

Carbometallation Reactions in Organic Synthesis

Topic Review
September 24th , 2015

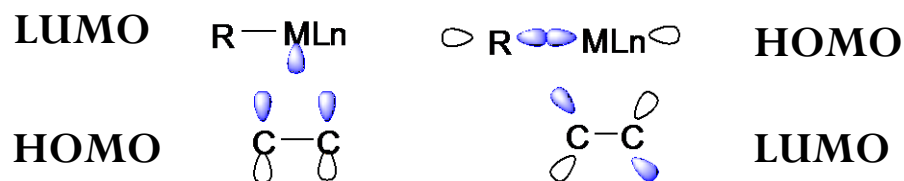
Presented by Sankar Rao Suravarapu

Prof. Dr. Philippe Renaud
University of Bern, Department of Chemistry and Biochemistry

Definition

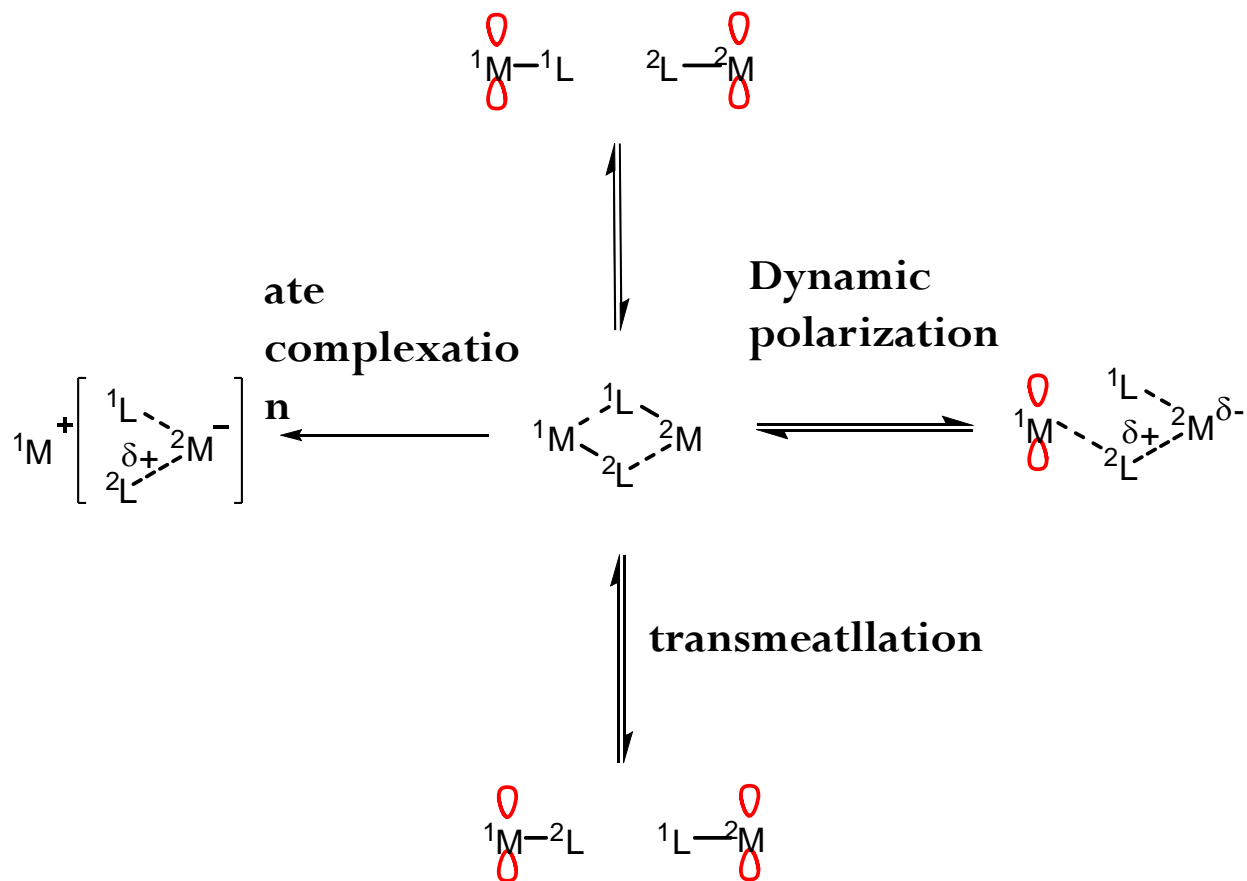
Carbometallation : A chemical process involving a net addition of carbon-metal bond to an unsaturated carbon-carbon multiple bonds.

- Carbometallation reactions that are proceeding *via* pericyclic reactions are stereoselective (**4-centered *syn* addition mechanism**)

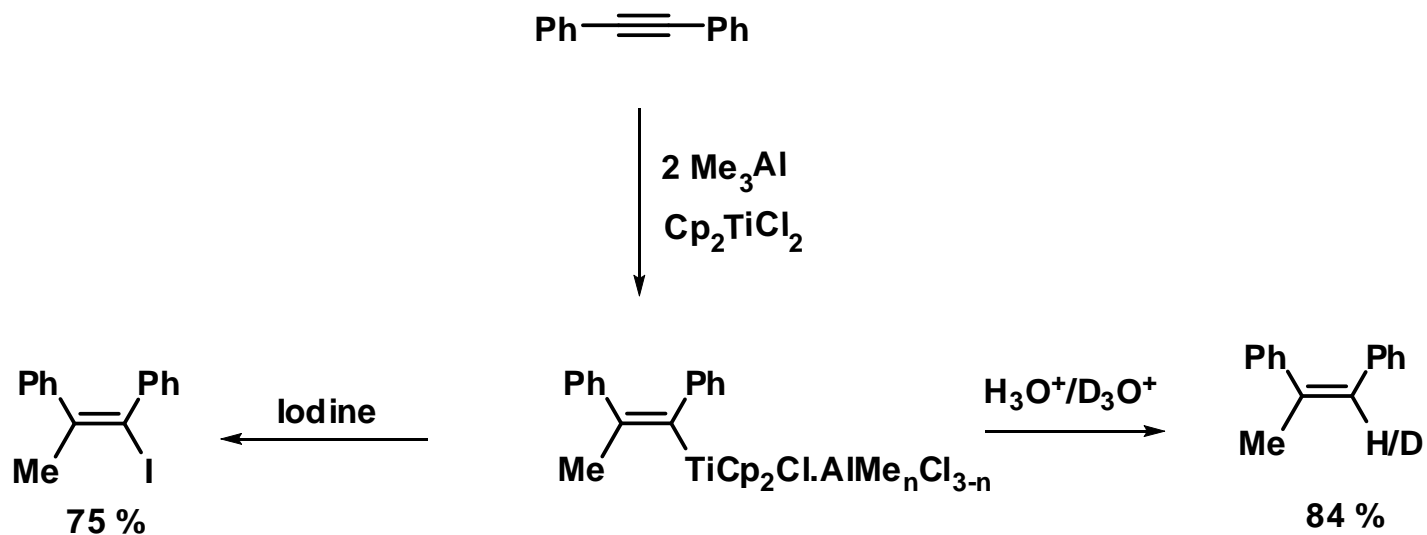


- Structural requirement for organometallic species is the presence of a low-lying empty metal orbital
- Activation energy for the carbometallation would be more than that of corresponding hydrometallation

Interaction between two metal containing Lewis acids

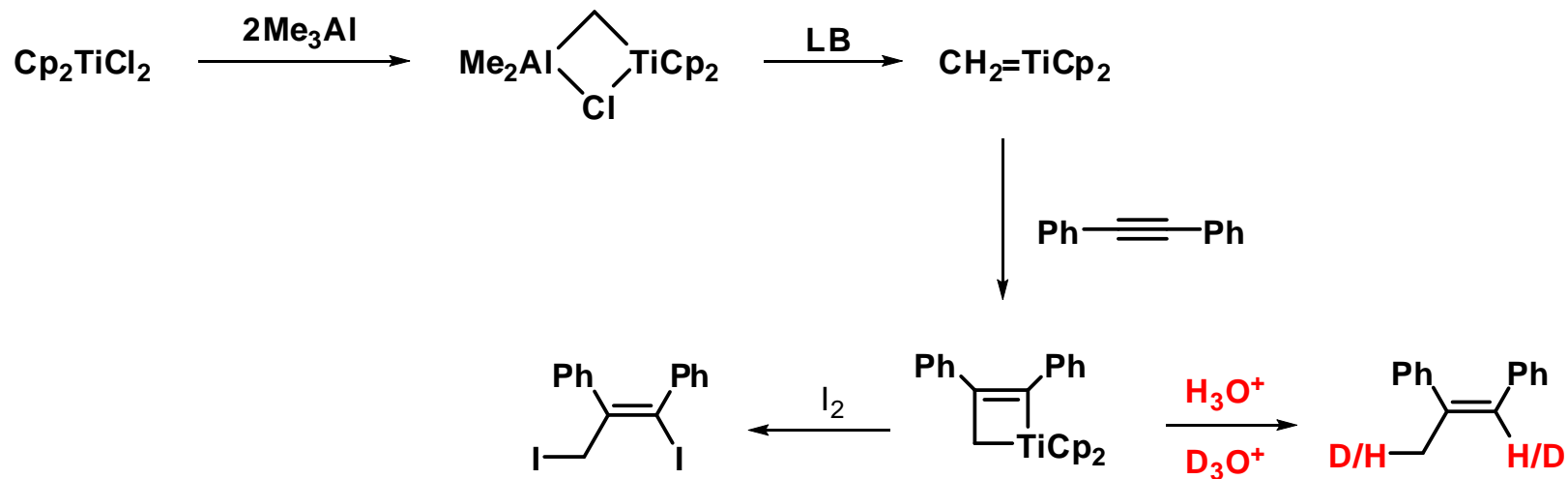


Stoichiometric **carbotitanation** of alkynes



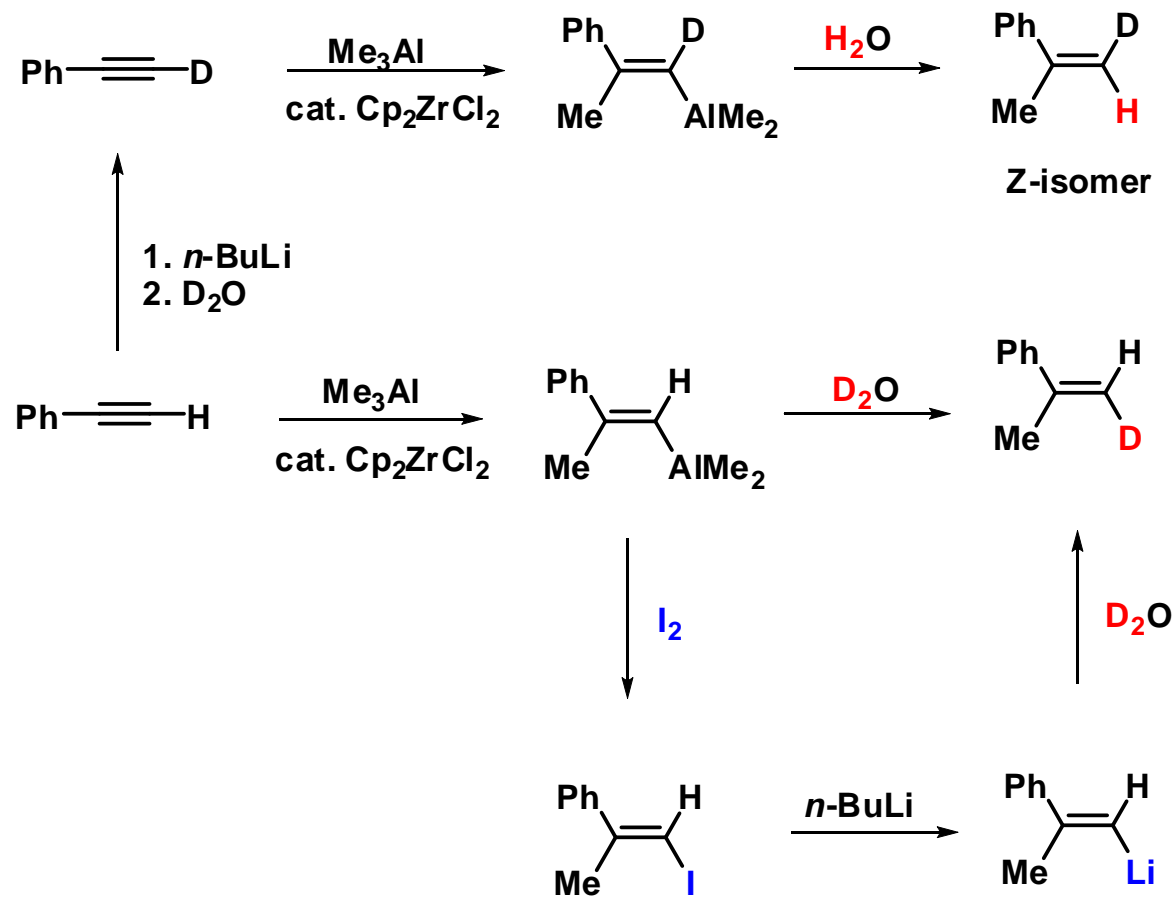
Negishi, E. et al., *Organomet. Chem.* **1978**, 156, C20

