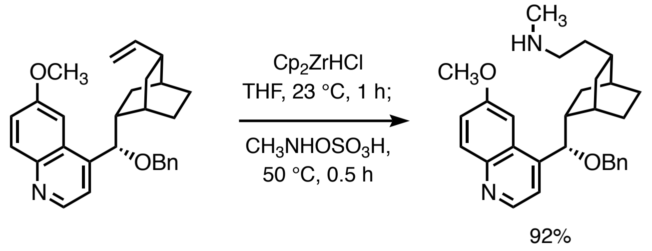
Sun, A.; Huang, X. *Synthesis* **2000**, *6*, 775–777.

Wipf, P.; Xu, W. *Synlett* **1992**, *9*, 718–721.

### Other Applications of Organozirconium Intermediates

#### Anti-Markovnikov Hydroamination

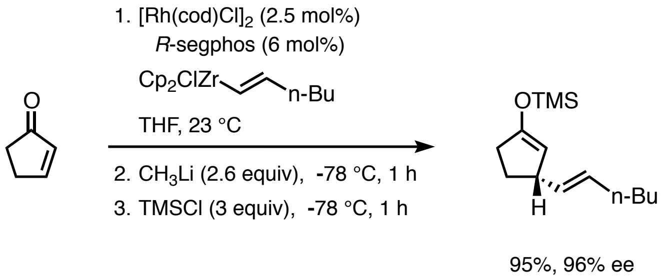
- Amination of zirconocene alkyl chloride intermediates can be achieved using commercially available *N*-methylhydroxylamine-*O*-sulfonic acid.

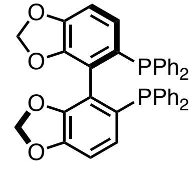


Strom, A. E.; Hartwig, J. F. *J. Org. Chem.* **2013**, *78*, 8909–8914.

### Synthesis of Cyclic Silyl Enol Ethers

- Tandem asymmetric conjugate addition of alkenylzirconocenes to cyclic enones can be catalyzed by Rh(I) to give silyl enol ethers in good yield with high enantioselectivity.





*R*-segphos

Westmeier, J.; Pfaff, C.; Siewert, J.; von Zezschwitz, P. *Adv. Synth. Catal.* **2013**, *355*, 2651–2658.

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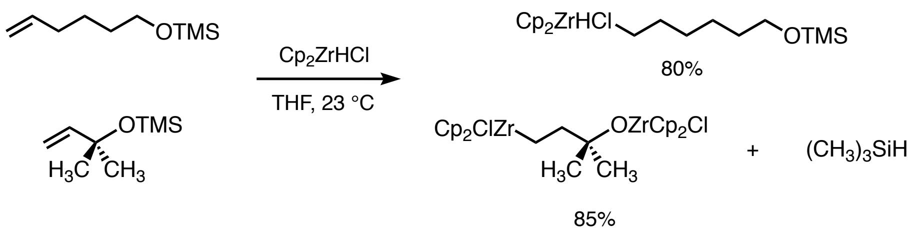
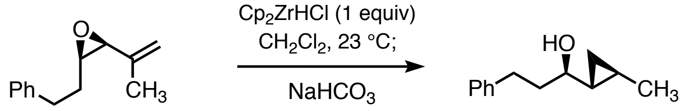
**Hydrozirconation – Functional Group Compatibility**

- Reduction of most epoxides, isonitriles, aldehydes, ketones, nitriles and esters by $Cp_2ZrHCl$ is competitive with hydrozirconation of alkenes and alkynes.
- Alcohols and acids are deprotonated by $Cp_2ZrHCl$ with loss of $H_2$; α,β-unsaturated ketones undergo 1,2-reduction with $Cp_2ZrHCl$.
- Acetals and THP ethers are inert to $Cp_2ZrHCl$ unless they are allylic or vinylic, in which case β-elimination can occur. Allylic or vinylic trimethylsilyl ethers can be reductively cleaved by $Cp_2ZrHCl$.



