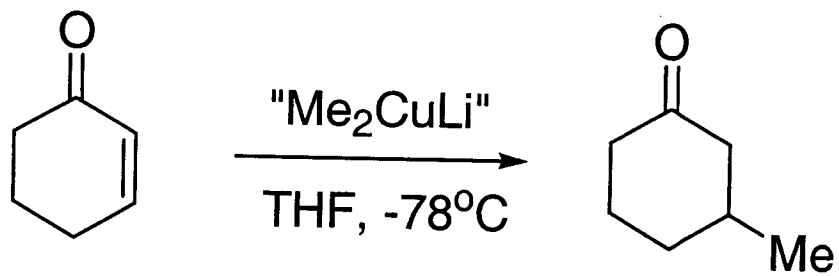
The Mechanism of Organocuprate Conjugate Additions: The Complexity of Simple Systems

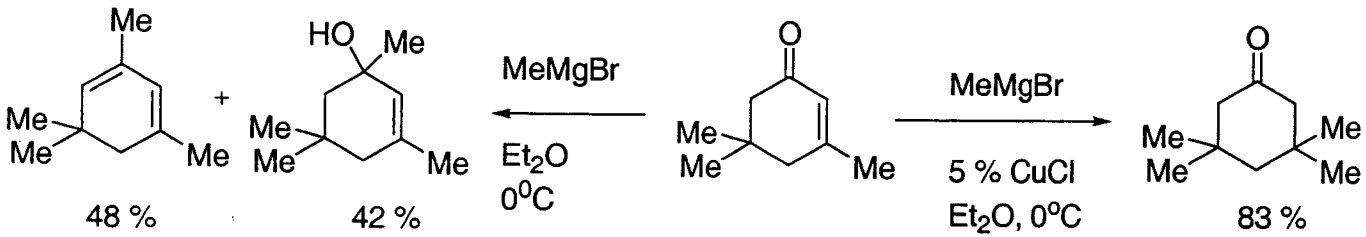


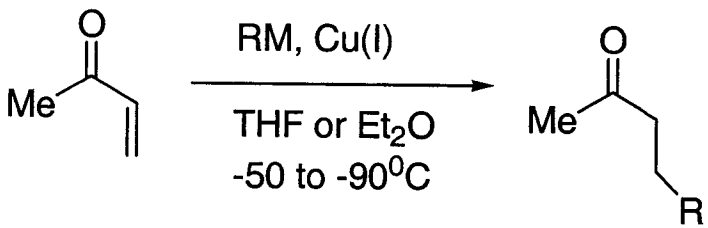
Steve Tymonko

SED Group Meeting

7/20/04

The "Black Box"





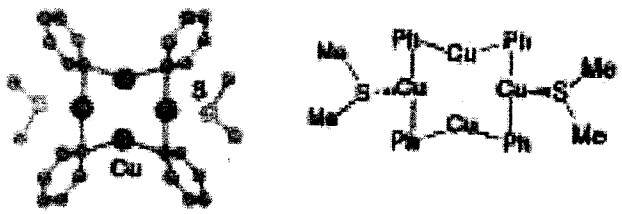
M= Li, Mg, Zn
Cu used stoicheometrically or catalytically
Practically, usually add at low temp and allow to warm
TMSCl and Lewis acids (BF_3) can greatly accelerate reaction
Non-transferable "dummy ligands" often used to avoid waste of R groups
Excellent enantioselectivities have been achieved with chiral ligands

"Predictions based on the hypotheses in vogue are so uncertain as to be practically useless."

Kharasch, M.; Tawney, P. *JACS*, **1941**, 2308
Nakamura, E.; Mori, S. *Angew. Chem. Int. Ed.* **2000**, 3751

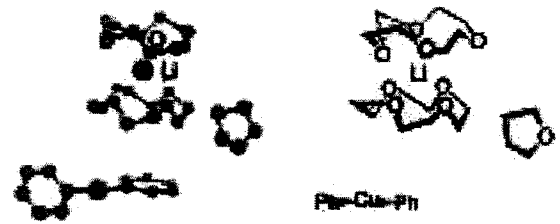
Structures of Organocopper Compounds

Neutral Cu(I): RCu



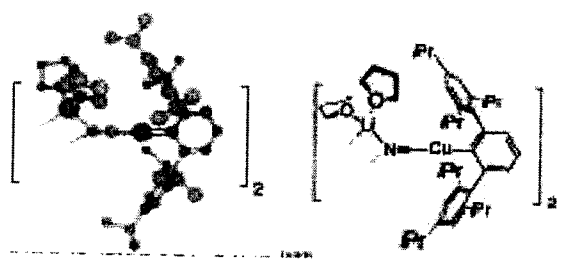
Monomers, dimers, and tetramers in solution
Unreactive

Linear Free Cuprates: R_2Cu^-



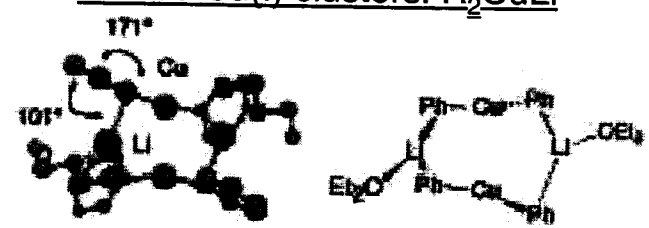
Unreactive monomers in conjugate addition chemistry

Minimum Cu(I) clusters: R_2CuLi



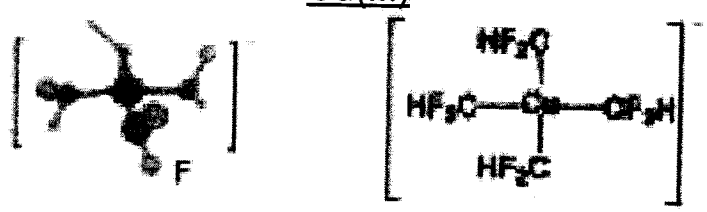
Linear C-Cu-C structure; Higher energy than closed clusters

Closed Cu(I) clusters: R_2CuLi



Resting state for most Cu(I) complexes; also known for Mg

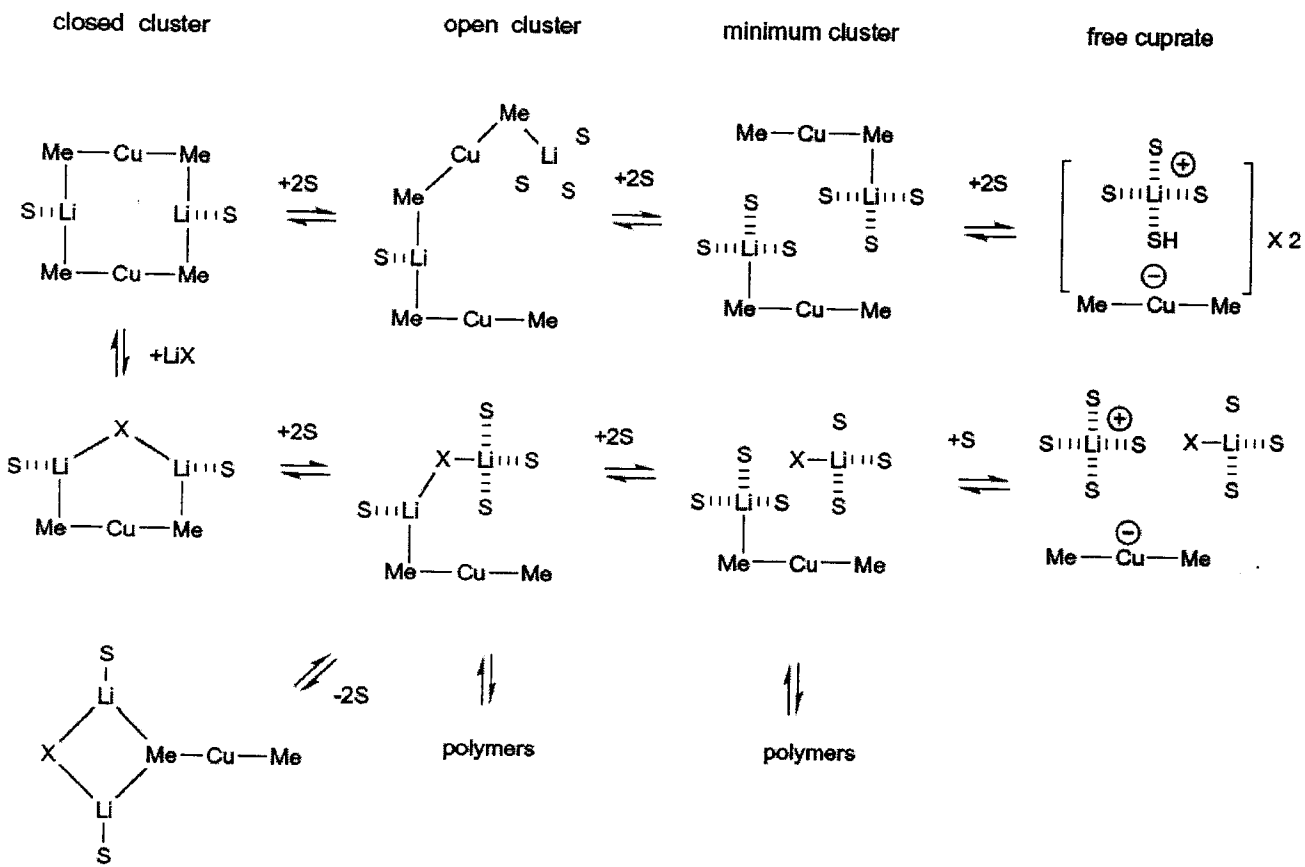
Cu(III)



Exceptionally rare

Nakamura, E.; Mori, S. *Angew. Chem. Int. Ed.* **2000**, 3750

Solution Equilibria

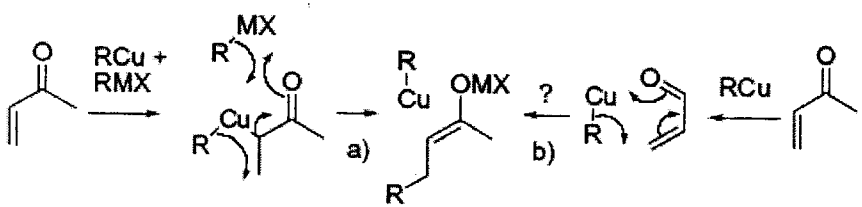


Closed cluster predominates in solution

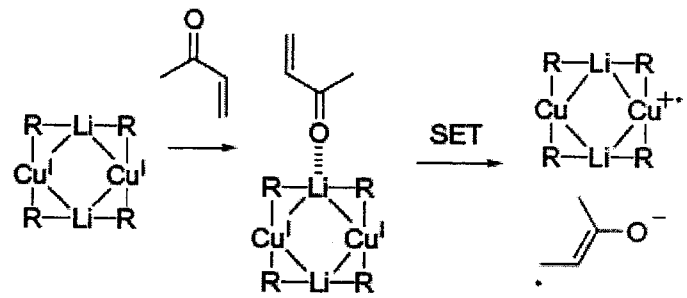
Nakamura, E.; Mori, S. *Angew. Chem. Int. Ed.* **2000**, 3750