Different sequence and time intervals of addition in same molar ratio



Tebbe *et al.*, *J. Am. Chem. Soc.*, **1978**, *100*, 3611

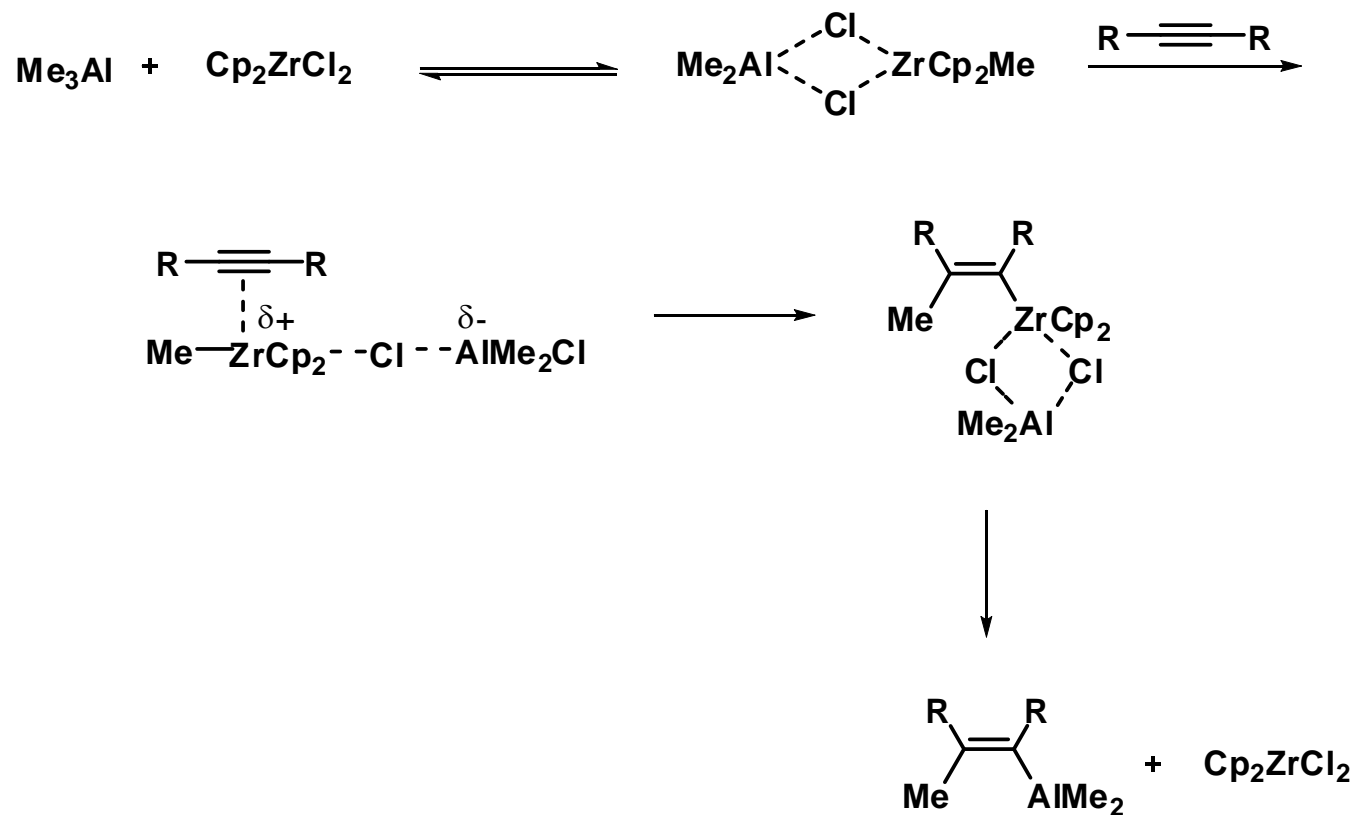
Zirconium-catalyzed **carboalumination** of alkynes



Negishi, E. et al., *J. Am. Chem. Soc.* **1985**, *107*, 6639

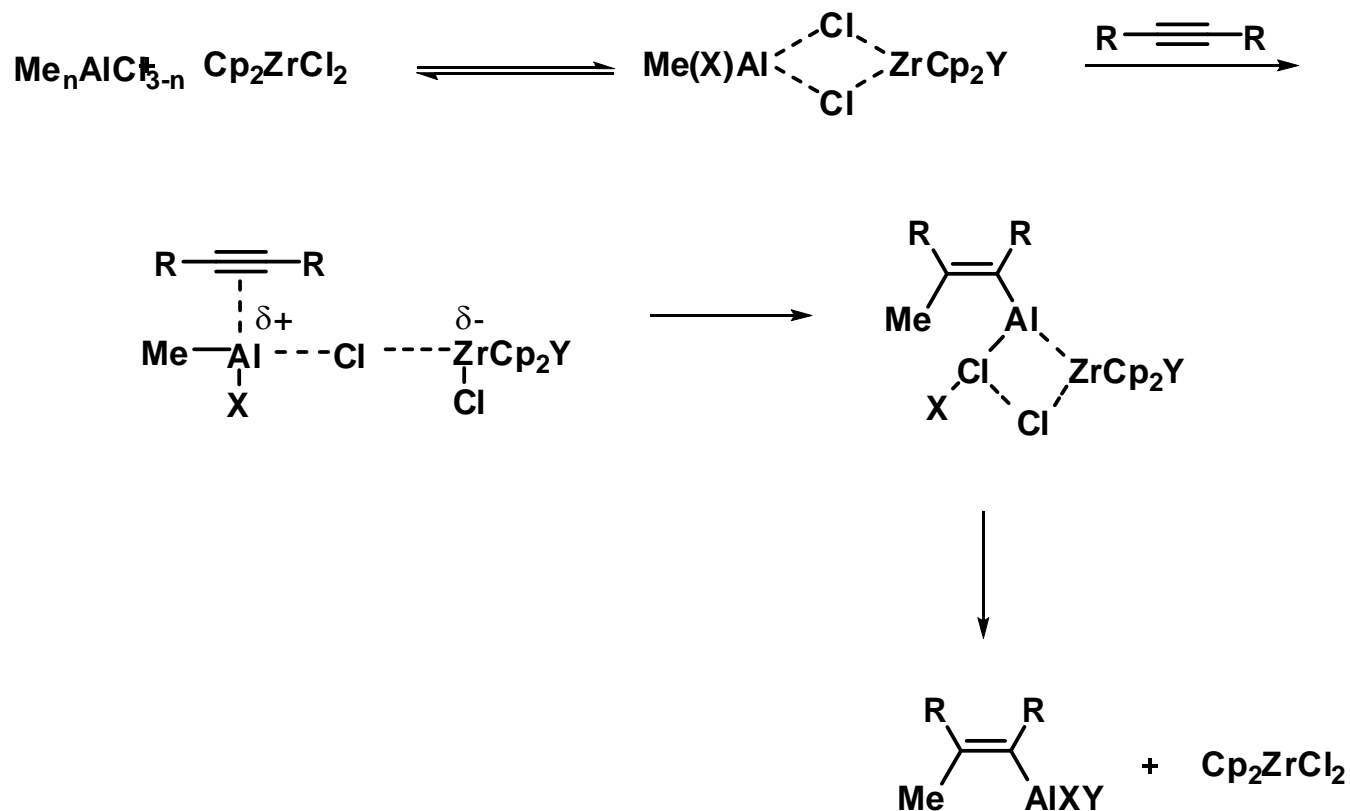
Zirconium-catalyzed **carboalumination** of alkynes

Mechanistic investigations



Zirconium-catalyzed **carboalumination** of alkynes

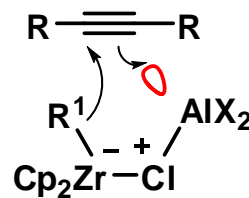
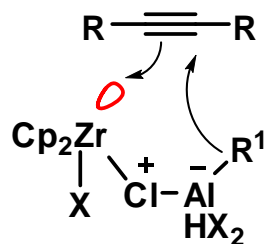
Mechanistic investigations



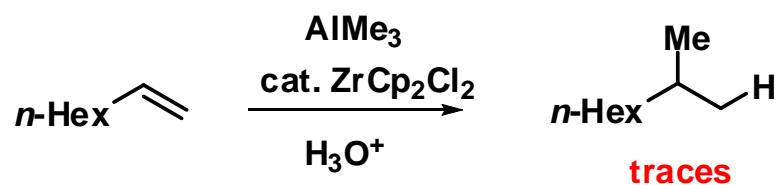
Zirconium-catalyzed **carboalumination** of alkynes

Mechanistic investigations

Two other possible six- centered mechanisms

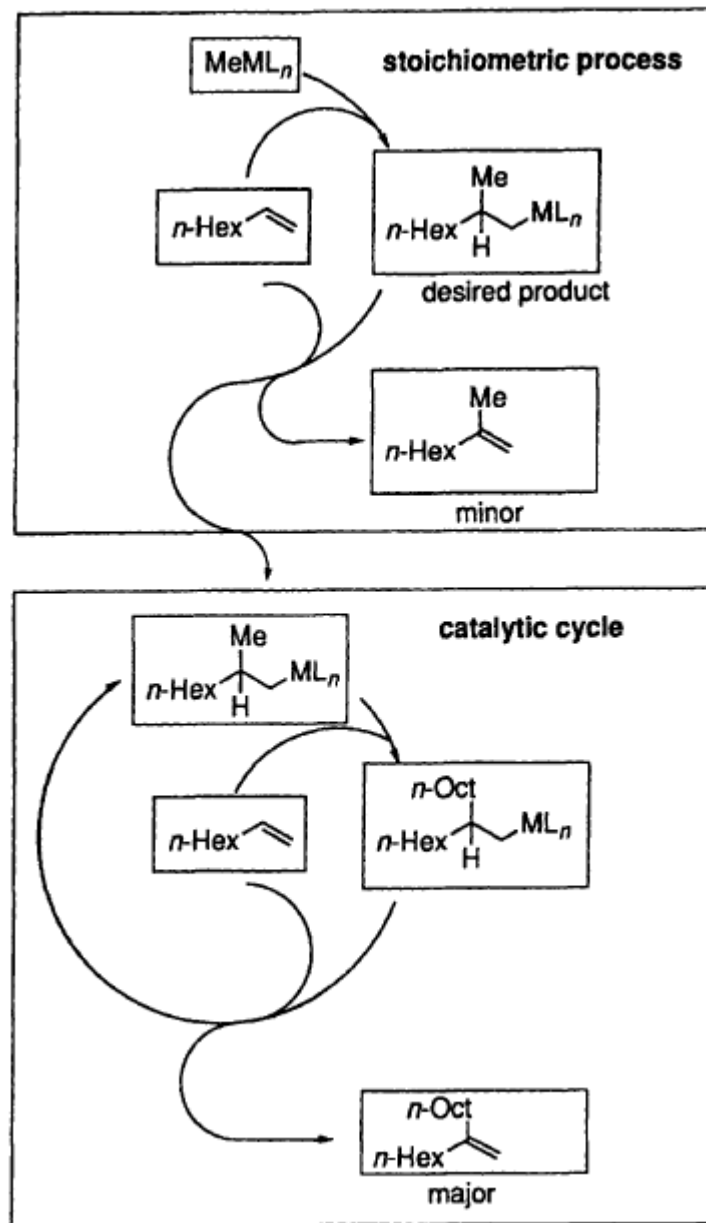


Zirconium-catalyzed **carboalumination** of alkenes

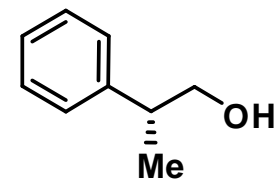
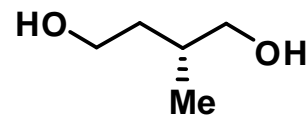
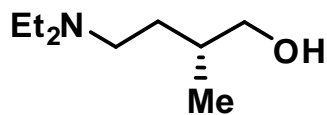
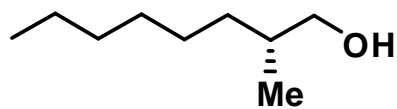
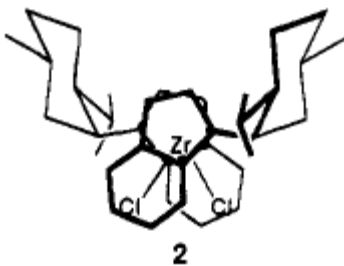
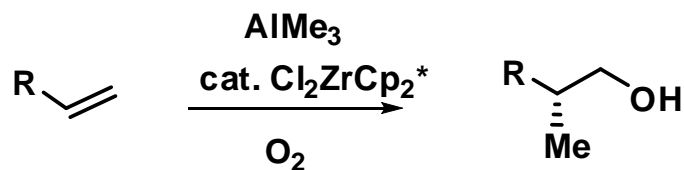


Negishi, E. et al., *J. Am. Chem. Soc.* **1995**, *117*, 10771

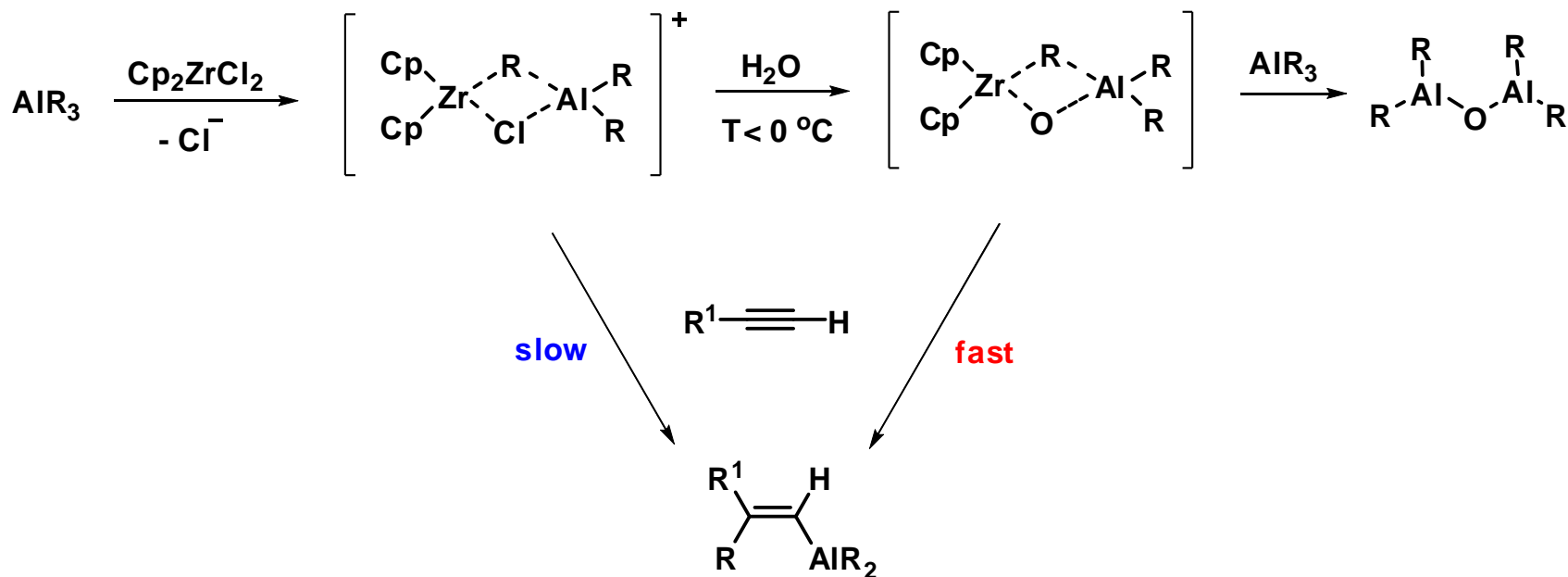
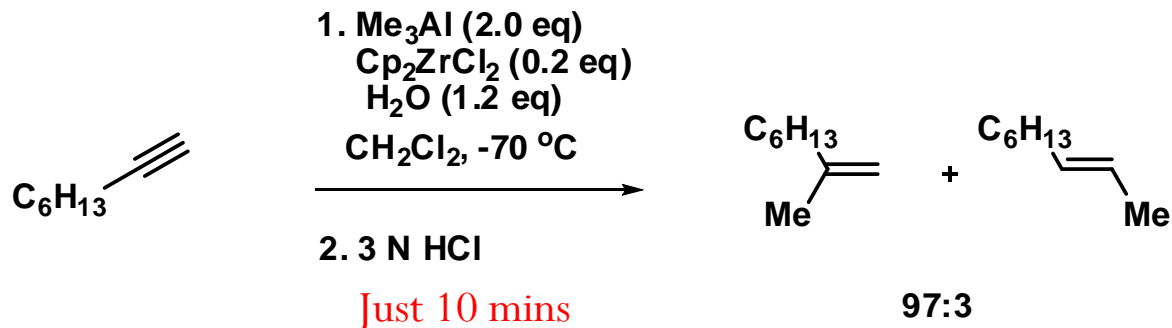
Negishi, E. et al., *Chem. Soc. Rev.* **1996**, *25*, 427



