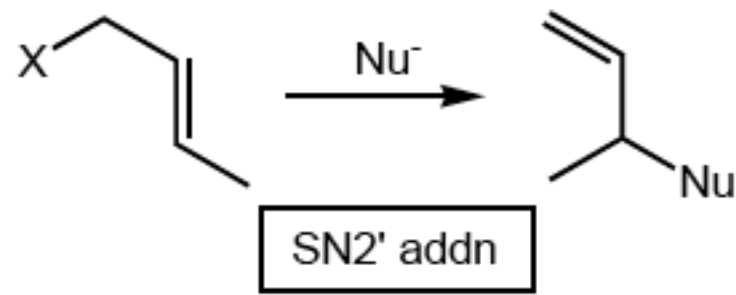
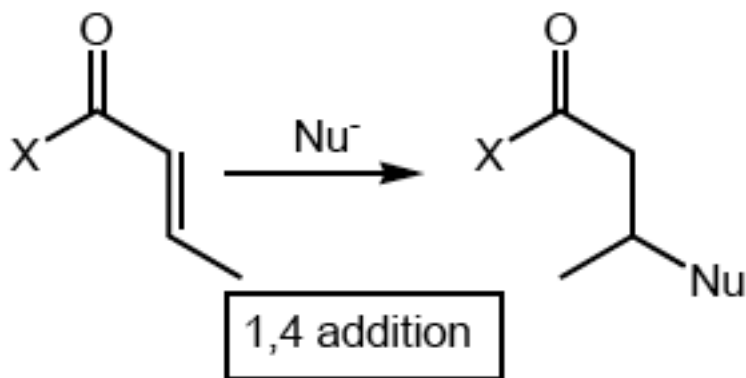


## Topics covered

- 1,4 addition involving copper
  - a. stoichiometric reactions
  - b. catalytic reactions
  - c. allylic substitution
2. Conjugate addition without copper
  - a. Ni-based systems
  - b. Rh-based systems
3. Catalytic addition of heteroatoms

Topics not covered: enolate conjugate additions, Friedel-Crafts-type conjugate additions



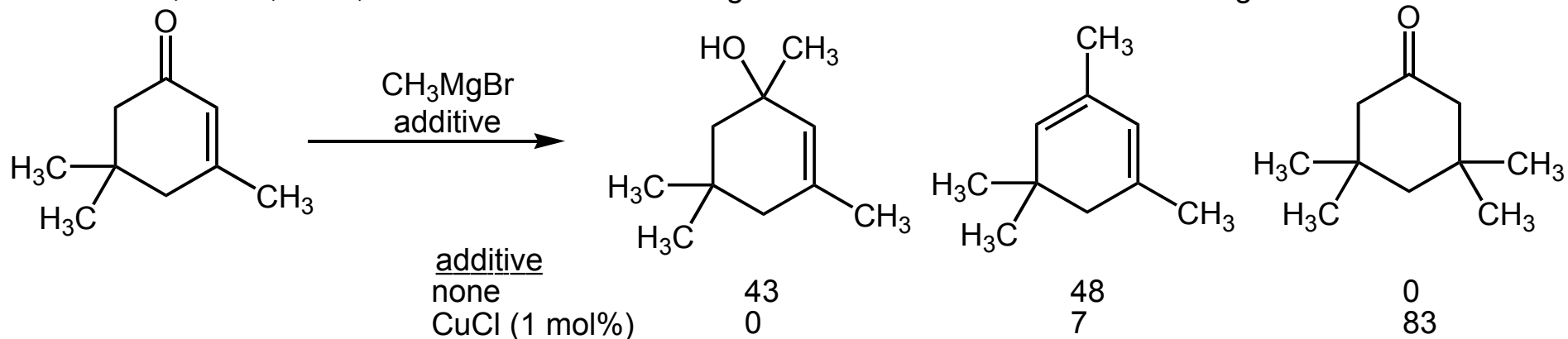
Concerns  
reactivity  
regioselectivity  
stereoselectivity

1,4 addition reactions involving copper

Review: Org. Rxns, **1992**, 41, 135-631

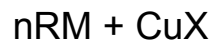
1st report:

Kharasch, JACS, 1941, 2308 "Factors Determining the Course and Mechanisms of Grignard Reactions"



an unusual example of the catalytic reaction predating the stoichiometric one

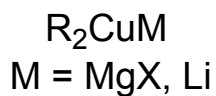
classes of copper reagents:



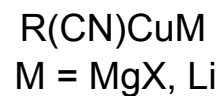
$n = 1, 2$   
 $X = \text{halide, CN}$



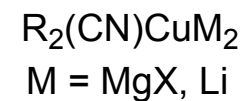
organocopper



organocuprate  
(Gilman reagent)



lower order cuprate



higher order cuprate

Ready; Catalysis

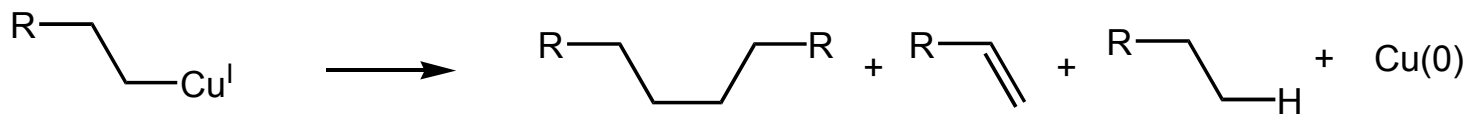
Conjugate Addition: general

$R_2CuM$  (M = MgX, Li)

Most common for simple conjugate additions

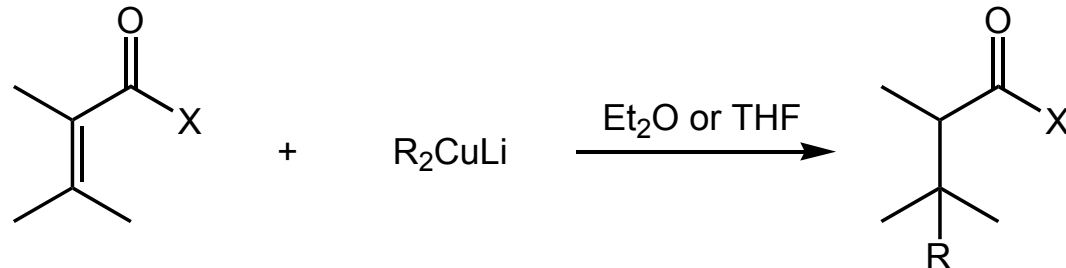
Soluble in Et<sub>2</sub>O, THF

Thermally unstable (usually keep temp < 0° for R = aryl, vinyl; -78 °C for R = alkyl)



General reactivity trends

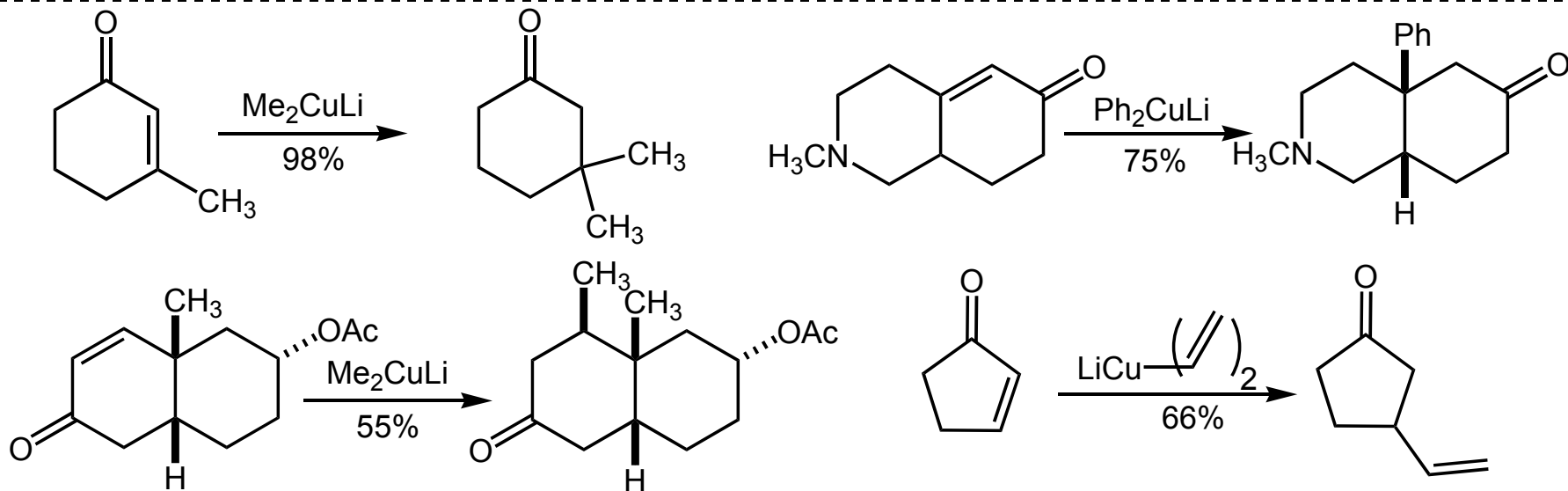
R = 1°~2° > 3° > Ar >> alkynyl



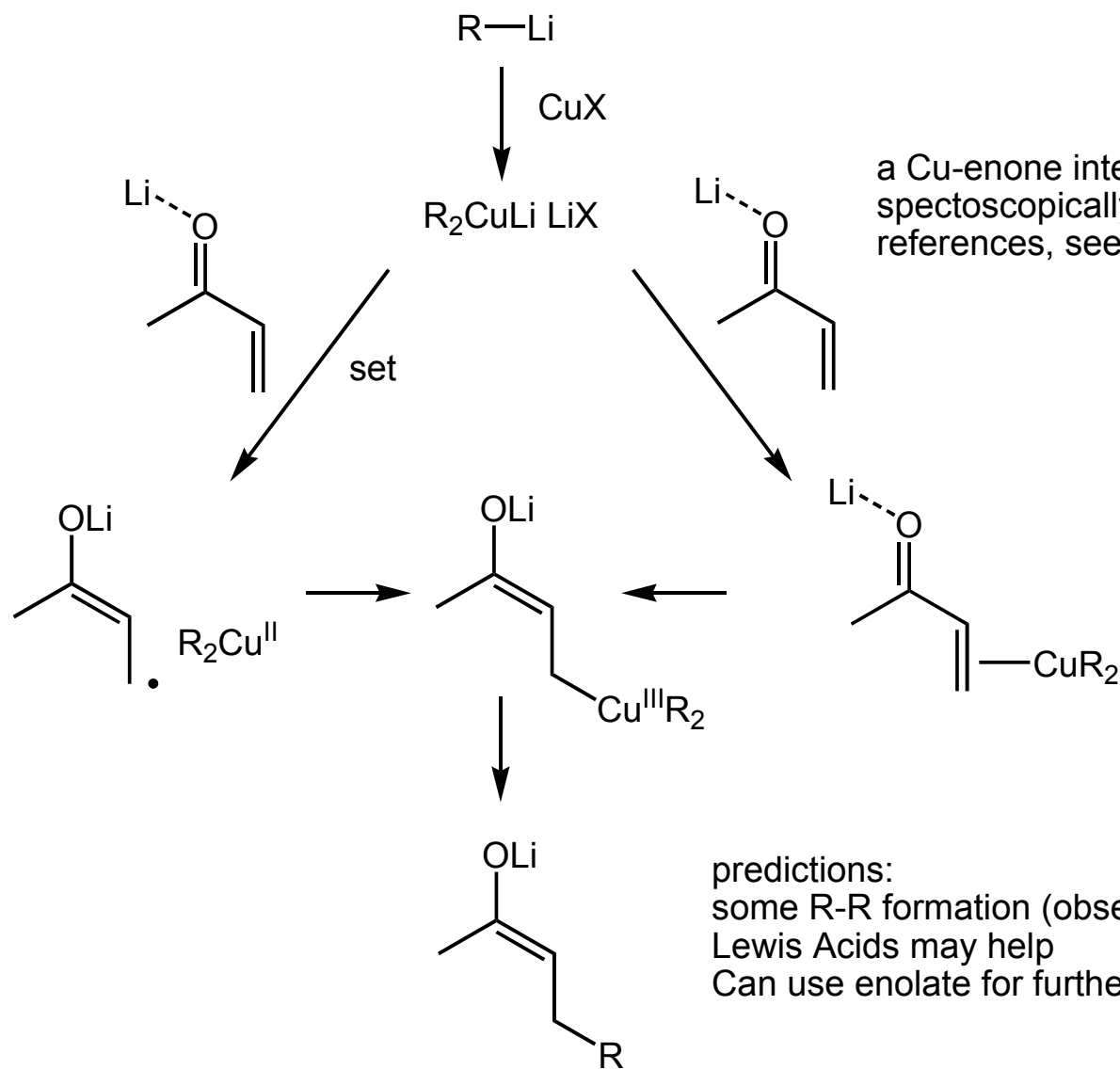
$\alpha$  or  $\beta$  sub. OK  
 $\alpha, \beta$  sub usually OK  
 $\beta, \beta$  usually difficult, but possible

ketones > esters > amides

aldehydes: 1,2 addition competes



mechanism

Recall:  $\epsilon_C - \epsilon_{Cu} = 0.6$  (polarization: C-Sn > C-Si ~ C-Cu > C-B)

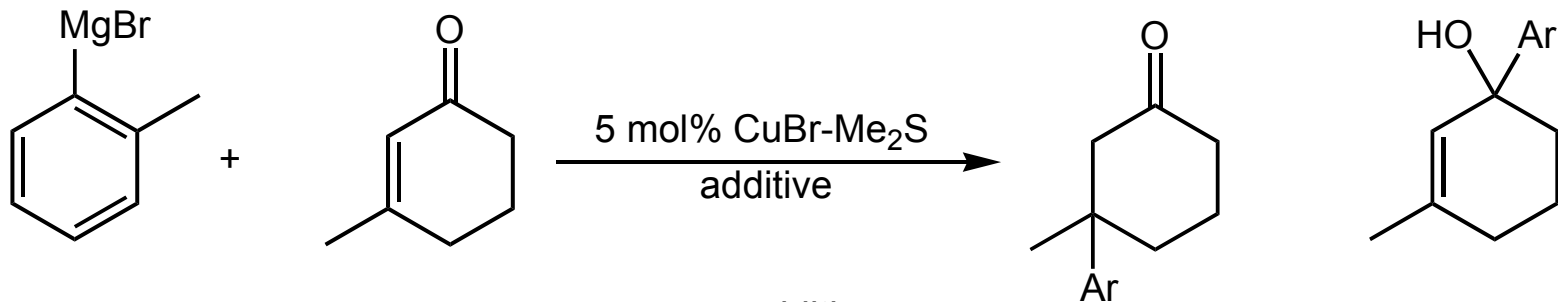
a Cu-enone intermediate has been observed spectroscopically and implicated kinetically. For lead references, see Krause, ACIEE, 1999, 1644

predictions:  
 some R-R formation (observed, usually use >1 equiv cuprate)  
 Lewis Acids may help  
 Can use enolate for further reaction