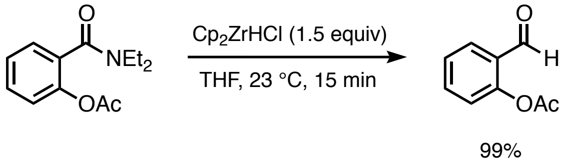
Uhlig, E.; Bürglen, B.; Krüger, C.; Betz, P. *J. Organomet. Chem.* **1990**, *382*, 77–88.

- Hydrozirconation of vinyloxiranes leads to formation of α-hydroxycyclopropyl derivatives. Ring formation proceeds with inversion of configuration at the allylic carbon.



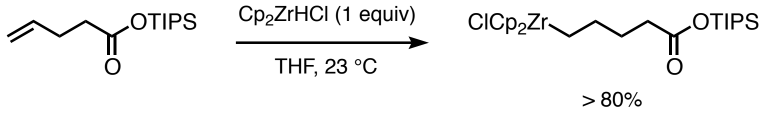
Harada, S.; Kowase, N.; Tabuchi, N.; Taguchi, T.; Dobashi, Y.; Dobashi, A.; Hanzawa, Y. *Tetrahedron* **1998**, *54*, 753–766.

- Tertiary amides can be reduced to aldehydes in the presence of excess Schwartz's reagent. Note that amides can be selectively reduced in the presence of esters:



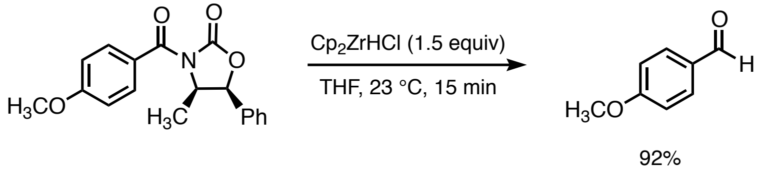
Spletstoser, J. T.; White, J. M.; Runoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2007**, *129*, 3408–3419.

- Triisopropylsilyl, *t*-butyl, and benzyl esters are tolerated with fast-reacting, unhindered C–C double and triple bonds as substrates.



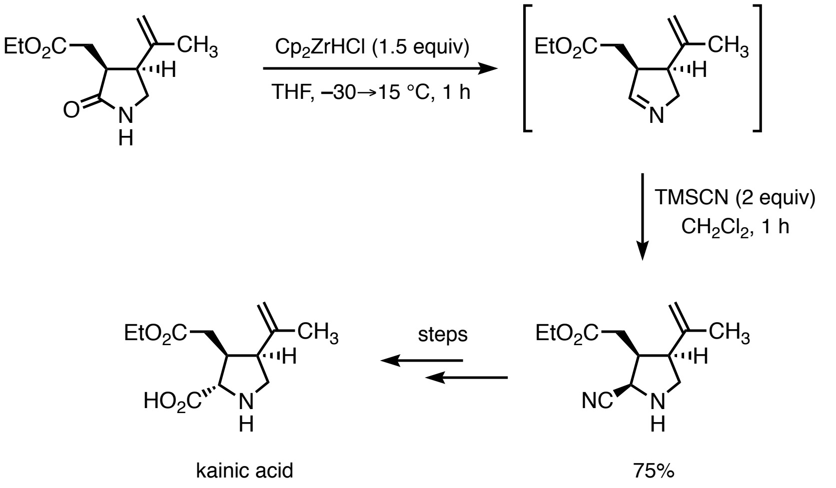
Wipf, P.; Xu, W.; Smitrovich, J. H.; Lehmann, R.; Venanzi, L. M. *Tetrahedron* **1991**, *50*, 1935–1954.

- Schwartz's reagent also reduces Evans' *N*-acyl oxazolidinones to give aldehydes:



White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2000**, *122*, 11995–11996.

- In their synthesis of kainic acid, Xia and Ganem successfully reduced a lactam using Schwartz's reagent in the presence of an isopropenyl group.



