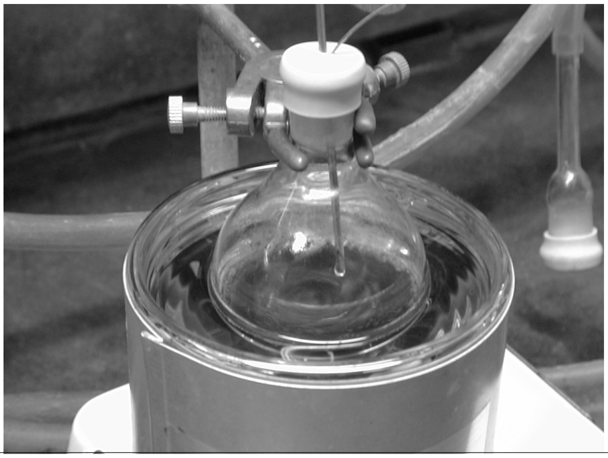
II. Special Topics

IIC. Organometallics

Boger Notes: p. 395 - 426 (Chapter XII)
Carey/Sundberg: **B** p. 477-546 (Chapter **B** 8)

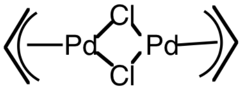


A. Organometallic Mechanisms

<u>Oxidation State</u>: The oxidation state of a metal is defined as the charge left on the metal after all ligands have been removed in their natural, closed-shell configuration. This is a formalism and not a physical property!

<u>d-Electron Configuration</u>: position in the periodic table *minus* oxidation state.

<u>18-Electron Rule</u>: In mononuclear, diamagnetic complexes, the total number of electrons never exceeds 18 (noble gas configuration). The total number of electrons is equal to the sum of d-electrons *plus* those contributed by the ligands.
18 electrons = coordinatively saturated
< 18 electrons = coordinatively unsaturated.



bridging by lone pairs on Cl;
each Cl acts as a 2-electron, mono negative ligands to <u>*one*</u> *of the Pd's, and a 2-electron neutral donor ligand like PPh_3 to the other*

for each Pd: Ox. state  , $Cl^{\ominus}$

Pd(II)

d: 10 ($4d^{10}$ $5s^0$) - 2 = <u>8</u>

electron count:

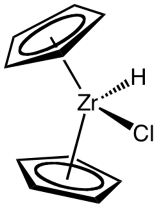
 : $4e^-$

$Cl^{\ominus}$  : $2e^-$

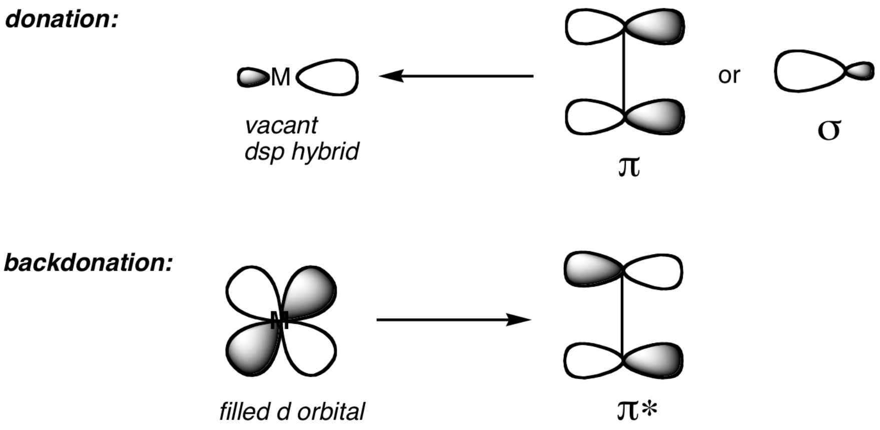
Cl : $2e^-$

$8e^- + d^8 =$ <u>$16e^-$</u>

unsaturated



Bonding considerations



donation:

M

vacant
dsp hybrid

π

or

σ

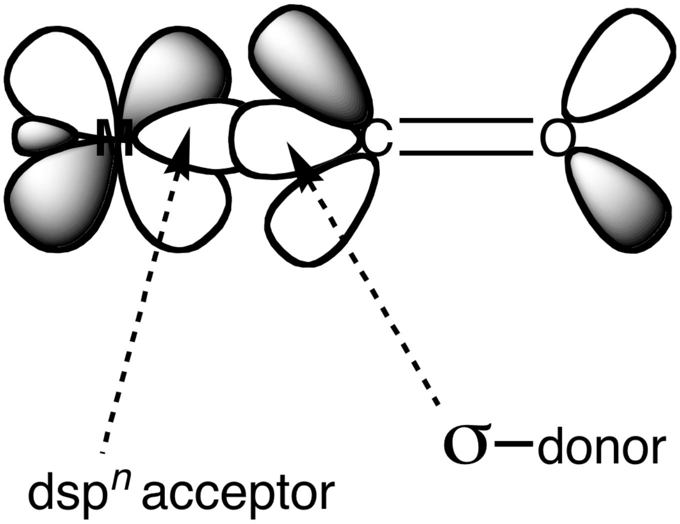
backdonation:

M

filled d orbital

π^*

for M-CO:



dsp^n acceptor

σ–donor

Quantification of the Steric and Electronic Properties of Phosphorus Ligands

Cf. Andersen, N. G.; Keay, B. A., "2-Furyl phosphines as ligands for transition-metal-mediated organic synthesis." *Chem. Rev.* **2001**, *101*, 997-1030.