Ready; Catalysis

Conjugate Addition: TMSCl

Added TMSCl+HMPA  
very common method



Nakamura, Tet, 1989, 349

additive		
none	2	11
TMSCl (2.4 equiv)	31	4
TMSCl + HMPA (2.4 equiv)	99	<1

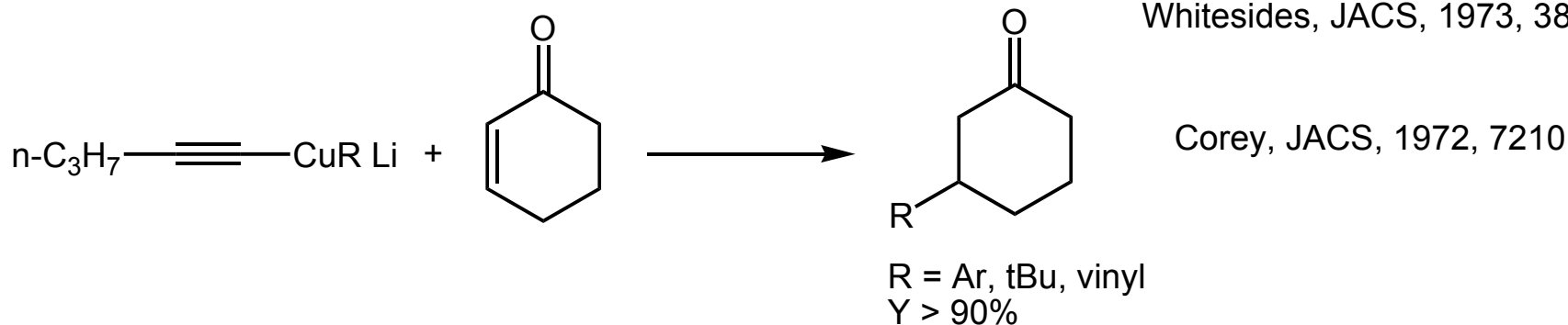
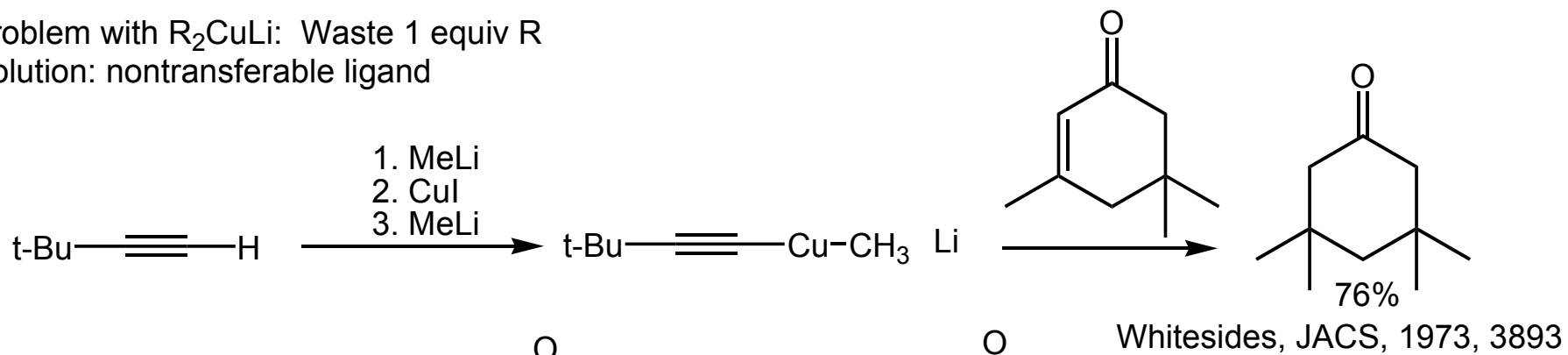
enals usually very difficult b/c 1,2 addition competes  
using RMgBr + 5 mol% CuBr-Me<sub>2</sub>S with added TMSCl/HMPA:

R	%Y	E/Z
hex	83	94:6
Ph	90	91:9

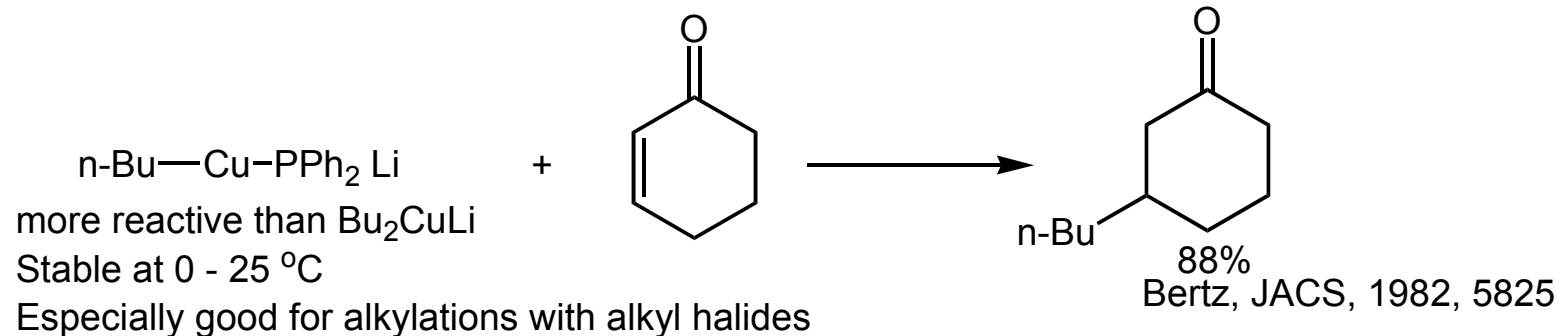
R	%Y	E/Z
hex	89	96:4
Ph	91	96:4

R	%Y	E/Z
Bu	89	87:13
Ph	55	92:8

Problem with  $R_2CuLi$ : Waste 1 equiv R  
 Solution: nontransferable ligand



Reagents of the form  $RR'Cu$  have reactivity intermediate between  $R_2Cu$  and  $R'_2Cu$



similar:  $t\text{BuCu}(\text{SPh})\text{Li}$  Posner, JACS, 1973, 7788

Origin of selectivity with mixed cuprates: Nakamura, JACS, 2005, 4697

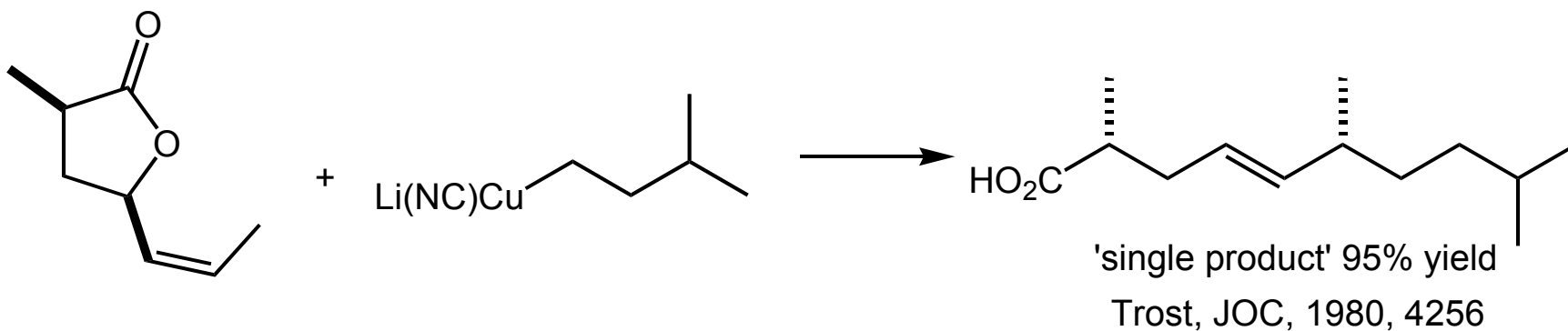
alkyl-cyano-cuprates review: Tet, 1984, 5005

$\text{RCu}(\text{CN})\text{Li}$  - lower order cuprates

$\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$  - Higher order cuprates

Lower order cuprates have reactivity intermediate between  $\text{RCu}$  and  $\text{R}_2\text{CuLi}$   
i.e. CN similar to alkyne (non-transferable ligand)

usually moderate reactivity for 1,4 addns, but OK for  $\text{S}_{\text{N}}2$ '

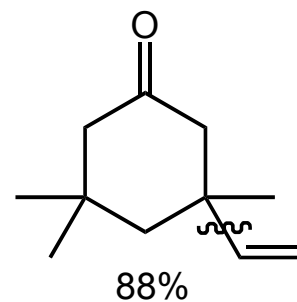
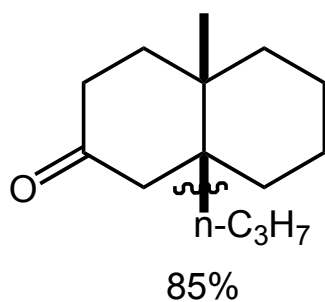
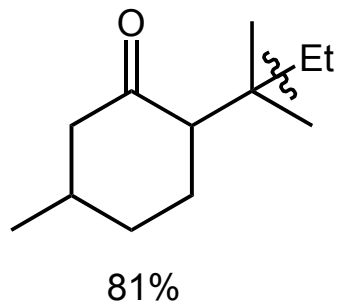
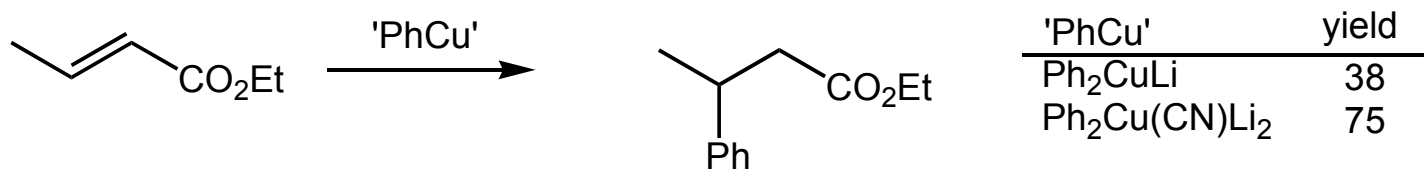
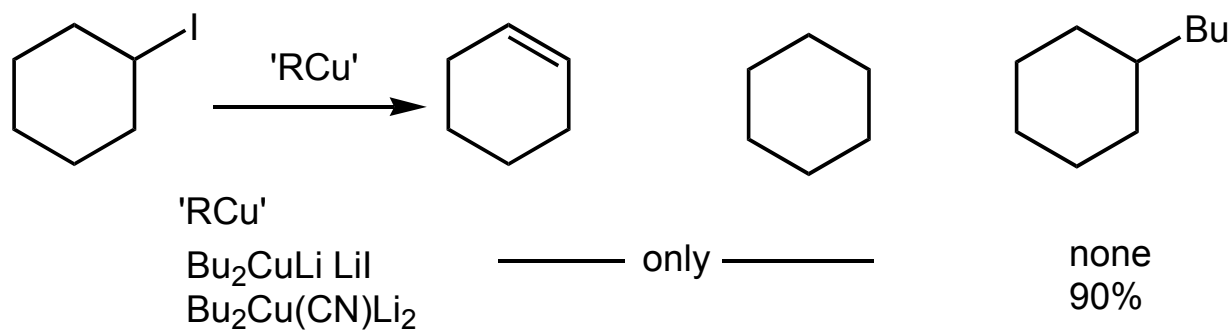


alkyl-cyano-cuprates review: Tet, 1984, 5005

$\text{RCu}(\text{CN})\text{Li}$  - lower order cuprates

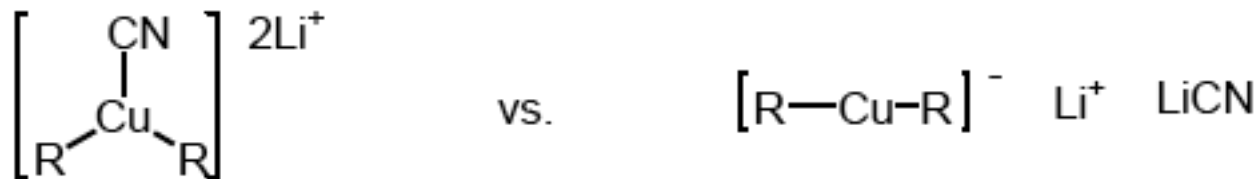
$\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$  - Higher order cuprates

experimental observation that higher order cuprates display improved reactivity relative to Gilman reagents.





