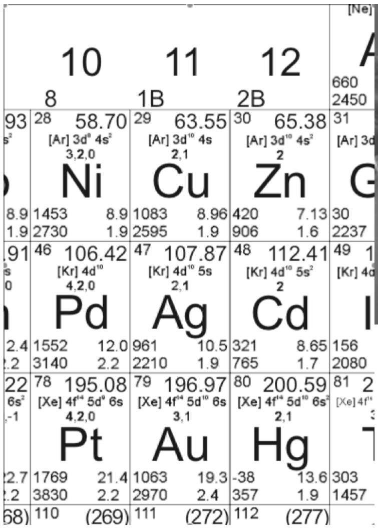
I. Basic Principles

IF. The Synthetic & Mechanistic Chemistry of Cuprates



10 8	11 1B	12 2B
28 58.70 [Ar] $3d^8 4s^2$ 3,2,0 Ni 1453 8.9 2730 1.9	29 63.55 [Ar] $3d^{10} 4s$ 2,1 Cu 1083 8.96 2595 1.9	30 65.38 [Ar] $3d^{10} 4s^2$ 2 Zn 420 7.13 906 1.6
46 106.42 [Kr] $4d^{10}$ 4,2,0 Pd 1552 12.0 3140 2.2	47 107.87 [Kr] $4d^{10} 5s$ 2,1 Ag 961 10.5 2210 1.9	48 112.41 [Kr] $4d^{10} 5s^2$ 2 Cd 321 8.65 765 1.7
78 195.08 [Xe] $4f^{14} 5d^9 6s$ 4,2,0 Pt 1769 21.4 3830 2.2	79 196.97 [Xe] $4f^{14} 5d^{10} 6s$ 3,1 Au 1063 19.3 2970 2.4	80 200.59 [Xe] $4f^{14} 5d^{10} 6s^2$ 2,1 Hg -38 13.6 357 1.9
110 (269)	111 (272)	112 (277)

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….

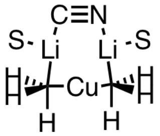
- In 1981, Lipshutz proposed the formation of “higher-order mixed cyanocuprates” (H.O. cuprates) by the addition of 2 equiv of an organolithium reagent to 1 equiv of copper cyanide.
- These $Me_2Cu(CN)Li_2$ reagents were assumed to be dianionic salts with the cyano group bound to copper (Lipshutz et al. *J. Am. Chem. Soc.* **1981**, *103*, 7672).
- Furthermore, it was reported 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

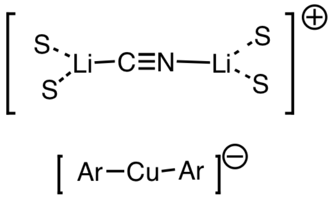
- Whether or not the cyanide ligand is bound to copper has been a controversial topic (Bertz, S. H. *J. Am. Chem. Soc.* **1991**, *113*, 5470).
- The Bertz proposal has the cyano group coordinated as lithium cyanide to a Gilman-like species. In the presence of HMPA, some free LiCN is indeed detected (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 Cyano Cuprates

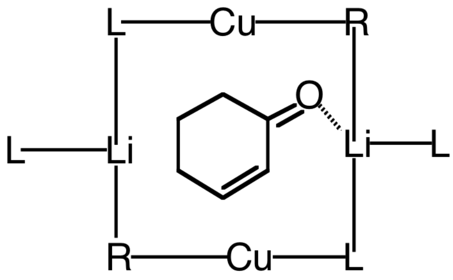
Proposed solution structure for Me_2CuLi-LiCN



