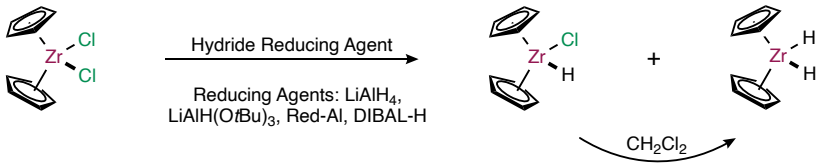
Schwartz's Reagent - $Cp_2Zr(H)Cl$

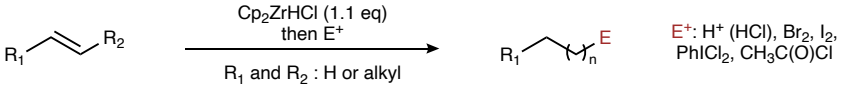
Schwartz's Reagent

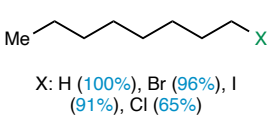
- Introduced to organic synthesis by Schwartz and coworkers in 1976
- Since the seminal report (included below), many transformations have been affected with Schwartz reagent reacting with olefins, alkynes, and other C=X functionalities
- The reagent can be made and stored as a dry powder for a few weeks (longer if kept under an inert atmosphere)
- Several ways to generate Schwartz reagent in situ



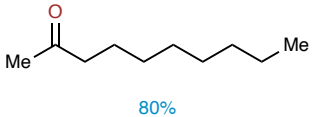
Hydrozirconation of Alkenes and Alkynes

Halogenation

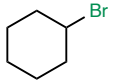




X: H (100%), Br (96%), I (91%), Cl (65%)



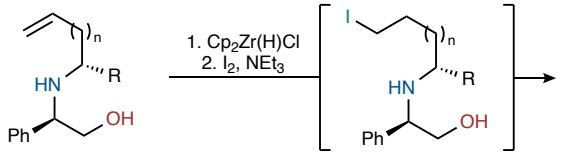
80%

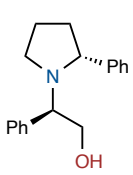


95%

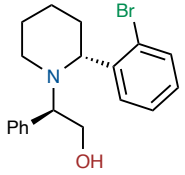
J. Am. Chem. Soc. **1974**, 96, 26, 8115-116

Halogenation and Ring Forming Intramolecular N-Alkylation

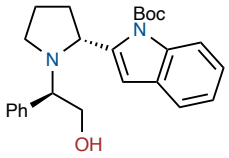




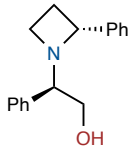
68%



60%



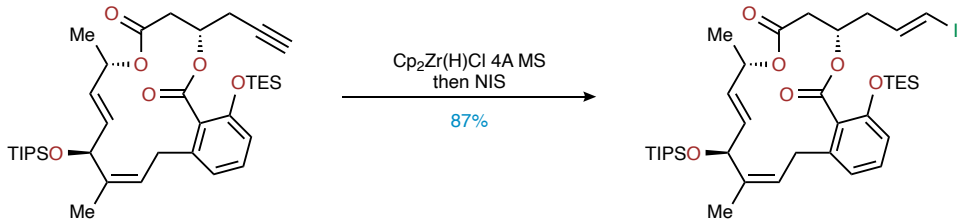
40%



53%

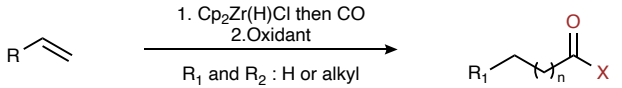
Synthesis **2008**, 1, 61-68

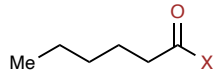
Application In Total Synthesis: Lobatomides A + C



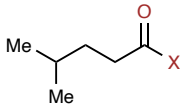
Angew. Chem. Int. Ed. **2024**, e202402335

Insertion of Carbon Monoxide

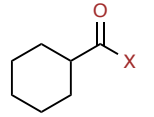




X: H (99%), OH (51%), OMe (77%)