Mechanistic Possibilities

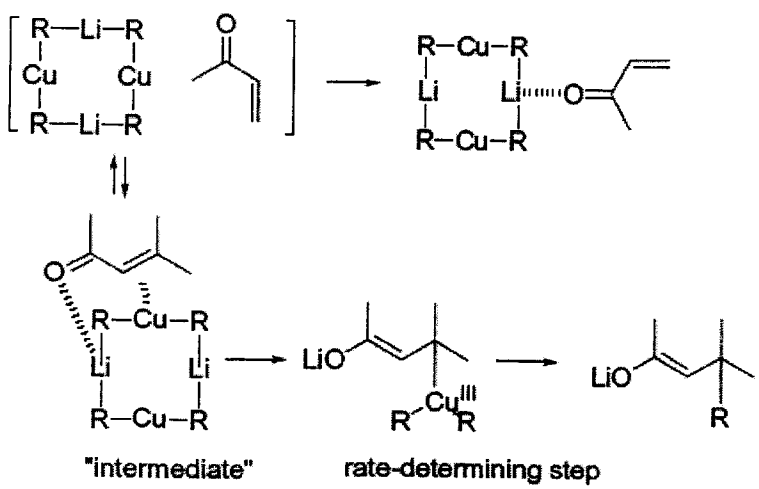
1,2- and 1,4-Addition

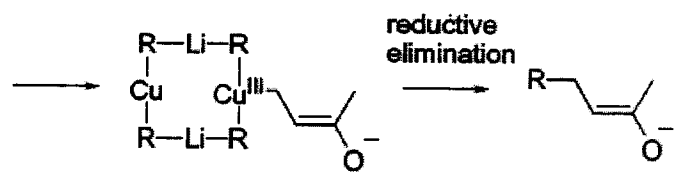


SET



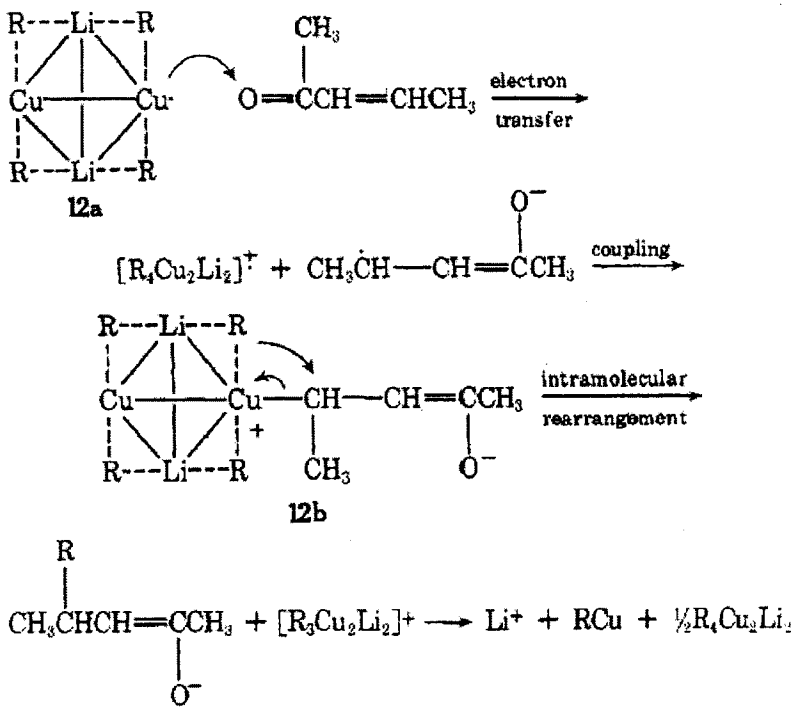
Cu^{III} Complex Formation



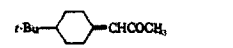
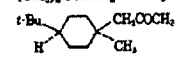
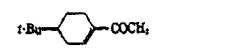
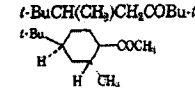
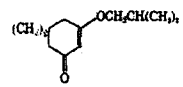


Nakamura, E.; Mori, S. *Angew. Chem. Int. Ed.* **2000**, 3750

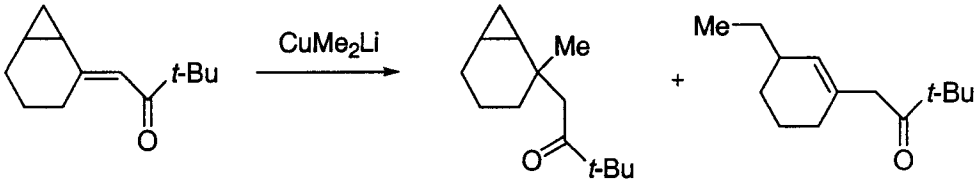
Evidence for a SET Mechanism



1. Polarographic measurement of reduction potentials less negative than -2.4 V correspond to productive reaction (22 cases)

Compound	$E_{1/2}$, V vs. sce[a]	Product (% yield)[b]
	−2.07	 (98)[c]
trans-$CH_3CH{=}CHCOCH_3$	−2.08	$(CH_3)_2CHCH_2COCH_3$ (96)[c]
	−2.12	 (*ca.* 89)[c]
trans-*t*-$BuCH{=}CHCOBu$-*t*	−2.22	*t*-$BuCH(CH_3)CH_2COBu$-*t* (79)[c]
	−2.25	 (75)[c]
	−2.43	(90% recovery)
	−2.45	(95% recovery)[c]

2. E/Z isomerization observed in unreacted SM
3. β-cyclopropyl substrates give ring opened products

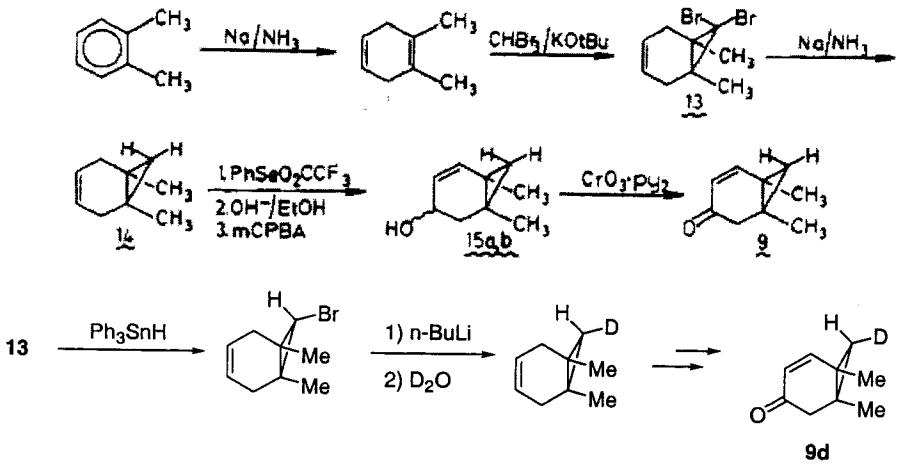


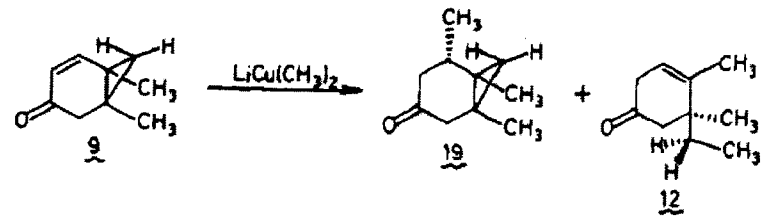
28 %

72 %

House, H. *Acc. Chem. Res.* **1976**, 59
House, H. et al. *JACS*, **1972**, 5495

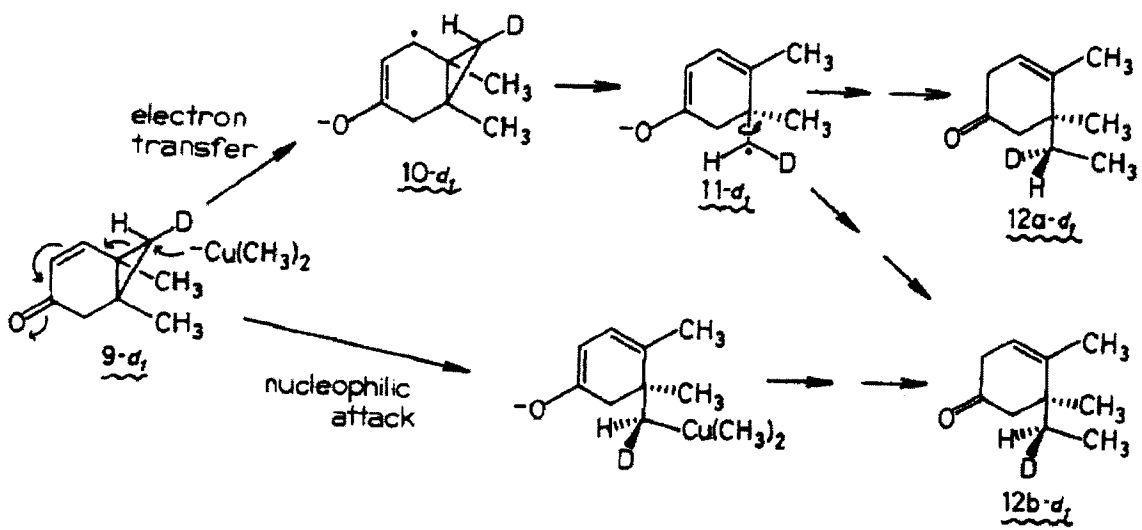
Refuting the SET Mechanism





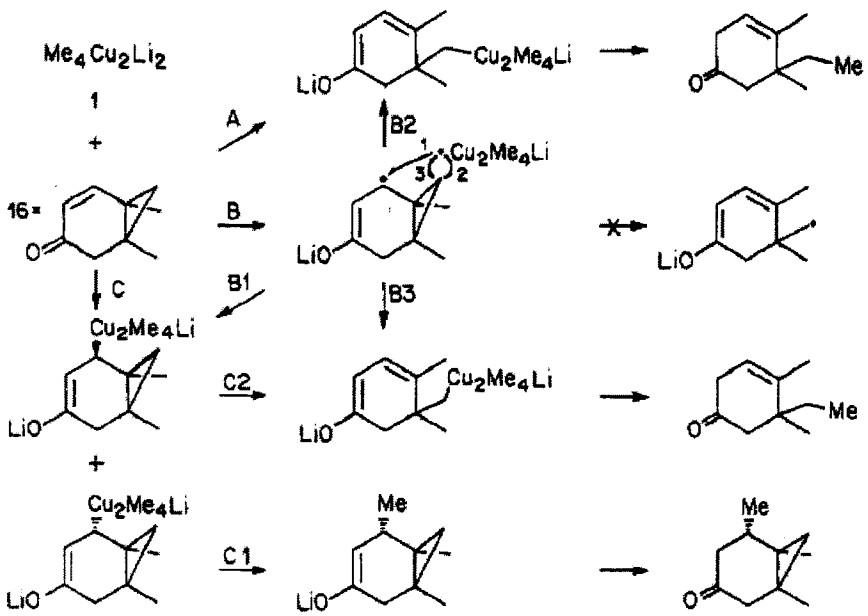
48 : 52

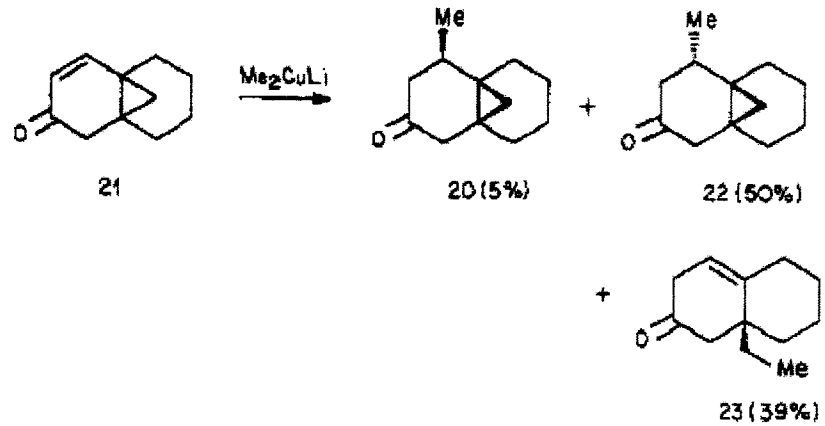
Deuterated **9** gave a single diastereomer of **12**



Casey, C.; Cesa, M. *JACS*, **1979**, 4236

Cyclopropyl Opening cont.