X-ray structure for Ar_2CuLi-LiCN

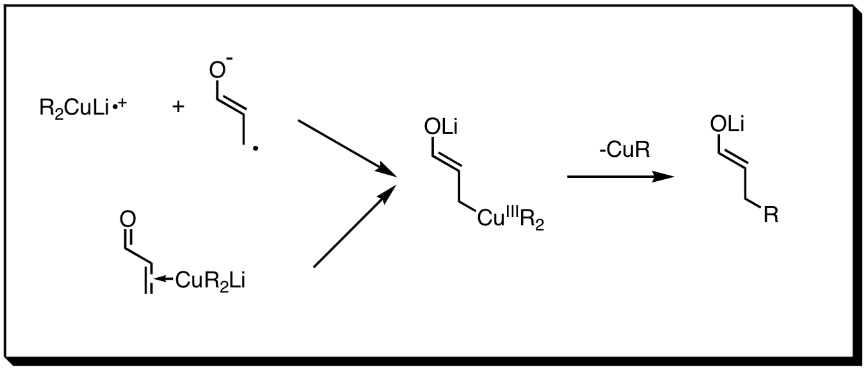


Conjugate Additions

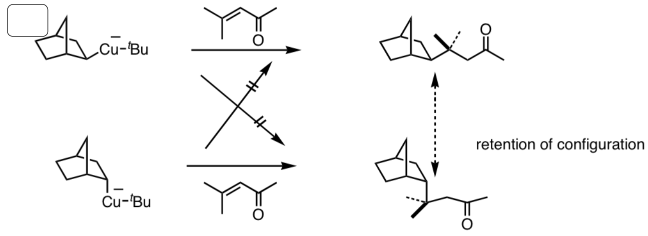


The formation of a π–complex appears to be followed by σ-complex formation and reductive elimination. The reductive elimination is rate-determining (Frantz, D. E.; Singleton, D. A.; Snyder, J. P., "^{13}C Kinetic isotope effects for the addition of lithium dibutylcuprate to cyclohexenone. Reductive elimination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

Conjugate Additions - To Be or Not To Be A Radical

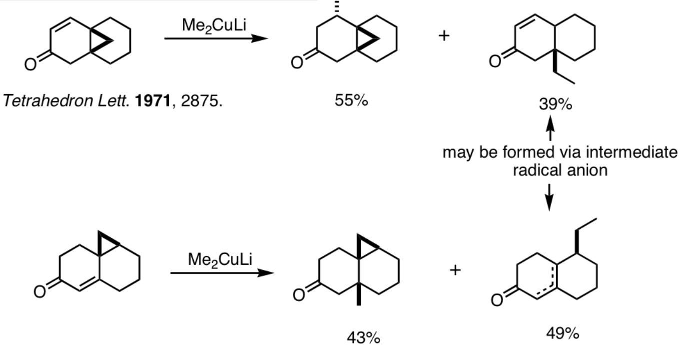


Evidence for ionic mechanism



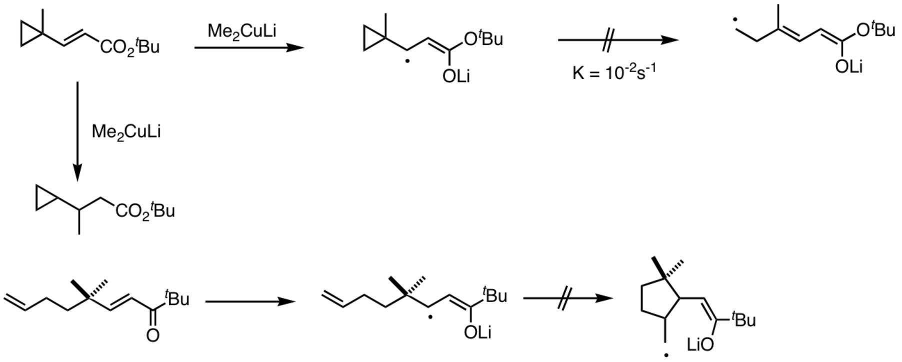
Whitesides *J. Org. Chem.* **1972**, *37*, 3718.
Whitesides *J. Am. Chem. Soc.* **1969**, *91*, 6542.

Evidence for radical anion mechanism



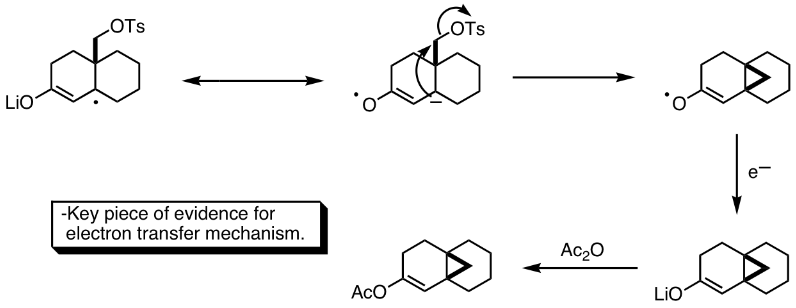
Marshall *Tetrahedron Lett.* **1971**, 2875.