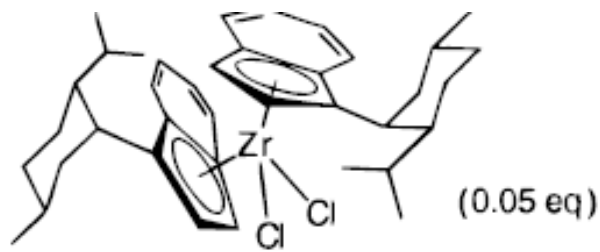
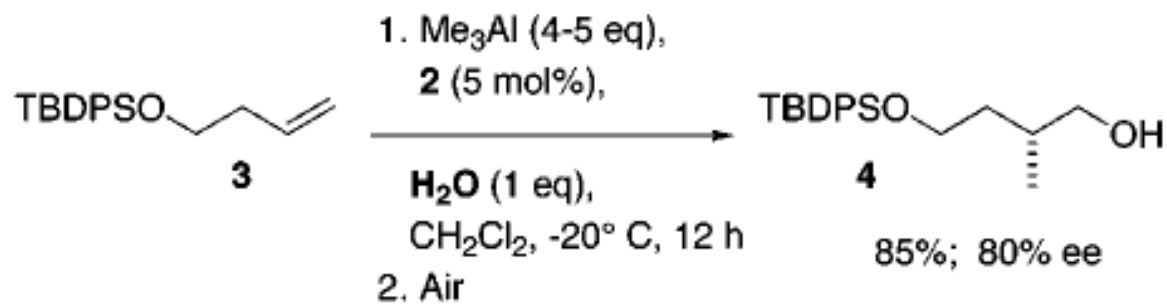
Zirconium-catalyzed enantioselective **methylalumination** of alkenes



Water accelerated carboalumination

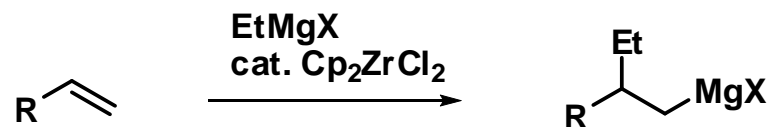


Asymmetric methylalumination

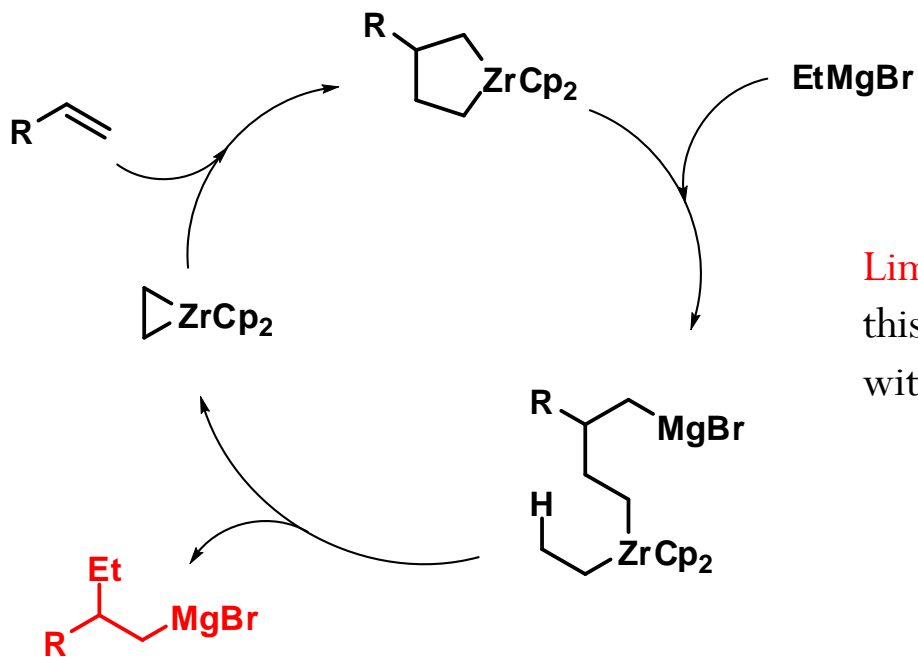


Zirconium catalyzed- Ethylmagnesiatio**n** of alkenes

Dzhemilev ethylmagnesiatio**n**



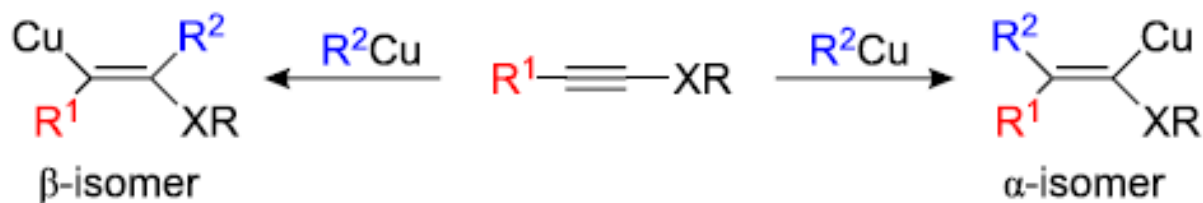
Catalytic cycle



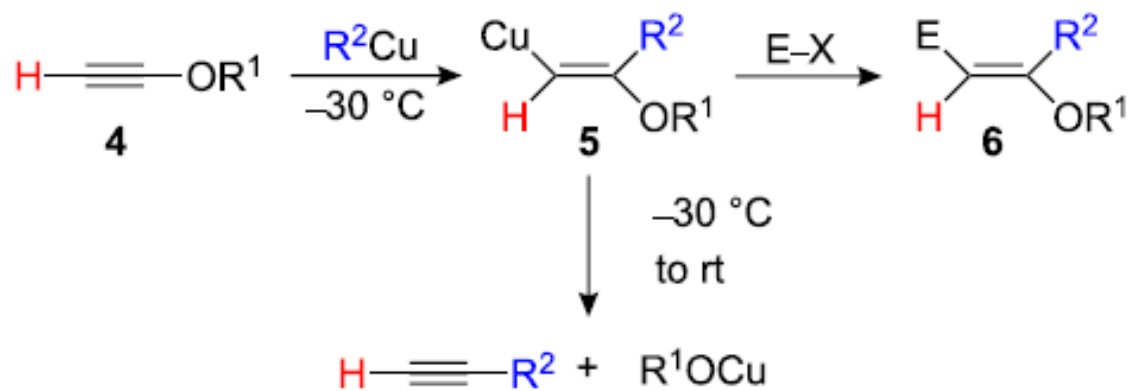
Limitation:
this reaction only works
with ethyl Grignard

Carbocupration reactions

Regioselectivity in the **carbocupration** reaction



Alkoxy-substituted terminal alkynes

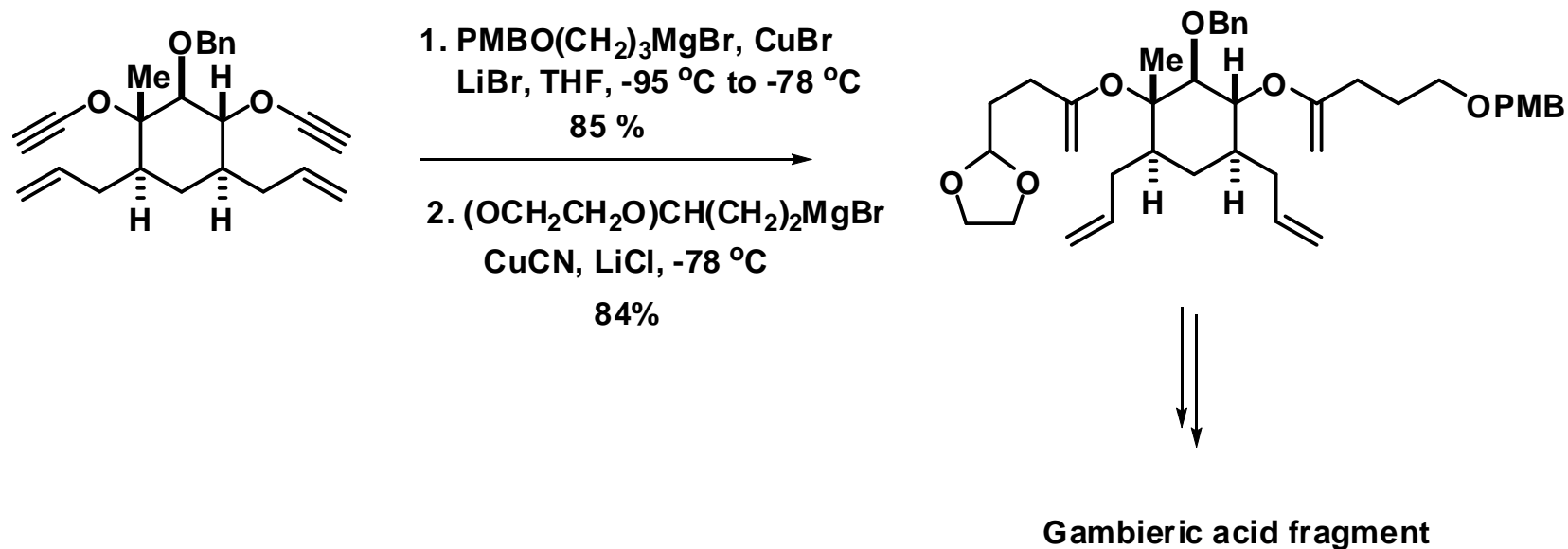


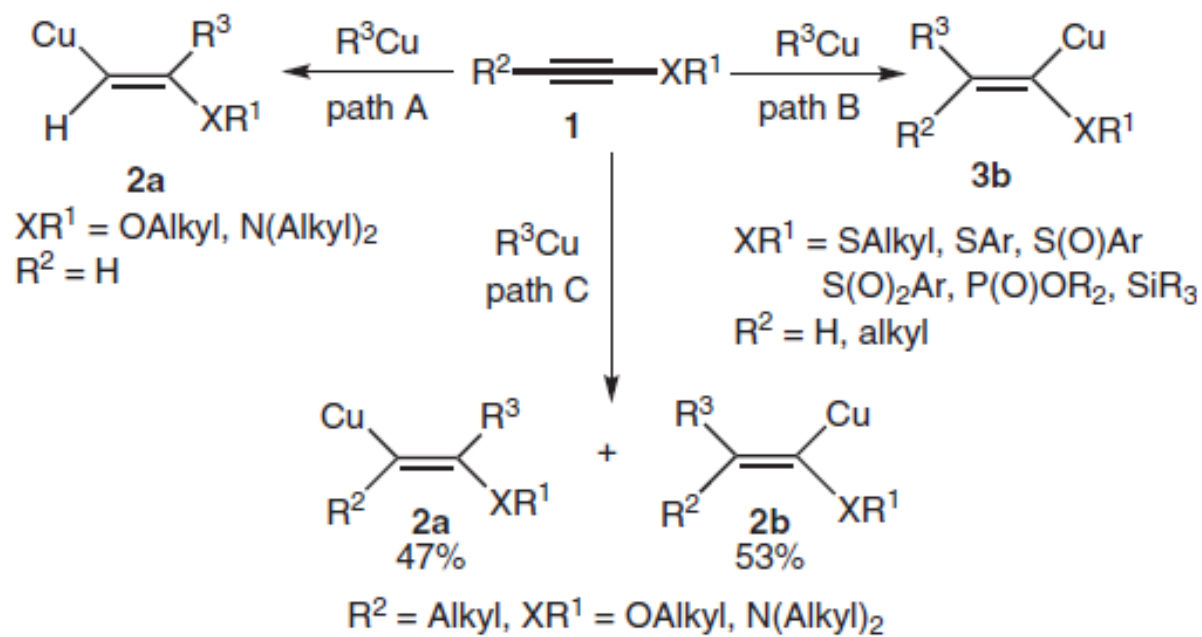
Nakamura, E. et al., *J. Am. Chem. Soc.* **1992**, *114*, 6686

J. Am. Chem. Soc. **1997**, *119*, 4887

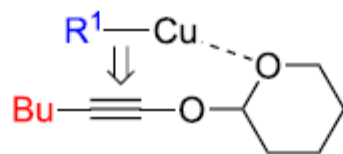
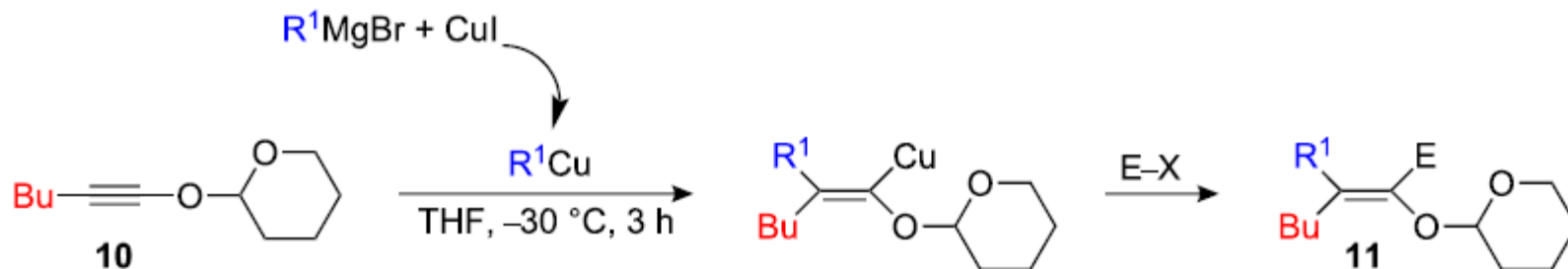
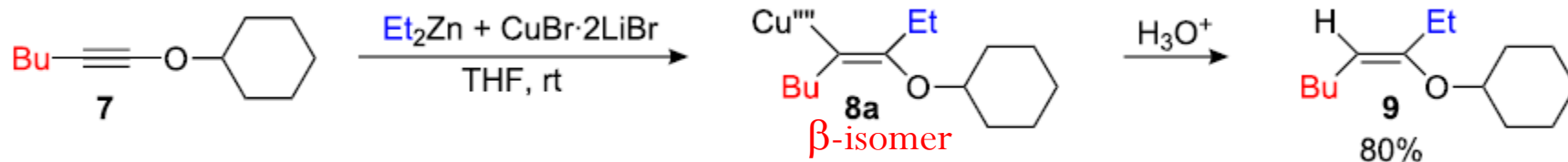
Sequential carbocupration reaction