The structure of higher-order cuprates has been debated:



*J. Org. Chem.* **1994**, *59*, 7585–7587

**New  $^1\text{H}$  and  $^{13}\text{C}$  NMR Spectral Data on “Higher Order” Cyanocuprates. If the Cyano Ligand Is Not on Copper, Then Where Is It?**

Bruce H. Lipshutz\* and Brian James

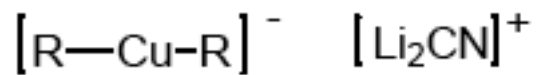
*Department of Chemistry, University of California, Santa Barbara, California 93106*

815 From Chem Comm. 1996

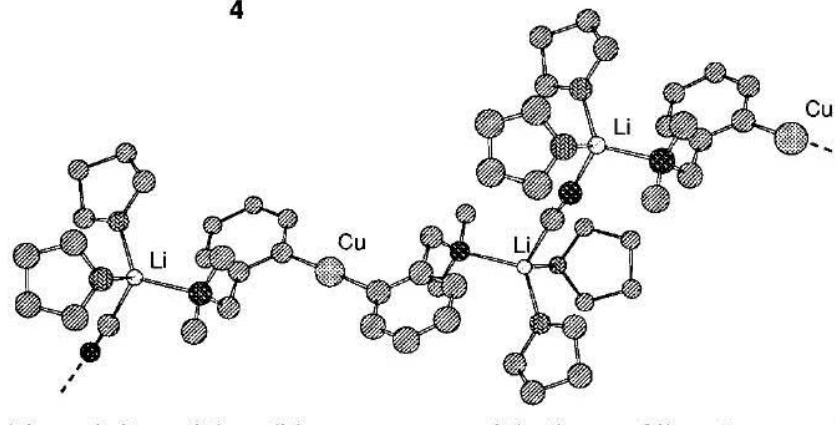
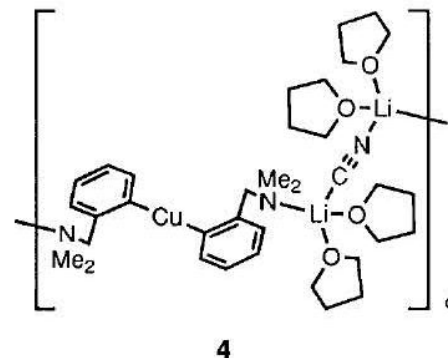
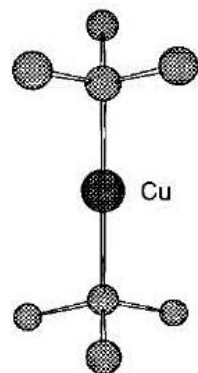
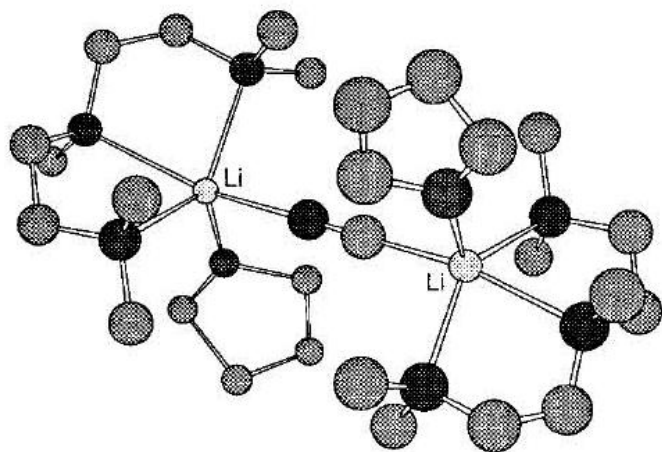
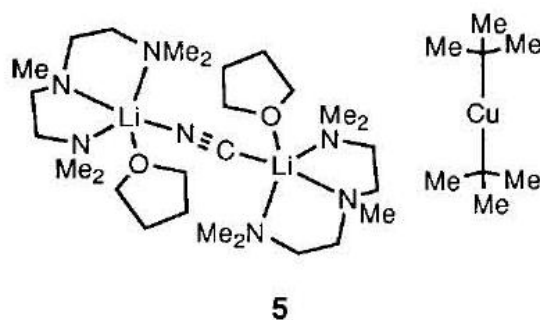
**It's on lithium! An answer to the recent communication which asked the question: 'If the cyano ligand is not on copper, then where is it?'**

*Steven H. Bertz, Guobin Miao, Magnus Eriksson*





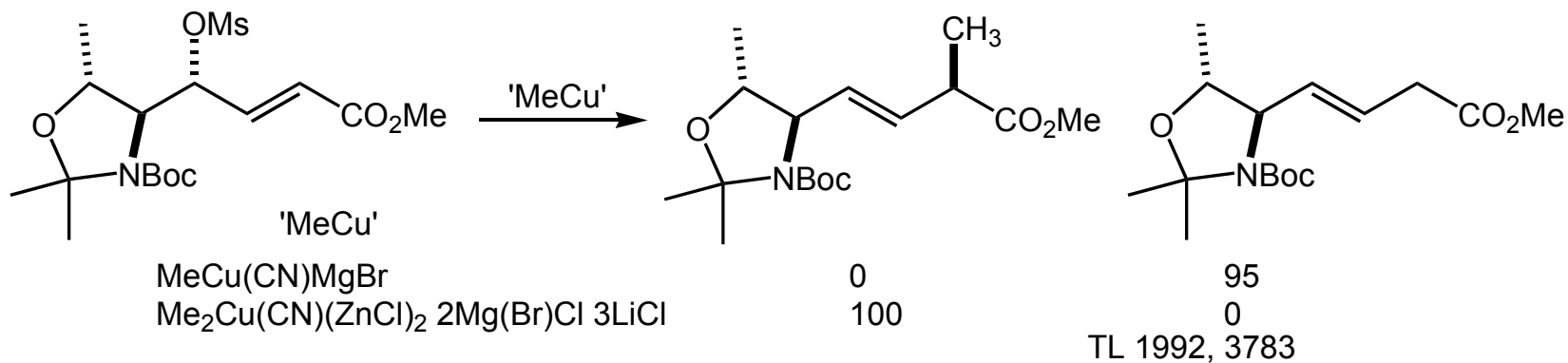
Brief review: Krause, ACIEE, 1999, 79



So why are higher order cuprates more effective?? Not clear

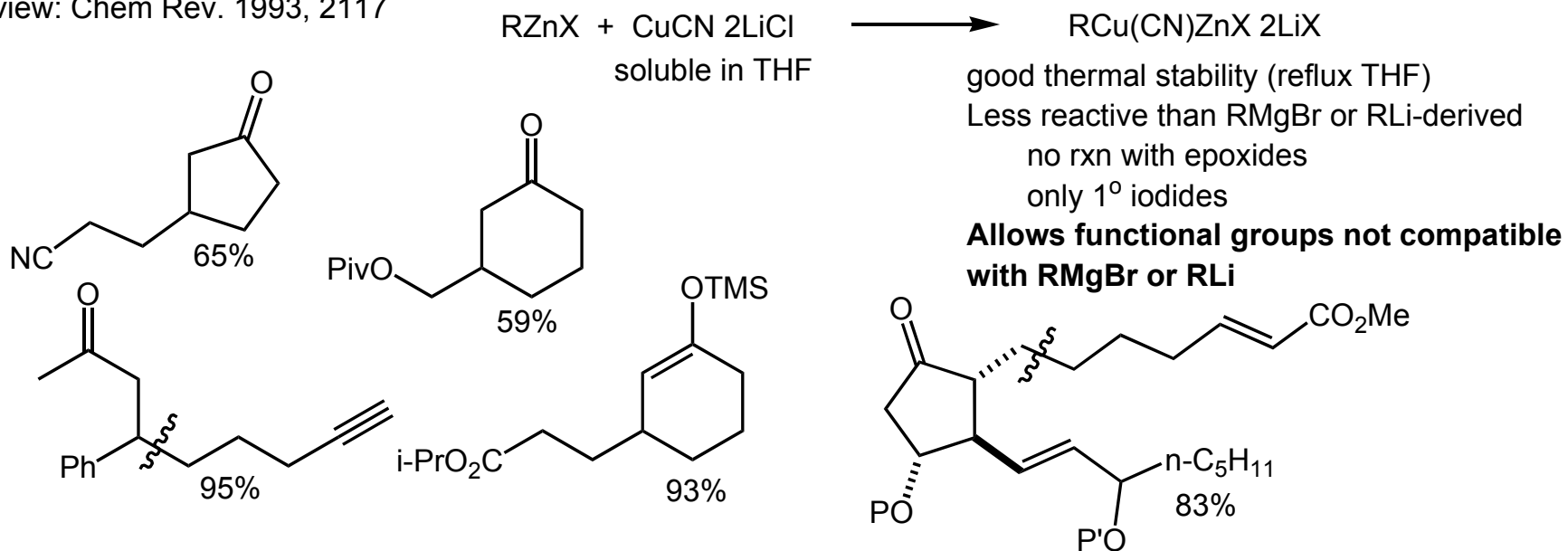
**Copper-mediated addition of alkylzinc reagents**

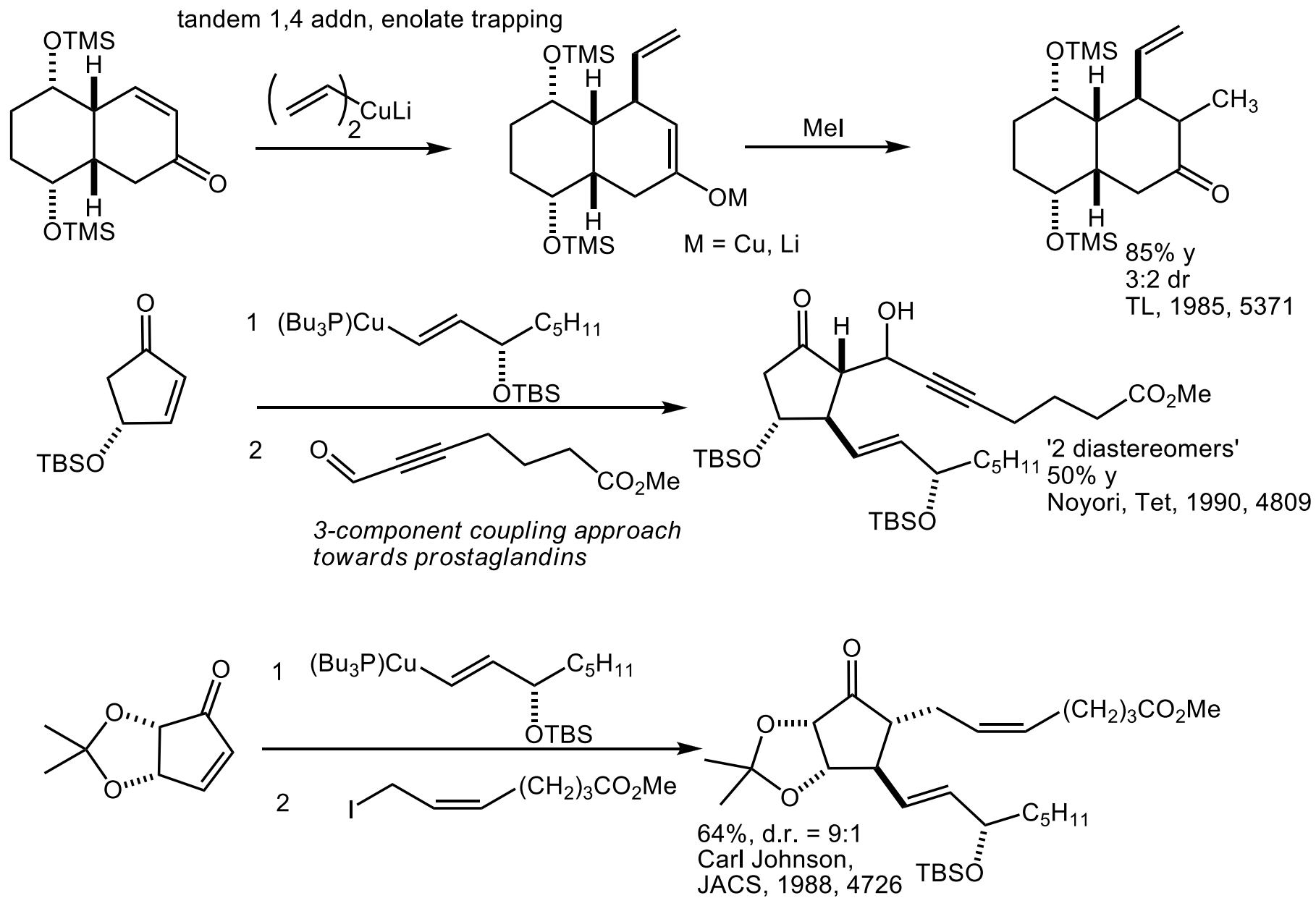
Often characterized by complicated reaction mixtures:

MeMgBr + ZnCl<sub>2</sub> --> white suspensionMeMgBr + ZnCl<sub>2</sub> + LiCl --> solution

for conjugate additions:

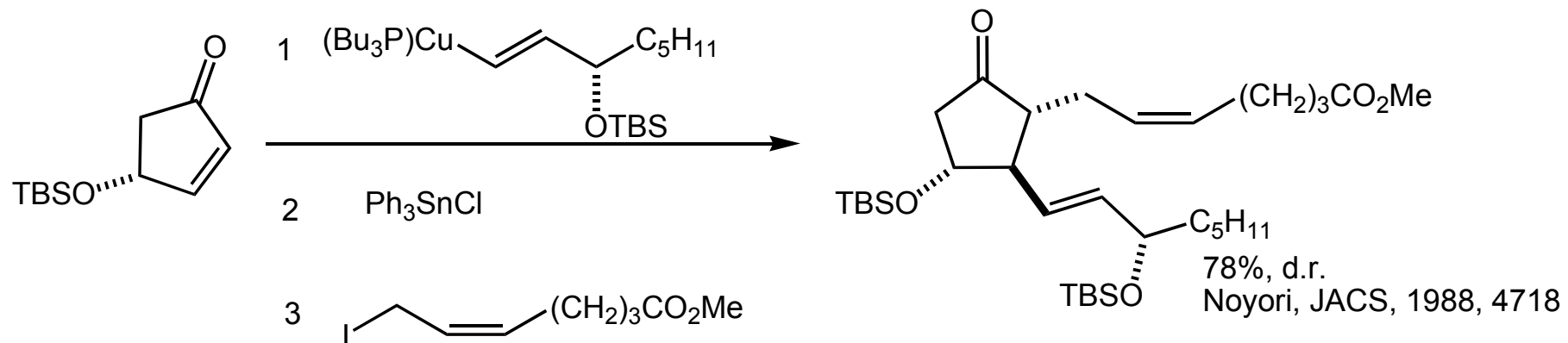
review: Chem Rev. 1993, 2117



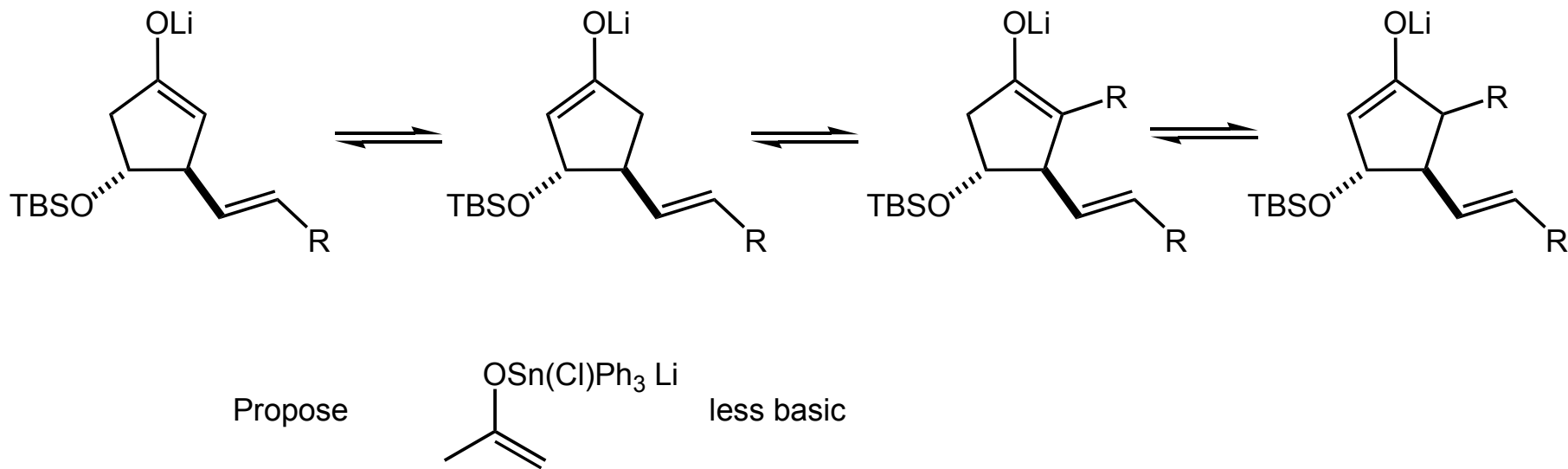


Problem: often hard to alkylate intermediate Li enolate

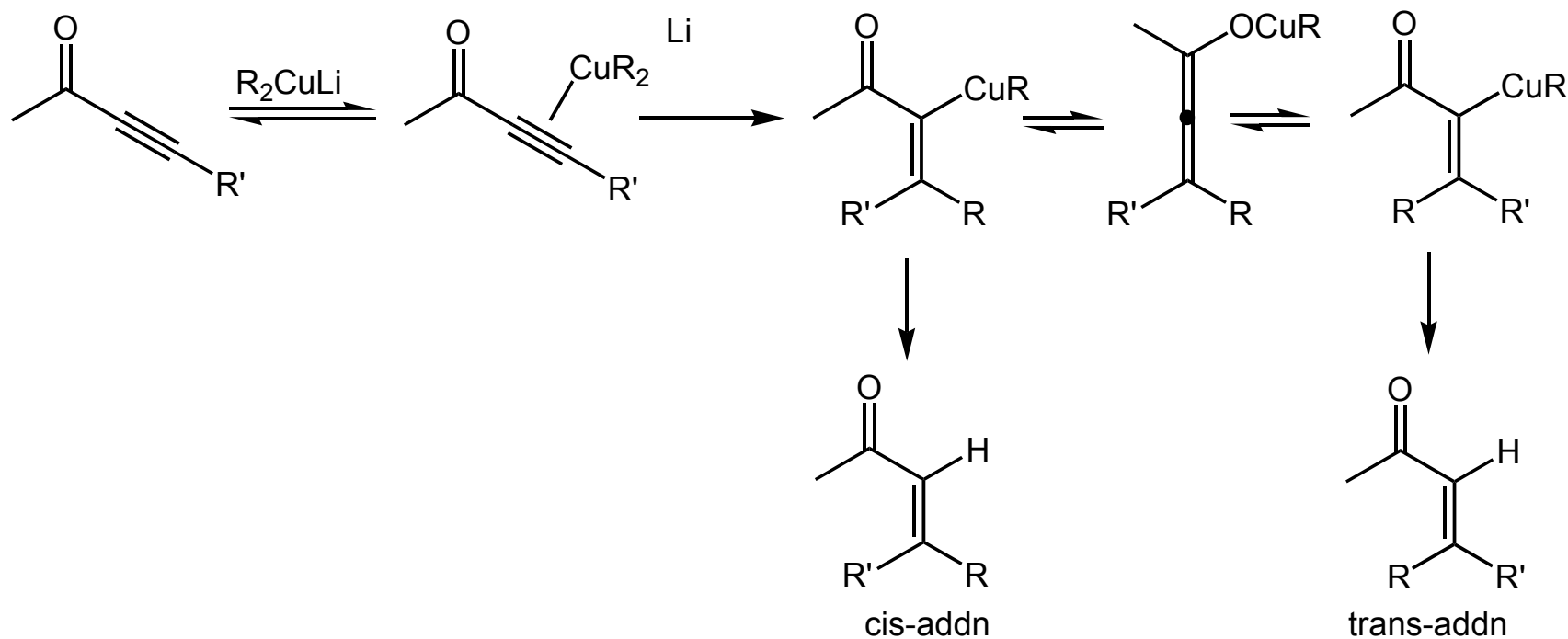
Solution: transmetalate to Sn



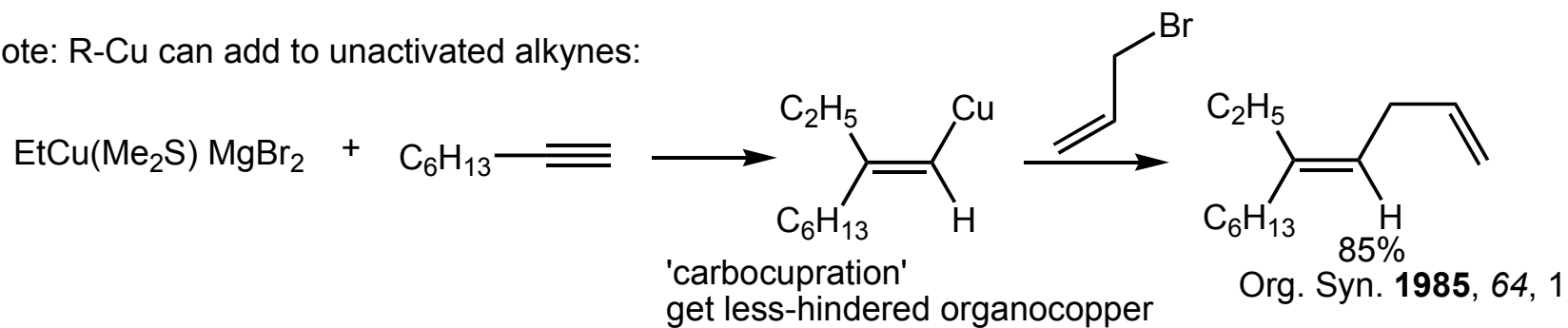
w/o Sn, get complex mixture resulting from enolate equilibration.



## 1,4 additions to alkynes

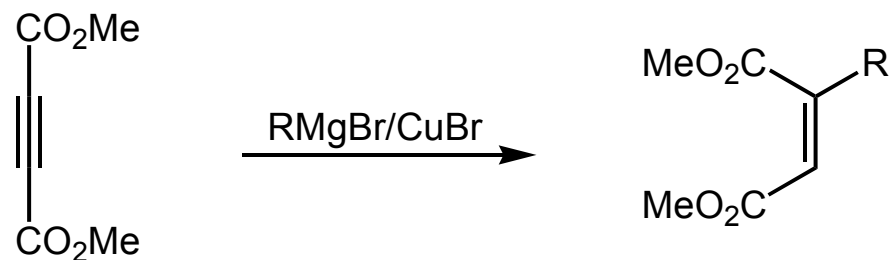


Note: R-Cu can add to unactivated alkynes:

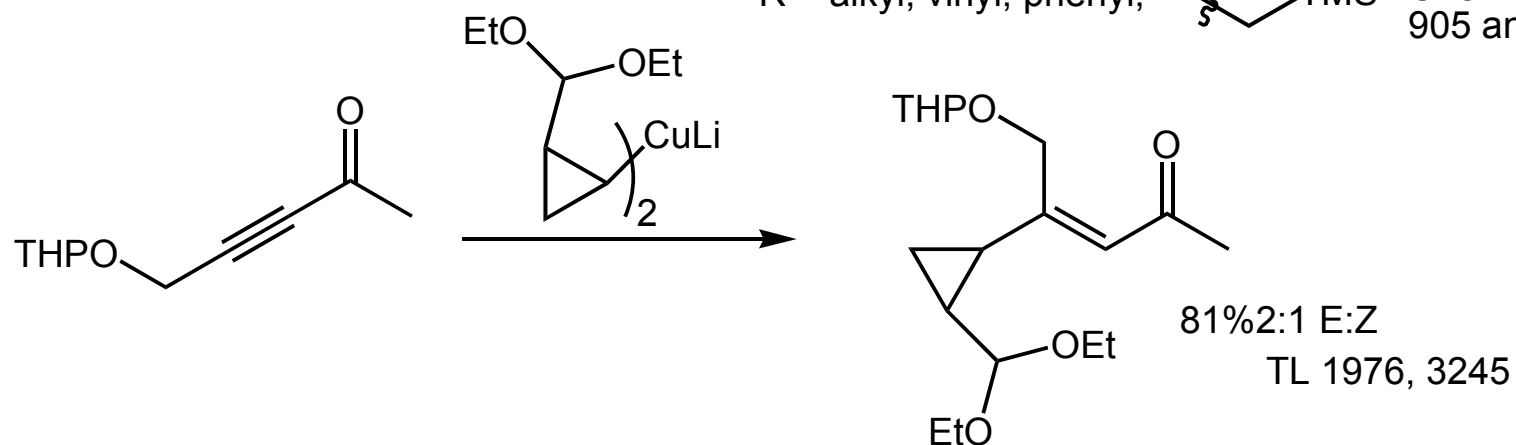


so 1,4 addn mechanistically between 1,4 addn and carbocupration

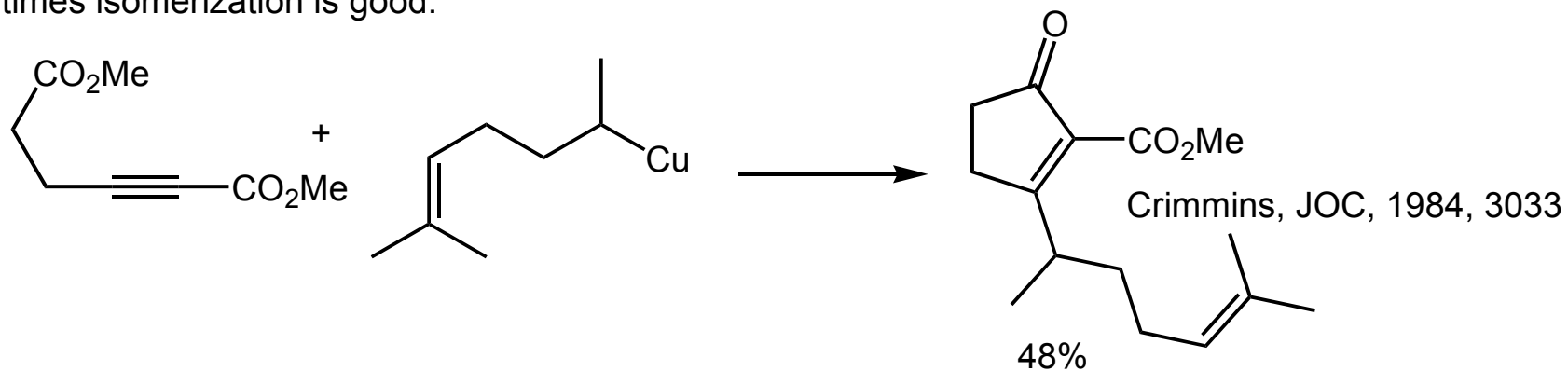
alkynones and alkynoates are more reactive than enones, so  $\text{RCu}$  is enough



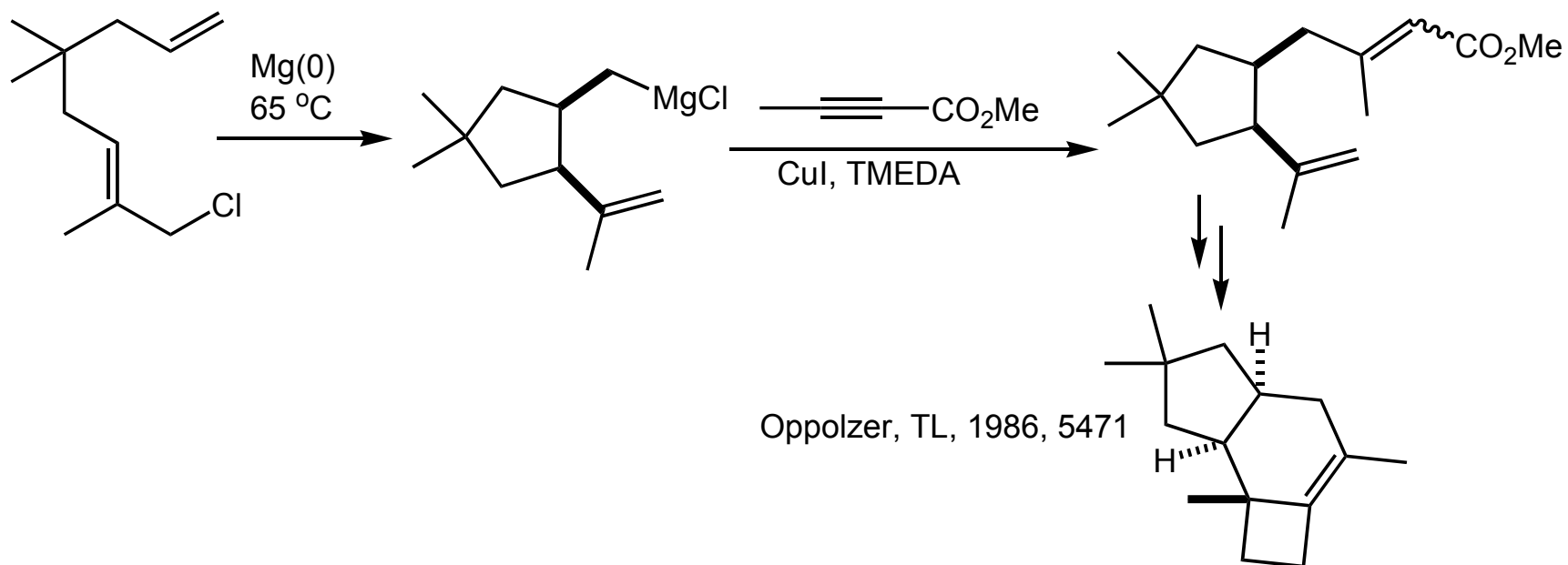
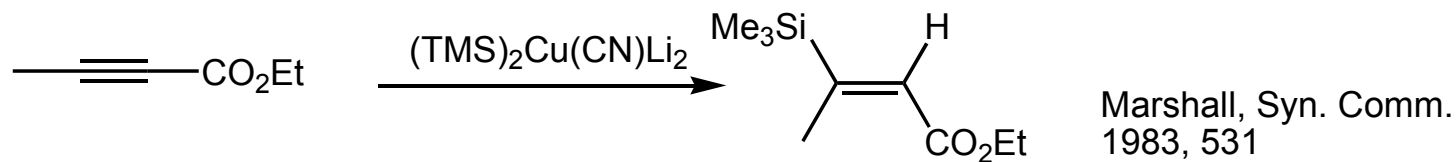
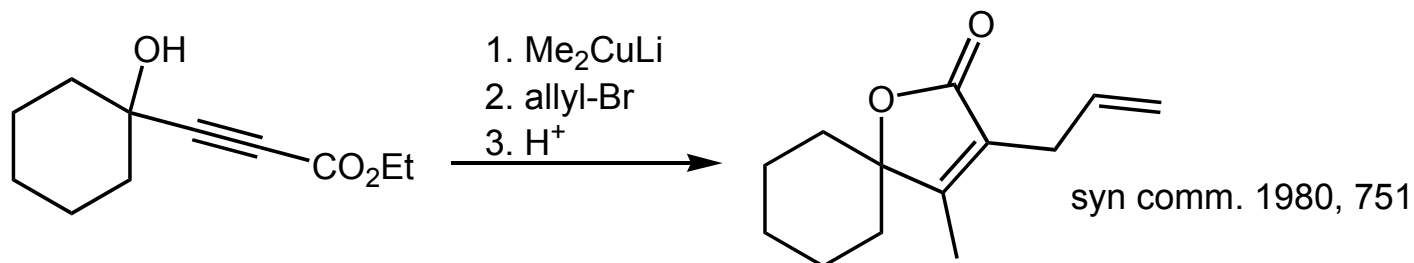
$\text{R} = \text{alkyl, vinyl, phenyl, } \text{CH}_2\text{-TMS}$  Chem Lett, 1981, 905 and 1363



sometimes isomerization is good:



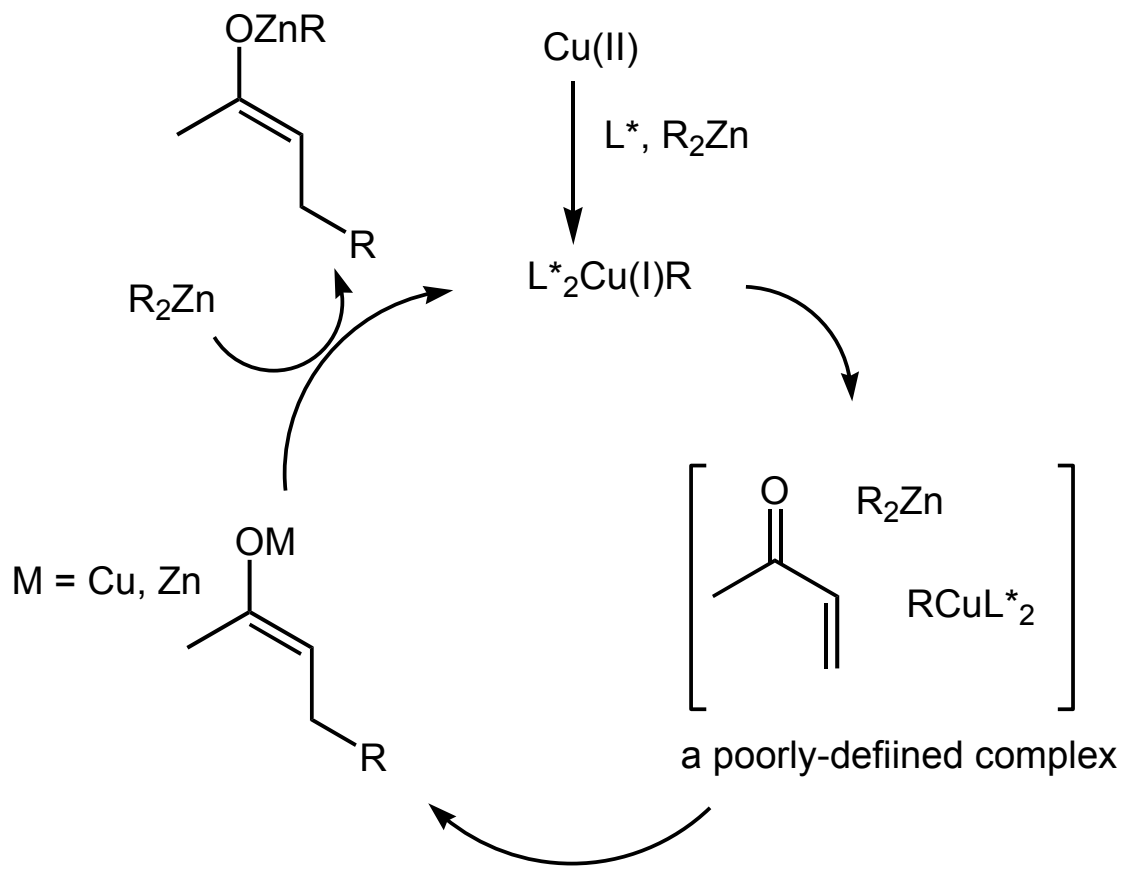
more examples of enoate addn





## Asymmetric 1,4 addn

Breakthrough came with observation that  $R_2Zn$  are effective alkyl sources  
 -functionalized Nu's  
 -can do catalytically without competing rxns of nucleophile



details of mechanism not known  
 stereoselectivity not understood

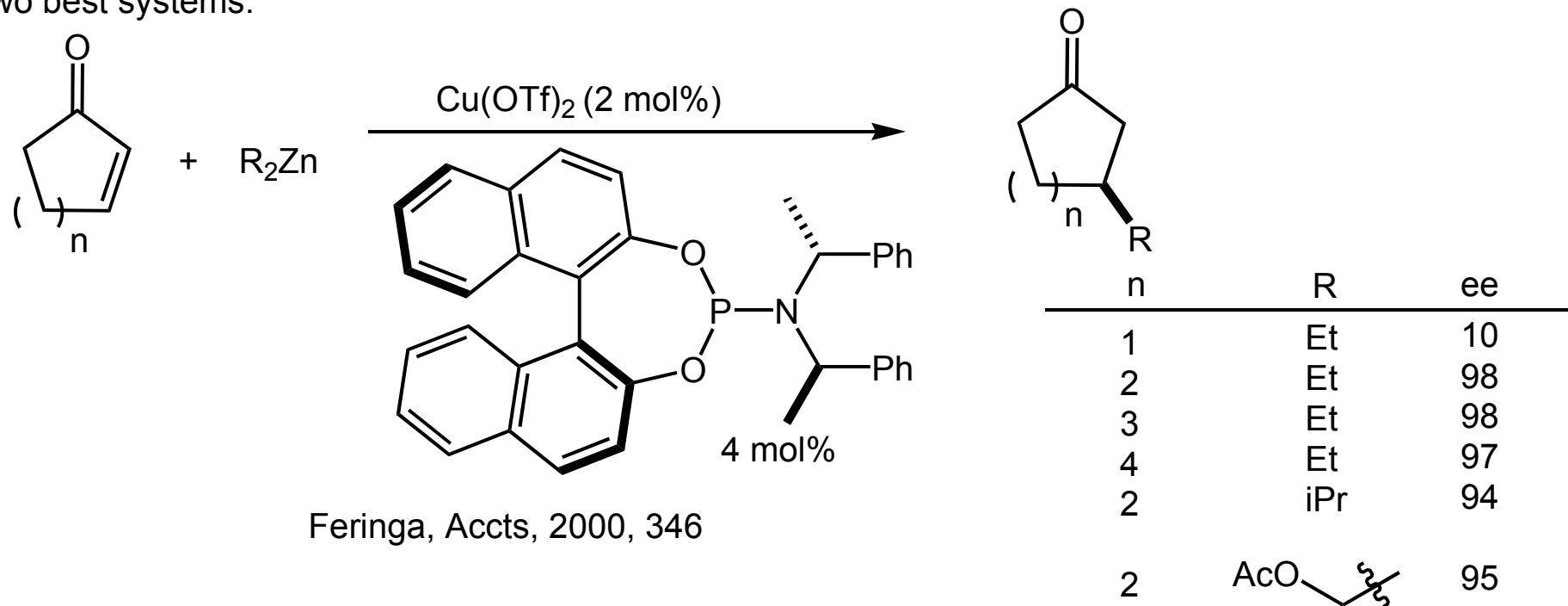
**Proposals**

Concerted transfer (ie no  $Cu(III)$  intermediate:  
 Noyori, Bull. Chem. Soc. 2000, 999; Kitamura,  
 Chem Lett. 2003, 224.

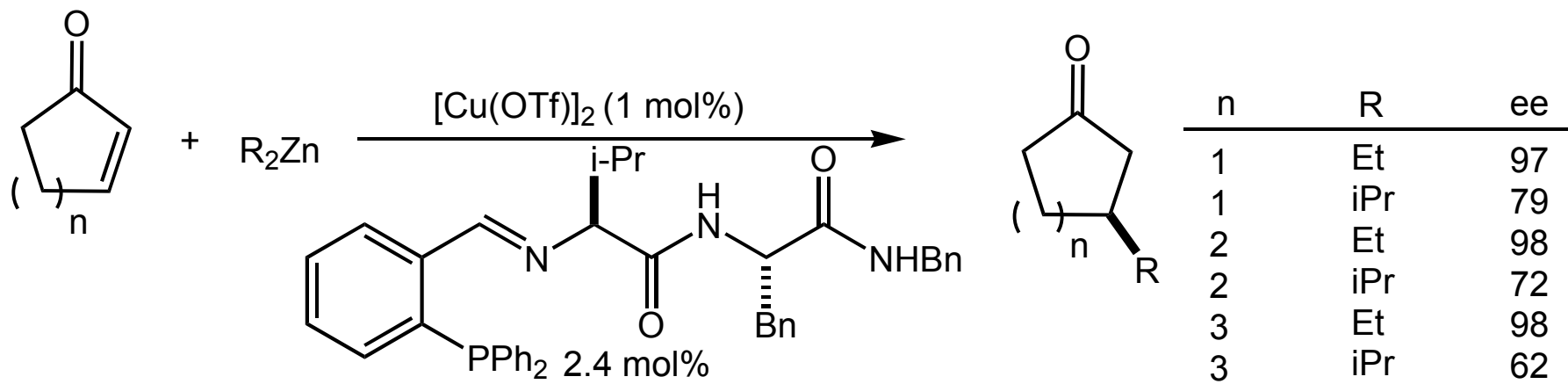
Rate limiting OA: Gennari, JOMC, 2005, 689,  
 2169

Rate limiting RE: Schrader, Chem-E.J. 2004,  
 6049.

two best systems:



Feringa, Accts, 2000, 346



overall best ligand,  
can optimize for individual substrates

Hoveyda, JACS, 2001, 755

## Asymmetric addition of Grignards

### Chemo- and stereoselectivity

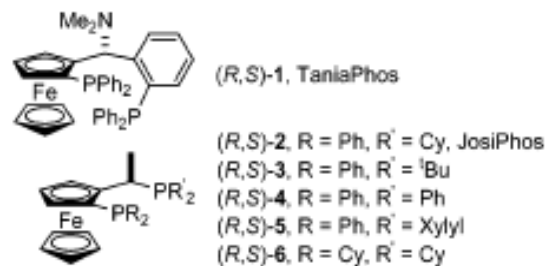


Figure 1. Chiral ferrocenyl-based diphosphines.

Scheme 1

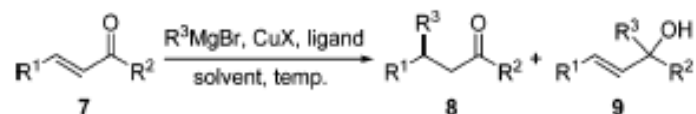


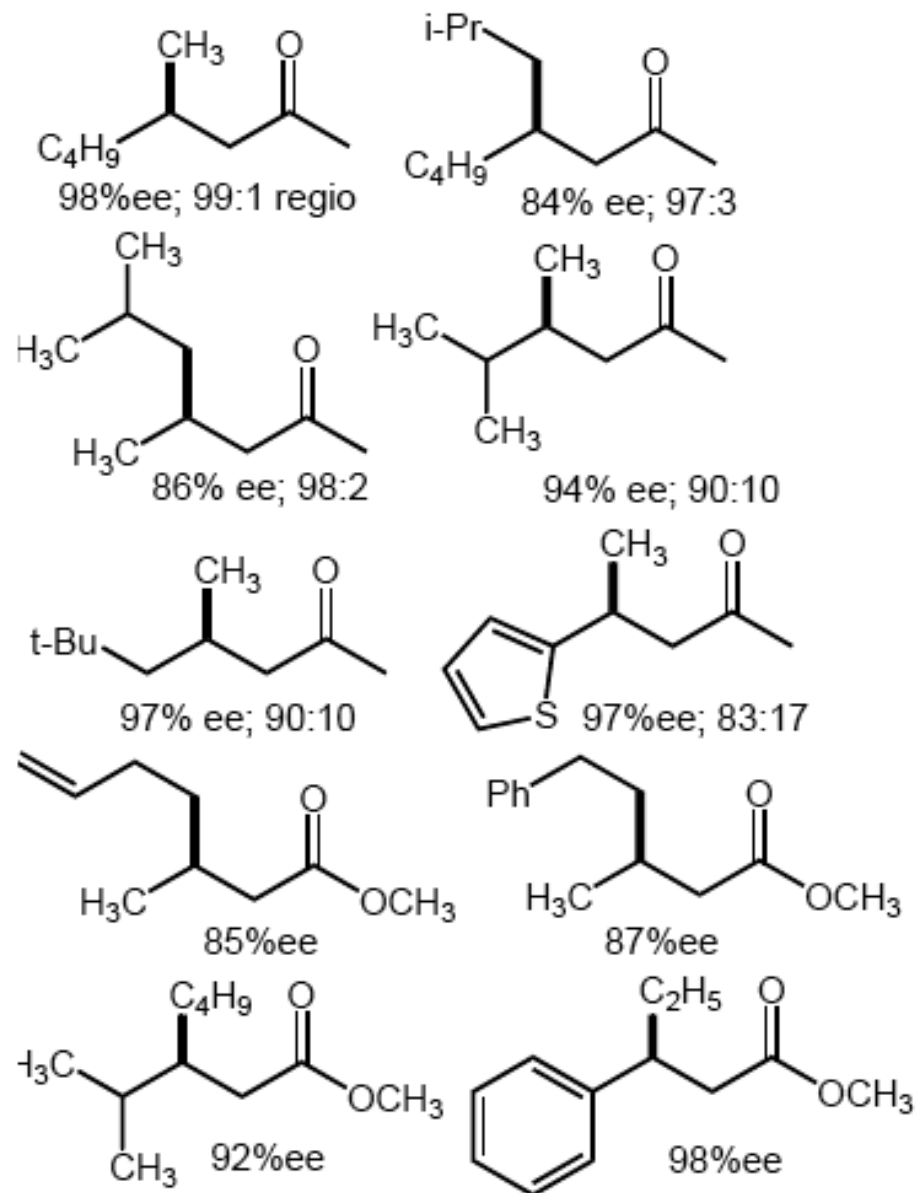
Table 1. Enantioselective CA of EtMgBr to (*E*)-3-Nonen-2-one 7a (R<sup>1</sup> = *n*-Pent, R<sup>2</sup> = Me, R<sup>3</sup> = Et)<sup>a,b</sup>

entry	ligand	CuX	solvent	temp (°C)	8a:9a <sup>c</sup>	ee <sup>d</sup> ( <i>R/S</i> )
1	1	CuCl	Et <sub>2</sub> O	0	84:16	1
2	1	CuCl	Et <sub>2</sub> O	-75	70:30	48 ( <i>R</i> )
3	2	CuCl	Et <sub>2</sub> O	-75	86:14	80 ( <i>R</i> )
4	2	CuI	Et <sub>2</sub> O	-75	83:17	72 ( <i>R</i> )
5	2	CuBr·SMe <sub>2</sub>	Et <sub>2</sub> O	-75	91:9	86 ( <i>R</i> )
6	2	CuBr·SMe <sub>2</sub>	<sup>t</sup> BuOMe	-75	99:1	90 ( <i>R</i> ) <sup>d</sup>
7 <sup>e</sup>	2	CuBr·SMe <sub>2</sub>	<sup>t</sup> BuOMe	-75	77:23	74 ( <i>R</i> )
8	3	CuBr·SMe <sub>2</sub>	<sup>t</sup> BuOMe	-75	86:14	44 ( <i>R</i> )
9	4	CuBr·SMe <sub>2</sub>	<sup>t</sup> BuOMe	-75	95:5	57 ( <i>R</i> )
10	5	CuBr·SMe <sub>2</sub>	<sup>t</sup> BuOMe	-75	80:20	21 ( <i>R</i> )
11	6	CuBr·SMe <sub>2</sub>	<sup>t</sup> BuOMe	-75	71:29	27 ( <i>R</i> )