- but

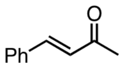
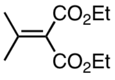
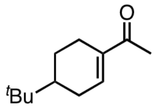
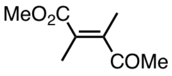
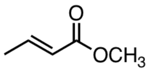
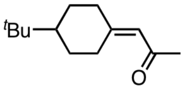
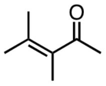
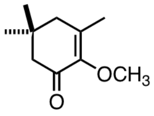


- Half-life of intermediate radical anion is very short.
- Subsequent coupling with cuprate reagent (after e-transfer) is faster than other radical reactions in some cases.
- However, competitive single electron reductions with cuprates have been observed and they may be used to effect reductive elimination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

Hannah *Tetrahedron Lett.* **1975**, 187.



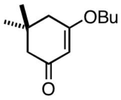
-Key piece of evidence for electron transfer mechanism.

	E$_{red}$		E$_{red}$
	-1.63 v	$^{n}\text{Pr}-\!\!\equiv\!\!-\text{CO}_2\text{Me}$	-2.26 v
	-2.13 v		-2.25 v
	-2.14 v		-2.33 v
	-2.12 v		-2.35 v
	-2.20 v		

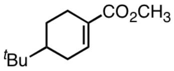
All can accept an e$^-$ (undergo reduction) by Me$_2$CuLi

E$_o$ = -2.35 v

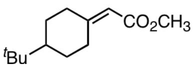
these substrates do not react with Me_2CuLi:



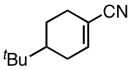
-2.43 v



-2.50 v

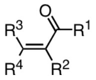


-2.54 v

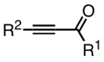


-2.55 v

-House estimation of

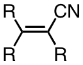


base value = -1.9 v



base value = -1.8 v

substituent	R^1	R^2	R^3/R^4		substituent	R^1	R^2
alkyl	-0.1	-0.1	-0.1		alkyl	-0.1	-0.1
alkoxy	-0.3	0	-0.3		alkoxy	-0.3	---
phenyl	+0.4	+0.1	+0.4				

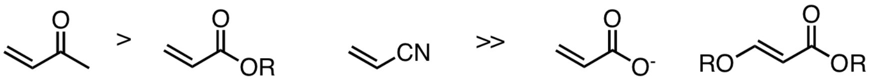


base value = -2.3 v

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:



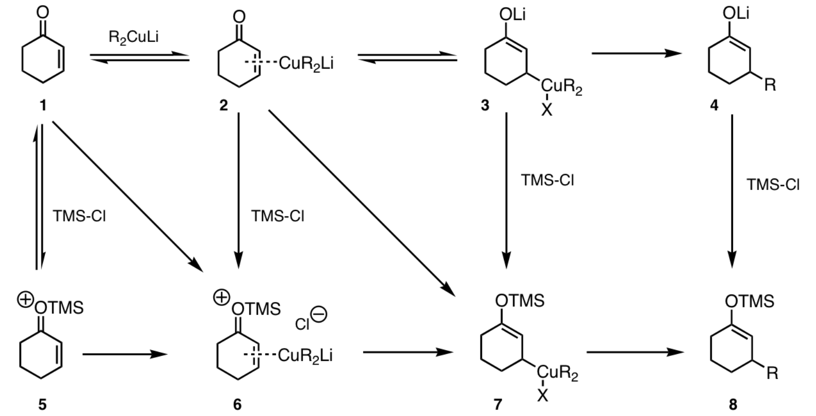
- Unsaturated esters are less reactive than enones.
- β,β−Disubstitution slows reaction.

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):

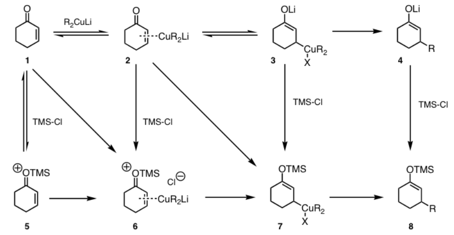
Mechanism of TMSCl-accelerated additions of cuprates to enones

- 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

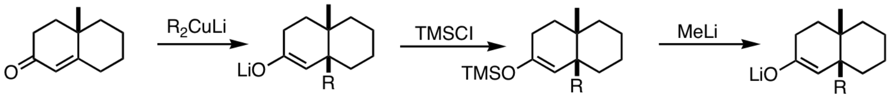
- Kuwajima, in contrast, suggested that TMS-Cl acted as a Lewis acid to activate the enone (e.g., **1→5**), and Lipshutz presented NMR evidence that the chloride acts as a Lewis base and associates with the lithium cation of cuprate dimers (e.g., **1→6).** Snyder and Bertz suggested that the chloride 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$_2$O, 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.