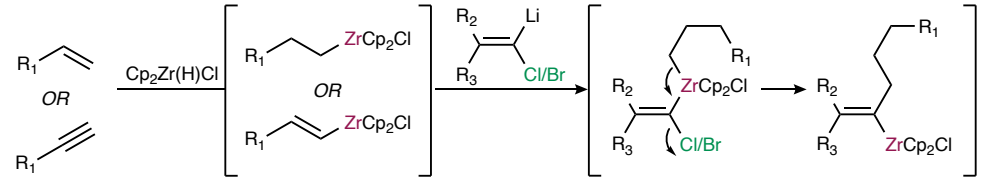
X: H (71%), OH (26%), OMe (50%)

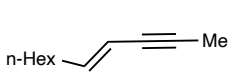


X: H (97%), OH (57%)

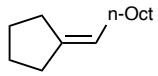
J. Am. Chem. Soc. **1975**, 97, 228-230

Insertion of Vinyl Carbenoids



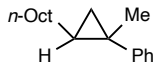


61%

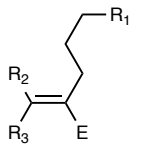


65%

Substrate scope extended by Whitby in 1999 JACS report! Tolerates alcohols, aldehydes, and halogens. New electrophiles: bromide, iodide, and fluoride sources.



61%

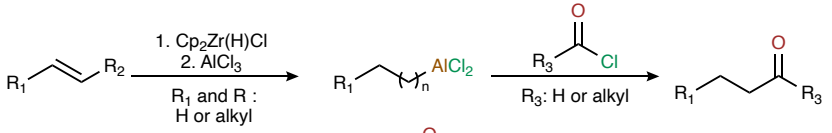


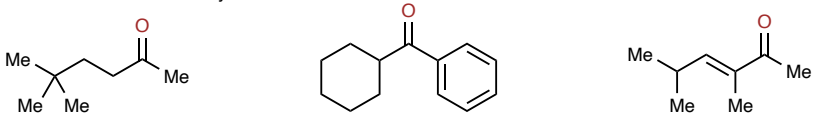
J. Am. Chem. Soc. **1989**, 111, 3089-91, *J. Am. Chem. Soc.* **1999**, 121, 30, and 7039-49,

Schwartz's Reagent - $Cp_2Zr(H)Cl$

Transmetalation

Despite substantial polarization of Zr-C bond, the steric hindrance of alkylzirconocenes significantly thwarts reactivity. Thus, transmetallation is conducted to generate more reactive metalated species.





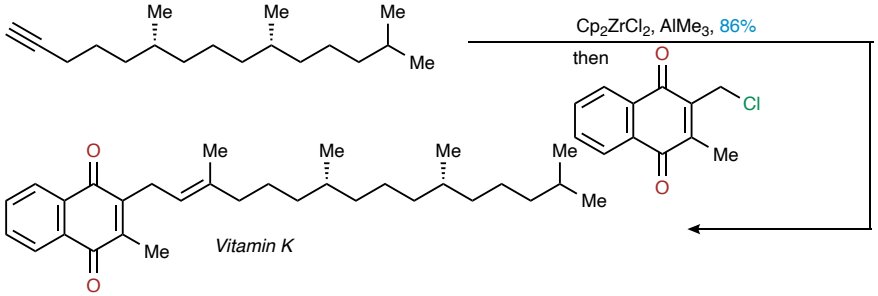
Zr only (60%, 29 hrs)
Zr → Al (98%, 30 min)

Zr only (8%, 48 hrs)
Zr → Al (64%, 45 min)

Zr only (—)
Zr → Al (98%, 45 min)

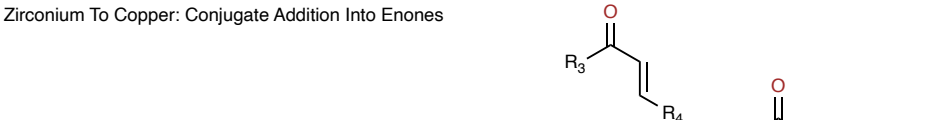
J. Am. Chem. Soc. **1977**, 99, 638-640.

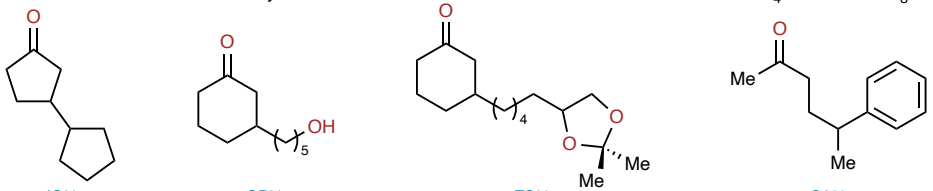
Applications In Total Synthesis: Vitamin K, Negishi (2001)



Org. Lett., **2001**, 3, 21.