Xia, Q.; Ganem, B. *Org. Lett.* **2001**, *3*, 485–487.

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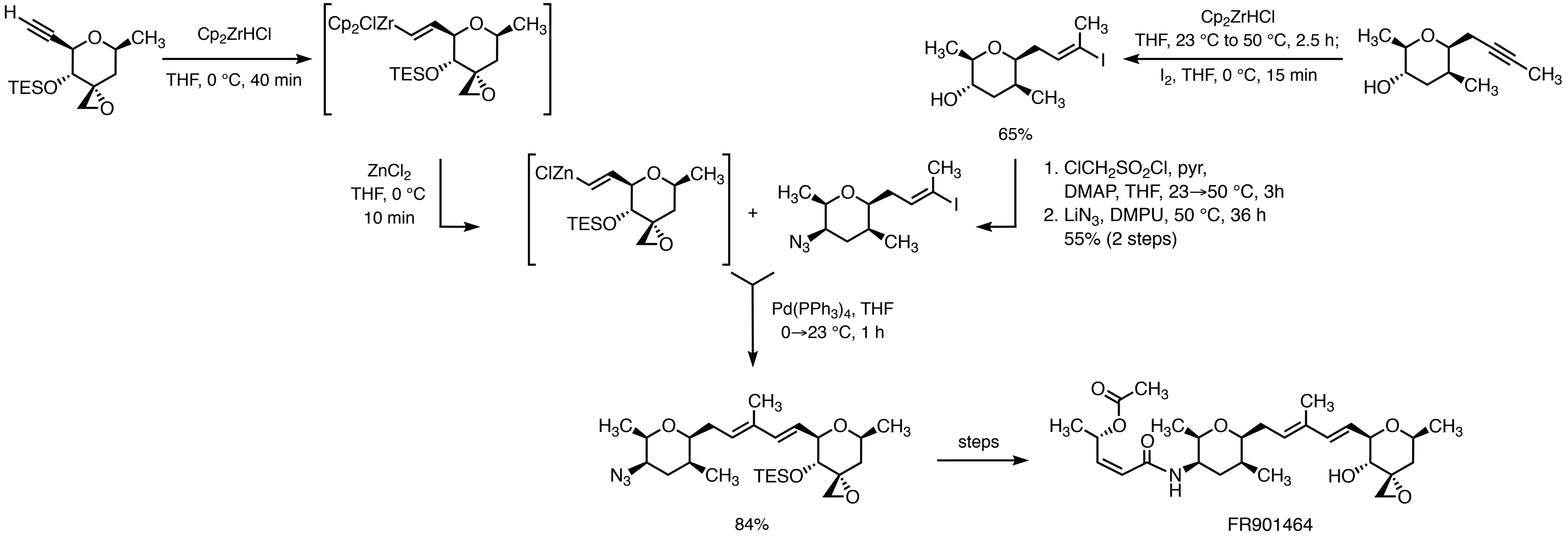
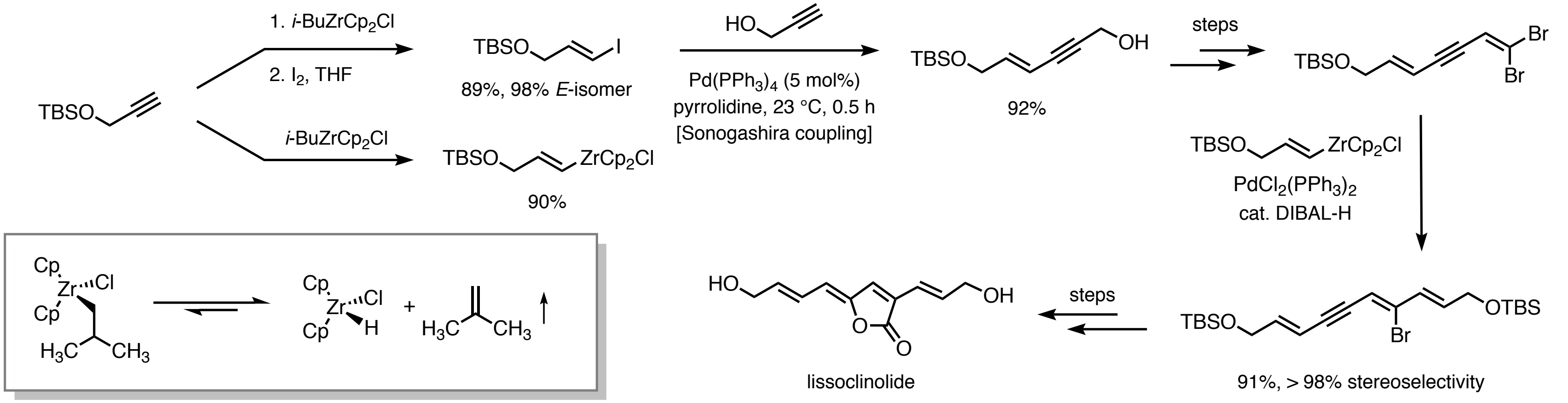
- A hydrozirconation–transmetallation–cross-coupling sequence was used in the synthesis of analogues of the natural product FR901464.