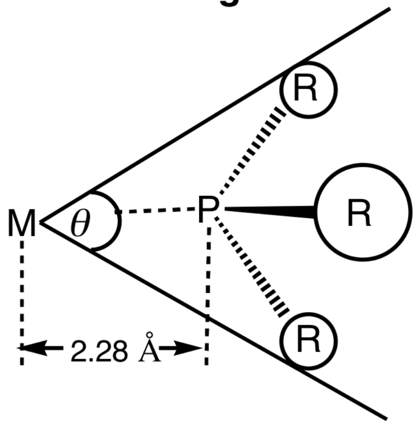
The steric and electronic properties of a tertiary phosphine ligand can dramatically influence the reactivity at the metal center and lead to marked changes in chemical reactivity. The steric bulk and electron-donor ability of a ligand are difficult properties to quantify, and indeed, the two properties are closely related. For example, as the steric bulk of the R groups in a tertiary phosphine of type PR_3 is increased, it is expected that the intervalence angles about the phosphorus atom will increase. Such a structural change would thereby reduce the s-character of the phosphorus lone pair orbital, making the ligand more Lewis basic. Therefore, it is often difficult to separate steric and electronic effects with respect to phosphorus donor ligands since the two factors are so intimately related.

Tolman suggested, using a geometrical parameter known as the cone angle, classifying phosphorus ligands according to size. For phosphines of type PR_3, the cone angle is defined as the apex of a cylindrical cone, centered 2.28 Å from the center of the phosphorus atom, which radiates out toward the R groups and just touches the van der Waals radii of the outermost atoms.

The Tolman Cone Angle:

In cases where the R groups contain internal degrees of freedom, the Tolman cone is taken to be the minimum angle which satisfies the condition that all of the R groups are completely contained within the geometrical construct.

For unsymmetrical phosphines or chelating diphosphines, the concept of cone angle is not as clear

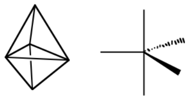


Tolman Cone Angle (θ) for a Variety of Phosphines and Phosphites

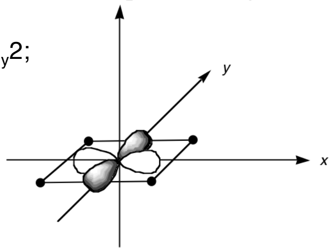
ligand	cone angle (θ)	ligand	cone angle (θ)
PH_3	87°	P(*p*-Tol)$_3$	145°
$P(OMe)_3$	107°	P(*m*-Tol)$_3$	165°
PMe_3	118°	PCy_3	170°
$P(OPh)_3$	128°	P(O-*t*-Bu)$_3$	172°
PEt_3	132°	P(*t*-Bu)$_3$	182°
TFP	133°	$P(C_6F_5)_3$	184°
$P(CF_3)_3$	137°	P(*o*-Tol)$_3$	194°
PPh_3	145°	P(mesityl)$_3$	212°

Structure

- saturated (18 e^-) complexes:
  - tetracoordinate: $Ni(CO)_4$, $Pd(PPh_3)_4$ are tetrahedral
  - pentacoordinate: $Fe(CO)_5$ is trigonal bipyramidal
  - hexacoordinate: $Cr(CO)_6$ is octahedral



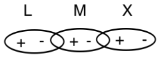
- unsaturated complexes have high $d_{x^2-y^2}$;
  - 16e^- prefers square planar



Basic reaction mechanisms

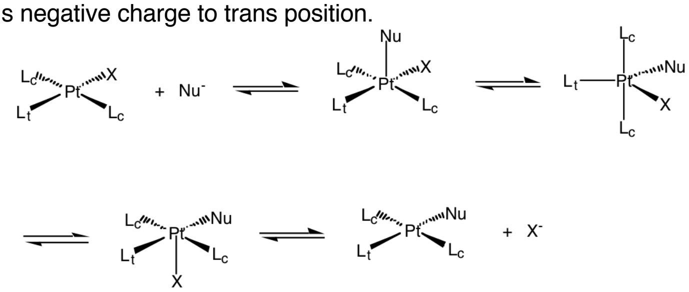
- **ligand substitution**: M-L + L' → M-L' + L

can be associative, dissociative, or radical chain.

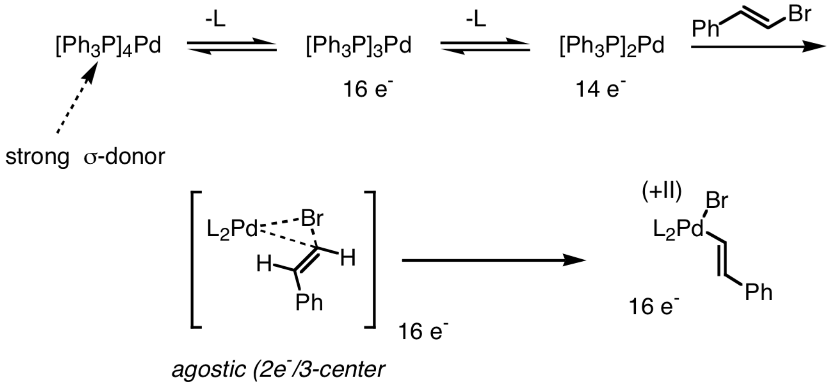


trans-effect: kinetic effect of a ligand on the role of substitution at the position trans to itself in a square or octahedral complex (ground-state weakening of bond).

L → M, repels negative charge to trans position.