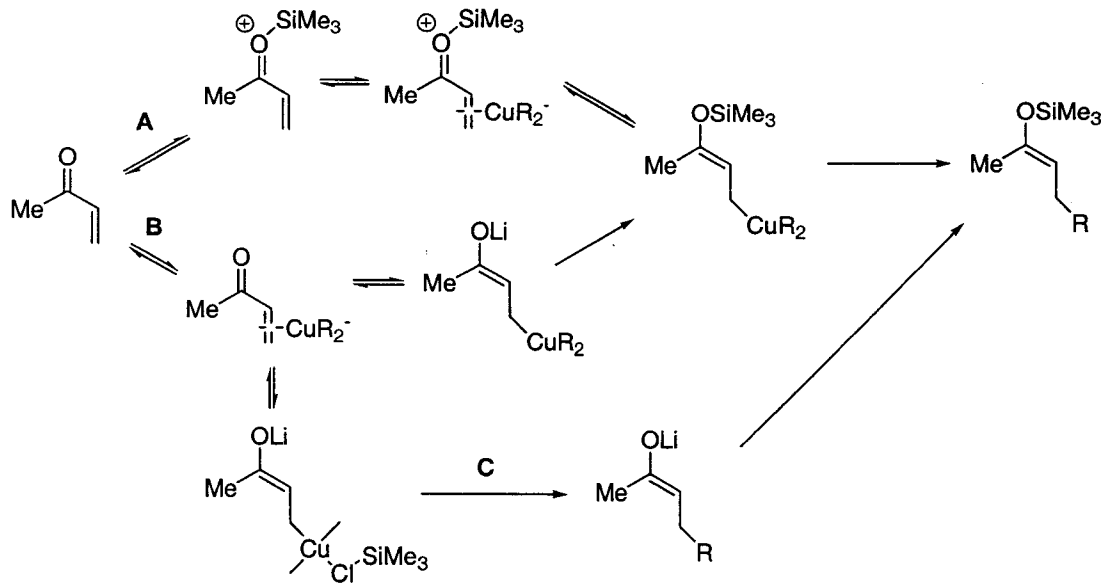
Cyclopropyl ketones are not opened

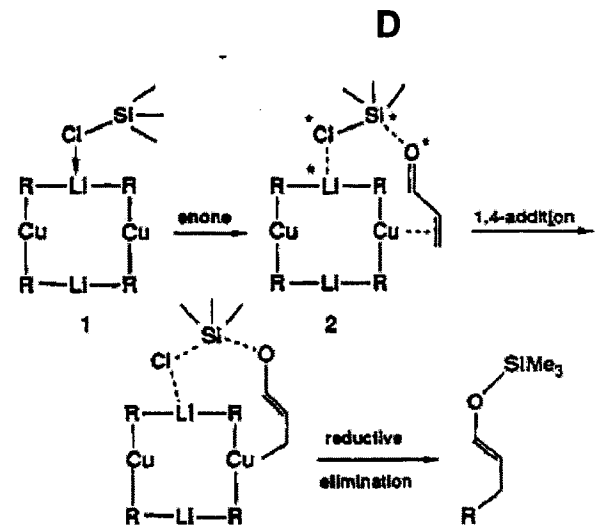
Freely rotating β–cyclopropyl substrates do not give ring opened products

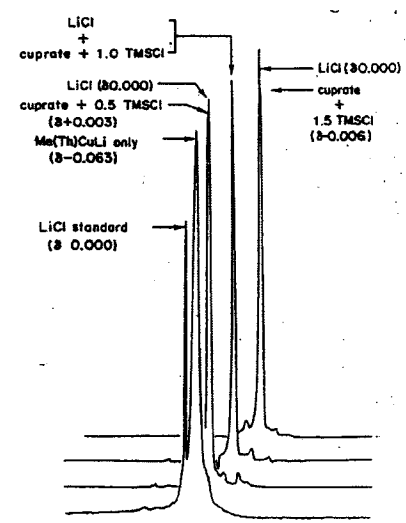
Path C through a common Cu(III) intermediate best explains results

Bertz, S.; Dabbagh, G.; Cook, J.; Honkin, V. *JOC.* **1984**, 1739

The Role of TMSCl





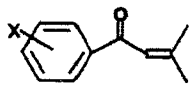


Experimental Observations

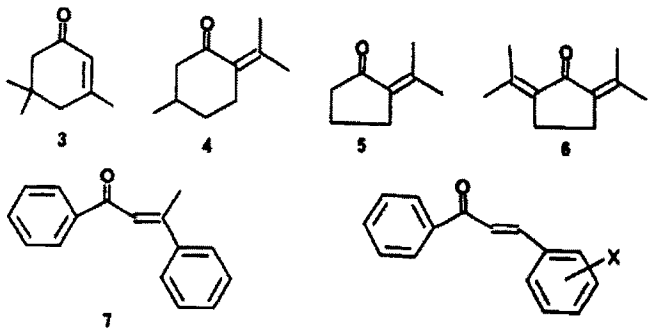
1. No change in ^{1}H NMR with enone/TMSCl mixes
2. ^{7}Li NMR changes with TMSCl addition
3. Ketone is often recovered alongside silyl enol ether
4. Calcuated Me_3Cu has reduced barrier to reductive elimination when complexed with TMSCl (E_a 3.2 kcal vs 10.1 kcal)

Corey, E. J.; Boaz, N. *Tetrahedron Lett.* **1985**, 6019
Lipshutz, B. et al. *JACS,* **1993**, 9283
Snyder, J. el al. *JACS*, **1995**, 11023

Kinetics of Cuprate Addition



2a, X = H
b, X = p-OC_6H_5
c, X = p-CH_3
d, X = p-Cl
e, X = m-CF_3



3 4 5 6 7

8a, X = H
b X = p-OCH_3
c, X = p-CH_3
d, X = p-Cl
e, X = m-CF_3

All substrates gave identical rate law

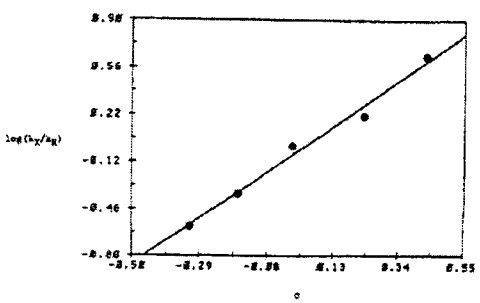
$$-\frac{d[\text{intermediate}]}{dt} = \frac{kK[(CH_3)_4Cu_2Li_2][\text{ketone}]}{1 + K[(CH_3)_4Cu_2Li_2]}$$

$$\text{ketone} + (CH_3)_4Cu_2Li_2 \overset{K}{\rightleftharpoons} \text{intermediate} \xrightarrow{k} \text{products}$$

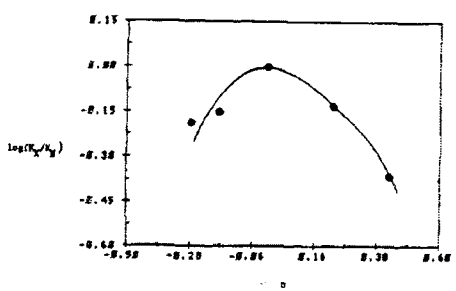
ketone	K, M^{-1}	k, s^{-1}
1	30 (7.9[a])	1.12 (3.9[a])
3	110	0.089
4	40	0.062
5	36 (7.0[a])	0.17 (0.99[a])
6	11	0.21
7	20	1.45

[a] Halide-free reagent.

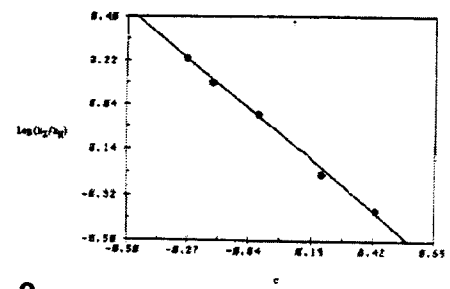
ketone	E_{red}[a]	K, M^{-1}	k, s^{-1}
8a	−1.41	162	5.0
2a	−1.86	8.6	13.8
1	−2.21	30	1.12
3	−2.22[b]	110	0.089