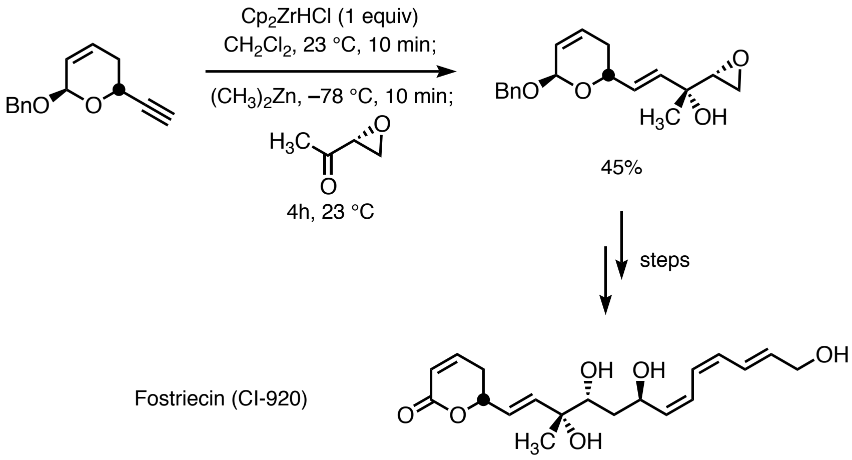
Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974–9983.

- A vinylzirconium compound was successfully coupled with a vinyl iodide *en route* to lissoclinolide. Schwartz's reagent was generated *in situ* by β-hydride elimination of *i*-BuZrCp$_2$Cl (inset).



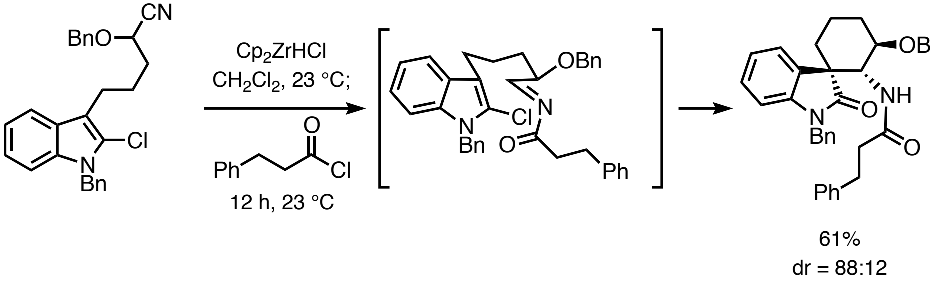
Xu, C.; Negishi, E.-i. *Tetrahedron Lett.* **1999**, *40,* 431–434.