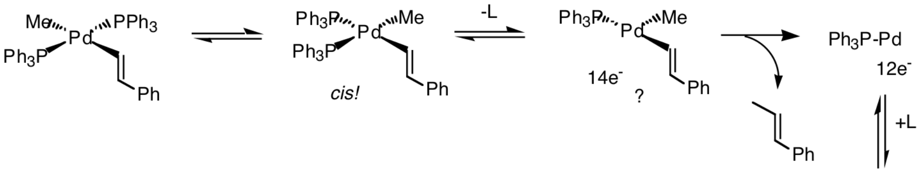


- **oxidative addition**:

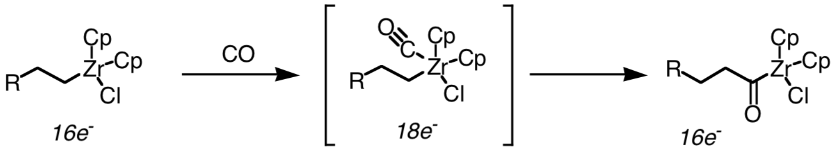


agostic (2e-/3-center bond) interactions

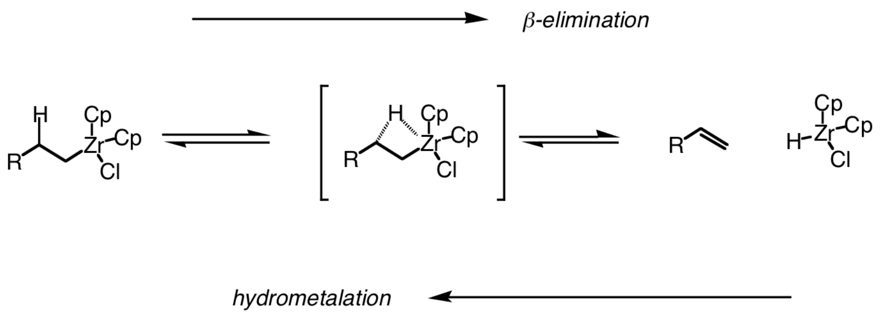
- **reductive elimination**: the major way in which transition metals are used to make C,C- and C,H-bonds!



- **migratory insertion**:

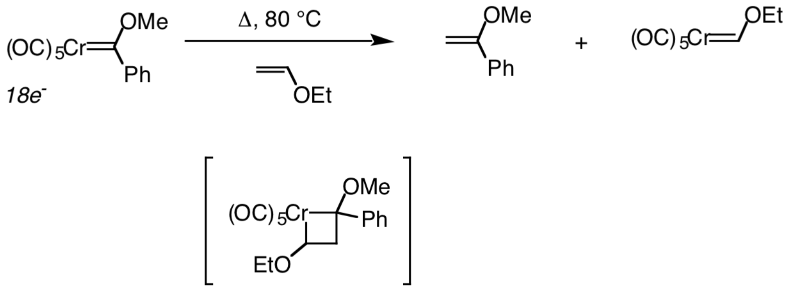


- **β-elimination/hydrometalation**:



- **olefin metathesis**:

Fischer carbene complex



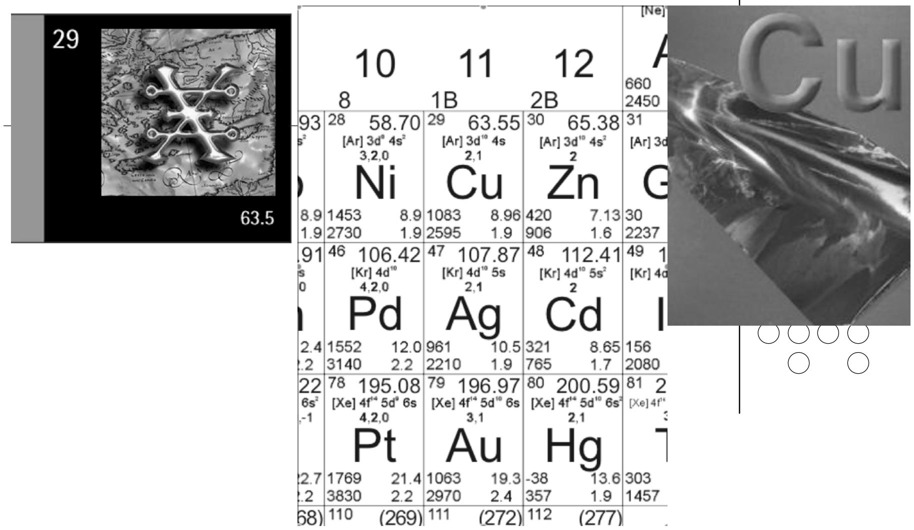
- **transmetalation**:

R-M + M'-X → R-M' + M-X

Summary of Mechanisms:

- ligand substitution
- oxidative addition/reductive elimination
- migratory insertion/β-elimination (carbo-, hydrometalation)
- alkene metathesis
- transmetalation

B. The Synthetic & Mechanistic Chemistry of Cuprates



History & Structure of Cuprates

- In 1952, Gilman reported the *in situ* preparation of Me_2CuLi (*J. Org. Chem.* **1952**, *17*, 1630).
- House and others subsequently demonstrated that the chemistry of CuI-derived organometallics was distinctively different from their lithium- or magnesium-based precursors (House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3138).
- Structural information on organocopper derivatives is scarce. Mixing MeLi-MeCu in different stoichiometric ratios provides an equilibrium mixture of Me_2CuLi, Me_3Cu_2Li, and Me_3CuLi_2. The latter reagent is supposed to be more stereoselective and more reactive than Me_2CuLi (Ashby, E. C. et al. *J. Am. Chem. Soc.* **1977**, *99*, 5312; *J. Org. Chem.* **1977**, *42*, 2805).

Structure of Cuprates - The Controversy Begins….

- In 1981, Lipshutz proposed the formation of "higher-order mixed cyanocuprates" (H.O. cuprates) by the addition of 2 equiv of an organolithium reagent to 1 equiv of copper cyanide.
- These $Me_2Cu(CN)Li_2$ reagents were assumed to be dianionic salts with the cyano group bound to copper (Lipshutz et al. *J. Am. Chem. Soc.* **1981**, *103*, 7672).
- Furthermore, it was claimed that H.O. cuprates are more reactive than lower order Gilman cuprates and be more stable due to backbonding from the filled d-orbital on copper to the empty π^*-orbital on the nitrile (Lipshutz et al. *Synthesis* **1987**, 325; *J. Org. Chem.* **1983**, *48*, 546).