ρ = 1.58

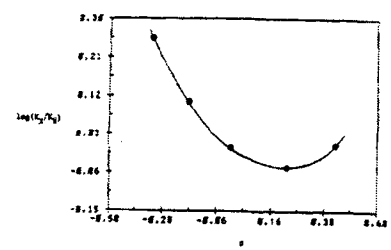


2



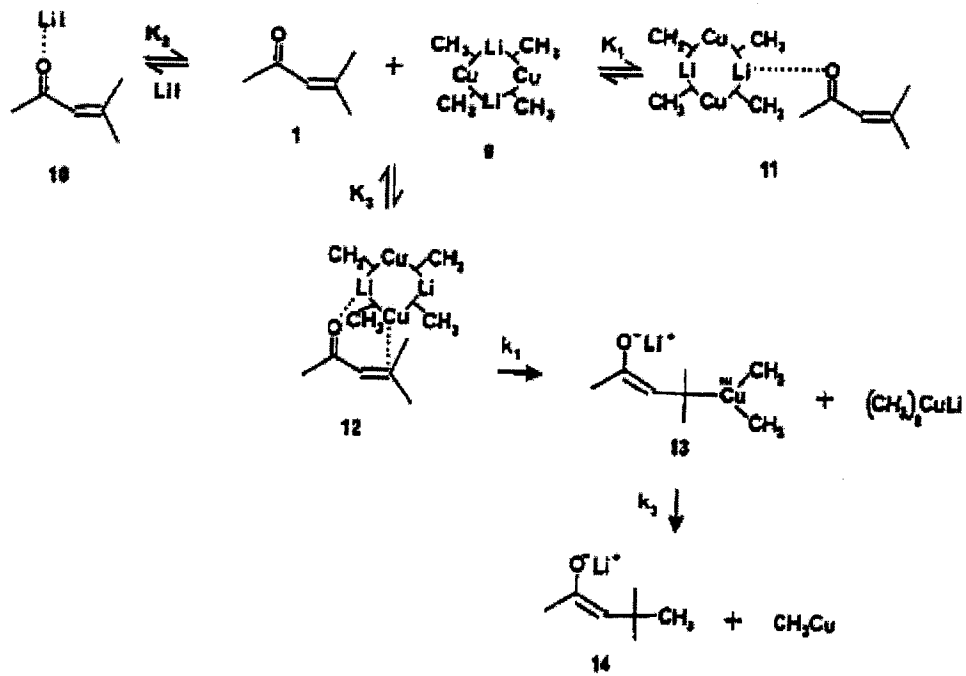
ρ = -0.88

8



Krauss, S.; Smith, S. *JACS*, **1981**, 141

Interpreting the Kinetics

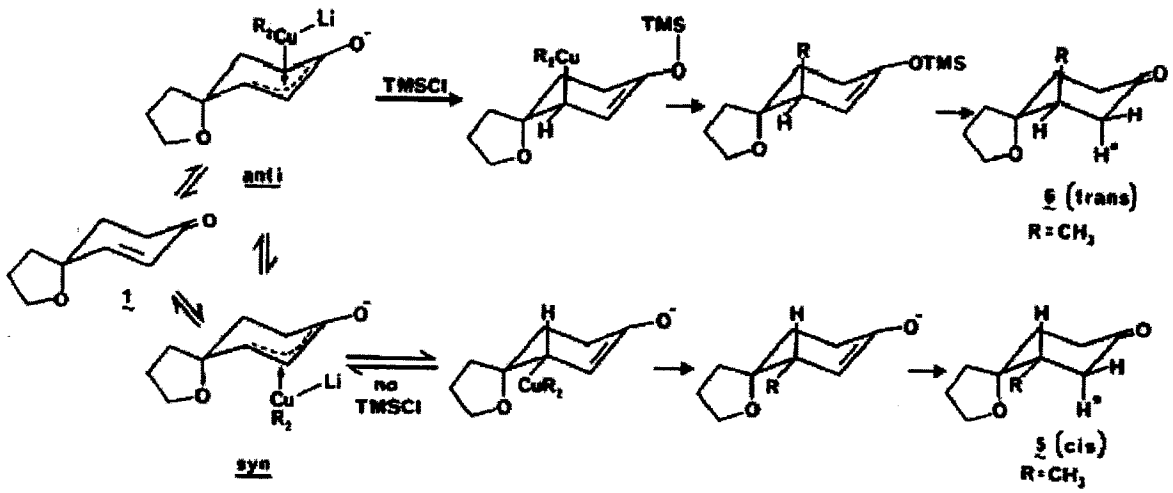


Hammett study is consistent with development of negative charge at the carbonyl and positive charge at the β-carbon (**12 ->13)**

Curved Hammett plots of K_{eq} suggest multiple complexes with competing electronics in intial equilibrium

Krauss, S.; Smith, S. *JACS,* **1981**, 141

A d-π^* complex?



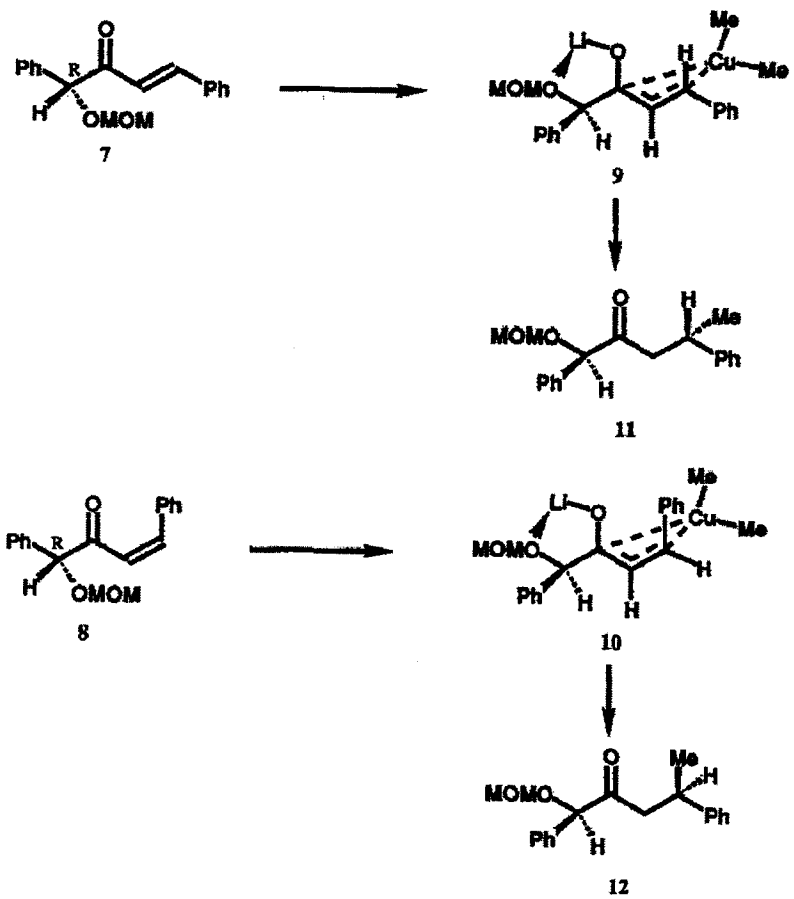
In THF addition of dimethylcuprate at -78^{0}C-rt gave 92:8 **5:6** with the addition of TMSCl exclusively **6** at -78^{0}C

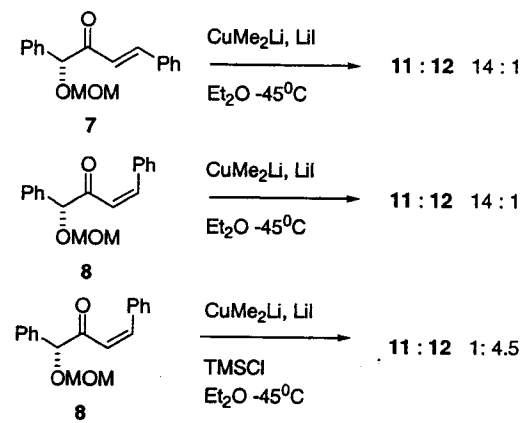
In Et_2O at -78^{0}C solid precipitate forms. Isolated at -78^{0}C, added to THF with TMSCl gave exclusively **6**

Reversibly formed d-π^* complex proposed to explain selectivity

Corey, E. J.; Boaz, N. *Tetrahedron Lett.* **1985**, 6015

Application of the d-π^* Model



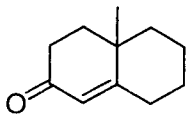


8 rapidly isomerizes under reaction conditions

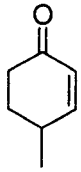
Model successfully predicts stereochemical outcome

Corey, E. J.; Hannon, F.; Boaz, N. *Tetrahedron* **1989**, 545

Further Evidence

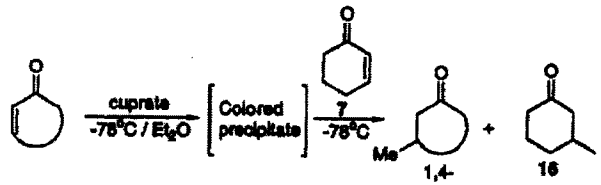


1



14

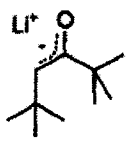
Table 2. Reaction of 2-Cyclohexenone (7) with the Colored Precipitates Obtained from 1 and 14 and Lithium Dimethylcuprates at −78 °C



enone	cuprate	products[a] (%) enone	1,4-	7	16
1	$Me_2CuLi{\cdot}(LiX)_3$	95[b]	0	<5	60
14	$Me_2CuLi{\cdot}LiI$	92	5	0	95

[a] GC yields unless stated otherwise. [b] NMR yield.

-80°C to -50°C ^{13}CNMR Experiments

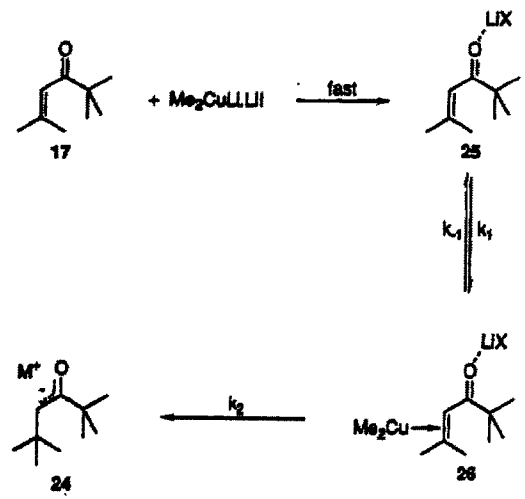


27

Table 3. ^{13}C NMR Chemical Shifts of 17 and Derived Complexes in Diethyl Ether

	carbon chemical shift, ppm C-1	C-2	C-3	C-4	C-5	C-6	C-7
17	26.5	43.8	203.5	119.7[a]	155.1	28.1	20.7
17 + LiI	26.6	44.1	204.8	120.0	156.1	28.2	21.1
17 + $LiClO_4$	26.5	44.2	205.9	120.0	157.9	28.3	21.2
24	29.9	37.9	166.8	99.0[b]	31.6	32.3	
25	27.1[c,d]	e	209.0[c]	120[c]	158.9[c,f]	28.4[c,d]	21.9[c,d]
26	e	e	195.8[c]	e	67.7[c,g]	e	e
27	29.9	37.9	166.7	99.1[h]	31.6	32.3	

[a] $^1J_{CH}$ = 153 Hz. [b] $^1J_{CH}$ = 145 Hz. [c] Broad resonance. [d] Assignments interchangeable. [e] Not observed. [f] 158.3 ppm when low halide Me_2CuLi used. [g] 67.3 ppm when low halide Me_2CuLi used. [h] $^1J_{CH}$ = 148 Hz.