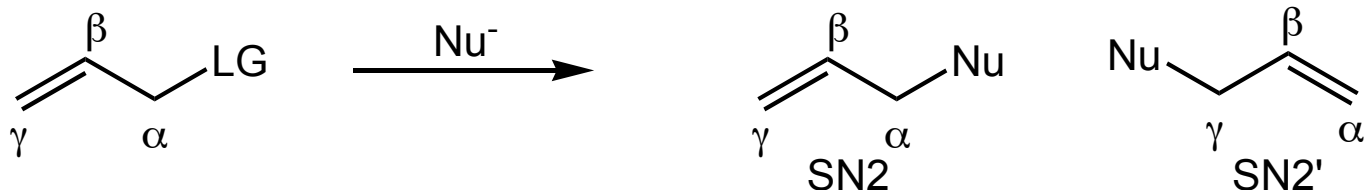
Feringa: PNAS, 2004, 5834

JACS, 2004, 12784

ACIEE, 2005, 2752



## SN2' additions



issues:

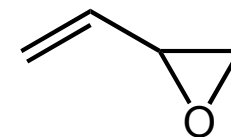
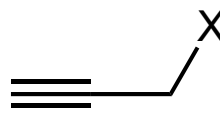
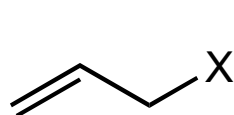
regioselectivity ( $\alpha$  vs  $\gamma$ ) (usually SN2')

SN2' favored:  $\text{RCu-BF}_3$ ;  $\text{R}_2\text{CuLi-ZnCl}_2$ ;  $\text{RCu}$ ;  $\text{R}_2\text{Cu}(\text{Cl or Br})(\text{MgBr})_2$ , THF

SN2 favored:  $\text{R}_2\text{CuI}(\text{MgBr})_2$ ;  $\text{Et}_2\text{O}$

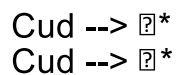
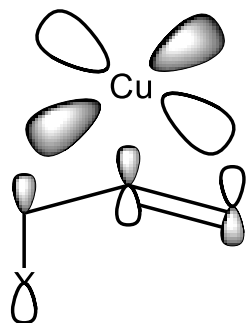
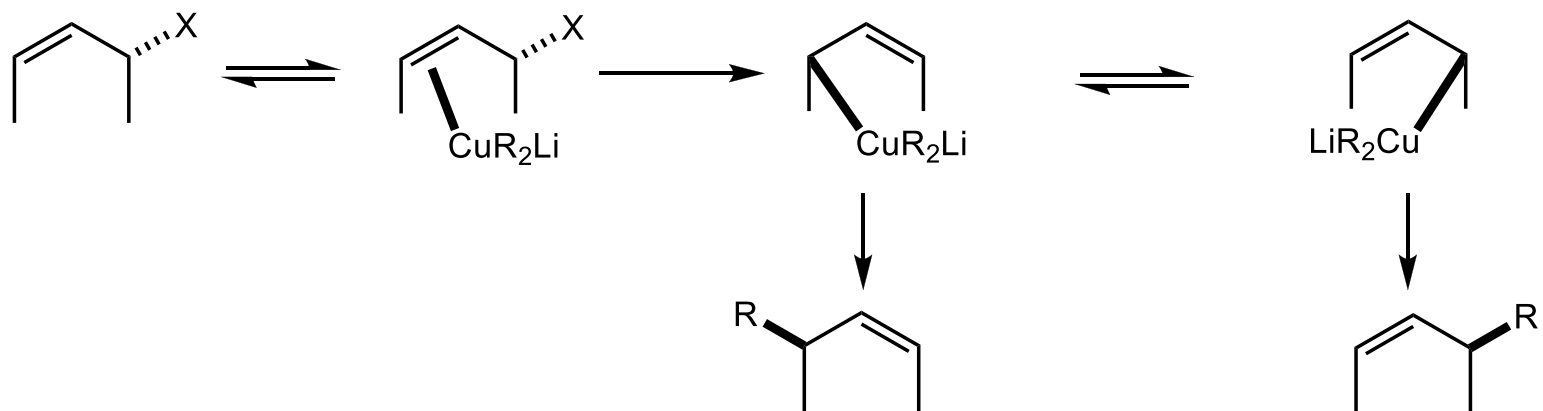
stereoselectivity (syn vs anti) (usually anti)

substrates



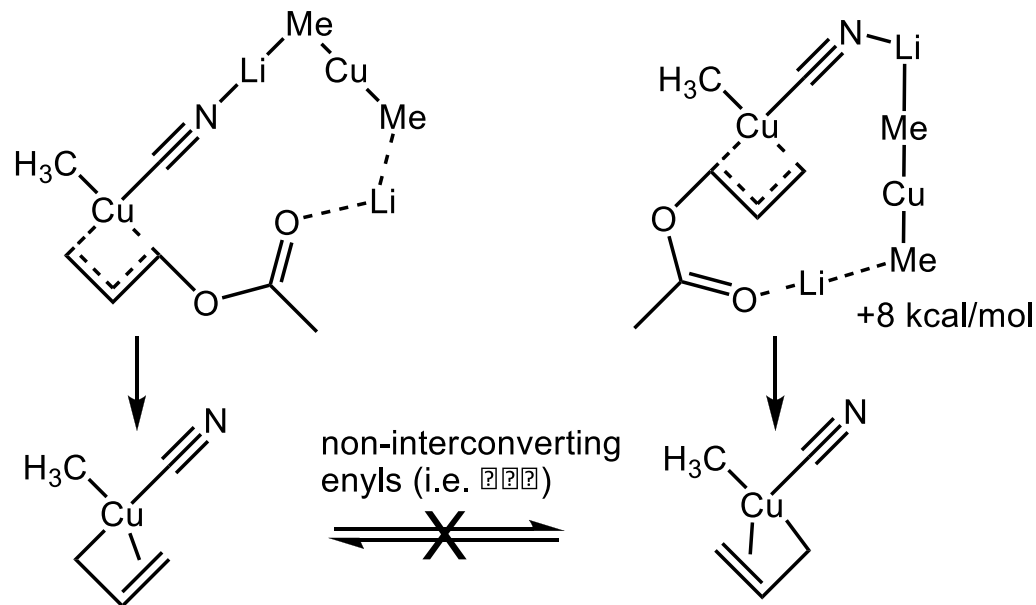
$\text{X} = \text{halide, OAc, OCO}_2\text{R, OP(O)(OR)}_2, \text{OS(O)R}$

accepted mechanism:



unresolved questions:  
 why SN2' favored?  
 Why little R-R formation?

Details may be very complicated; from computation:

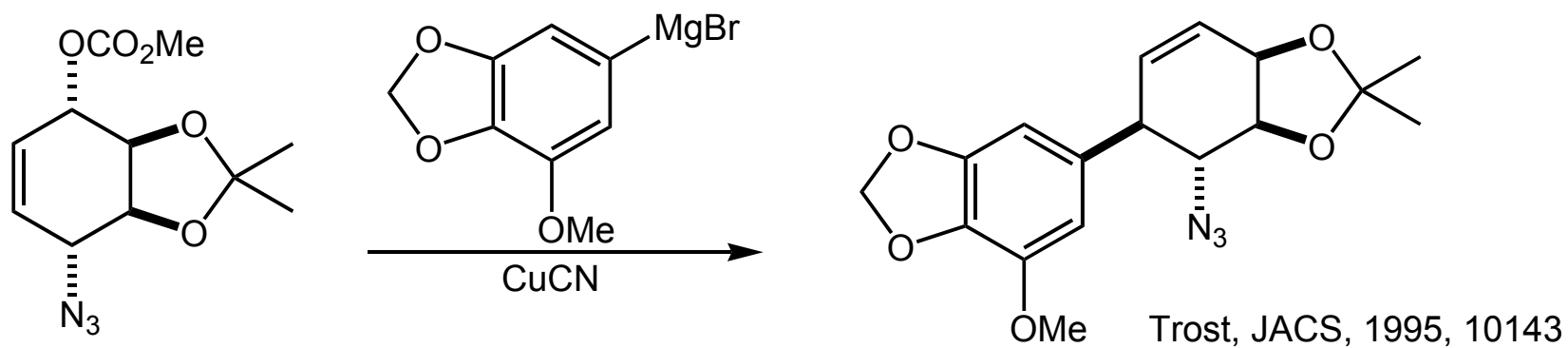
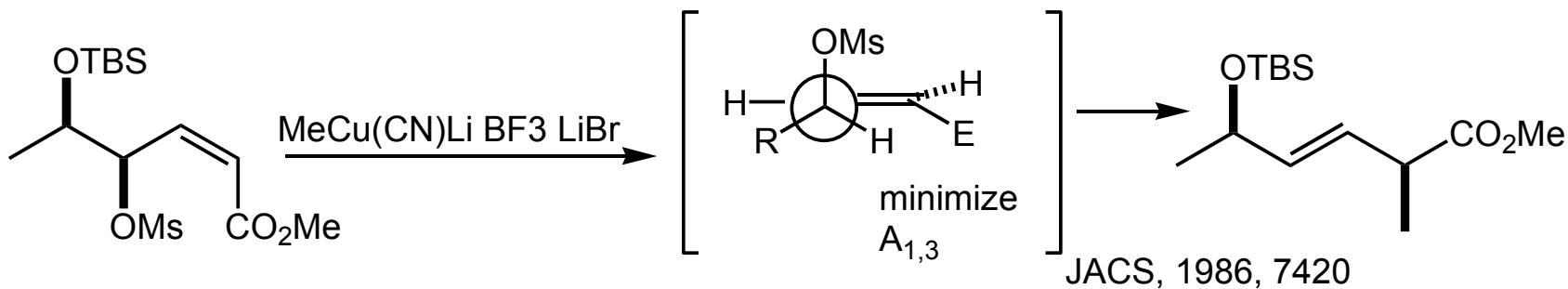
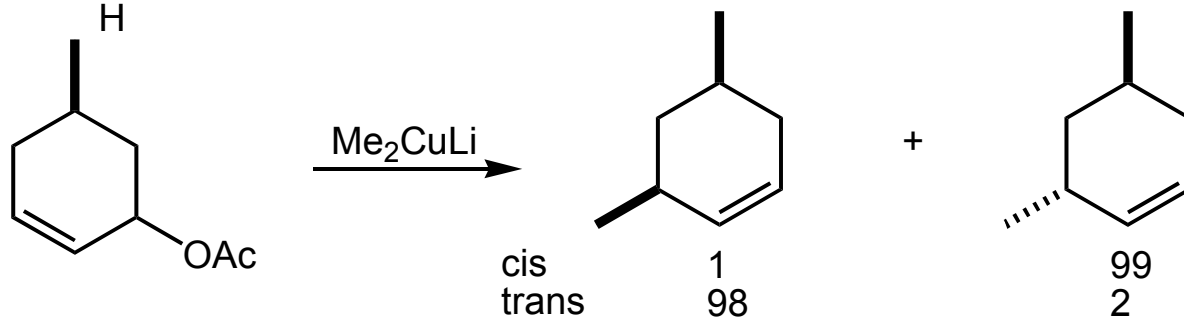
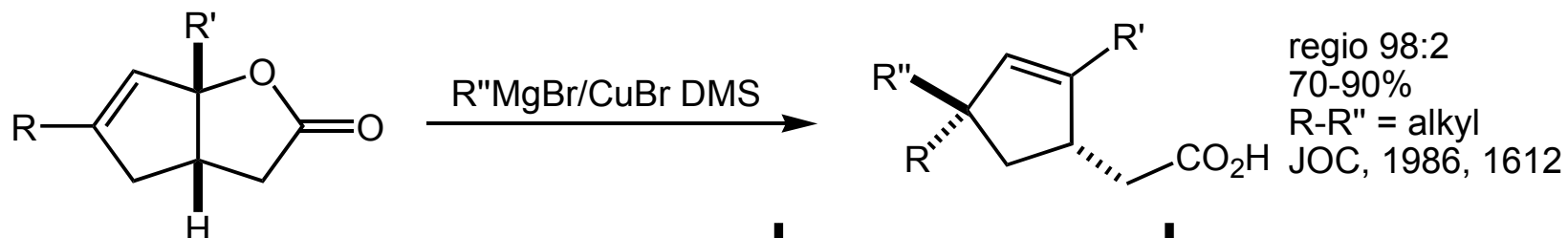


Nakamura, JACS, 2008, 12862  
 but why are the 2 cuprates different?