Structure of HO (?) Cuprates

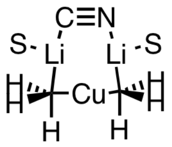
- Whether or not the cyanide ligand is bound to copper has been a controversial topic (Bertz, S. H. *J. Am. Chem. Soc.* **1991**, *113*, 5470).
- The Bertz proposal has the cyano group coordinated as lithium cyanide to a Gilman-like species. In the presence of HMPA, some free LiCN is indeed detected (Cabezas, J. A.; Oehlschlager, A. C. *J. Am. Chem. Soc.* **1997**, *119*, 3878; no trace of LiCN is found if the cuprate is prepared in THF only).
- Also, EXAFS and XANES studies have shown that the addition of cyanide to dimethylcuprate does not cause a significant change at the copper center (Barnhart, T. M.; Huang, H.; Penner-Hahn, J. E. *J. Org. Chem.* **1995**, *60*, 4310).
- However, addition of methyl *E*-cinnamate led to changes attributed to a cuprate-enoate π-complex.

Structure of Cuprates

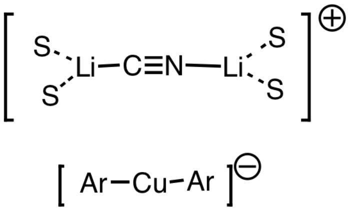
- Interpretation of NMR data has been somewhat controversial (Lipshutz, B. H. *J. Org. Chem.* **1994**, *59*, 7585), but IR characterization and *ab initio* calculations indicate that CN^- only interacts with Li^+ (Huang, H.; Alvarez, K.; Lui, Q.; Barnhart, T. M.; Snyder, J. P.; Penner-Hahn, J. E. *J. Am. Chem. Soc.* **1996**, *118*, 8808. Stemmler, T. L.; Barnhart, T. M.; Penner-Hahn, J. E.; Tucker, C. E.; Knochel, P.; Böhme, M.; Frenking, G. *J. Am. Chem. Soc.* **1995**, *117*, 12489).
- An NMR study confirmed that a cyanide-bridged compound is a reasonable possibility (*J. Am. Chem. Soc.* **1997**, *119*, 3878, see also: Bertz, S. H. et al. *Angew. Chem. Int. Ed.* **1998**, *37*, 314).
- A solid state structure, however, stresses the separation of $[Ar_2Cu]^-$ and $[Li_2CN]^+$ units (Kronenburg, C. M. P.; Jastrzebski, J. T. B. H., "A model structure for the resting state of cyanocuprate reagents $R_2Cu(CN)Li_2$. The x-ray crystal structure of $[Ar_2Cu(CN)Li_2(THF)_4]_\infty$." *J. Am. Chem. Soc.* **1998**, *120*, 9688).

Structure of Cyano Cuprates

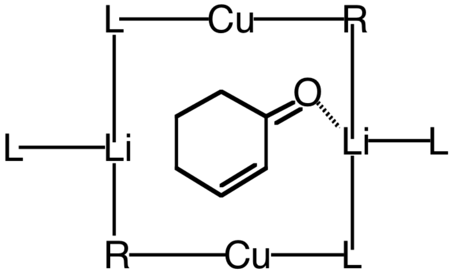
Proposed solution structure for $Me_2CuLi\text{-}LiCN$



X-ray structure for $Ar_2CuLi\text{-}LiCN$

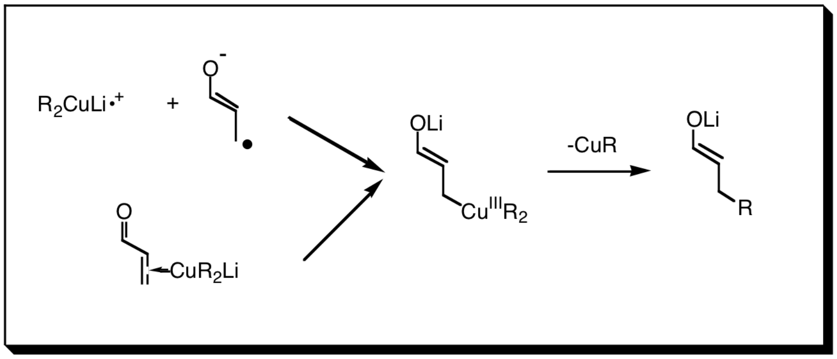


Conjugate Additions



The formation of a π–complex appears to be followed by σ-complex formation and reductive elimination. The reductive elimination is rate-determining (Frantz, D. E.; Singleton, D. A.; Snyder, J. P., "^{13}C Kinetic isotope effects for the addition of lithium dibutylcuprate to cyclohexenone. Reductive elimination is rate-determining." *J. Am. Chem. Soc.* **1997**, *119*, 3383).

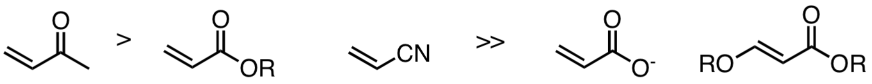
Conjugate Additions - To Be or Not To Be A Radical



Conjugate Additions

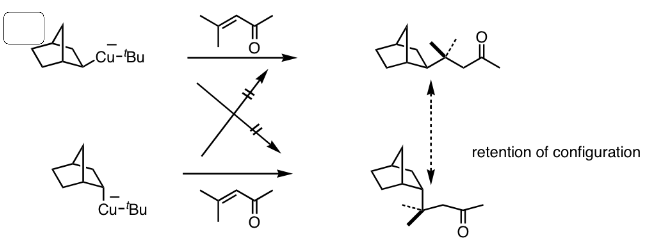
- Caveat: The mechanism of cuprate additions depends on cuprate structure, substrate, solvent, additives (e.g. TMS-Cl), and the specific reaction conditions.
- Review: Woodward, S., "Decoding the "black box" reactivity that is organocuprate conjugate addition chemistry." *Chem. Soc. Rev.* **2000**, *29*, 393-401.