25:26 ~1:2 at -80°C

Vellekoop, A.; Smith, R. *JACS*, **1994**, 2902

^{13}C-^{13}C Coupling

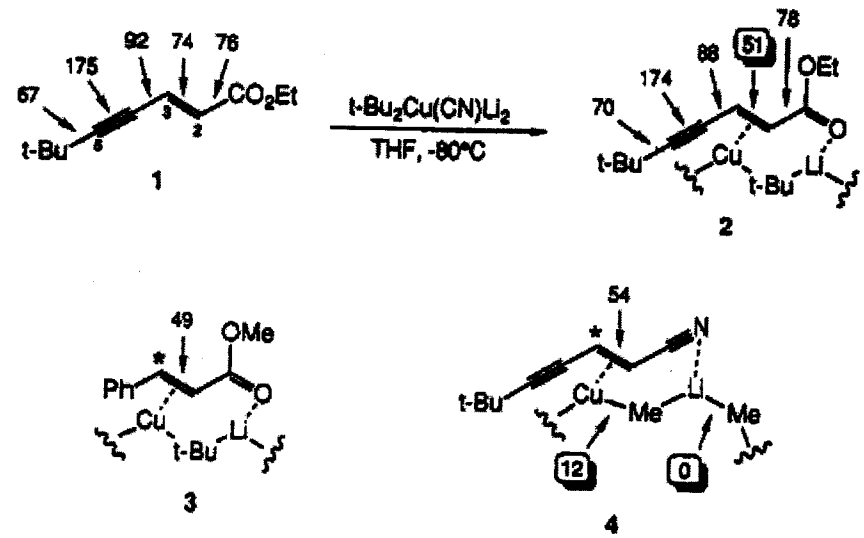
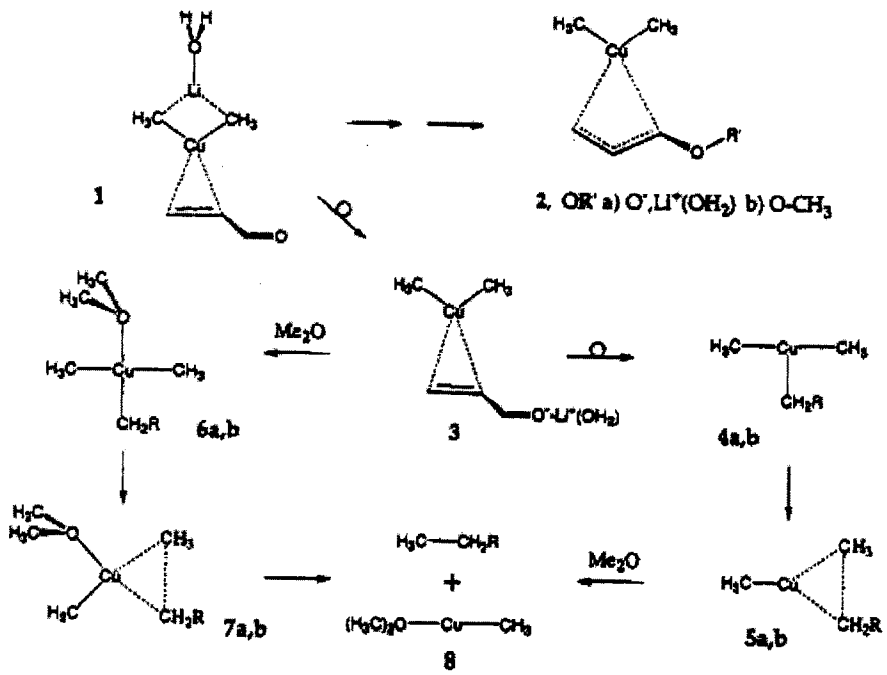


Figure 1. ^{13}C-labeled π-complexes examined in this work ($^{1}J_{C,C}$ coupling constants given in hertz).

In complex **4** with labeled Michael acceptor 2 methyl groups bound to Cu/Li seen at δ= -5.1 and -10.7ppm
Signal at -10.7ppm has 12 Hz coupling constant

Krause et al. *JACS*, **1994**, 381

Calculations on $CuMe_3$



[a] R = (a) CH=CHO⁻Li⁺, (b) H.

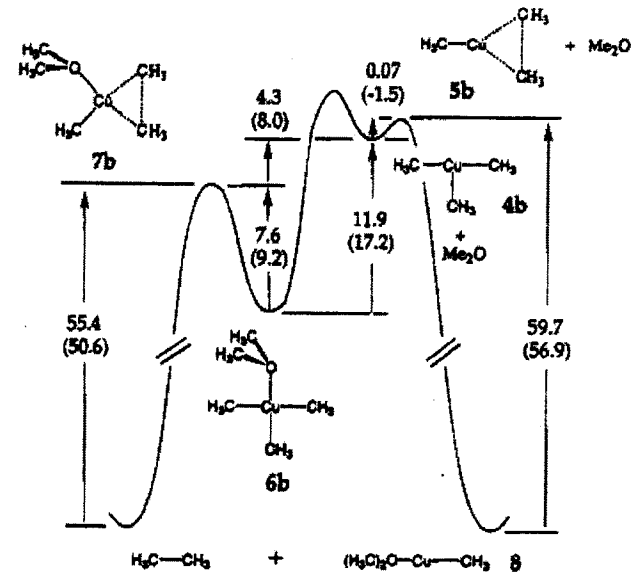


Figure 1. Relative B3LYP/LANL2DZ//B3LYP/LANL2DZ (MP2/HW3//B3LYP/LANL2DZ) energies, kcal/mol, including B3LYP/LANL2DZ zero-point energies for the transformation of **6b** to **4b** and CH_3CH_3 + **8**.

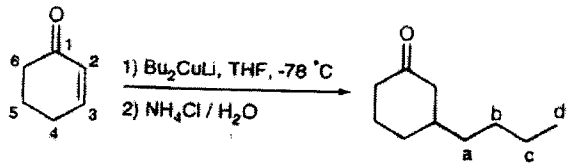
Argue complex **6** is a Cu(I) species and not Cu(III)

" Quite clearly, trialkylcopper derivatives have little or no independent existence and, therefore, cannon serve as intermediates in cuprate conjugate addition, reversible or otherwise."

Snyder, J. *JACS*, **1995**, 11025

Natural Abundance Isotope Effects

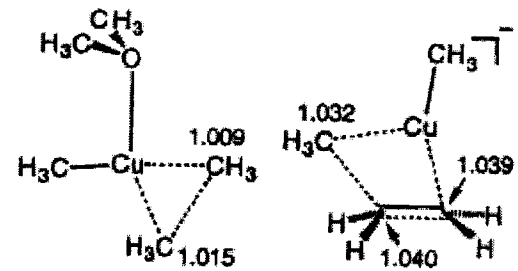
Table 1. ^{13}C KIEs ($^{12}k/^{13}k$) for the Addition of Bu_2CuLi to Cyclohexenone (−78 °C)



KIEs based on starting material[a,b]	experiment 1	2	3
C_1	1.004(2)	0.999(2)	1.002(5)
C_2	1.006(2)	1.005(2)	1.005(3)
C_3	1.026(2)	1.020(4)	1.024(4)
C_4	0.999(3)	0.998(3)	0.998(3)
C_5	1.002(2)	1.005(3)	1.009(4)
C_6		1.000 assumed[d]	

KIEs from product[b,c]	experiment 4	5	6
C_a	1.016(4)	1.011(4)	1.015(4)
C_b	0.999(4)	0.993(4)	0.997(4)
C_c		1.000 assumed[d]	
C_d	1.002(7)	1.003(7)	1.002(7)

[a] Experiments 1−3 are reactions carried to 91.0(8), 92.1(7), and 81.1(1.4)% completion, respectively, to determine the KIEs for cyclohexenone. [b] Standard deviations are shown in parentheses. [c] Experiments 4−6 are reactions carried to ≈10% completion to determine the KIEs for the incoming butyl group. [d] See ref 11.

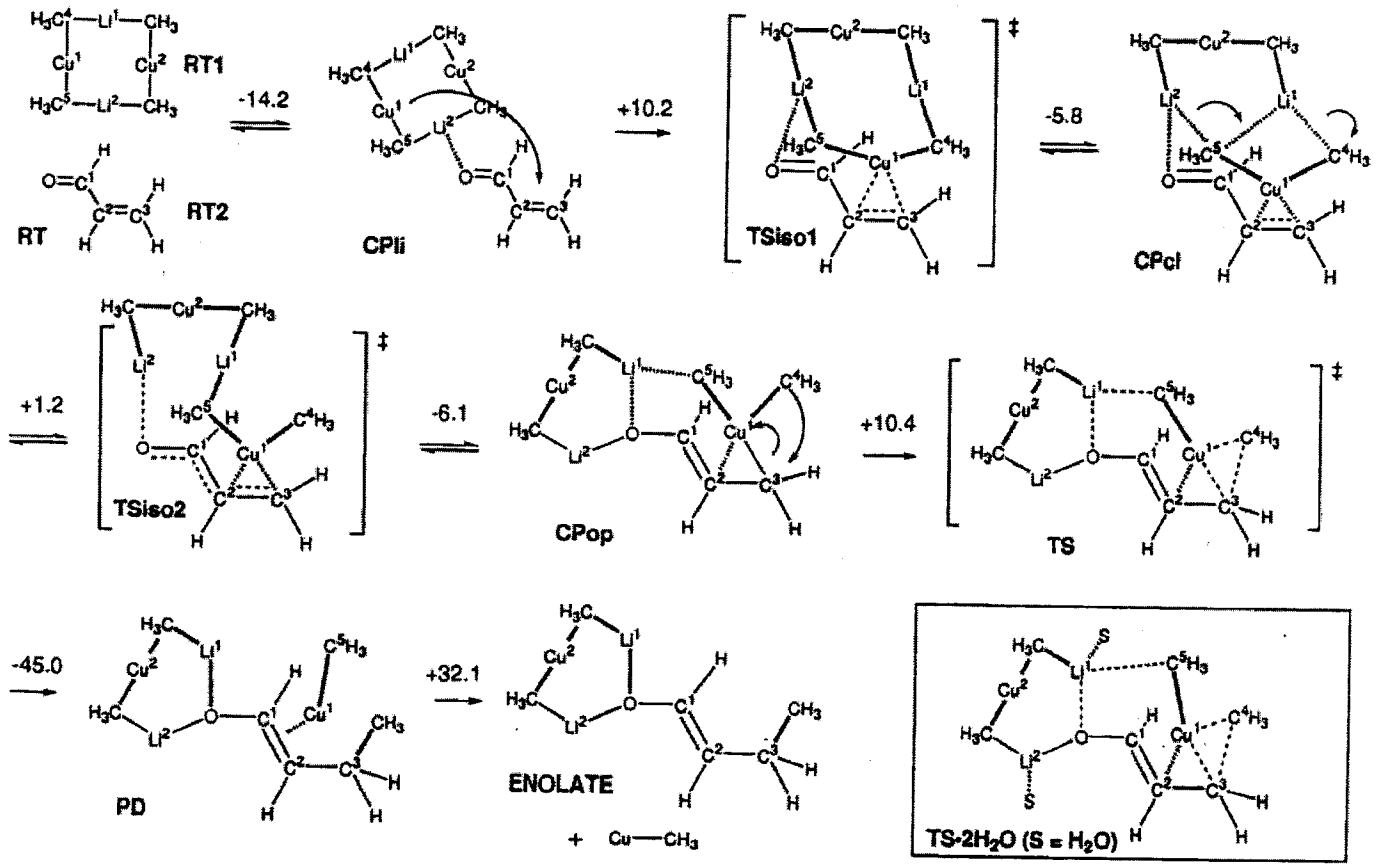


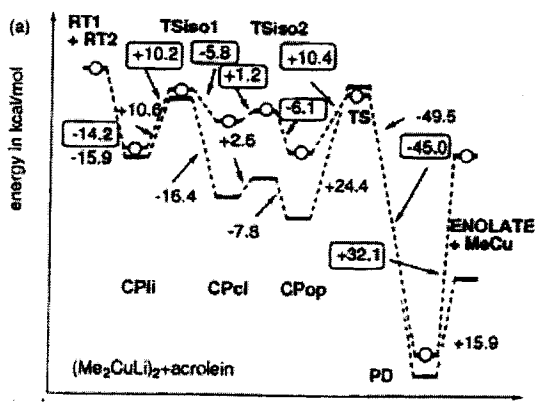
1 2

KIEs consistent with rate-determining reductive elimination via **1**

Frantz, D.; Singleton, D.; Snyder, J. *JACS*, **1997**, 3383.