Zirconium To Copper: Conjugate Addition Into Enones





48%

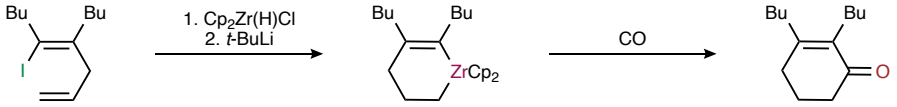
85%

78%

61%

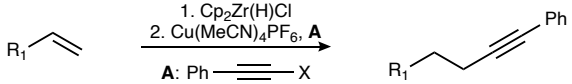
J. Org. Chem. **1991**, *56*, 6496-97.

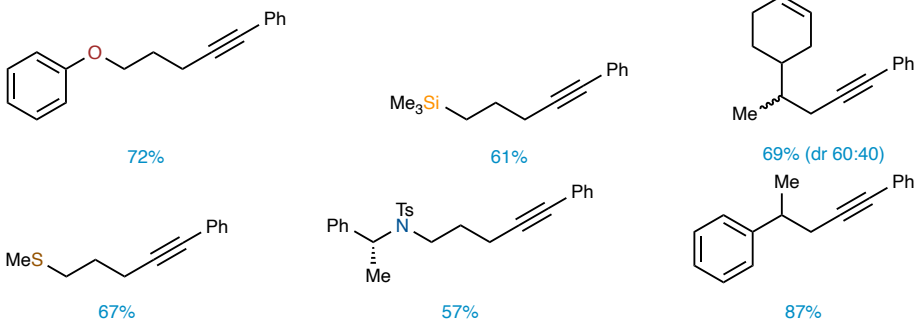
Zirconium to Lithium: Metallacycle Formation



Organometallics **2007**, *26*, 775.

Zirconium to Copper: Ullman Type Coupling





72%

61%

69% (dr 60:40)

67%

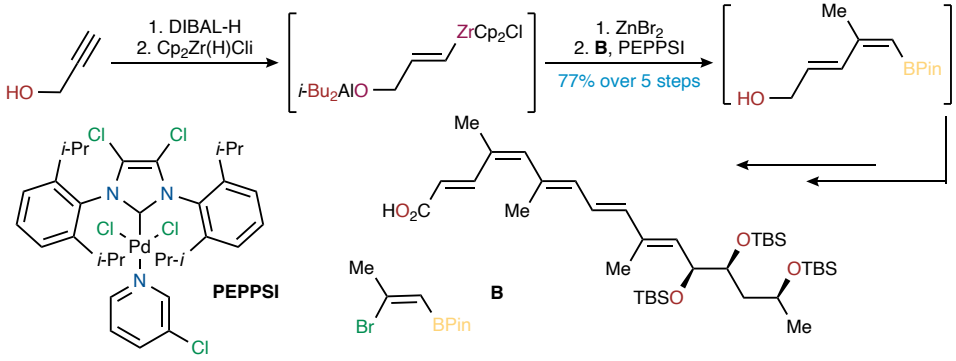
57%

87%

"…[cross-coupling] reactions using alkylzirconocenes have received less attention, likely owing to a lack of suitable pi-systems to stabilize the binding ability of zirconium to achieve suitable trasmetalation."

Adv. Synth. Catal. **2017**, 359 2425-2433, *Synthesis* **2021**, *53*, 1061-76

Applications In Total Synthesis: mycolactone A side chain, Negishi, (2009)