Alkoxy-substituted alkynes





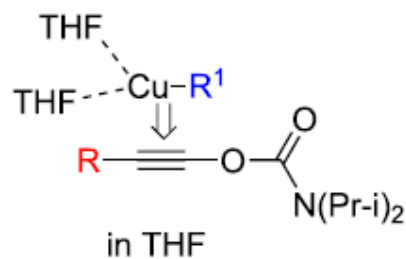
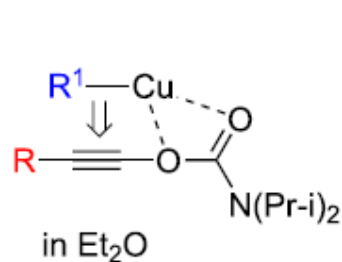
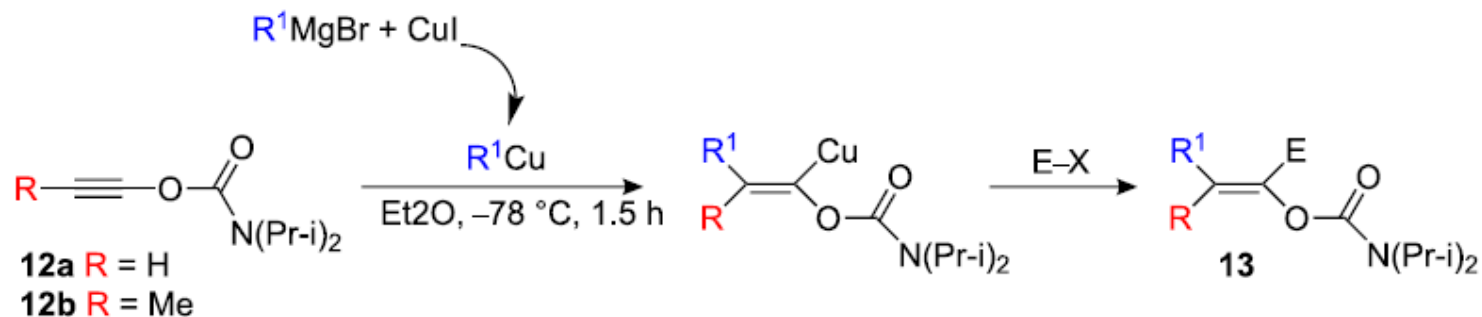
Solving the regioselectivity problem in di-substituted alkynes



α-isomer

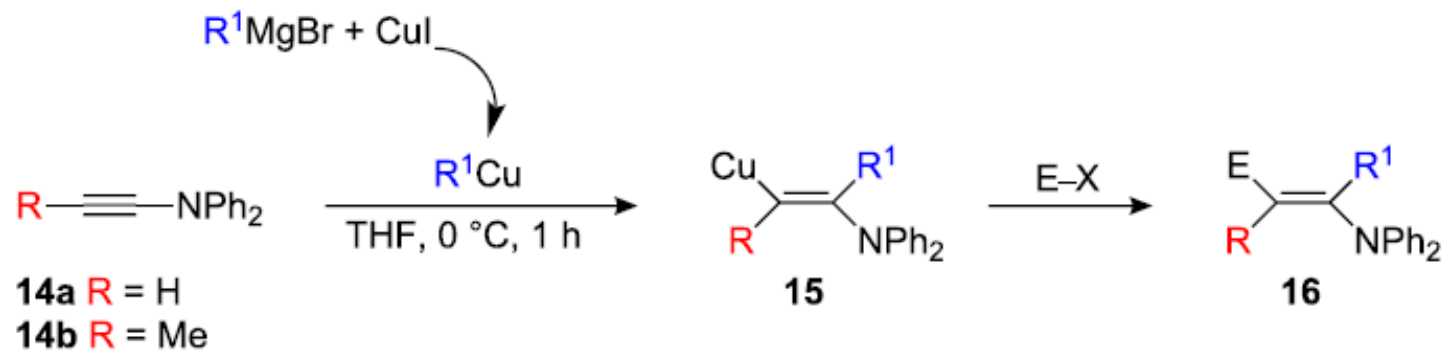
- $R^1 = \text{Et}, E = \text{H}$ 88%
- $R^1 = \text{Pr}, E = \text{H}$ 80%
- $R^1 = \text{Hex}, E = \text{H}$ 87%
- $R^1 = \text{i-Pr}, E = \text{H}$ 77%
- $R^1 = \text{CH}_2\text{Ph}, E = \text{H}$ 70%
- $R^1 = \text{Et}, E = \text{C}_3\text{H}_5$ 85%

carbocupration of O-alkynyl carbamates



- R = H, R¹ = Bu, E = H, 81%
- R = H, R¹ = *c*-C₆H₁₁, E = H, 72%
- R = H, R¹ = Ph, E = H, 86%
- R = H, R¹ = Me, E = H, 40%
- R = H, R¹ = Bu, E = I, 73%
- R = H, R¹ = Bu, E = C₃H₅, 81%
- R = Me, R¹ = Bu, E = H, 80%
- R = Me, R¹ = Ph, E = H, 80%

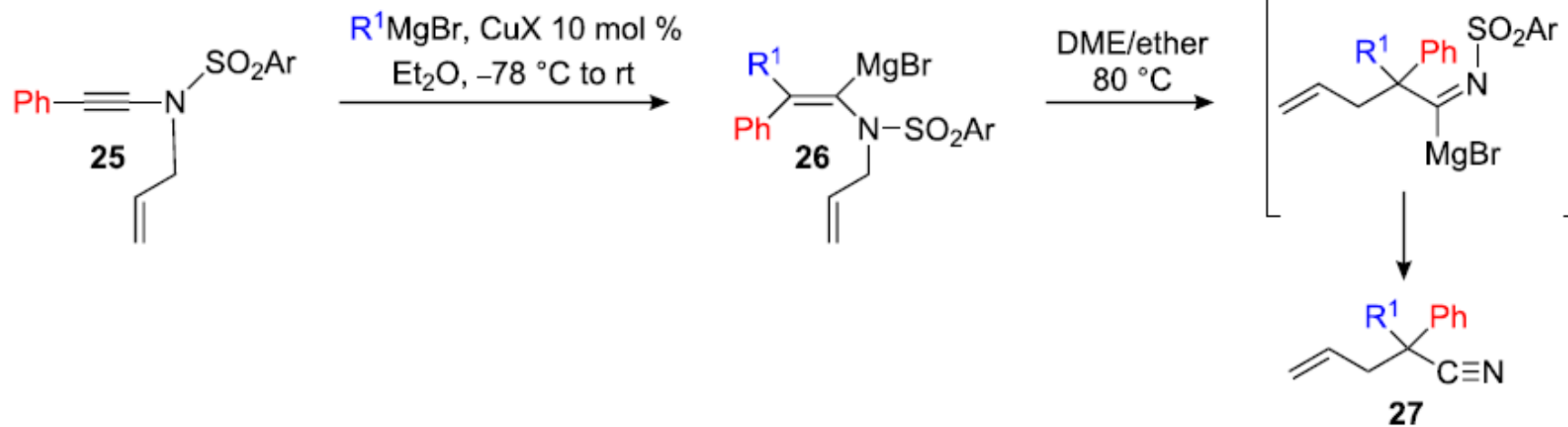
N-substituted alkynes



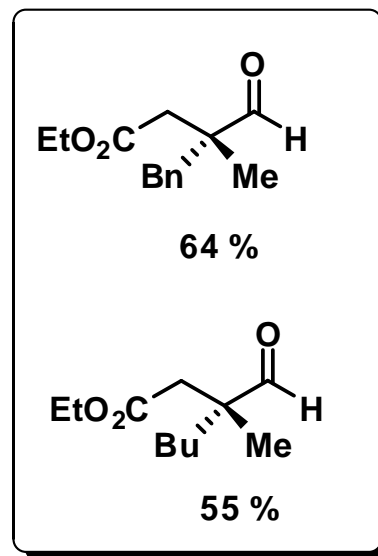
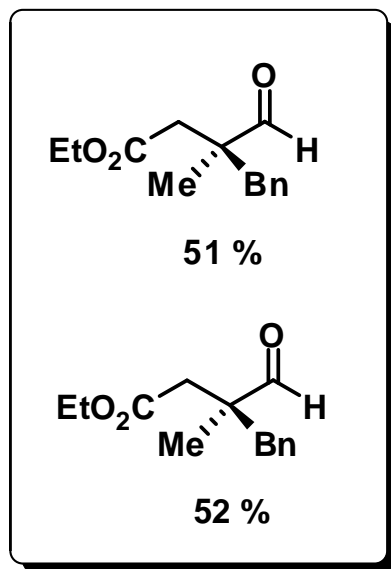
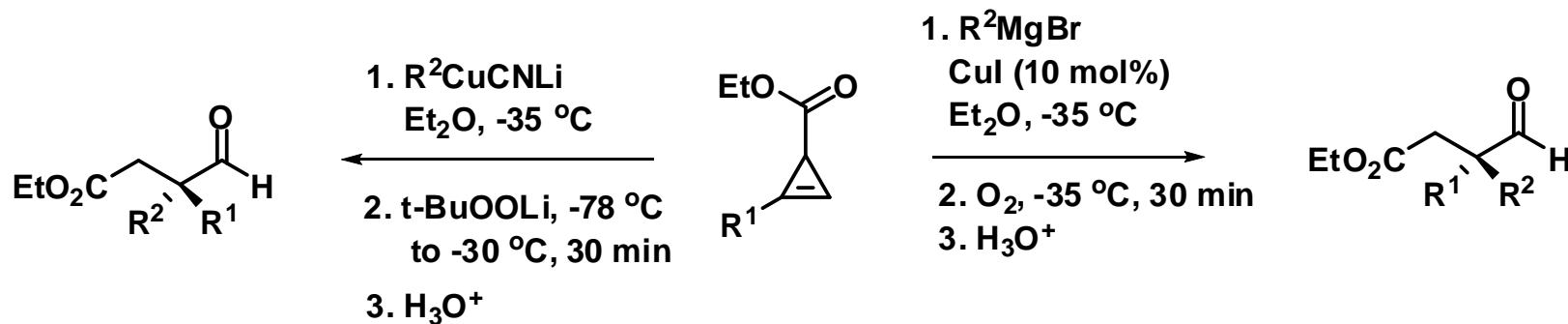
- R = H, R¹ = Et, E = H, 80%
- R = Me, R¹ = Et, E = H, 92%
- R = Me, R¹ = Bu, E = H, 54%
- R = Me, R¹ = Et, E = CO₂, 72%

15 is more stable than corresponding β -metalated enol ether

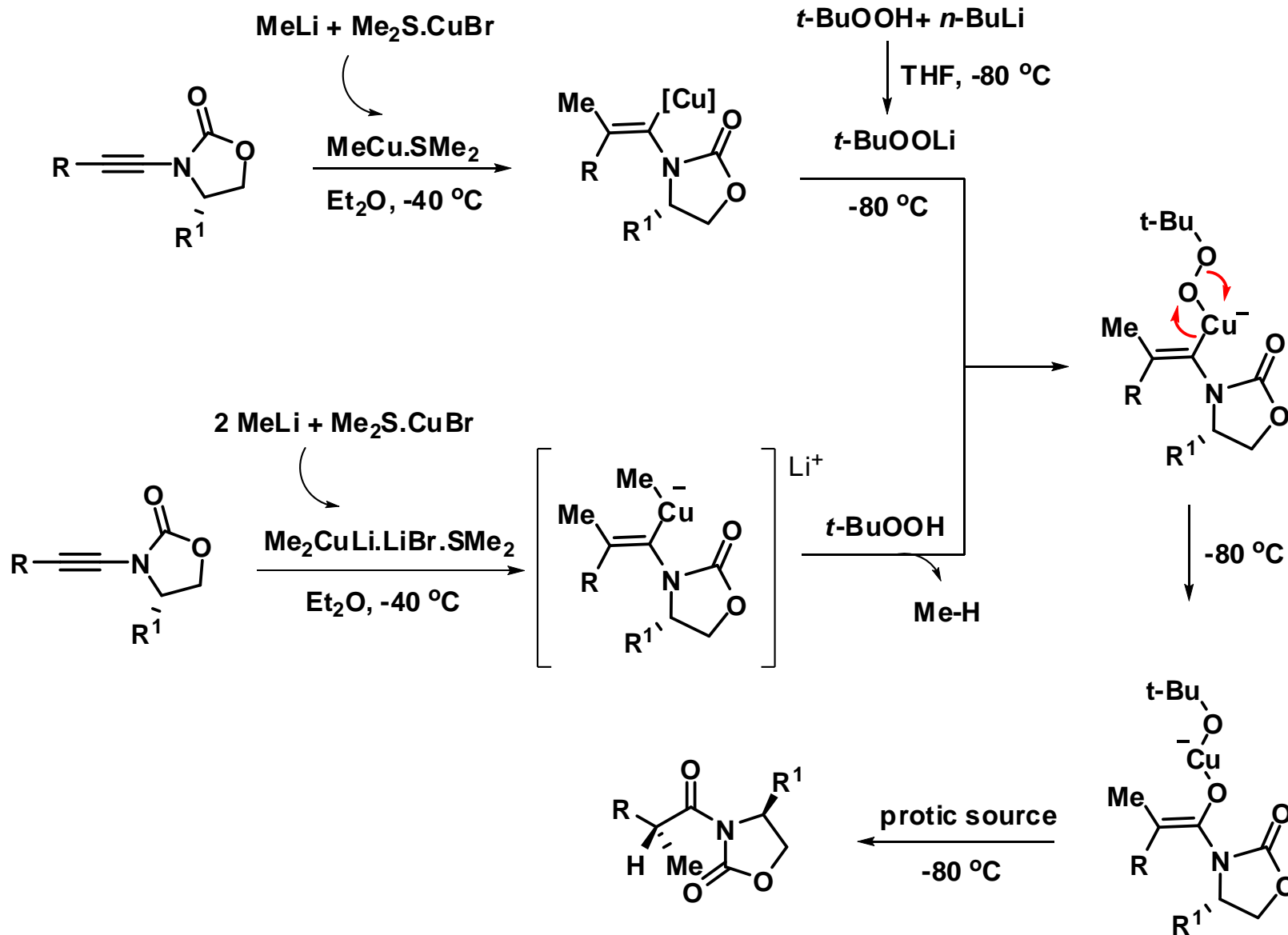
Tandem carbocupration sigmatropic rearrangement