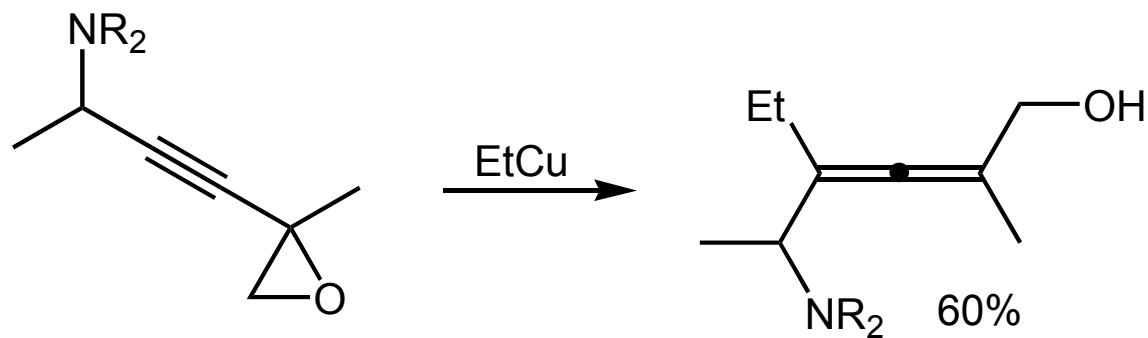
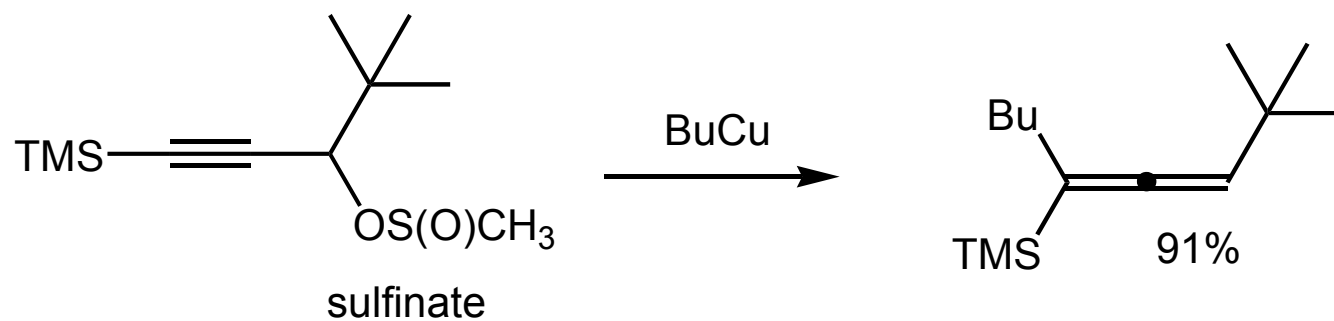
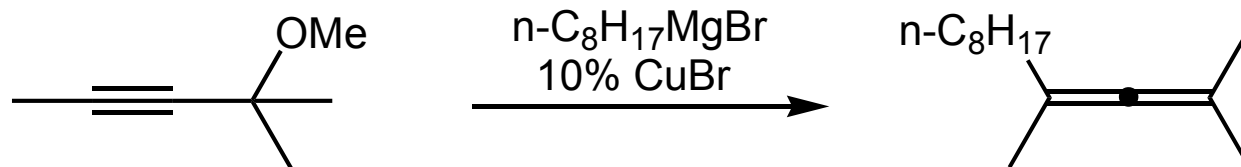
towards  $\beta$ -substitution  
 (SN2')

towards  $\alpha$ -substitution  
 (SN2)

SN2' addns: examples



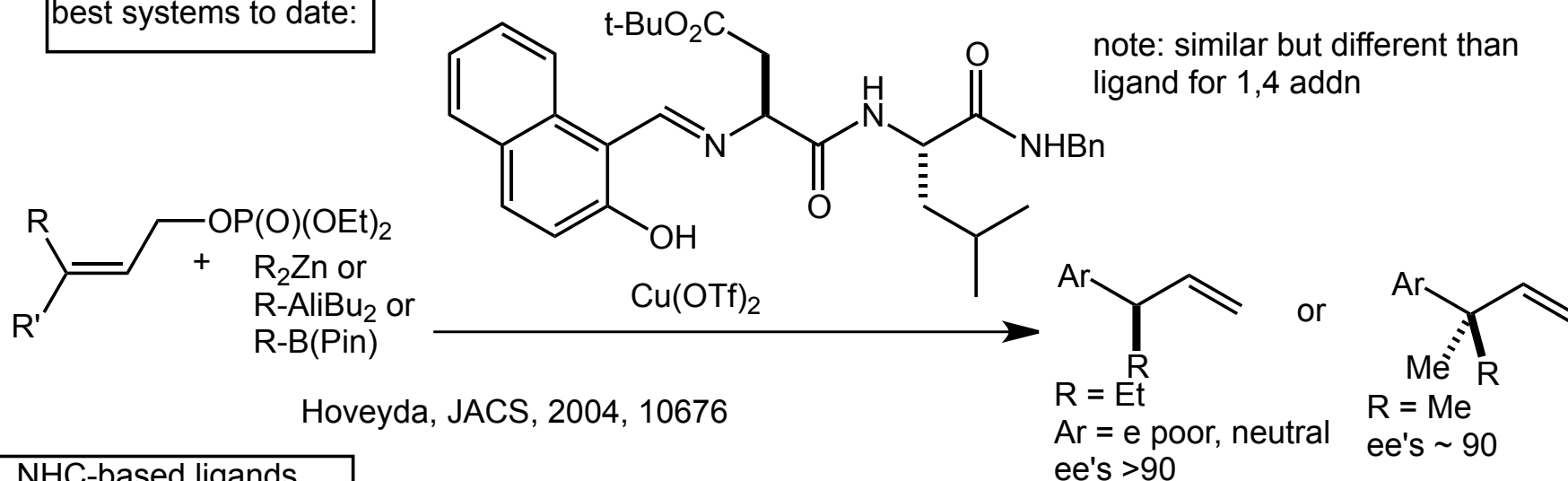
## SN2' addns involving alkynes



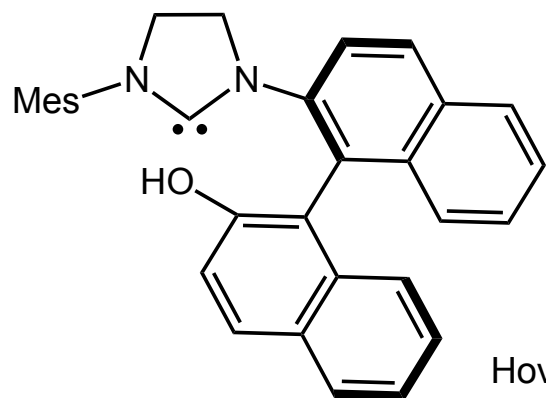
Ready; Catalysis

Conjugate Addition-28

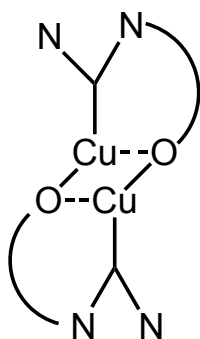
best systems to date:



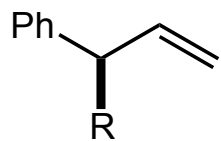
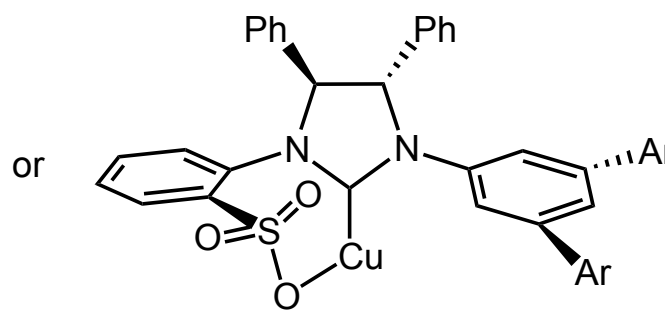
NHC-based ligands



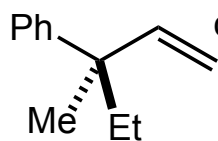
solid state:



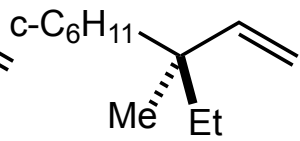
Hoveyda, JACS, 2004, 11130  
JACS, 2014, 2149



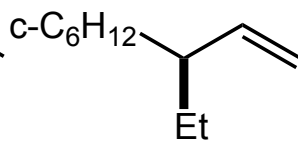
$R = Me$ , 74% ee  
 $R = Et$ , 86% ee



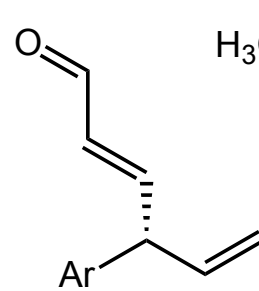
91% ee



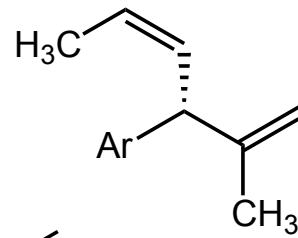
93% ee



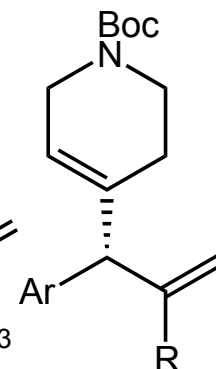
94% ee



$>80\% ee$



$>80\% ee$



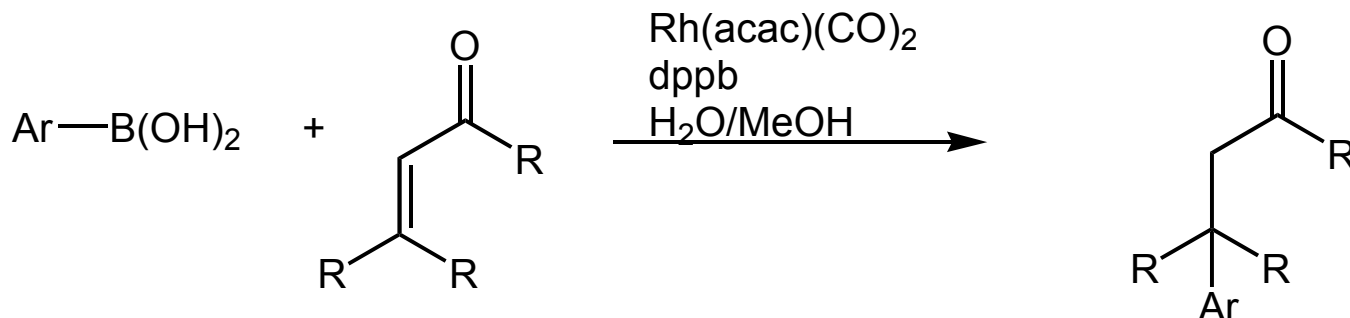
$>80\% ee$



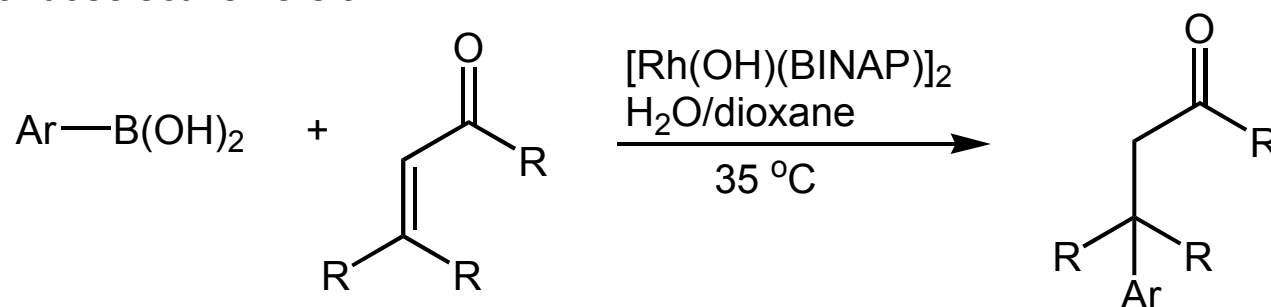
## Rh-catalyzed 1,4 addns of boronic acids - a remarkable rxn

review: Hayashi Chem Rev. 2003, 2829

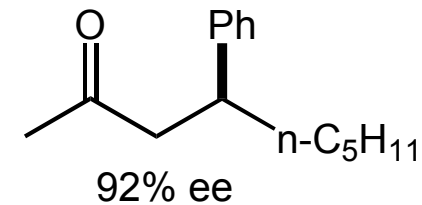
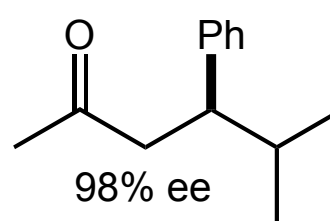
original report: Miyaura OM, 1997, 4229