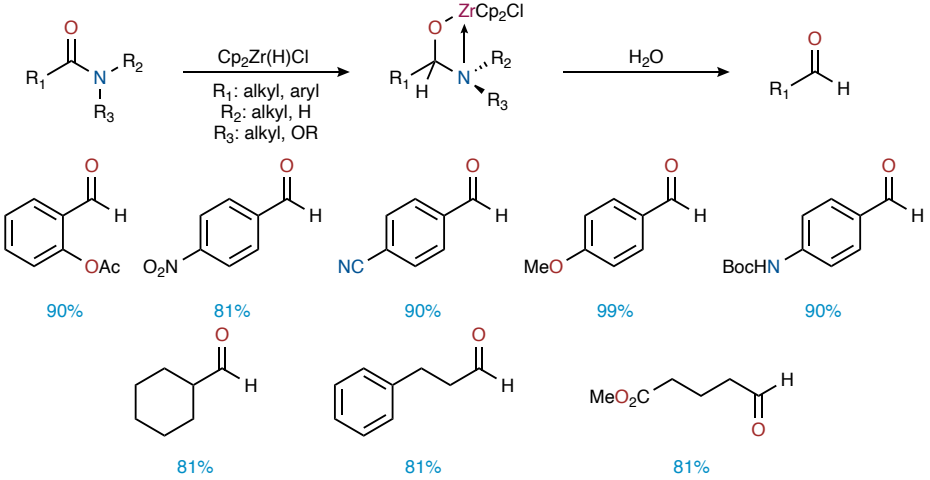
Org. Lett. **2009**, *11*, 18, 4093-95

Schwartz's Reagent - $Cp_2Zr(H)Cl$

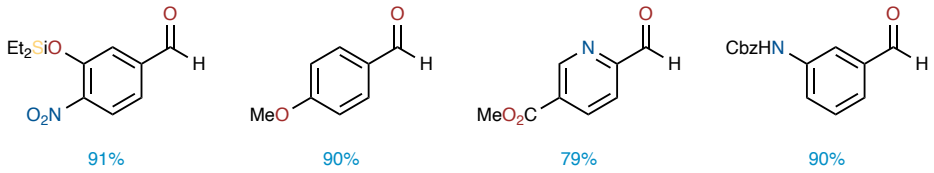
Chemoselective Reduction of Amides

Reduction of Amides To Aldehydes

The chemoselectivity of Schwartz Reagent is attributed to the high oxophilicity of Zr.



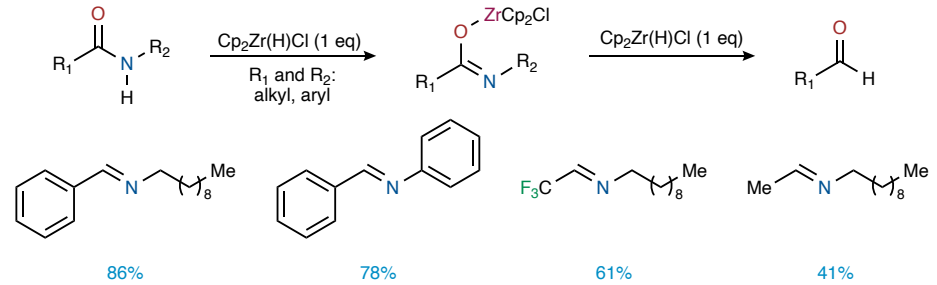
J. Am. Chem. Soc. **2000**, 122, 11996-96



Org. Lett. **2014**, *16*, 390-94

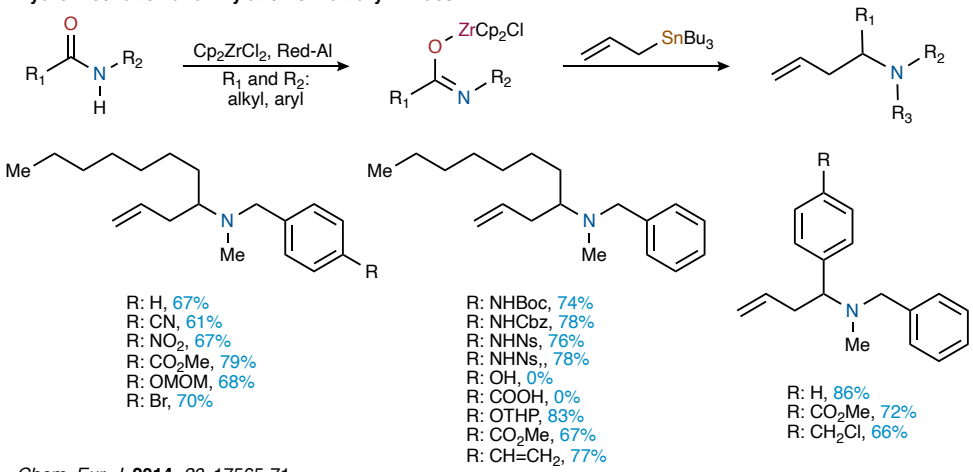
Elaborated substrate scope conditions: Cp_2ZrCl_2, $LiAlH(Ot\text{-}Bu)_3$