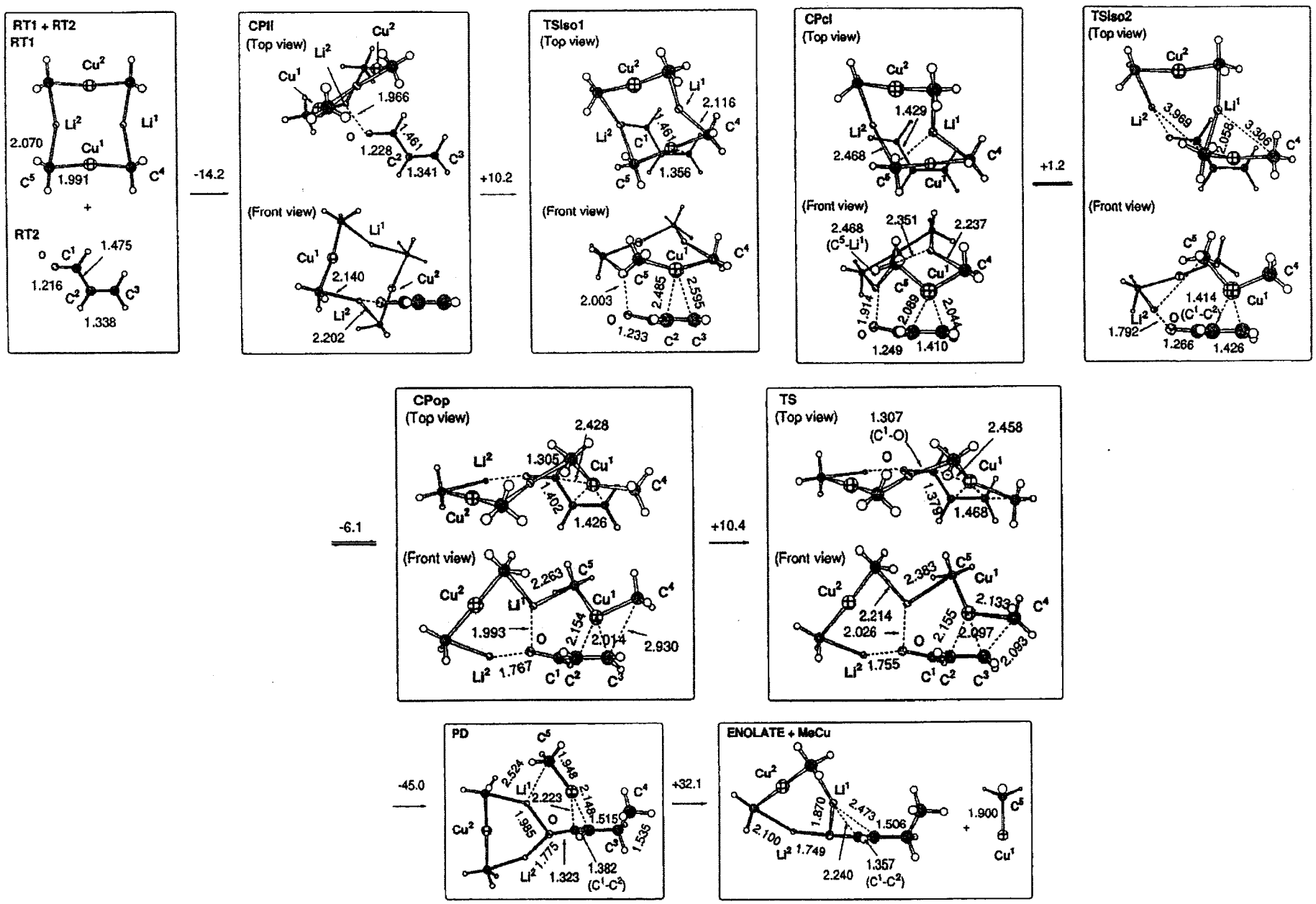
Calculated Mechanism



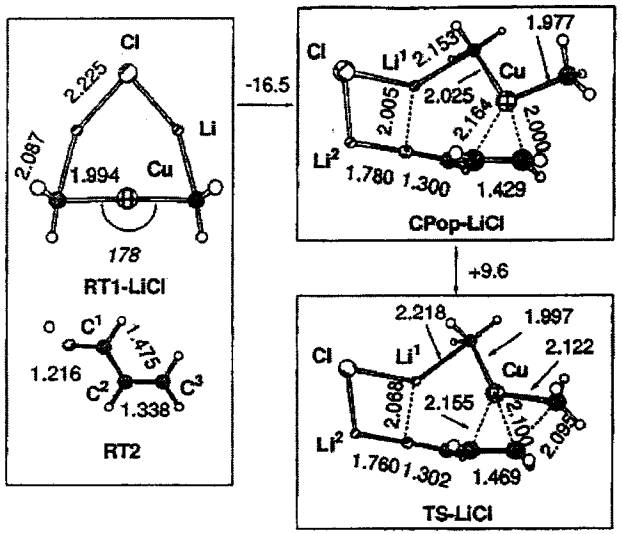


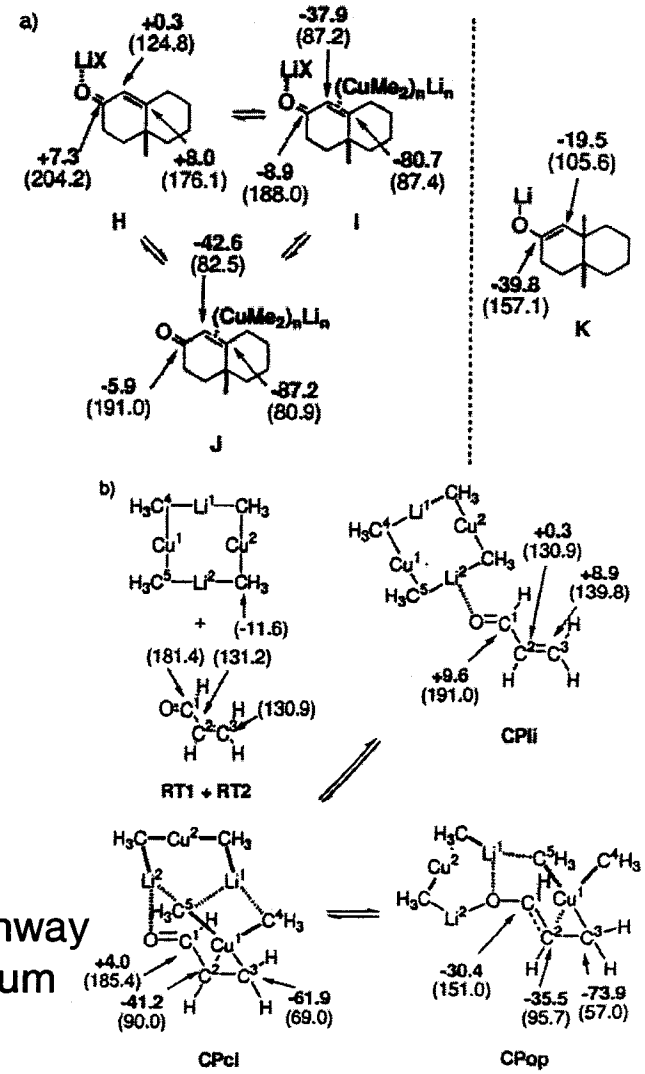
Nakamura et al. *JACS*, **1997**, 4900

3-D Representations



Solvation/ External LiCl



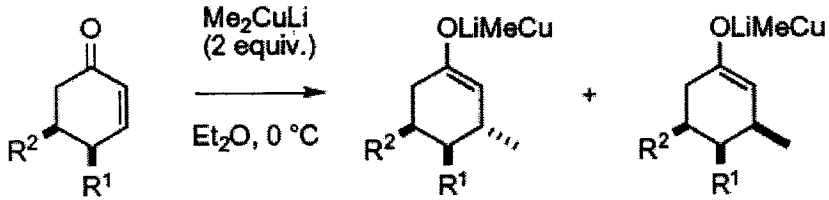


Partial solvation reduced activation energy 0.1 kcal/mol
External LiCl gave activation energy of 9.6 kcal
Monomeric $CuMe_2Li$ gave 12.1 kcal/mol activation energy

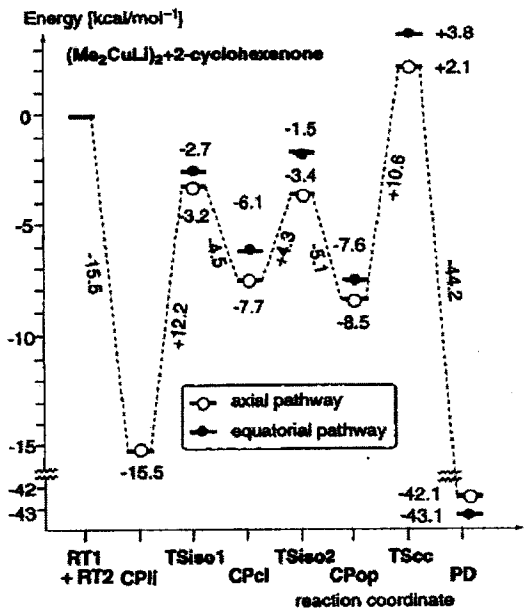
^{13}CNMR is consistent with predicted values for dimeric pathway
Carbonyl shift would correspond to 2:1 CPcl/CPop equilibrium
Calculated 4.9 kcal/mol difference

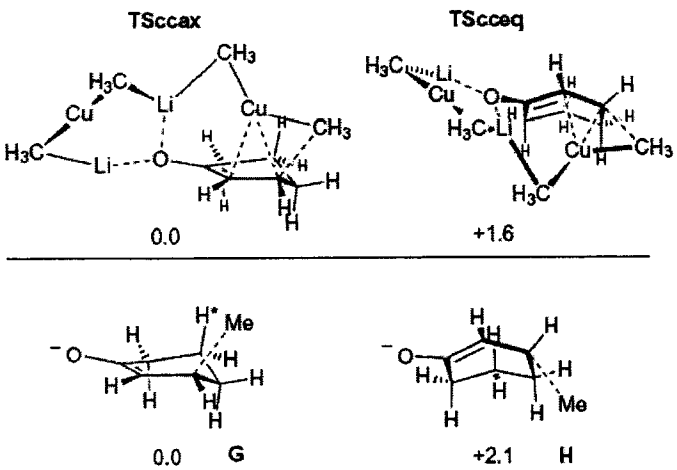
Nakamura et al. *JACS*, **1997**, 4900

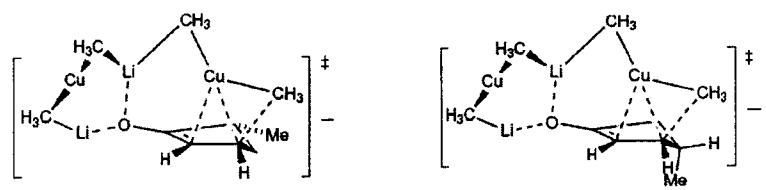
Origin of Diastereoselectivity



	trans		*cis*
(a) R^1 = Me, R^2 = H	91	:	9
(b) R^1 =H, R^2 = Me	98	:	2





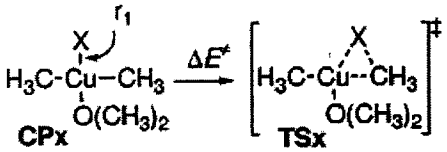


Calculations agree with axial approach in C-C bond forming step.