-Effect of substrates:



- Unsaturated esters are less reactive than enones.
- β,β-Disubstitution slows reaction.

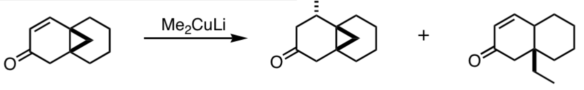
Evidence for ionic mechanism



retention of configuration

Whitesides *J. Org. Chem.* **1972**, *37*, 3718.
Whitesides *J. Am. Chem. Soc.* **1969**, *91*, 6542.

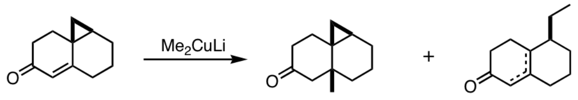
Evidence for radical anion mechanism



Marshall *Tetrahedron Lett.* **1971**, 2875.

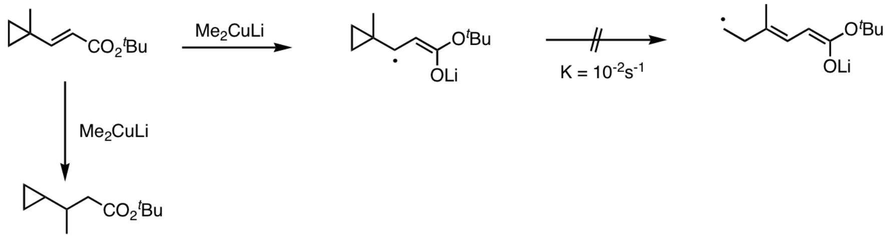
55% 39%

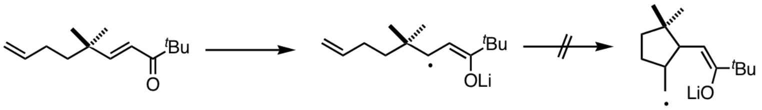
may be formed via intermediate radical anion



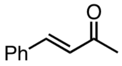
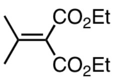
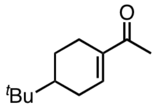
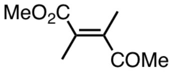
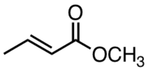
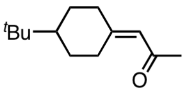
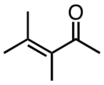
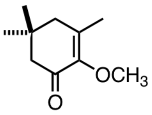
43% 49%

- but





- Half-life of intermediate radical anion is very short.
- Subsequent coupling with cuprate reagent (after e-transfer) is faster than other radical reactions in some cases.
- However, competitive single electron reductions with cuprates have been observed and they may be used to effect reductive elimination reactions analogous to dissolving metal or Zn reductions.

	E_{red}		E_{red}
	-1.63 v	$^{n}Pr-C\equiv C-CO_2Me$	-2.26 v
	-2.13 v		-2.25 v
	-2.14 v		-2.33 v
	-2.12 v		-2.35 v
	-2.20 v		

All can accept an e$^-$ (undergo reduction) by Me_2CuLi

↑

E_o = -2.35 v

Mixed Organocuprates - Enter the Dummies

- $R(X)Cu^-$ (X=alkynyl, CN, NR_2, SMe, PR_3 a. o.) in which the X^- group acts as a nontransferable ("dummy") ligand provided a breakthrough for the synthetic use of cuprates. Seemingly a paradox, cyano and alkynyl groups have low energy of activation for 1,2-migration as a consequence of participation of the π-orbitals in the transfer step. A long accepted hypothesis for the dummy ligand effect of these groups was that they form a strong Cu-X bond. However, it has been shown that the transfer selectivity is controlled by the metal-coordination ability of the X group in the polymetallic cluster rather than the Cu-X bond strength.

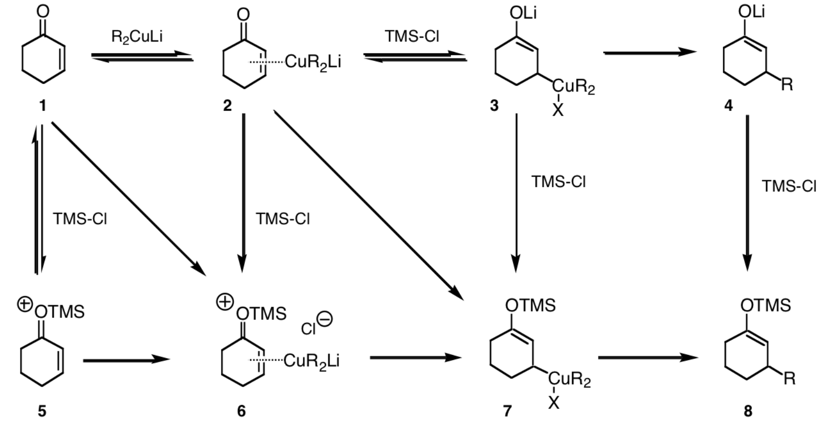
RLi, CuI, R_3P (1:1:2)	Suzuki *Tetrahedron Lett.* **1980**, 1247.
(COD)RCuMgX	Leyendecker *Tetrahedron Lett.* **1980**, 1311.
RCu(SPh)Li, RCu(O^tBu)Li, RCu(NMe_2)Li	Posner *j. Am. Chem. Soc.* **1973**, *95*, 7788.
RCu(SPh)Li	Alexakis *Tetrahedron Lett.* **1976**, 3461. *Org. Prep. Proc. Int.* **1976**, *8*, 13.
RCu($C\equiv C^tBu$)Li and RCu(CN)Li	Boeckman *J. Org. Chem.* **1977**, *42*, 1581. Marino *J. Org. Chem.* **1976**, *41*, 3213.
RCu(CN)Li	Acker *Tetrahedron Lett.* **1977**, 3407. Miyaura *Tetrahedron Lett.* **1977**, 3369.
RCu($C\equiv CPr$)Li	Corey *J. Am. Chem. Soc.* **1972**, *94*, 7210.
RCu($C\equiv CC(OMe)Me_2$)Li	Corey *J. Org. Chem.* **1978**, *43*, 3418.