Reduction of Secondary Amides To Imines



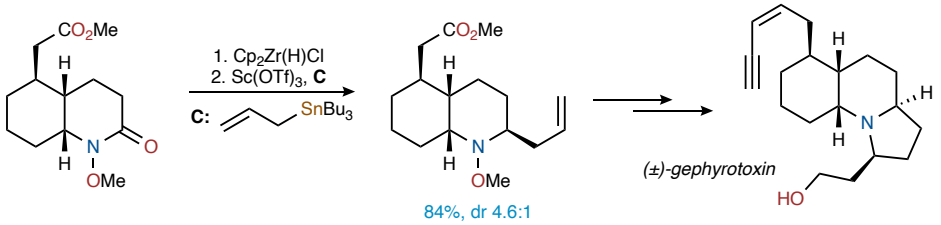
Tetrahedron Letters. **1993**, *32*, 5035-38

Hydrozirconation and Allylation of Tertiary Amides



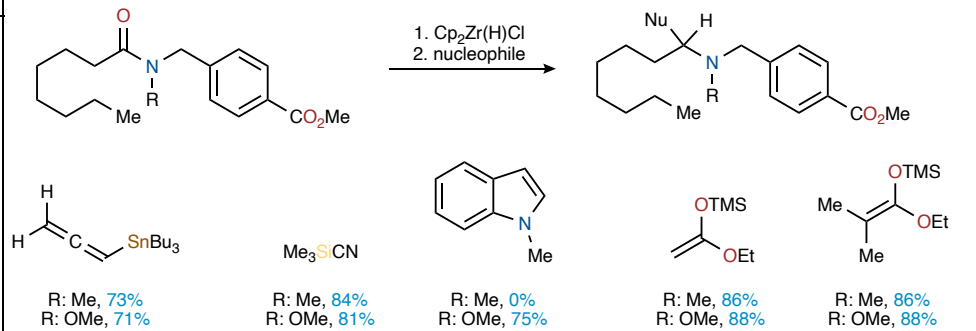
Chem. Eur. J. **2014**, *20*, 17565-71.

Applications In Total Synthesis: (±)-gephyrotoxin, Chida (2014)



Angew. Chem. Int. Ed. **2014**, *53*, 512-16

Other Nucleophilic Additions Into Tertiary Amides



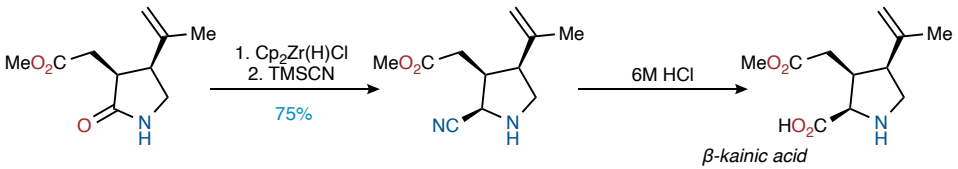
Chem. Eur. J. **2014**, *20*, 17565-71.

Schwartz's Reagent - $Cp_2Zr(H)Cl$

METHOD of the week

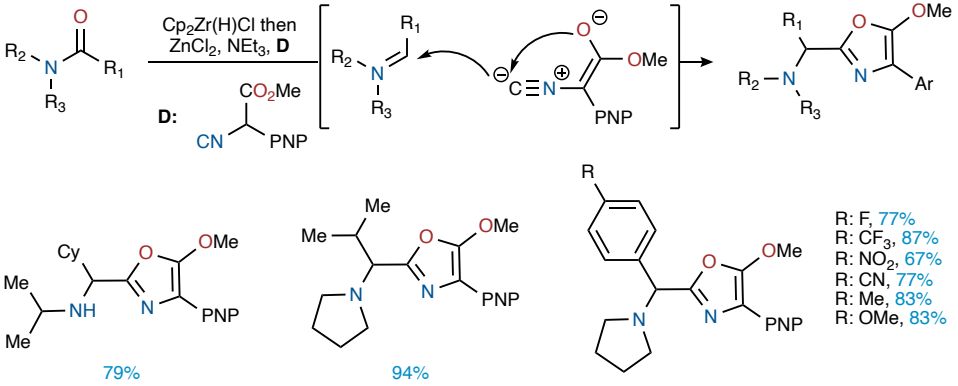
The SARLAH Group

Applications In Total Synthesis: β-kainic acid, Ganem (2001)