Mechanism of TMSCl-accelerated additions of cuprates to enones

- A consistent mechanistic hypothesis for the differing effects of TMSCl with changes in solvent and substrate starts with the observation that the coordination of lithium to the carbonyl oxygen is a critical factor in cuprate conjugate additions without additives. No reaction occurs in the presence of excess 12-crown-4.
- In ether the lithium coordination is sufficient for the reaction to proceed rapidly with cyclohexenone, and the TMSCl-accelerated process cannot compete (however, the more powerful electrophile trimethylsilyl triflate can).
- In the more basic THF the lithium coordination is attenuated and acceleration by irreversible silylation of an enone-cuprate complex dominates. The irreversible nature of the silylation brings about the change in the rate-limiting step from carbon-carbon bond formation in the absence of TMSCl. (It is important to remember that the cuprate reagent itself has changed in going from ether to THF, but emphasized here is the effect of lithium coordination.)
- With unsaturated esters and amides the lithium-carbonyl coordination is not sufficient, even in ether, to activate the conjugate addition (though more powerful Lewis acids such as BF_3 can) and the TMSCl-mediated process takes over.

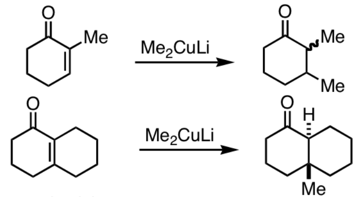
- TMS-Cl trapping is also useful in the regiospecific generation of enolates.



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

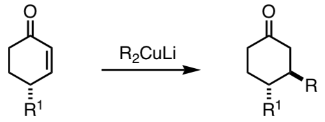
Stereochemistry of Conjugate Additions: Cyclic Substrates

2,3-diastereoselectivity



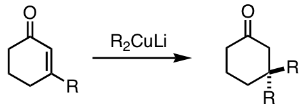
condition dependent:
cis preferred, but isomerization
to *trans* is facile.

3,4-diastereoselectivity

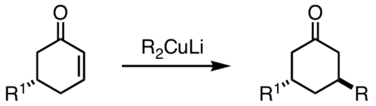


R^1	R	*trans: cis*	R^1	R	*trans: cis*
Me	Me	72:28	Et	Me	77:23
	Et	78:22		Ph	89:11
	^{i}Pr	88.12	^{i}Pr	Me	89:11
	Ph	96:4 (87:13)		Et	92:8

3-substituted enones

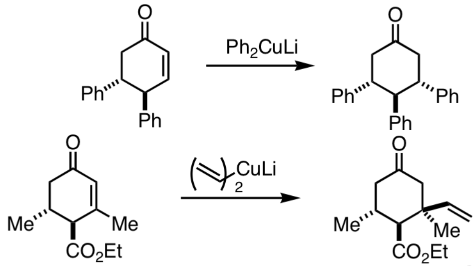


3,5-diastereoselectivity



R^1	R	*trans: cis*
Me	Me	98:2 (99:1) (93:7)
Me	CH_2Ph	*trans* only

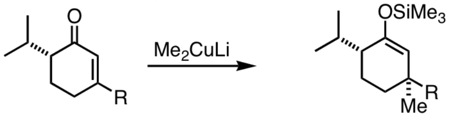
3,4-diastereoselectivity vs 3,5-diastereoselectivity



This will be dependent on the relative size of the C-3 and C-4 substituents.