Other Cuprates

- In addition to Gilman and Cyanocuprate reagents, Yamamoto-type cuprates (Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947) and cuprate/TMS-Cl mixtures have interesting reactivity. Organocopper compounds can also be obtained via transmetalation (Kharasch-Grignard; Wipf, P., "Transmetalation reactions in organocopper chemistry." *Synthesis* **1993**, 537-557):

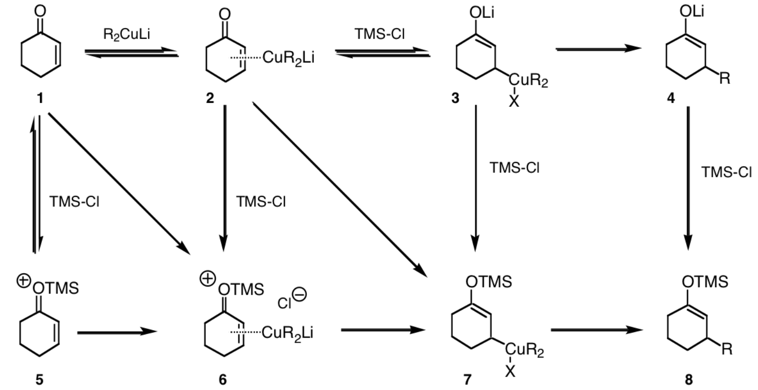
Mechanism of TMSCl-accelerated additions of cuprates to enones

- Several conflicting theories have been proposed to explain this effect. Corey and Boaz suggested that TMS-Cl accelerates the conjugate addition by the silylation of a d,π*-complex to produce the silyl enol ether of a Cu(III)-adduct and thus make the process irreversible (e.g., **2→7).**



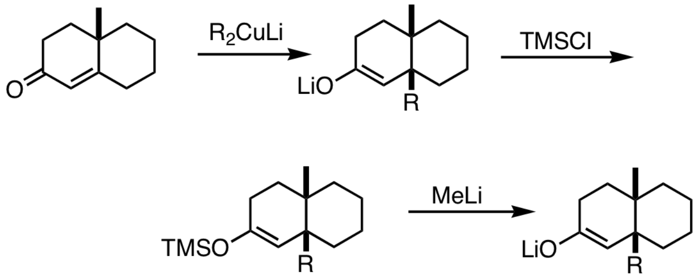
Mechanism of TMSCl-accelerated additions of cuprates to enones

- Kuwajima, in contrast, suggested that TMS-Cl acted as a Lewis acid to activate the enone (e.g., **1→5**), and Lipshutz presented NMR evidence that the chloride acts as a Lewis base and associates with the lithium cation of cuprate dimers (e.g., **1→6).** Snyder and Bertz suggested that the chloride coordinates with copper to stabilize formation of the Cu(III) intermediate **7** (X=Cl).



- The measurement of kinetic isotope effects is consistent with a rate-limiting silylation of the intermediate π-complex. These data support the Corey proposal, have no bearing on the push-pull proposal by Lipshutz, but do not support any importance for TMS-Cl coordination of the initial enone or a formal Cu(III) intermediate. Also, the basic mechanism appears to be the different in THF or Et_2O, and it is known that TMSCl has less effect on additions to enones in the latter where the rate-limiting step is reductive elimination.
- However, TMS-Cl does have a large impact on additions to α,β-unsaturated esters, amides, and nitriles in ether, and this might also go hand in hand with a change in the rate-limiting step.

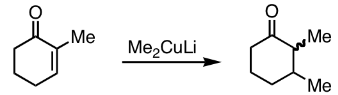
- TMS-Cl trapping is also useful in the regiospecific generation of enolates.



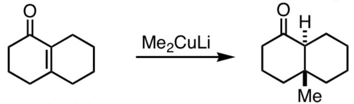
Stork *J. Am. Chem. Soc.* **1974**, *96*, 7114.
Stork *J. Am. Chem. Soc.* **1961**, *83*, 2965.
Horiguchi *Tetrahedron Lett.* **1989**, *30*, 7087.

Stereochemistry of Conjugate Additions: Cyclic Substrates

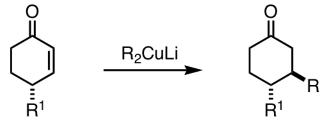
2,3-diastereoselectivity



condition dependent:
cis preferred, but isomerization
to *trans* is facile.