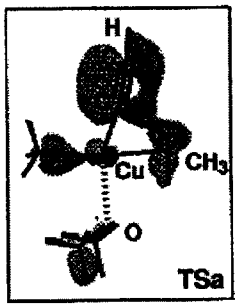
Mori, S.; Nakamura, E. *Chem. Eur. J.* **1999**, 1534

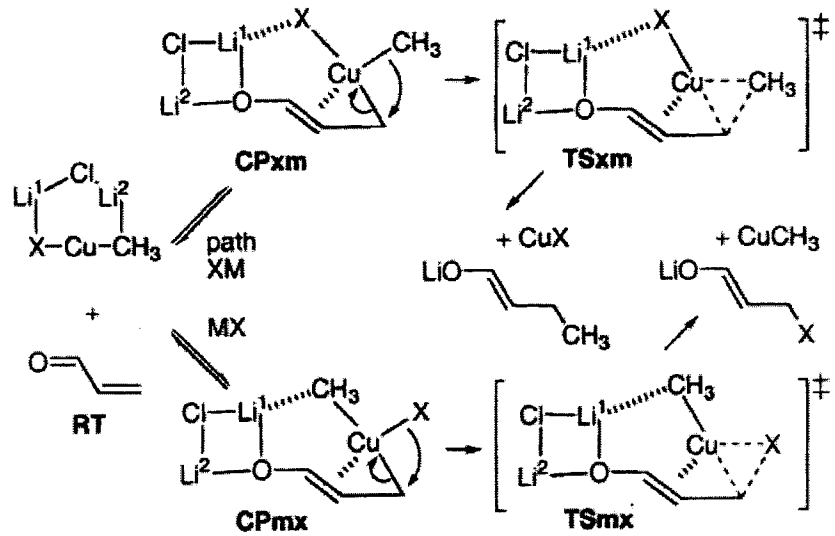
Dummy Ligands

Bond lengths vs. reductive elimination

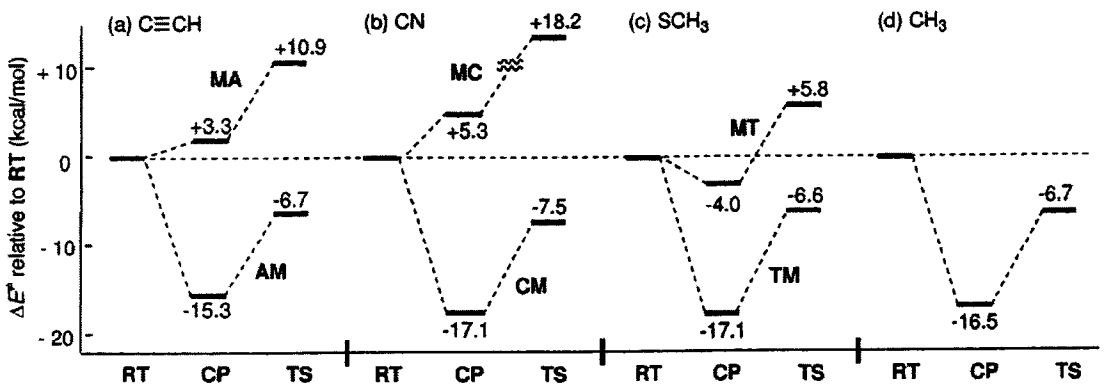


X	r_1 (Å)	$\Delta E^{\ddagger}$ (kcal/mol)
CH_3	1.94	+ 8.2
C≡CH	1.83	+ 2.9
C≡N	1.83	+ 4.0
SCH_3	2.18	+ 11.5
$N(CH_3)_2$	1.93	+ 10.3





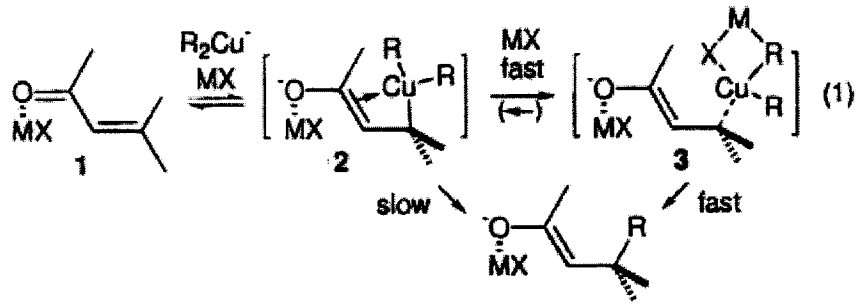
X = CH_3 (M), C≡CH (A), CN (C), SCH_3 (T)



Bridging ability and not bond strength determine transfer

Nakamura, E.; Yamanaka, M. *JACS*, **1999**, 8941

The Role of Lewis Acids



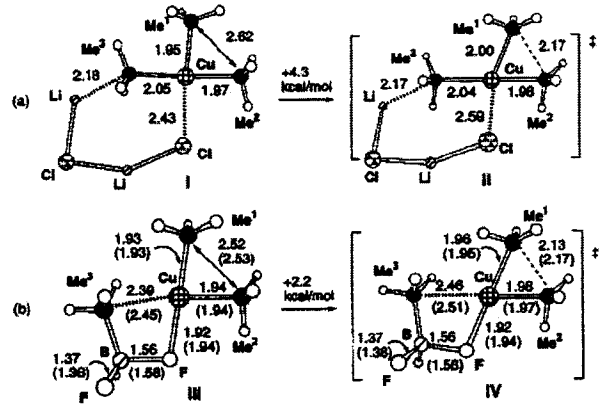
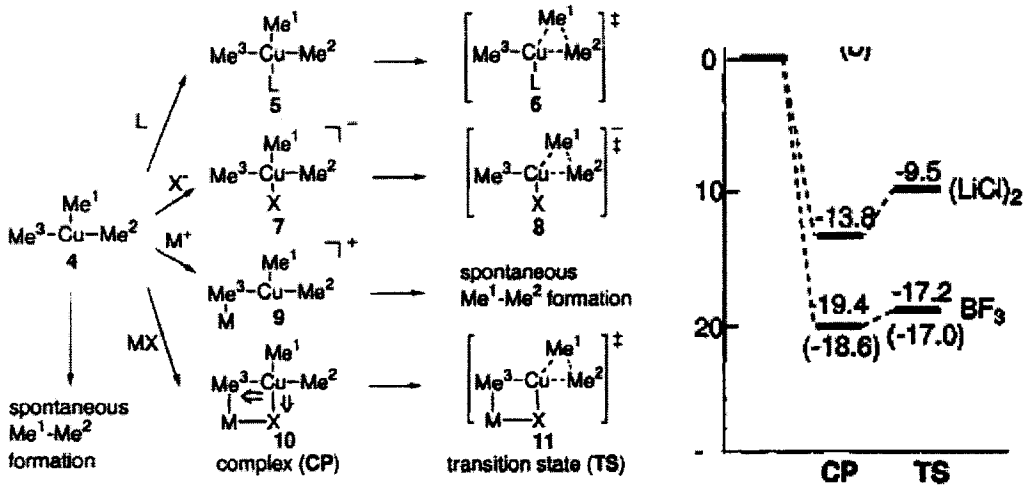


Figure 2. 3D structures of CP and TS of reductive elimination for (a) $Me_3Cu{\cdot}(LiCl)_2$ and (b) $Me_3Cu{\cdot}BF_3$. Bond lengths [Å] are at the B3LYP/631A level (those in parentheses are at the B3LYP/Ahlrichs-SVP for the Cu and 6-311G(d,p) for the rest.



Decreases charge accumulation on both C and Cu in TS

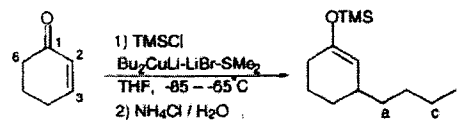
An explanation for Feringa's ligand?

Nakamura, E. Yamanaka, M.; Mori, S. *JACS*, **2000**, 1826

TMSCl Revisited

Isotope effects in THF

Table 1. ^{13}C and ^{17}O KIEs ($^{12}k/^{13}k$ or $^{16}k/^{17}k$) for the Addition of $Bu_2CuLi-LiBr-SMe_2$ to Cyclohexenone/TMSCl in THF (−85 to −65 °C)



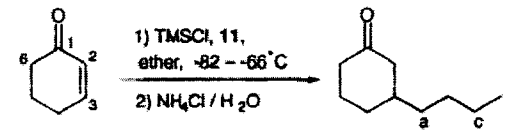
KIEs based on starting material[a–c]	experiment 1	2	3
C_1	1.005(2)	1.001(2)	1.000(2)
C_2	1.003(2)	1.007(1)	1.006(2)
C_3	1.007(2)	1.004(2)	1.008(2)
O	e	1.018(6)	1.019(7)

KIEs determined from *product*[b–d]	experiment 4	5	6
C_a	0.996(6)	0.999(4)	1.002(5)

[a] Experiments 1–3 are reactions carried to 87.6(9), 86.2(1.2), and 78.5(1.3)% completion, respectively, to determine the KIEs for cyclohexenone. [b] The numbers in parentheses are standard deviations in the last digit. [c] See ref 14. [d] Experiments 4–6 are reactions carried to ≈10% completion to determine the KIEs for the incoming butyl group. [e] Not determined.

Isotope effects in Et_2O

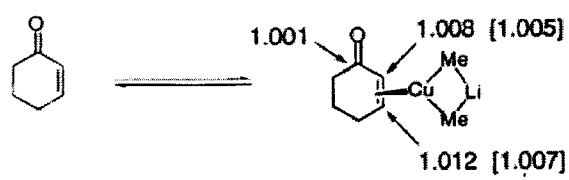
Table 2. ^{13}C and ^{17}O KIEs ($^{12}k/^{13}k$ or $^{16}k/^{17}k$) for the Addition of 11 to Cyclohexenone/TMSCl in Ether (−82 to −66 °C)

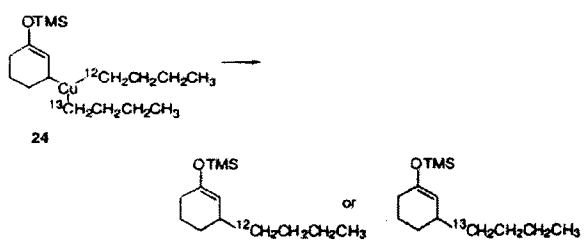


KIEs based on starting material[a–c]	experiment 7	8
C_1	1.002(4)	1.003(3)
C_2	1.001(4)	1.005(4)
C_3	1.014(6)	1.018(4)
O	*e*	1.003(10)

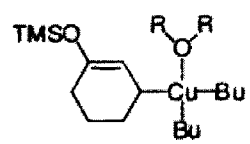
KIEs determined from *product*[b–d]	experiment 9	10
C_a	1.009(4)	1.010(3)

[a] Experiments 7–8 are reactions carried to 80.6(5) and 84.9(7)% completion, respectively, to determine the KIEs for cyclohexenone. [b] The numbers in parentheses are standard deviations in the last digit. [c] See ref 14. [d] Experiments 9–10 are reactions carried to ≈10% completion to determine the KIEs for the incoming butyl group. [e] Not determined.