- Diastereoselective addition to a ketone was achieved by hydrozirconation followed by *in situ* transmetallation to zinc.



Chavez, D. E.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2001**, *40*, 3667–3670.

- Hydrozirconation of nitriles provides metallo-imine complexes that can further react with acyl chlorides. This strategy was used in the synthesis of a spirooxindole library by interception of the imine intermediate through a Friedel–Crafts cyclization with a pendant indole substituent.

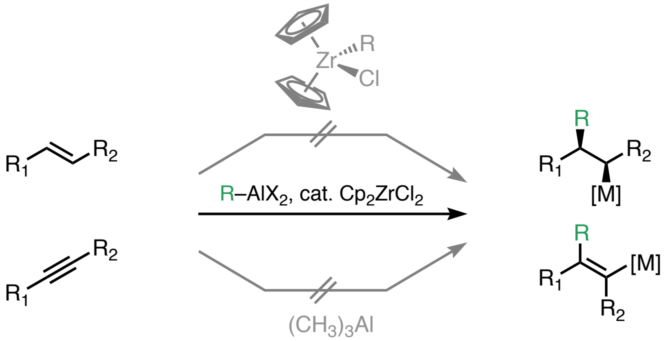


LaPorte, M. G.; Tsegay, S.; Hong, K. B.; Lu, C.; Fang, C.; Wang, L.; Xie, X.-Q.; Floreancig, P. E. *ACS Comb. Sci.* **2013**, *15*, 344–349.

**Carbozirconation**

Negishi, E.-i. *Arkivoc* **2011**, *8,* 34–53.

**General Reaction Scheme**

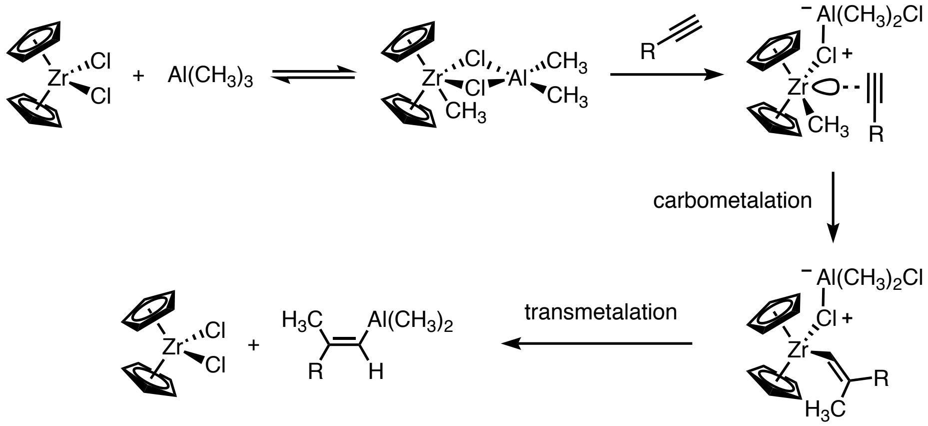


$R_1$ = alkyl, aryl; $R_2$ = alkyl, H; [M] = [Al], [Zr]

- Carbometalation is the addition of a carbon–metal bond across a carbon–carbon π-bond. The process is believed to be concerted.

- A stoichiometric amount of trialkylaluminum reagent is needed, but only a catalytic amount of $Cp_2ZrCl_2$ is required.