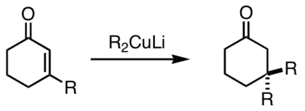


3,4-diastereoselectivity

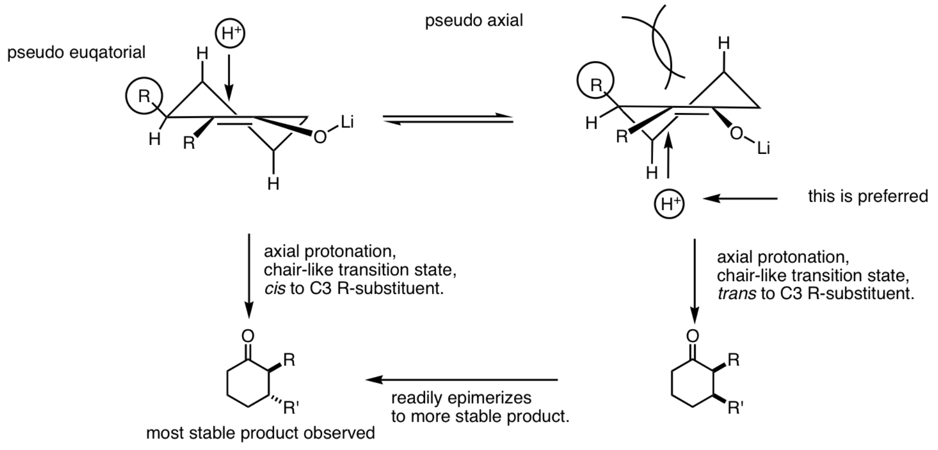


R^1	R	*trans: cis*	R^1	R	*trans: cis*
Me	Me	72:28	Et	Me	77:23
	Et	78:22		Ph	89:11
	^{i}Pr	88.12	^{i}Pr	Me	89:11
	Ph	96:4		Et	92:8
		(87:13)			

3-substituted enones



2,3-Diastereoselection determined by protonation of enolate



pseudo euqatorial

pseudo axial

Destabilizing 1,3-diaxial
interaction developing.

this is preferred

axial protonation,
chair-like transition state,
cis to C3 R-substituent.

axial protonation,
chair-like transition state,
trans to C3 R-substituent.

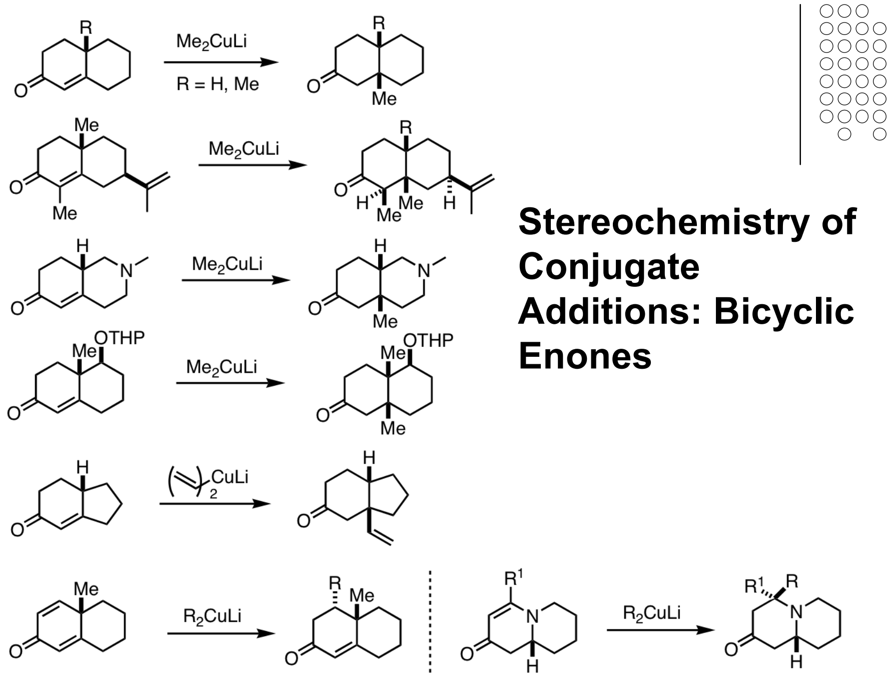
readily epimerizes
to more stable product.

most stable product observed

Face-selective Addition Reaction to a Heterocycle

Yamada, S.; Jahan, I. "A new route to 3,4-disubstituted piperidines: Formal synthesis of (-)-paroxetine and (+)-femoxetine." *Tetrahedron Lett.* **2005**, *46*, 8673-8676.

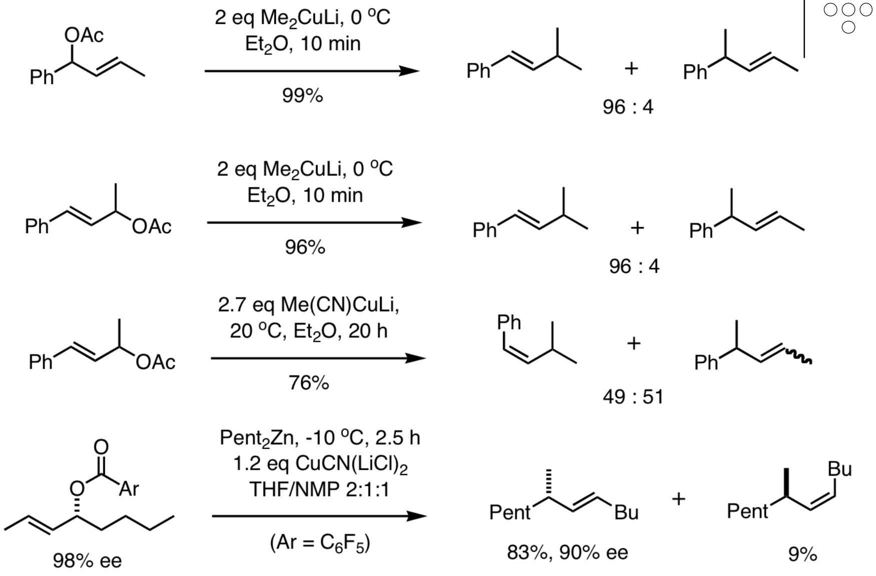
Stereochemistry of Conjugate Additions: Bicyclic Enones



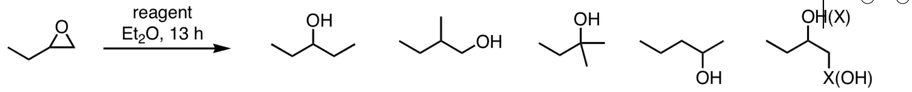
3-Component Conjugate Addition - Enolate Trapping

- Noyori, R. et al. *JACS* **1988**, *110*, 4718.