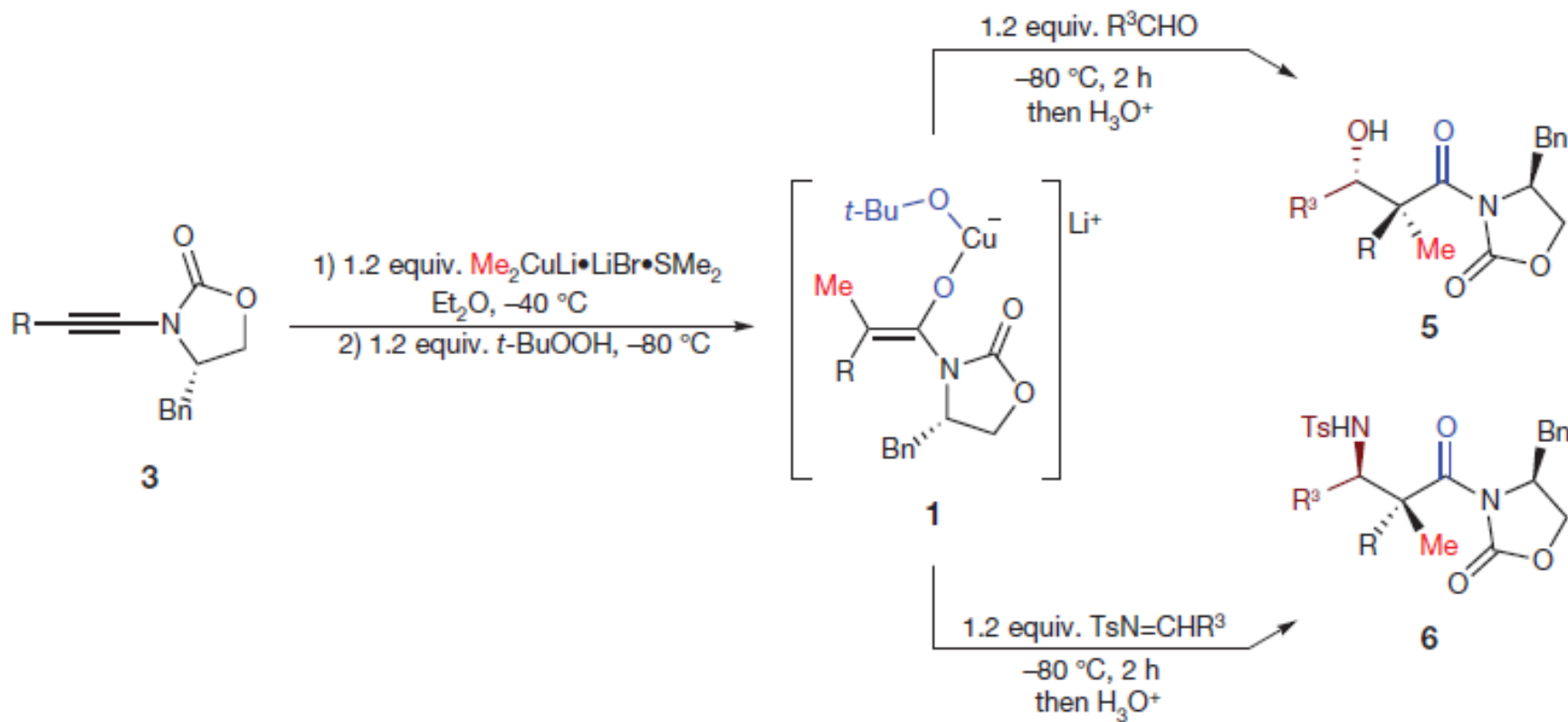
Carbometallation-Oxidation-Ring opening: formation of quaternary centers



Carbocupration-Oxidation

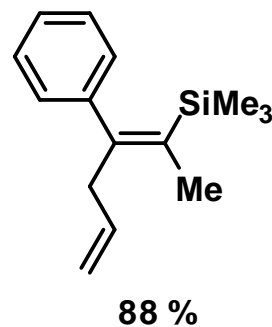
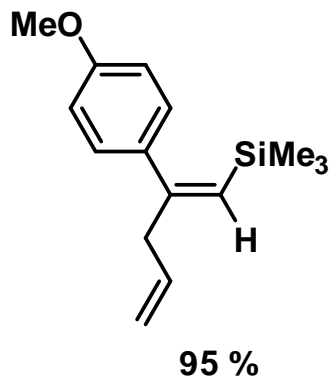
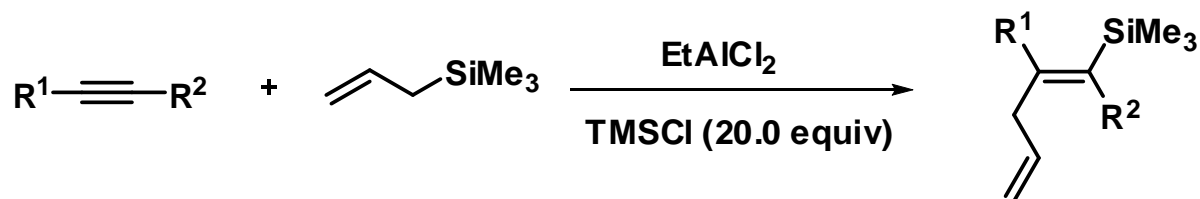


Application to the aldol and Mannich reactions

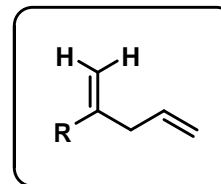


Carbosilylation reactions

Lewis acid-catalyzed *trans*- carbosilylation of simple alkynes

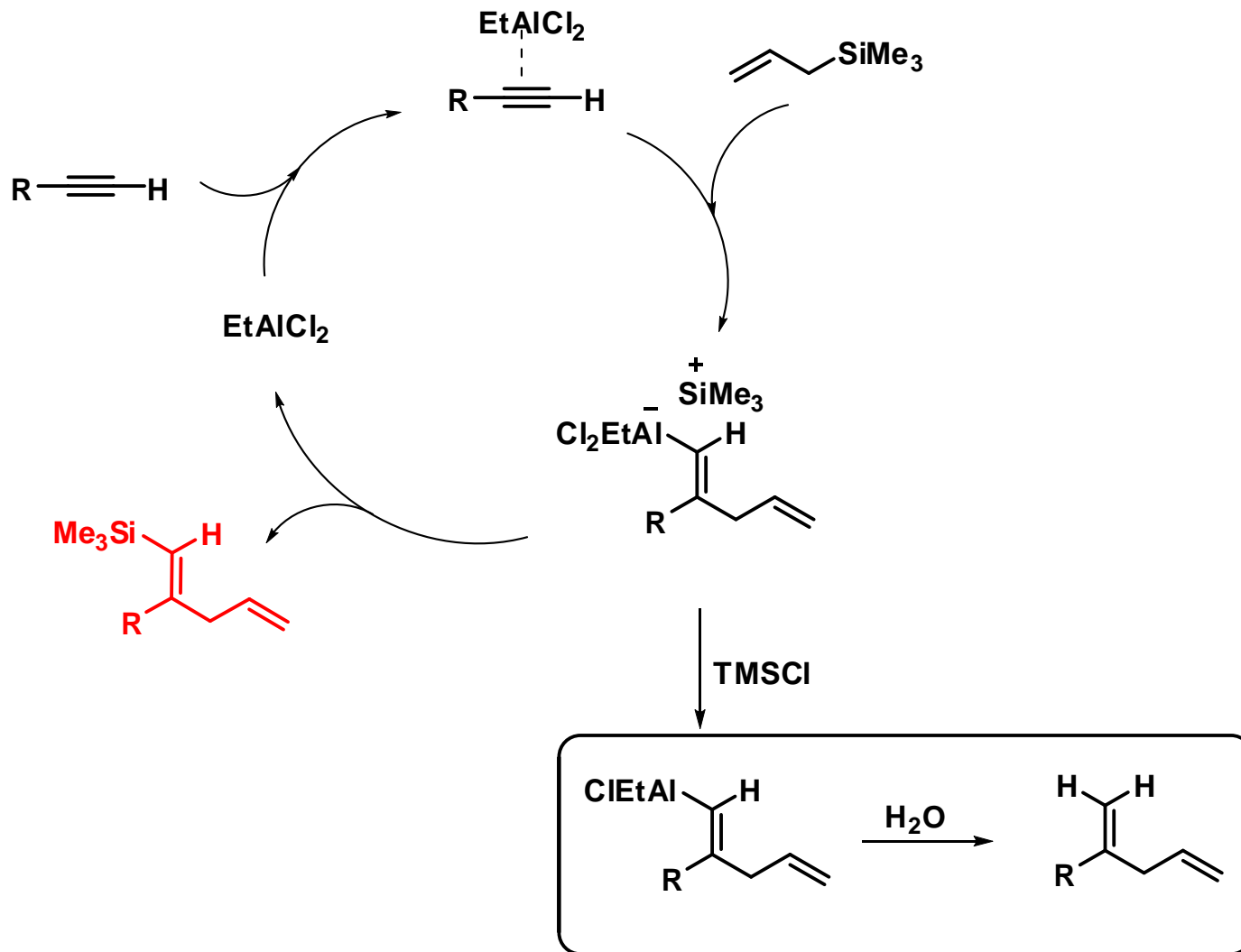


Bi product in this reaction although, traces

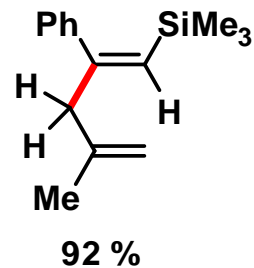
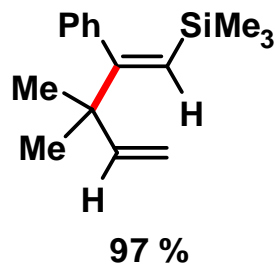
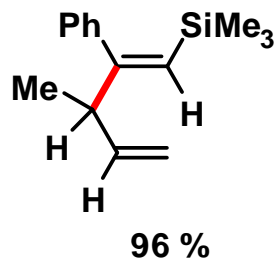
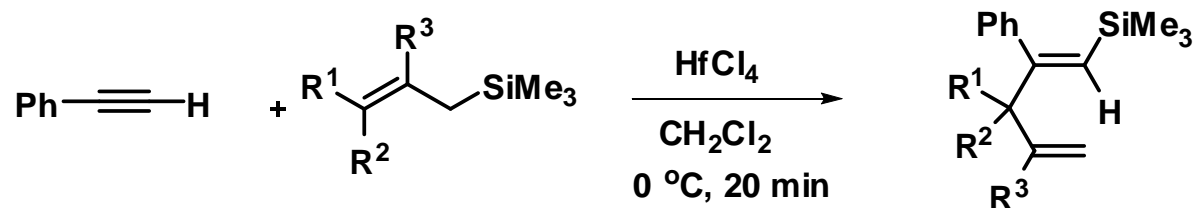


Yamamoto *et al.*, *J. Org. Chem.* **1996**, *61*, 4874

Mechanism carbosilylation of simple alkynes

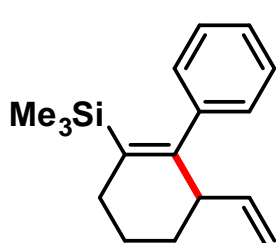
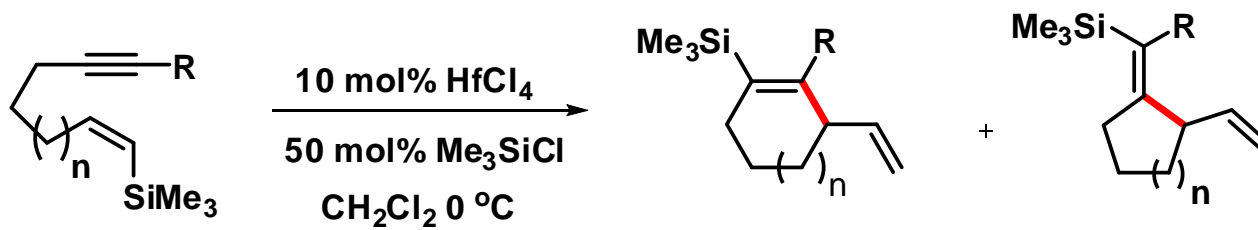


HfCl₄ -catalyzed carbosilylation reaction

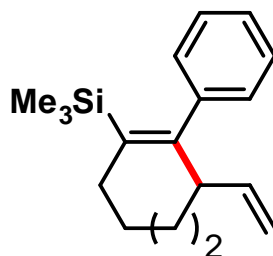


Yamamoto *et al.*, *J. Am. Chem. Soc.* **1997**, *119*, 6781.

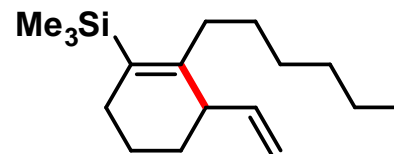
HfCl₄ –catalyzed intramolecular carbosilylation reaction



61 %



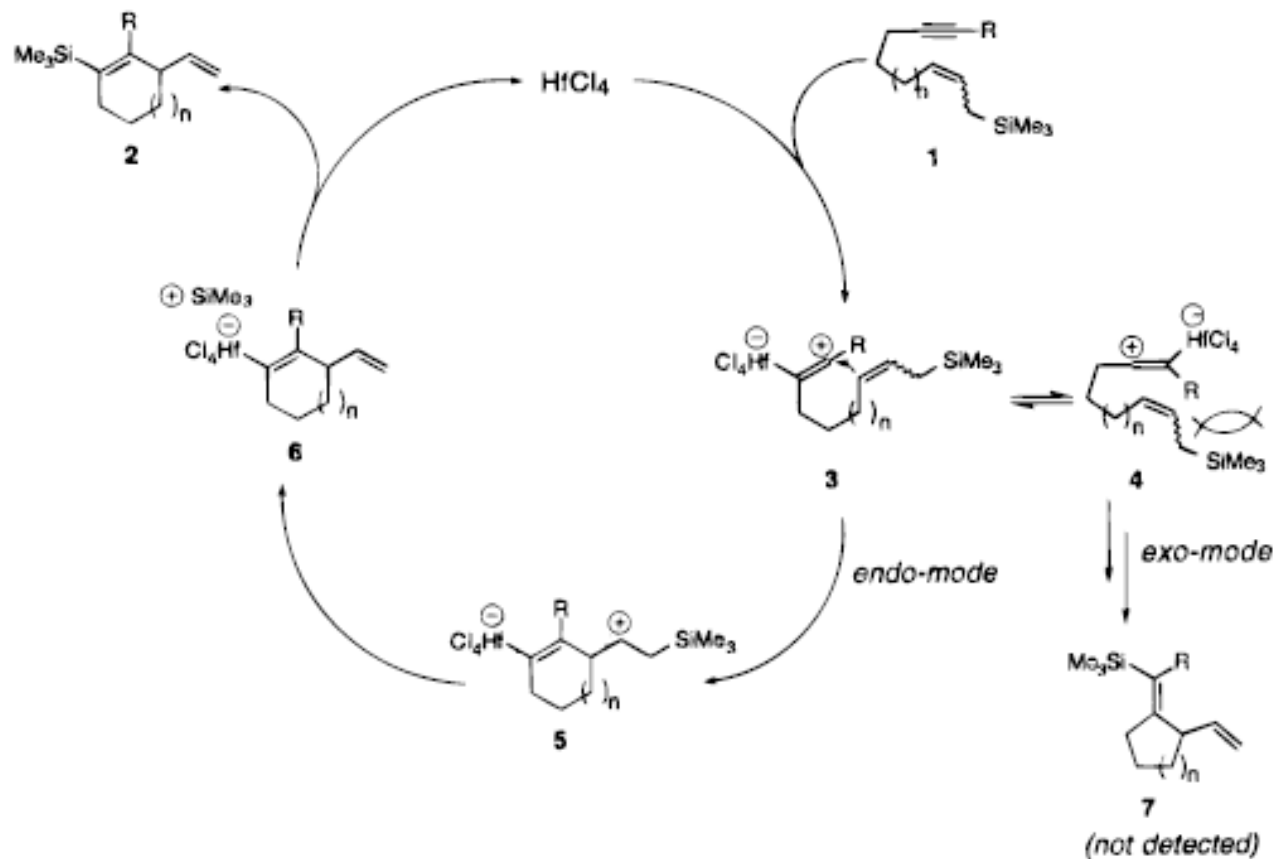
76 %



99 %

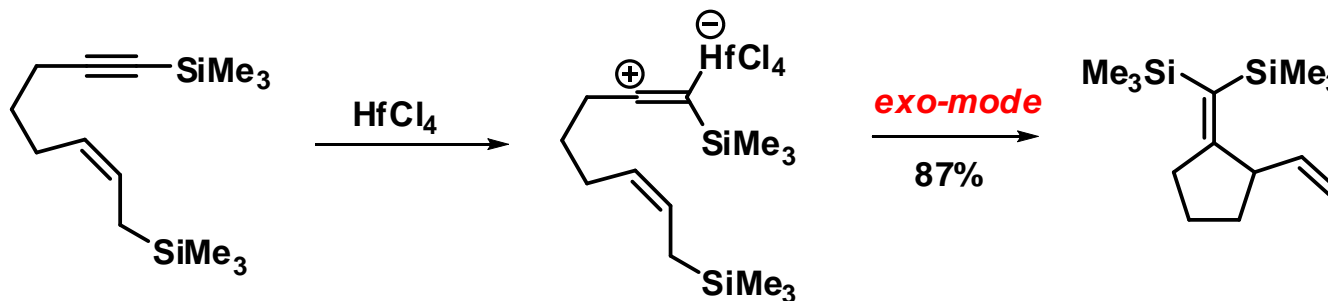
Yamamoto *et al.*, *J. Am. Chem. Soc.* **1998**, *120*, 5339.