moderate yields  
high temp  
long times

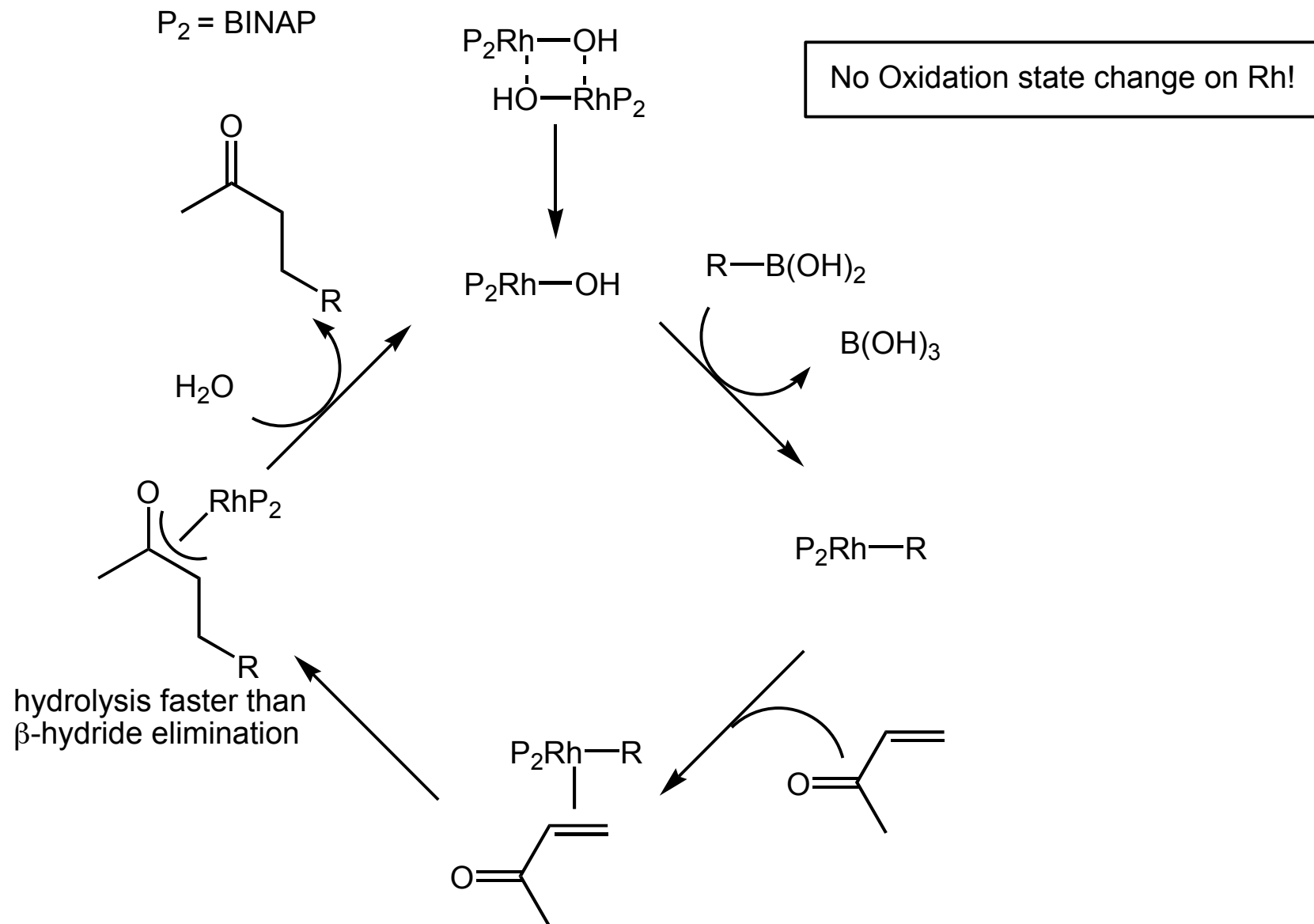
enantioselective version



n	R	ee
1	Ph	98
2	Ph	99
2	4OMe-Ph	99
2	4-F-Ph	99
2	Hexenyl	94
3	Ph	96

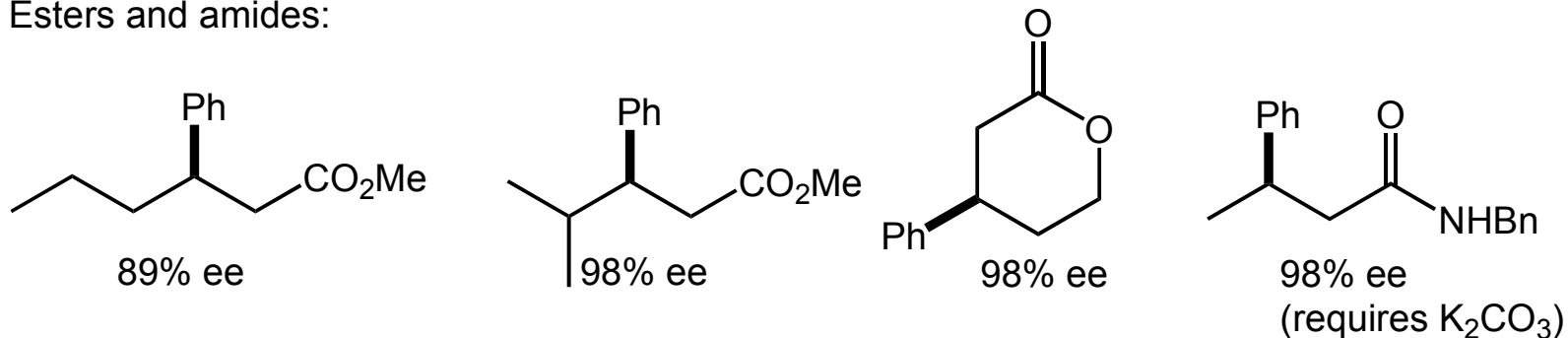


## Mechanism of Rh-catalyzed 1,4 addn

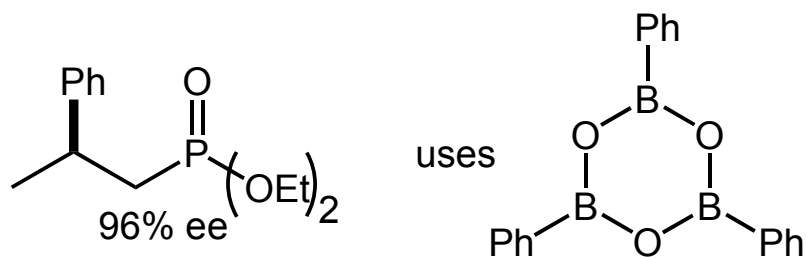


## Rh-catalyzed 1,4 addn: other substrates

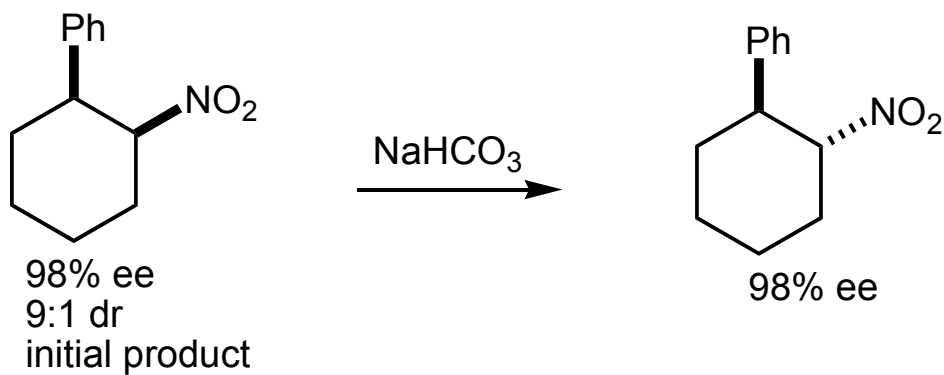
Esters and amides:



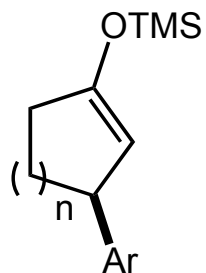
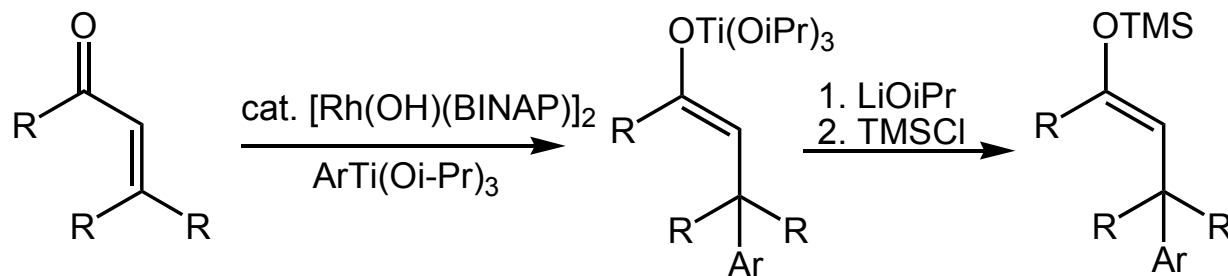
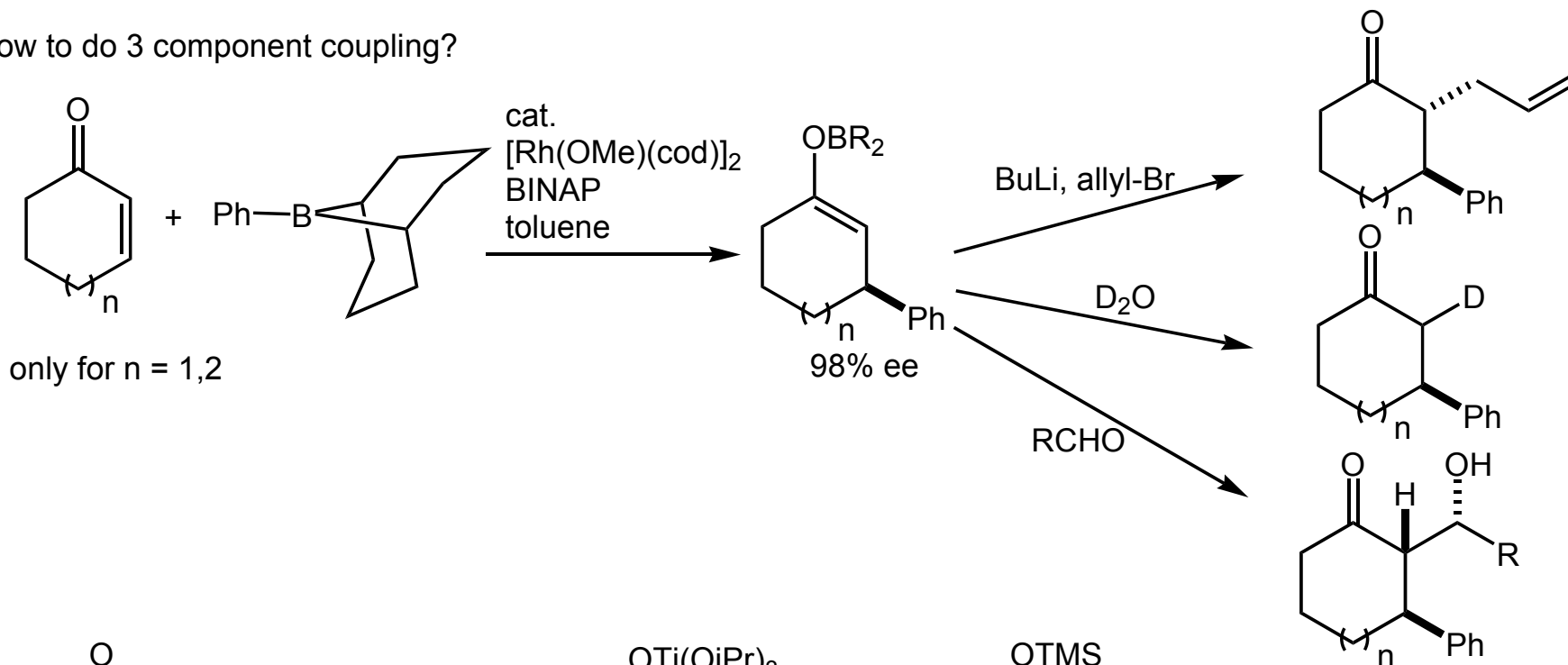
Phosponates



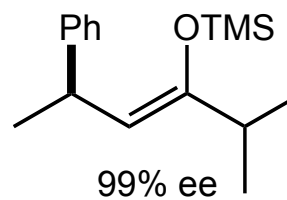
nitro olefins



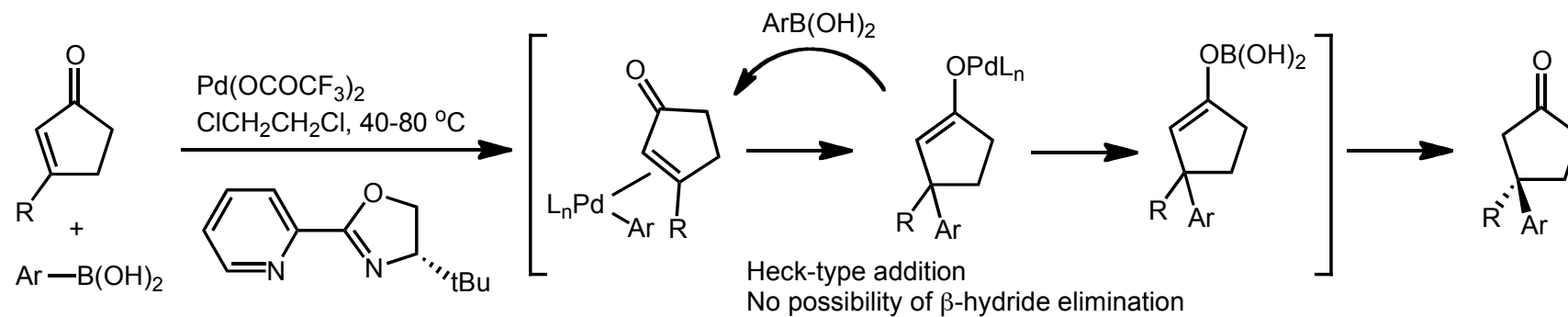
How to do 3 component coupling?



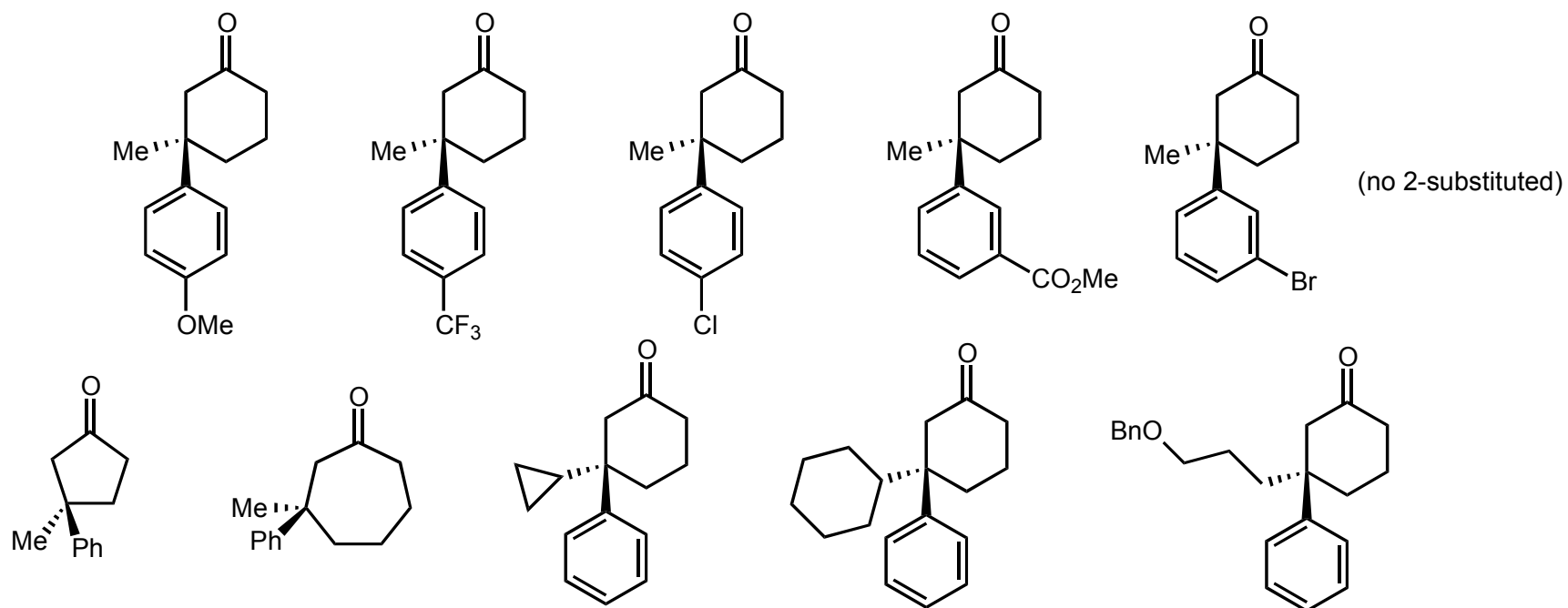
n	Ar	ee(%)
1	Ph	99
2	Ph	99
2	4F-Ph	99
2	4MeOPh	99
3	Ph	98



Pd-Catalyzed addition of aryl boronic acids: formation of quaternary stereocenters  
Stoltz, JACS, 2011, 6902

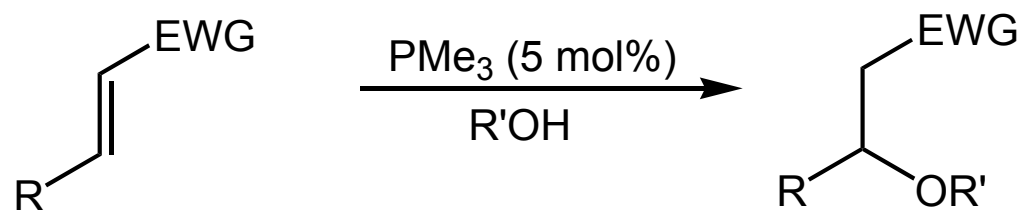


yields mostly >80%, ee's mostly >90%



## 1,4-addn of O nucleophiles

Bergman and Toste, JACS, 2003, 8696



EWG	R	R'OH	Y (%)
COMe	H	MeOH	56
COEt	Me	H <sub>2</sub> O	77
CO <sub>2</sub> Me	Me	MeOH	71
CN	H	MeOH	79
COMe	Ph	MeOH	0