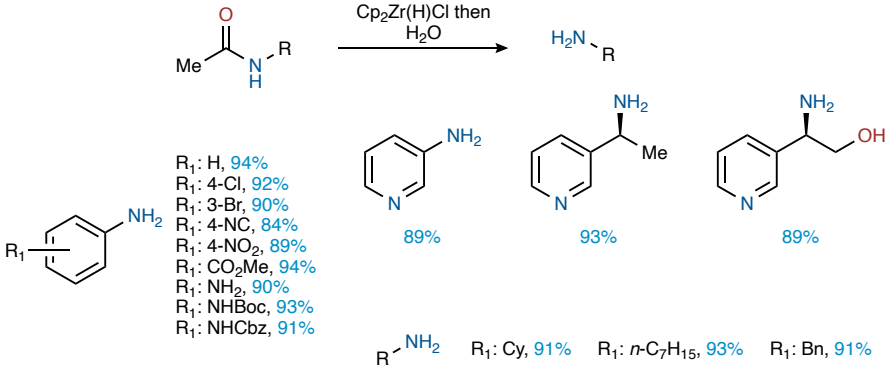
Org. Lett. **2001**, *3*, 485-87.

Reductive Addition of Tertiary and Secondary Amides With Isocyanoacetates



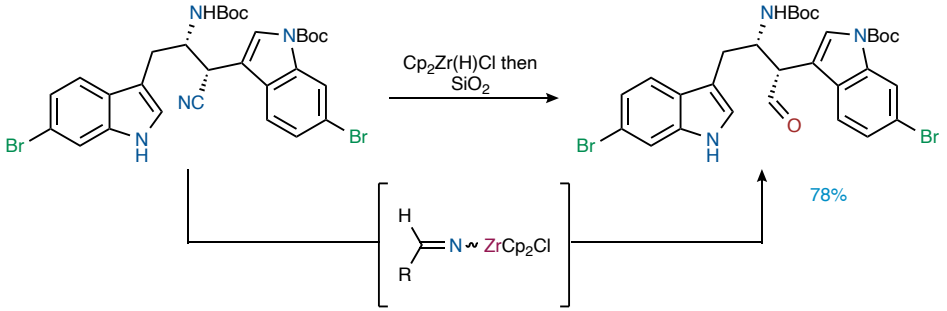
J. Org. Chem. **2017**, *82*, 9693-703.

Chemoselctive Amide Deprotection



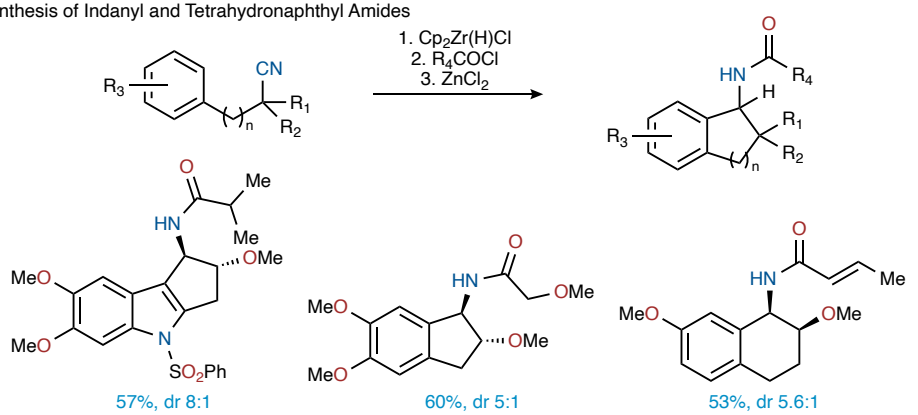
Org. Biomol. Chem. **2014**, *12*, 261-64.

Hydrozirconation of Nitriles



J. Am. Chem. Soc. **2016**, *138*, 43, 14234-237.

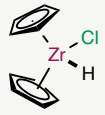
Synthesis of Indanyl and Tetrahydronaphthyl Amides



Org. Lett. **2008**, *10*, 1139-42.

Other Reactivity With Schwartz's Reagent Not Covered Here

Cleavage of lactones, anhydrides, and azlactones • Reduction of isocyanates to formamides
Reduction of phosphine oxides to phosphines • Reduction of β-ketoesters to unsaturated esters



Schwartz's Reagent

For more about Schwartz's Reagent See:

Reviews:

Synthesis **2021**, *53*, 1061-76
Eur. J. Org. Chem. **2018**, 6601-6623

Book Chapter: 8.23 Hydrozirconation of Alkenes and Alkynes, Comprehensive Organic Synthesis (2nd Edition)

Chem 534 Notes: Coupling and Organocopper Chemistry