Mechanism for the exclusive *endo-dig* carbosilylation reaction

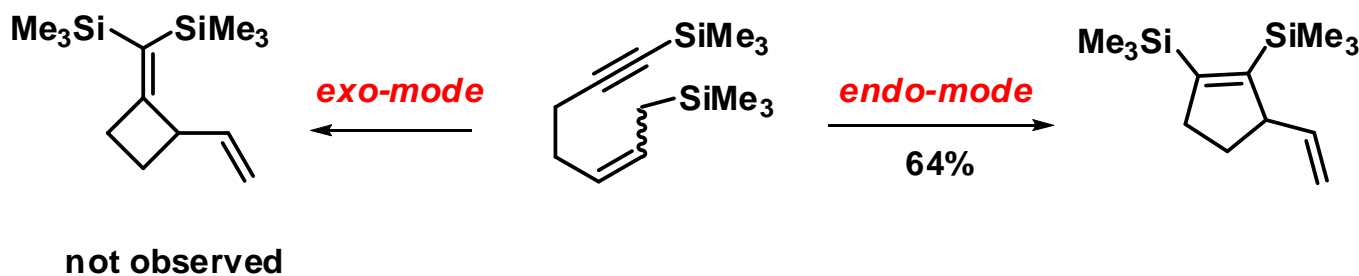


Yamamoto *et al.*, *J. Am. Chem. Soc.* **1998**, *120*, 5339.

Mechanistic insights

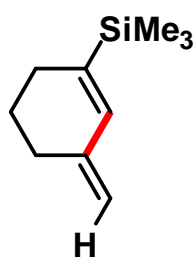
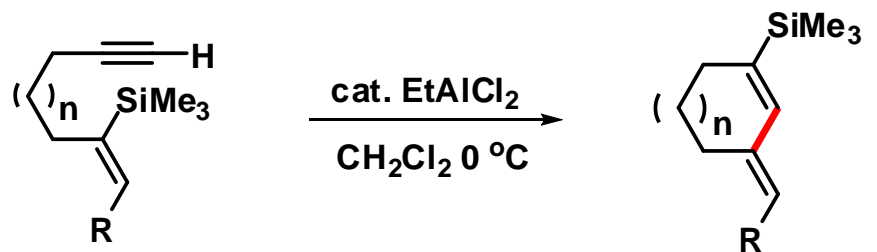


- *exo-mode* is favorable because of β -silicon effect

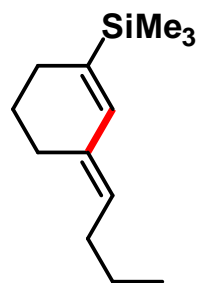


- Controversial result
- Electronic factor is not dictating the reaction
- Computational studies showed that the endo product is favored by 18.3 kcal/mol

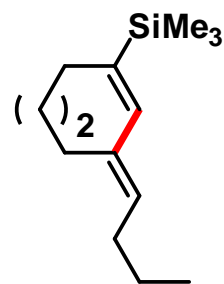
Lewis acid-catalyzed intramolecular vinylsilylation reaction



0 %

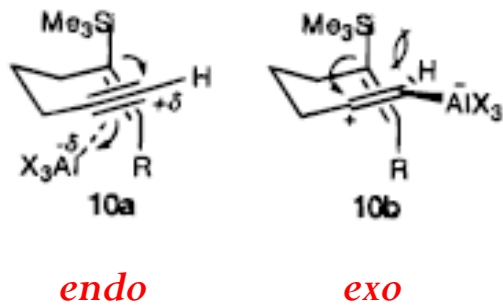
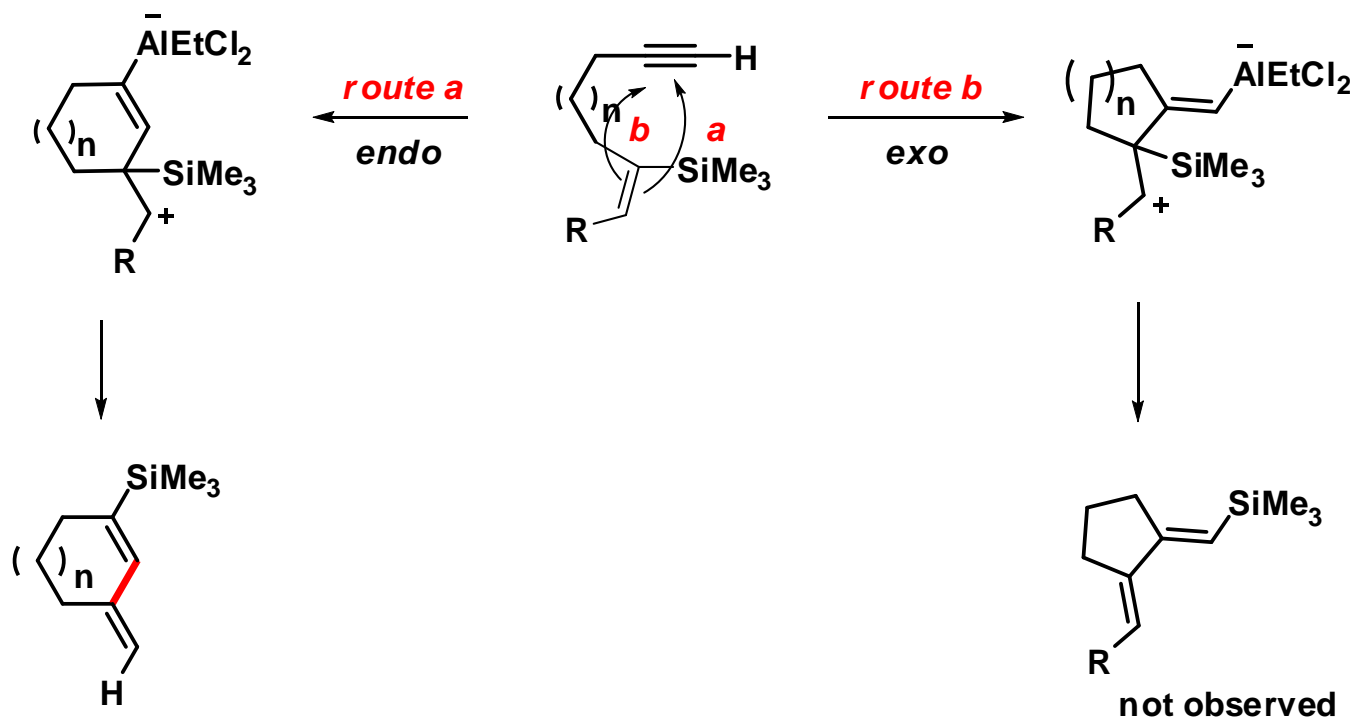


90 %



35 %

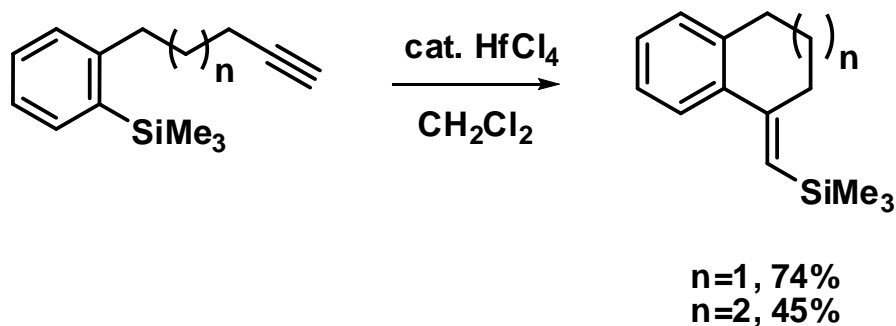
Yamamoto *et al.*, *J. Am. Chem. Soc.* **1999**, *121*, 3797.



Yamamoto *et al.*, *J. Am. Chem. Soc.* **1999**, *121*, 3797.

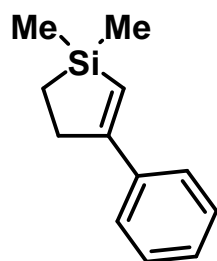
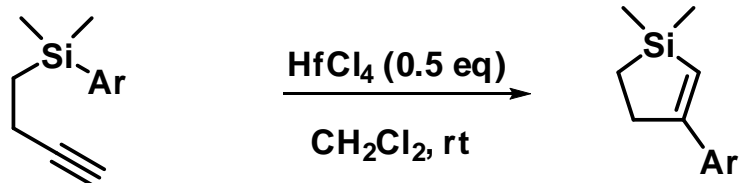
Lewis acid-catalyzed intramolecular *trans* vinylsilylation and arylsilylation of alkynes

Arylsilylation of alkynes

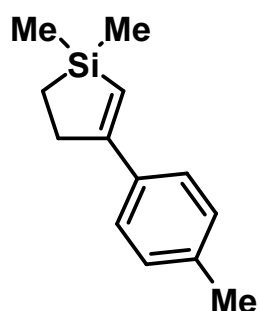


Yamamoto *et al.*, *J. Am. Chem. Soc.* **2001**, *121*, 3797.

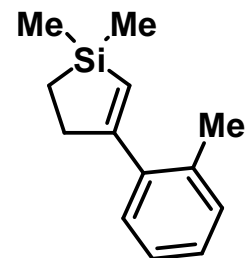
Arylsilylation of alkynes



71%



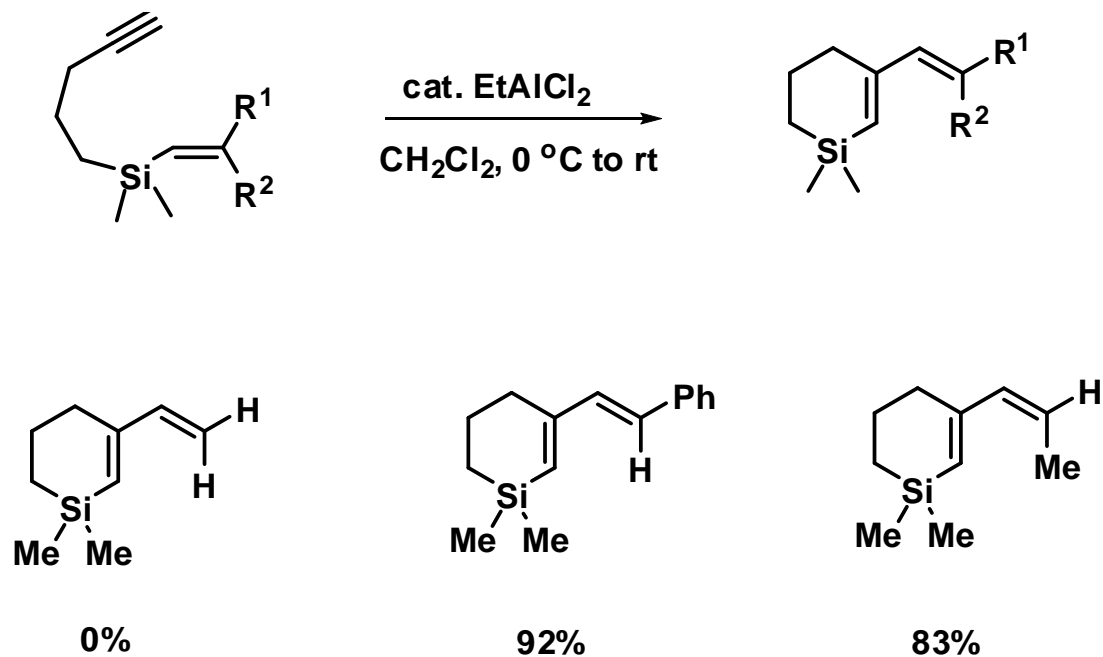
57%



20%

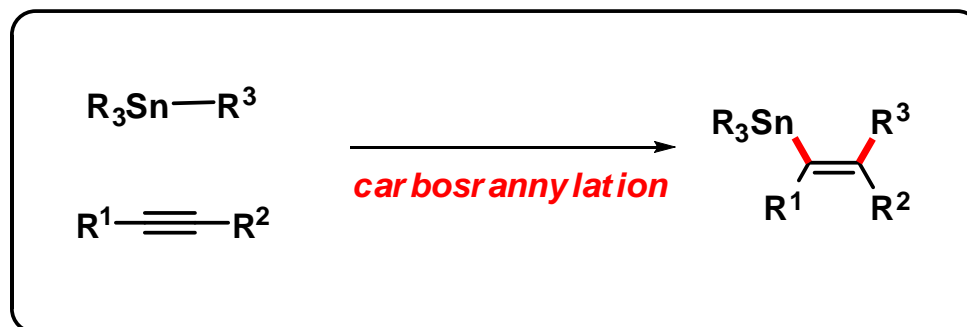
Yamamoto *et al.*, *J. Am. Chem. Soc.* **2001**, *121*, 3797.