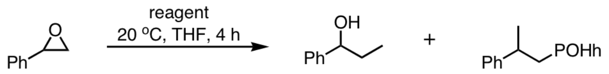
Allylic Displacements



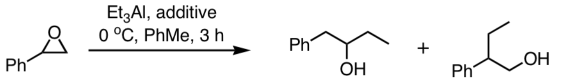
Epoxide Openings



3 eq MeMgBr, 34 °C	5%	5%	7%	15%	63% (X = Br)
3 eq MeMgCl, 34 ° C	45%	22%	1%	0%	31% (X = Cl)
3 eq MeLi, LiBr, 34 °C	90%	0%	1%	0%	0%
2 eq Me_2CuLi, 0 °C (14 h)	88%	0%	1%	0%	0%

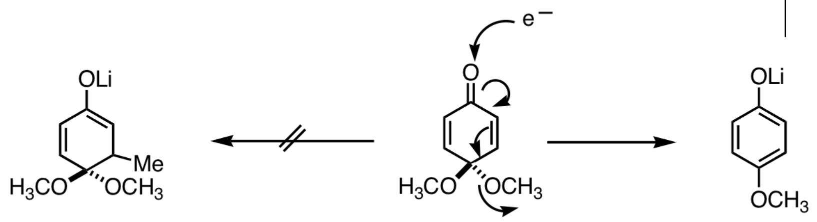


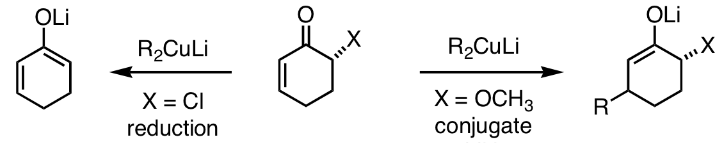
reagent:	
$Me_2Cu(CN)Li_2$	68 : 32 (93% yield)
MeLi	71 : 29 (trace)
Me_4ZnLi_2	51 : 49 (93% yield)



additive:	
none	33 : 67 (75% yield)
5% PPh_3	2 : 98 (95% yield)

Reduction Pathways





R_2CuLi

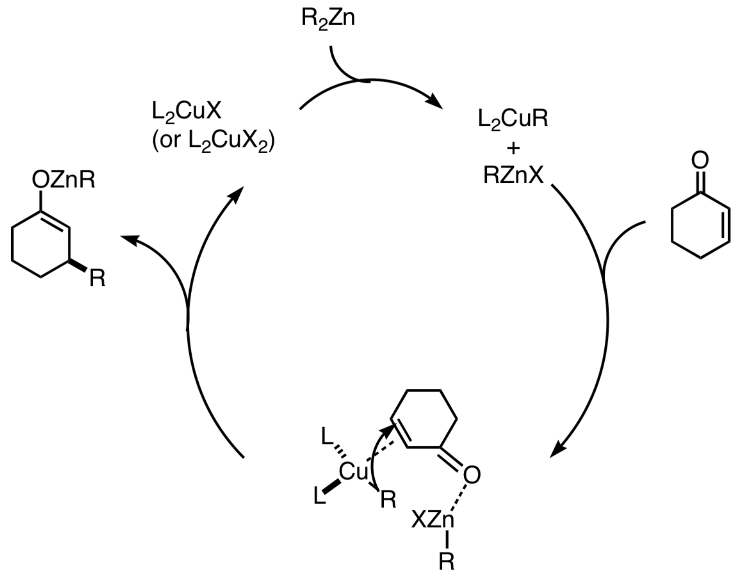
X = Cl
reduction

R_2CuLi

X = OCH_3
conjugate
addition

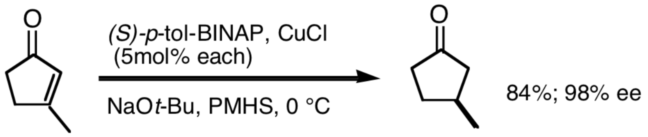
Synthetic Examples

- Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M., "Highly enantioselective catalytic conjugate addition and tandem conjugate addition - aldol reactions of organozinc reagents." *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2620.



Conjugate Reduction

- Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L., "Synthesis of β-alkyl cyclopentanones in high enantiomeric excess via copper-catalyzed asymmetric conjugate reduction." *J. Am. Chem. Soc.* **2000**, *122*, 6797-6798. The pioneering work by Stryker, Lipshutz and Hiyama demonstrated that achiral phosphine-copper hydrides such as $[(Ph_3P)CuH]_6$ reduce enones via 1,4-reduction. In this work, chiral cyclopentanones were obtained from polymethylhydrosiloxane (PMHS), CuCl, NaO*t*-Bu, and chiral bis-phosphines.
- Cyclohexenones and cycloheptenones are also reduced with good ee's, but 1,2-reduction competes to some extent.



Applications in Natural Product Synthesis

- 1,2-Shift of Copper-Ate Complexes
- Ashworth, P.; Broadbelt, B.; Jankowski, P.; Kocienski, P.; Pimm, A.; Bell, R. *Synthesis* **1995**, *2*, 199.