- Experimental evidence points toward a bimetallic mechanism:



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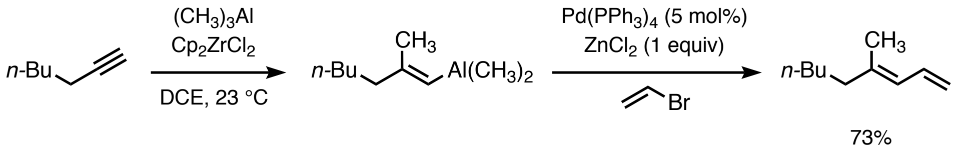
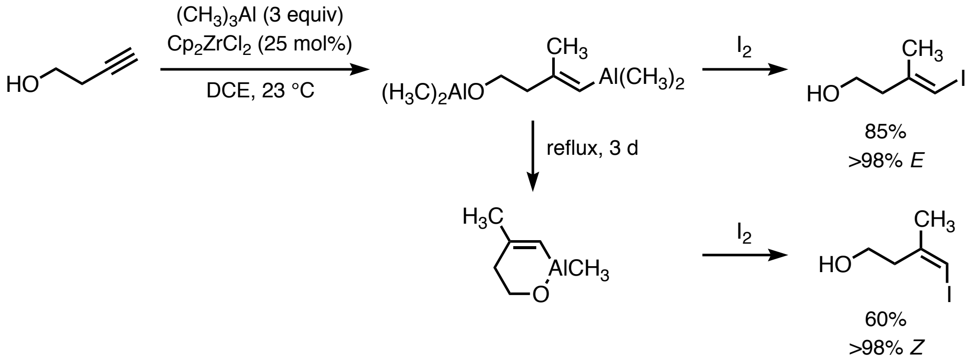
- The reaction of trimethylaluminum with terminal alkynes proceeds with excellent stereo- and regioselectivity.



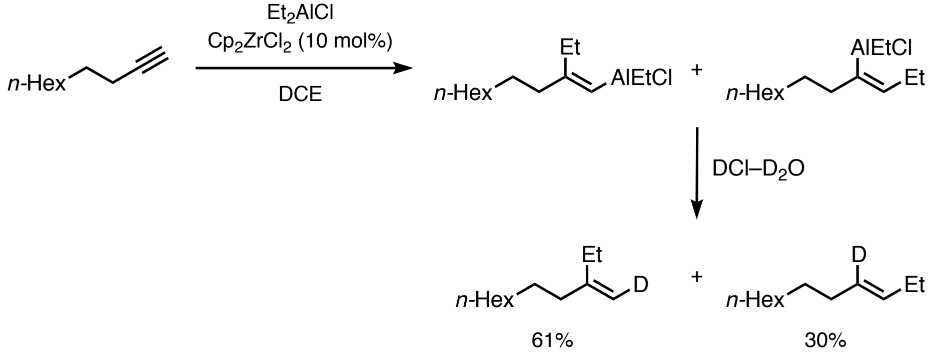
Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100,* 2254–2256.

- Carbometalation is compatible with free hydroxyl groups. In the case of homopropargylic alcohols, *anti*-carbometalation products can be obtained by thermal isomerization of the initial adducts:



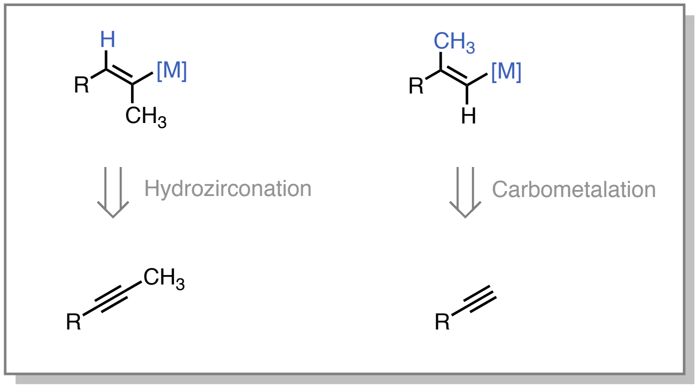
Ma, S.; Negishi, E.-i. *J. Org. Chem.* **1997**, *62*, 784–785.
Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4093–4096.

- Carboalumination with $Et_3Al$ or $Et_2AlCl$ can proceed through a variety of mechanisms and usually results in regioisomeric products. It has therefore found little use in organic synthesis.