Vinylsilylation of alkynes

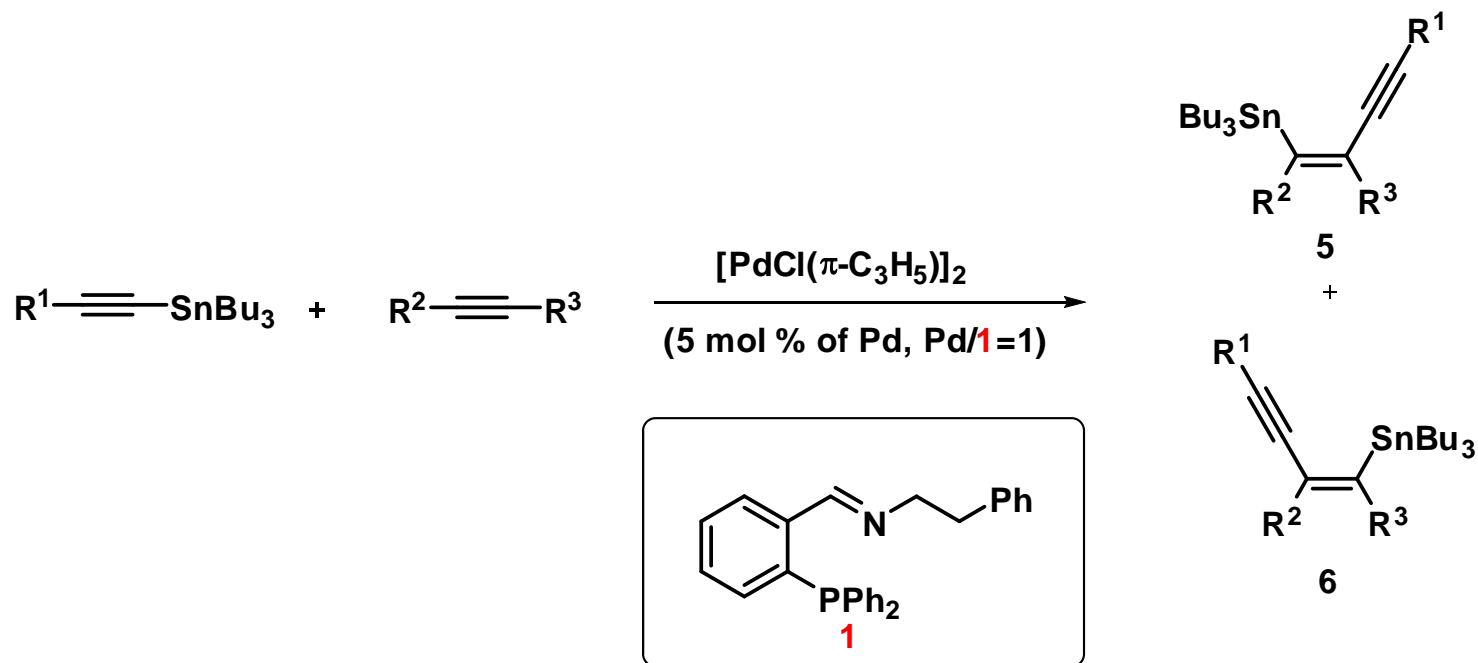


Yamamoto *et al.*, *J. Am. Chem. Soc.* **2001**, *121*, 3797.

Corrostannylation reactions

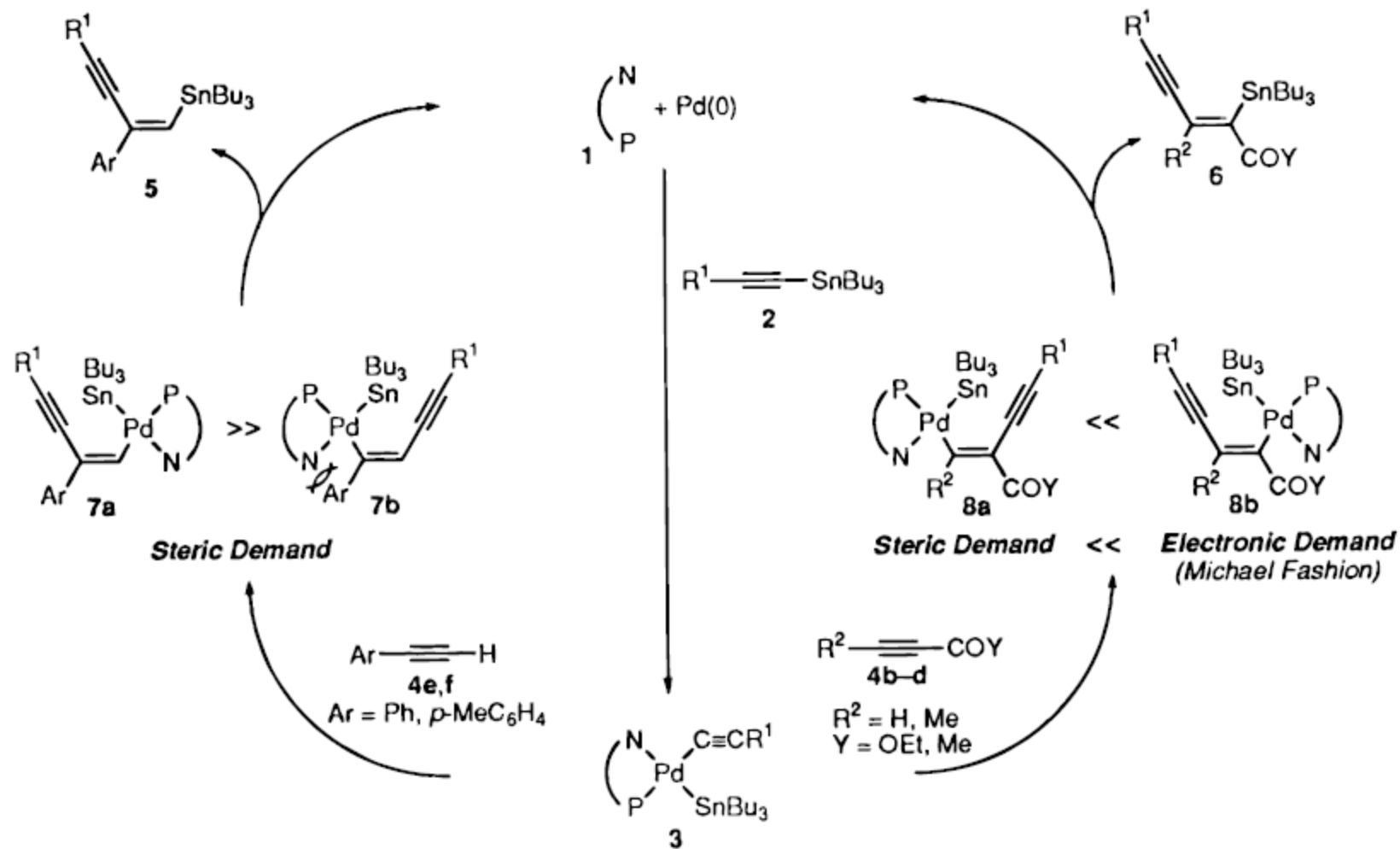


Carbostannylation of alkynes catalyzed by an iminophosphine-palladium complex



- Regioselectivity of the products depend on sterics and electronics of substituents

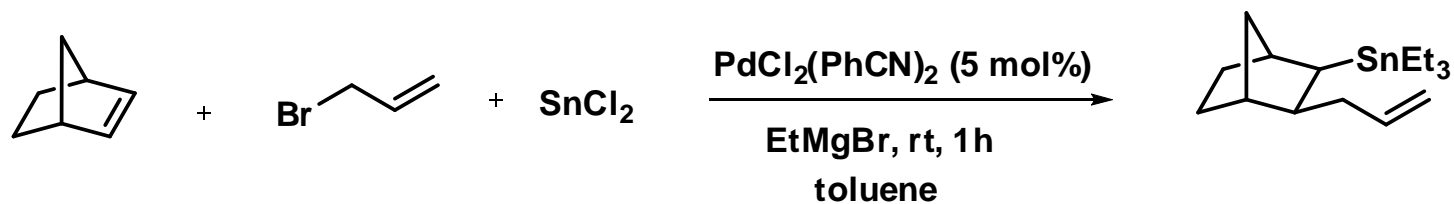
E. Shirakawa *et al.*, *J. Am. Chem. Soc.* **1998**, *120*, 2975.



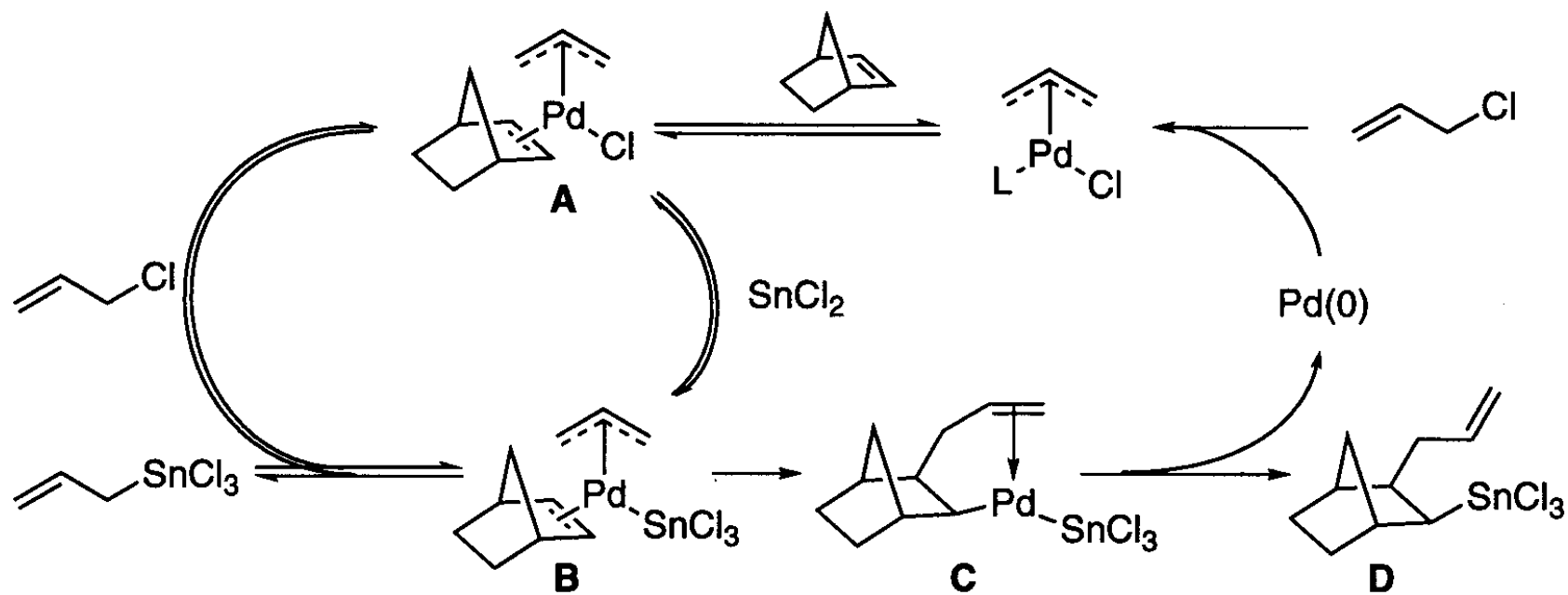
E. Shirakawa *et al.*, *J. Am. Chem. Soc.* **1998**, *120*, 2975.