80 : 20

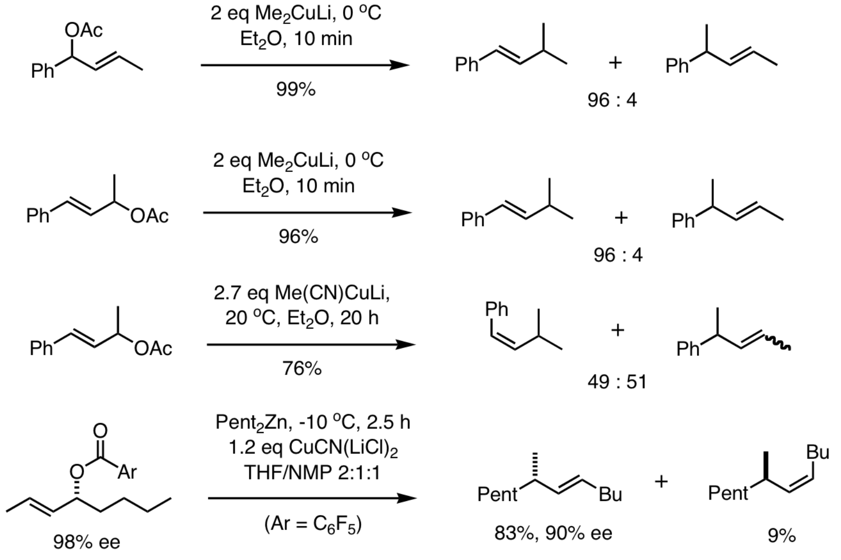
3,6-diastereoselectivity

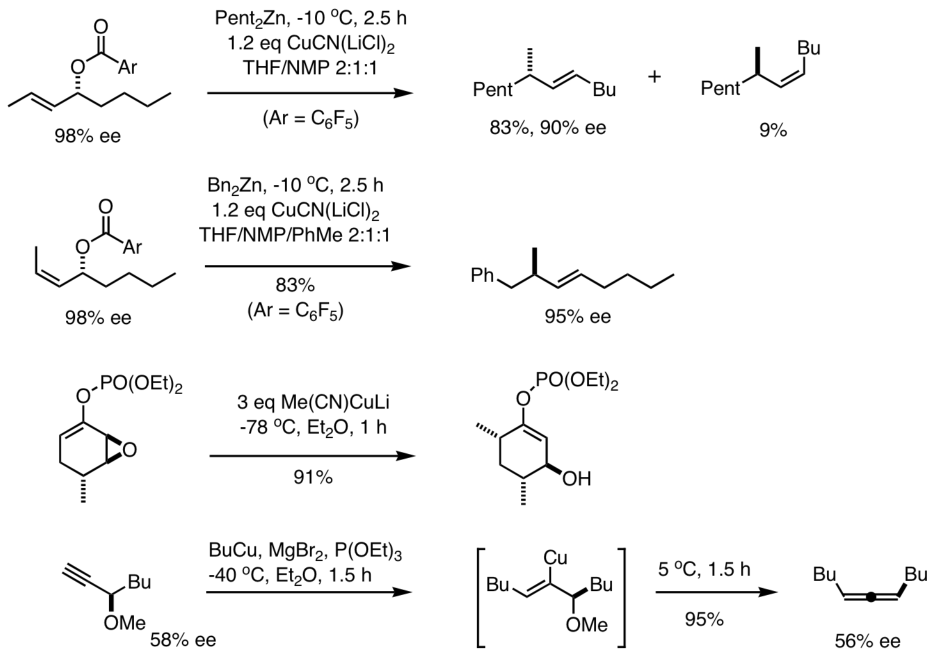


3-Component Conjugate Addition - Enolate Trapping

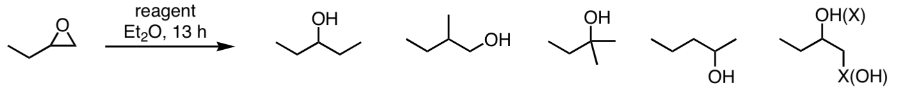
- Noyori, R. et al. *JACS* **1988**, *110*, 4718.

Allylic Displacements

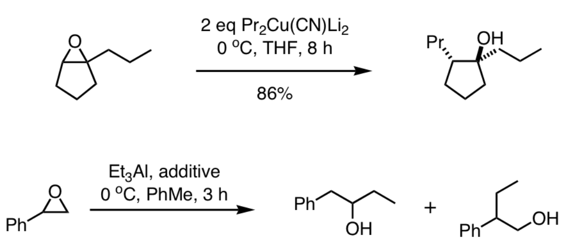




Epoxide Openings



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%



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