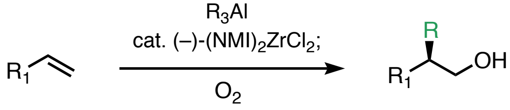
*Metallocenes in regio- and stereoselective synthesis*, *Vol. 8*, Takahashi, T. Ed.; Springer: Berlin; New York, **2005**; p.155.

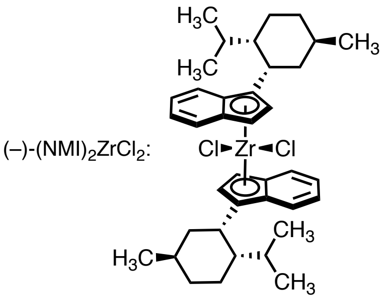
- Thus, carboalumination of alkynes is limited to methylation in practice. Together, hydrozirconation and carboalumination provide reliable access to two classes of trisubstituted olefins commonly encountered in synthesis:



**Zirconium-catalyzed asymmetric carboalumination of alkenes (ZACA)**

- By contrast, olefins reliably give regiodefined carbometalation products even with higher-order alkyls such as ethyl and propyl groups. Enantioselective methods employing chiral zirconocene catalysts have been developed.
- Negishi and coworkers have developed a protocol for asymmetric carboalumination of alkenes giving functionalized products in moderate to high yields with synthetically useful enantiomeric purities.





commercially available

| R | Yield | ee |
|---|---|---|
| $–CH_3$ | 68–92% | 70–90% |
| $–CH_2CH_3$ | 56–90% | 85–95% |
| $–(CH_2)_nCH_3$ | 74–85% | 90–95% |

Kondakov, D. Y.; Negishi, E.-i. *J. Am. Chem. Soc.* **1996**, *118*, 1577–1578.
Kondakov, D. Y.; Negishi, E.-i. *J. Am. Chem. Soc.* **1995**, *117*, 10771–10772.

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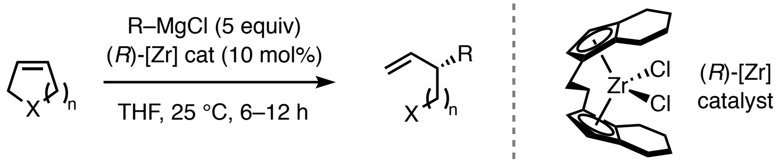
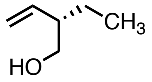
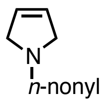
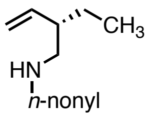
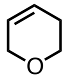
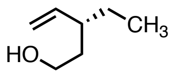
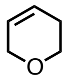
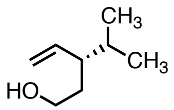
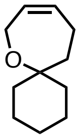
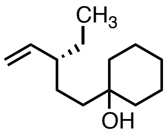
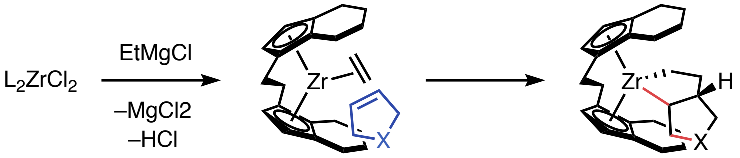
- Cyclic olefins are excellent substrates for ZACA. When heteroatoms are positioned β to the newly formed C–M bond, irreversible elimination occurs to give terminal alkenes with good stereoenrichment at the allylic position.



| Olefin | Grignard | Product | Yield | ee |
|---|---|---|---|---|
|  | EtMgCl |  | 65% | > 97% |
|  | EtMgCl |  | 75% | > 95% |
|  | EtMgCl |  | 73% | 95% |
|  | *n*-PrMgCl |  | 40%<br>(60% brsm) | 98% |
|  | EtMgCl |  | 75% | 92% |

- Stereoinduction is determined by the oxidative coupling step, wherein the substrate reacts with a Zr-olefin complex formed upon β-H elimination of $Cp_2ClZr–R$.



Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6997–6998.