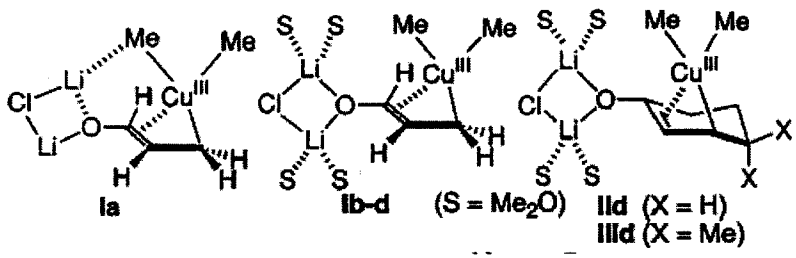
Consistent with rate-limiting silylation of π-complex in THF
No involvement in the reaction in ether



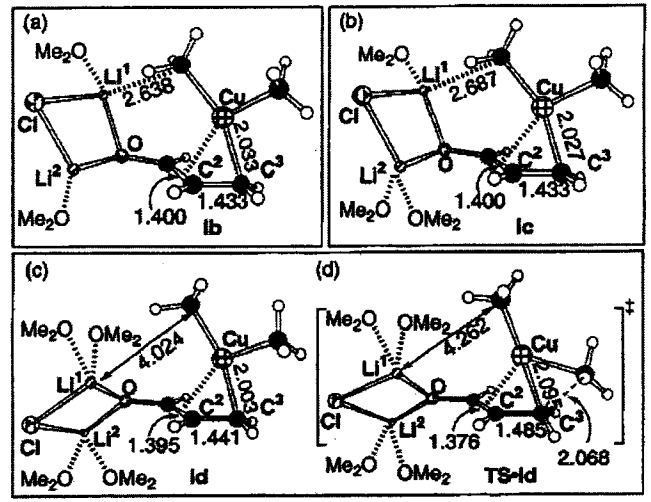
Non-equivalent alkyl groups based on C_a KIE!

Frantz, D.; Singleton, D. *JACS*, **2000**, 3288

Solvation- Toward a Closer E_a Match



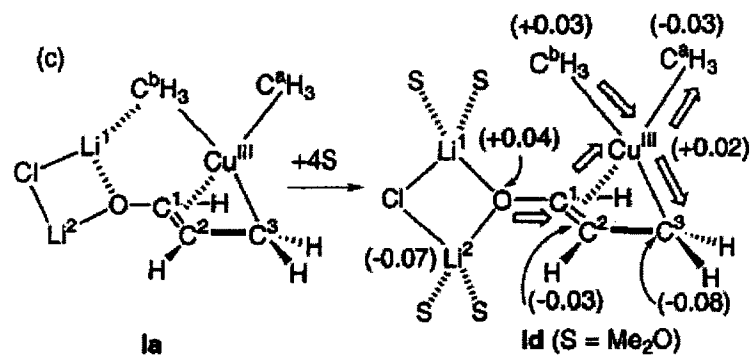
b = 2xMe_2O c = 3 Me_2O d = 4 Me_2O



E_a = 18.2 +/- 1.7 kcal/mol for 4,4-dimethylcyclohexenone (experimental)

	E_a (kcal/mol)
TS-Ia	9.1
TS-Ib	10.6
TS-Ic	10.9
TS-Id	12.3
TS-IId	12.4
TS-IIId	15.5

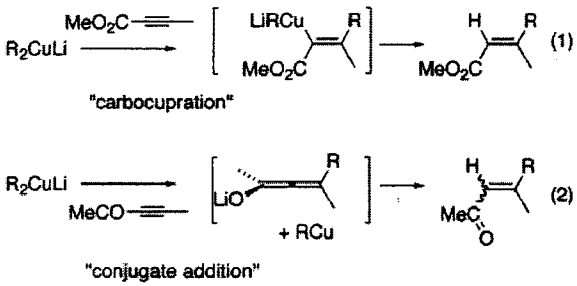
Change in Natural Charge

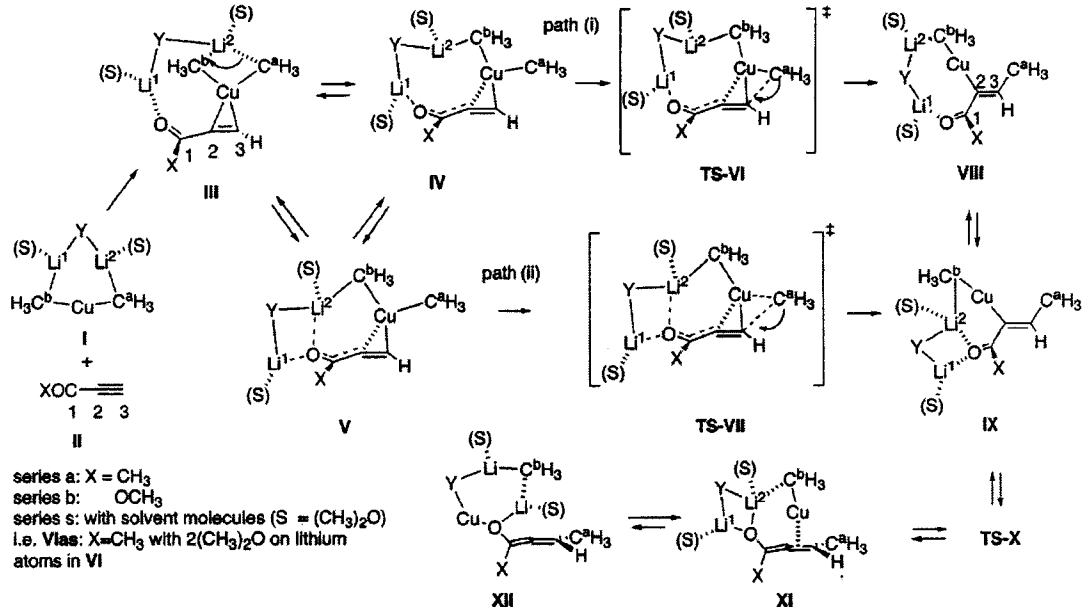


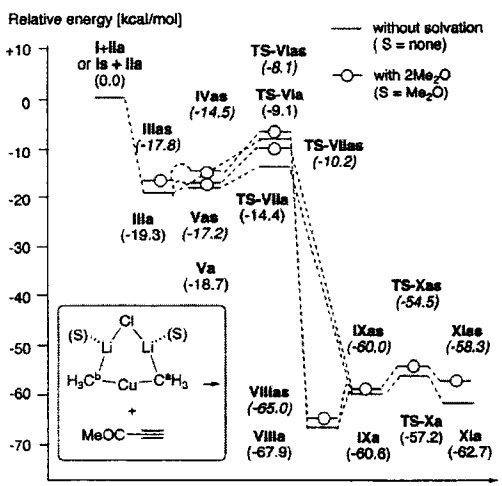
Solvation and steric hindrance provide improved agreement between theoretical and experimental values.

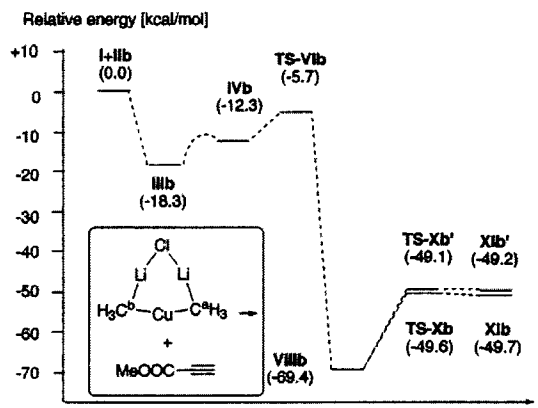
Yamanaka, M.; Nakamura, E. *Organometallics* **2001**, 5675

Addition to Alkynyl Carbonyls





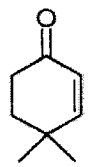




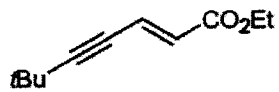
Both reaction mechanistically similar, difference arises in barrier to racemization.

Mori, S.; Nakamura, E.; Morokuma, K. *Organometallics*, **2004**, 1081

1,6 Additions



8



9

- 1,4-addition of $Me_2CuLi \cdot LiI$ to enone **8**: $E_A = 76 \pm 7$ kJ mol^{-1}, $\lg A = 16 \pm 2$ (correlation coefficient $r = -0.985$)
- 1,6-addition of $Me_2CuLi \cdot LiI$ to enynoate **9**: $E_A = 70 \pm 7$ kJ mol^{-1}, $\lg A = 15 \pm 2$ (correlation coefficient $r = -0.975$)

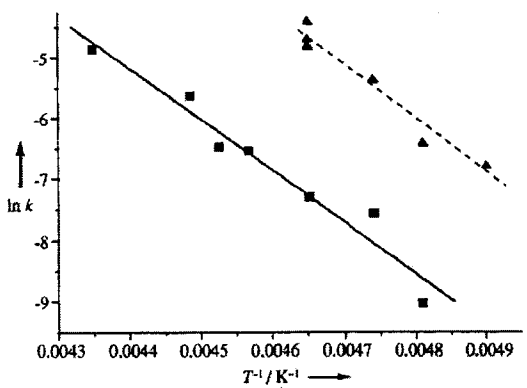


Figure 2. Arrhenius plot for the 1,4-addition of $Me_2CuLi \cdot LiI$ to enone **8** (▲) and for the 1,6-addition to enynoate **9** (■).

Rate independent of cuprate concentration

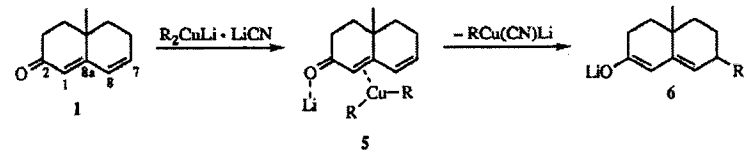
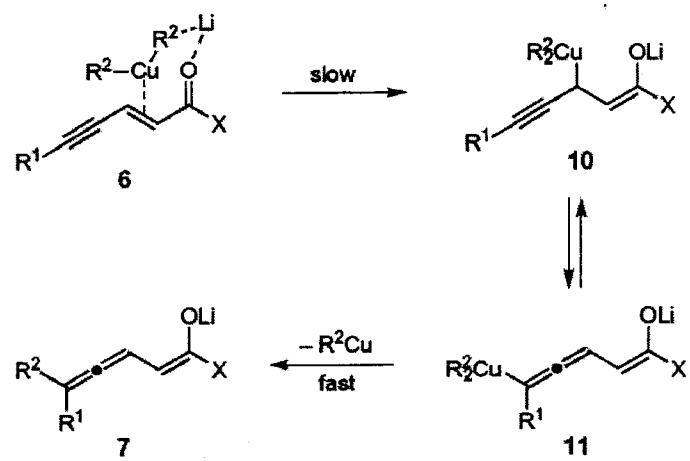


Table 2. ^{13}C NMR chemical shifts of dienone **1**, π-complexes **5** and enolates **6**

Compound	R	Solvent	C-1	C-2	C-7	C-8	C-8a
1	–	$CDCl_3$	123.4	199.9	137.9	127.6	162.1
5	Me	THF-d_8/Et_2O (~1:1)	83.0	[a]	133.5	118.5	84.4
5	*n*-Bu	THF-d_8	[a]	[a]	141.2	129.4	113.9
6	Me	THF-d_8/Et_2O (~1:1)	100.6	163.4	30.5	116.5	144.4
6	*n*-Bu	THF-d_8	99.9	163.1	[a]	114.2	144.2

[a] Not detected.

5 observed at -80°C, warming to -60°C gave complete conversion to **6**



Canisius, J.; Gerold, A.; Krause, N. *Angew. Chem. Int. Ed.* **1999**, 1644
Uerdingen, M; Krause, N. *Tetrahedron*, **2000**, 2799

Conclusions

- The emerging mechanistic picture relies on reversible formation of a d-π* complex with reduction from a Cu(III) species
- TMSCl traps the Cu complex and changes RDS
- Recent calculations allow for better experimental/theoretical match and improved understanding of solvation/ ligand effects
- Can continued work provide the same detailed explanations for catalytic enantioselective systems?