Pd-catalyzed allyl and arylstannylation of norbornenes

- Allylstannylation

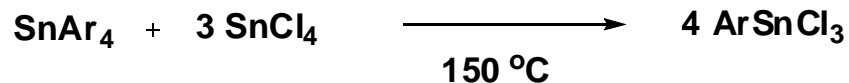


- Mechanism

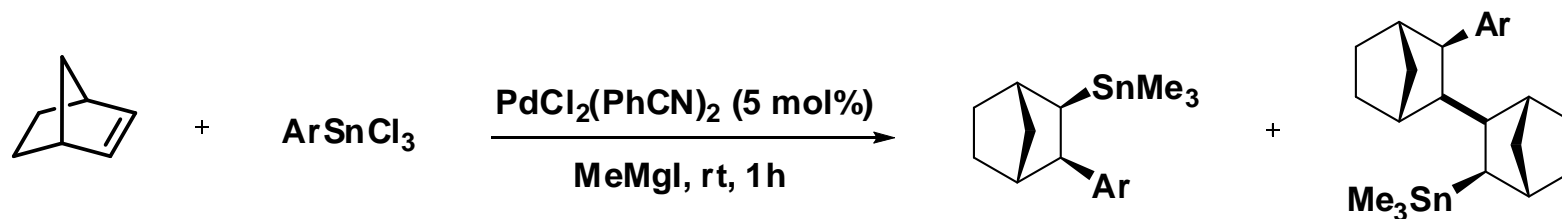


Pd-catalyzed ally and arylstannylation of norbornenes

- Preparation of aryltintrichloride

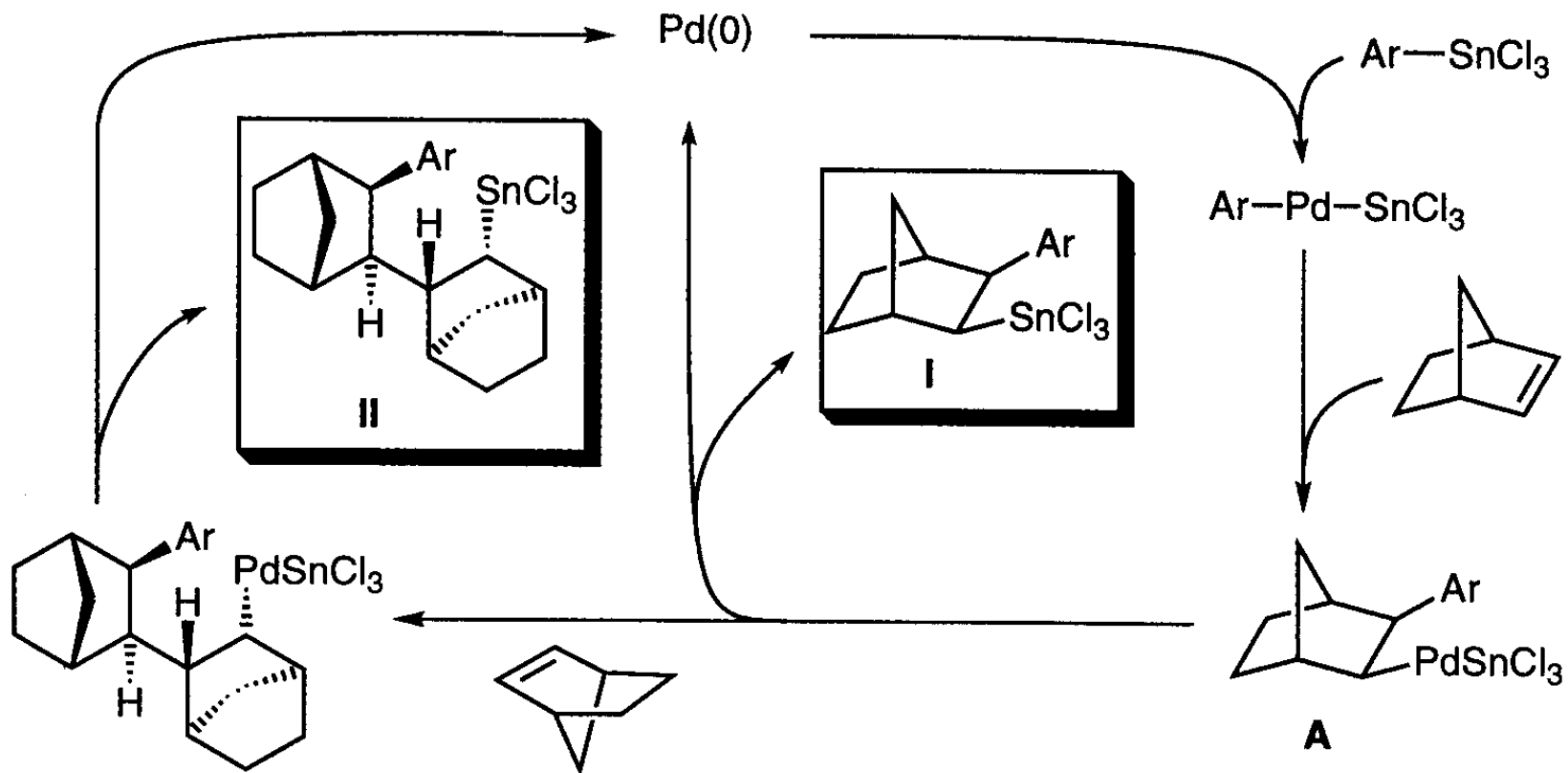


- Arylstannylation

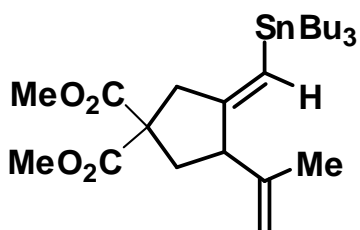
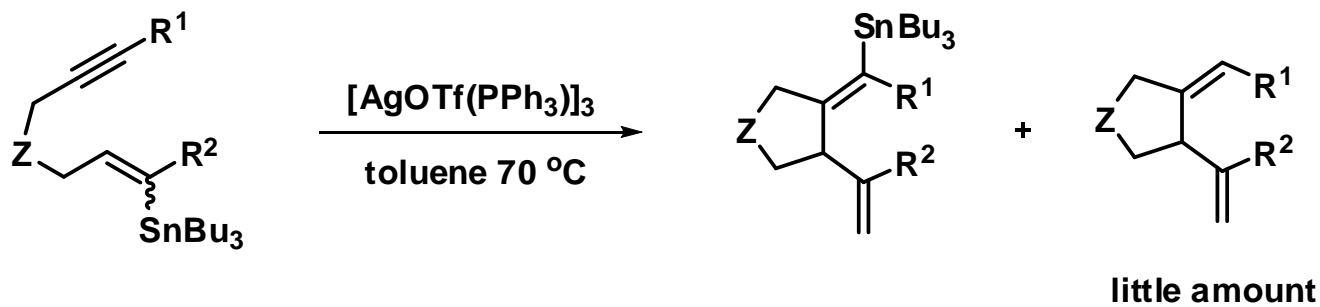


- This reaction does not proceed with tributyltin chloride reagent
- Question why???

• Mechanism

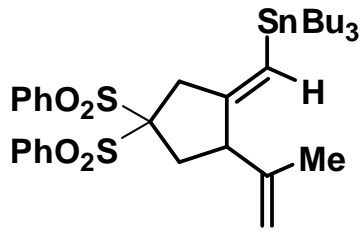


Ag-catalyzed intramolecular carbostannylation



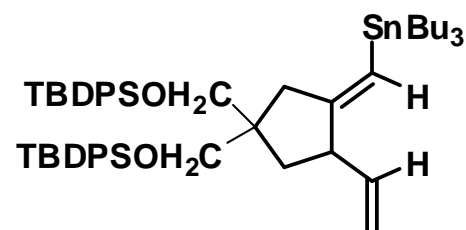
87 %

dsp: 3 %



91 %

dsp: 0 %

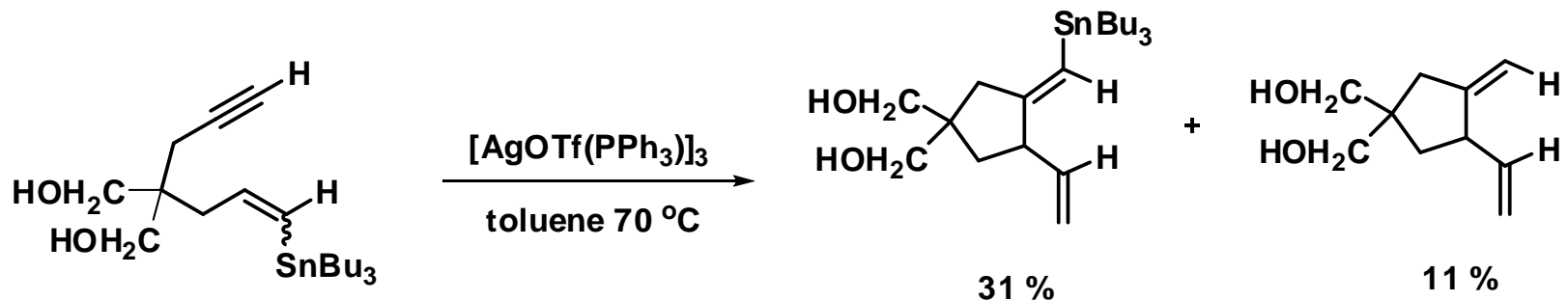


93 %

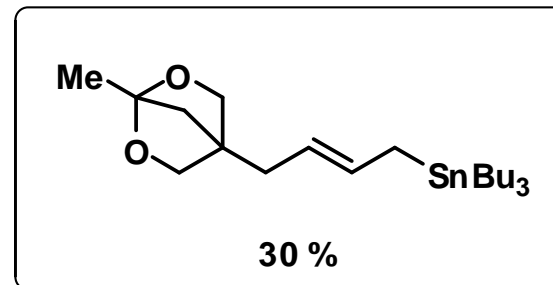
dsp: 0 %

dsp: destannylated product*

Ag-catalyzed intramolecular carbostannylation



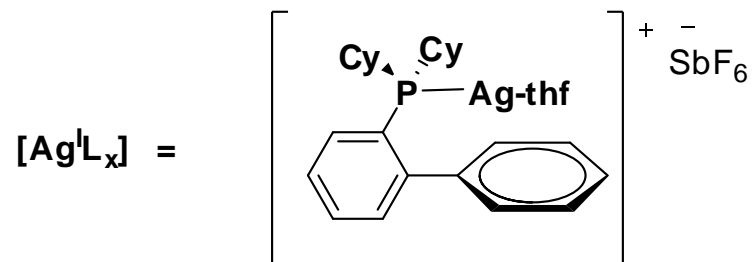
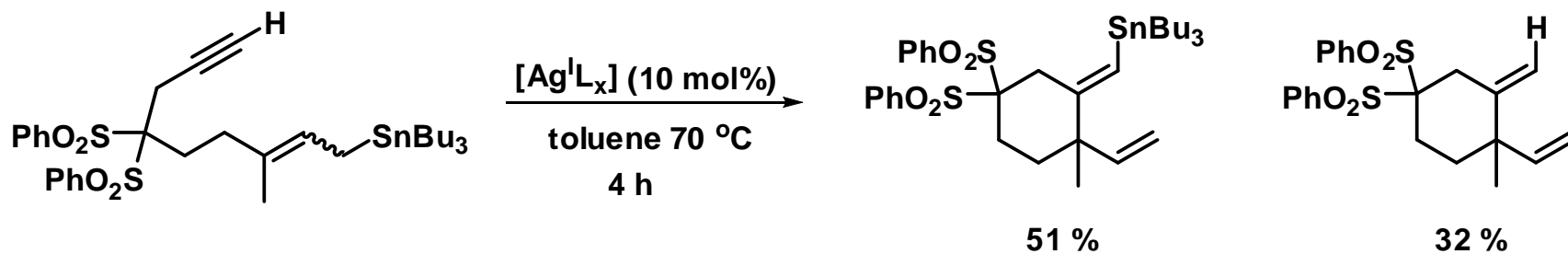
- The major byproduct in this reaction is bicyclic acetal



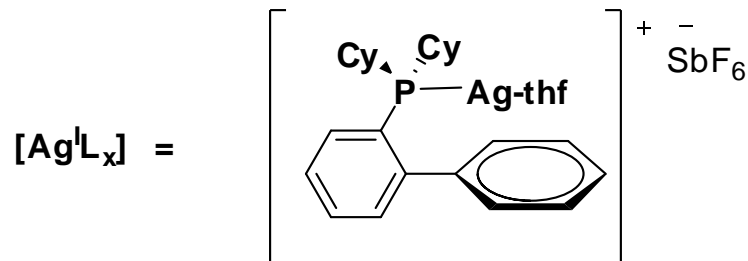
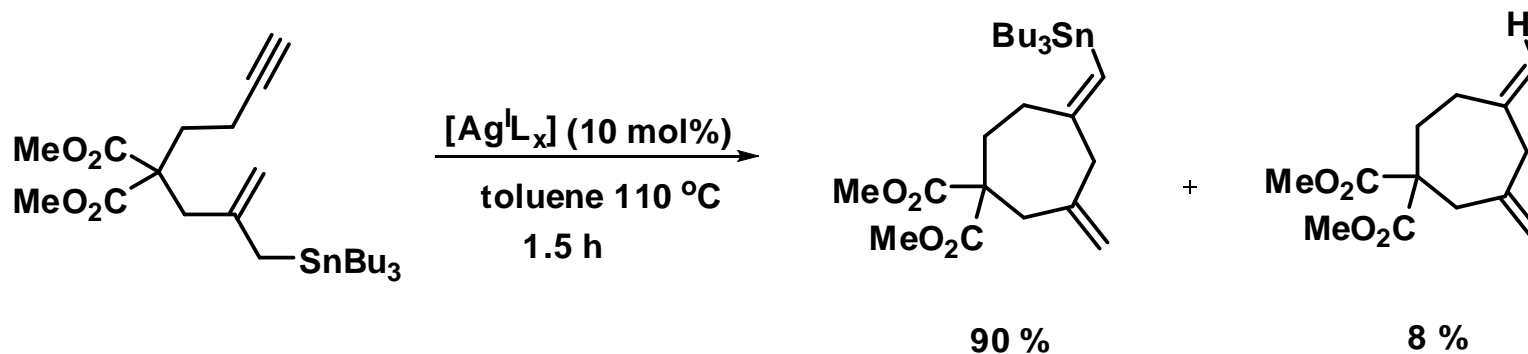
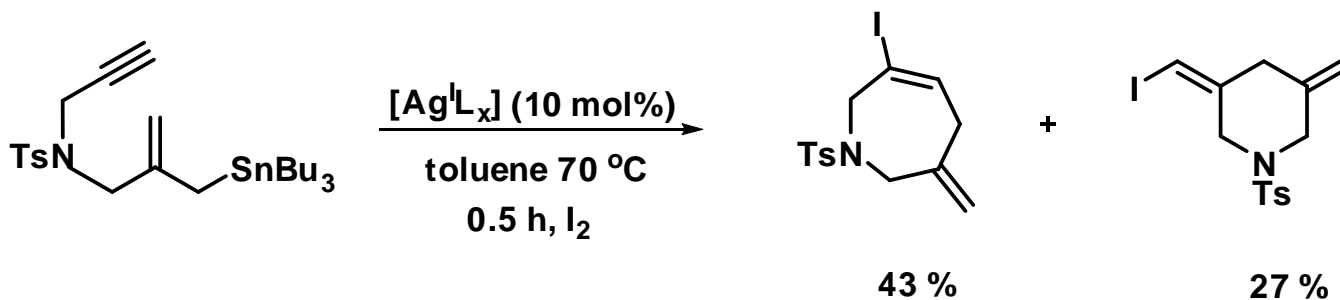
A, M. Echavarren et al., *Angew. Chem.* 2007, 119, 2726.

Ag-catalyzed intramolecular carbostannylation

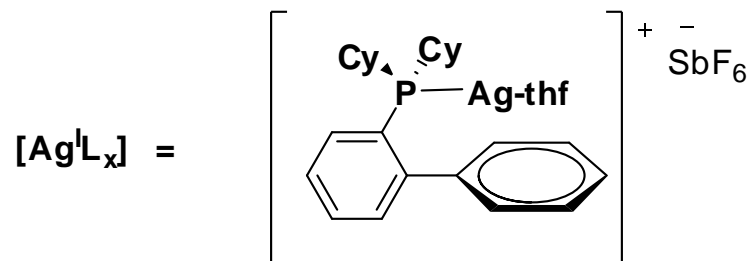
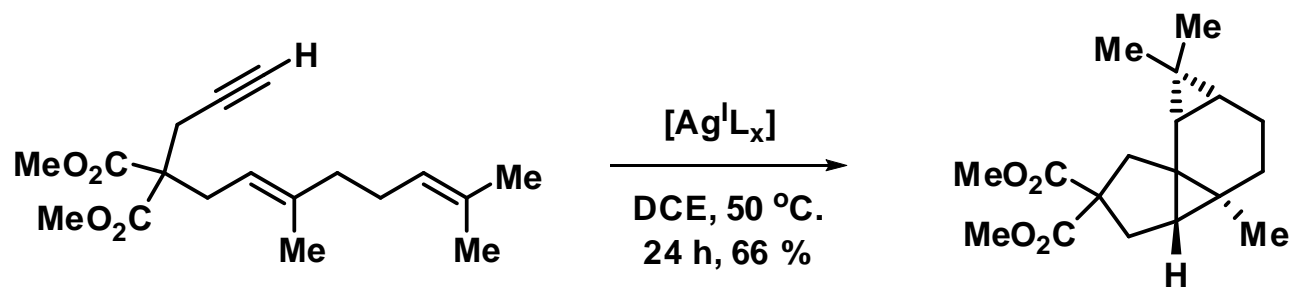
- Small application in six- and seven- membered-ring systems



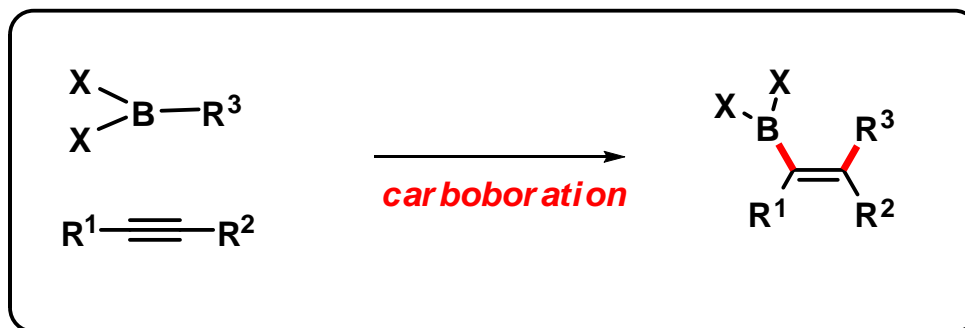
Small application in six- and seven-membered-ring systems



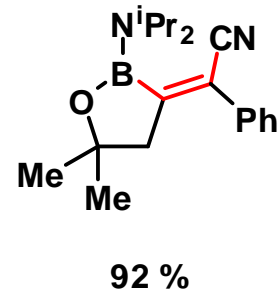
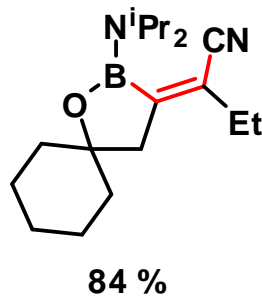
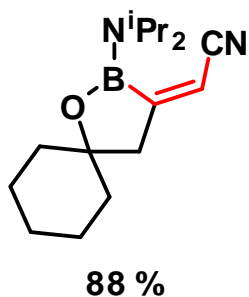
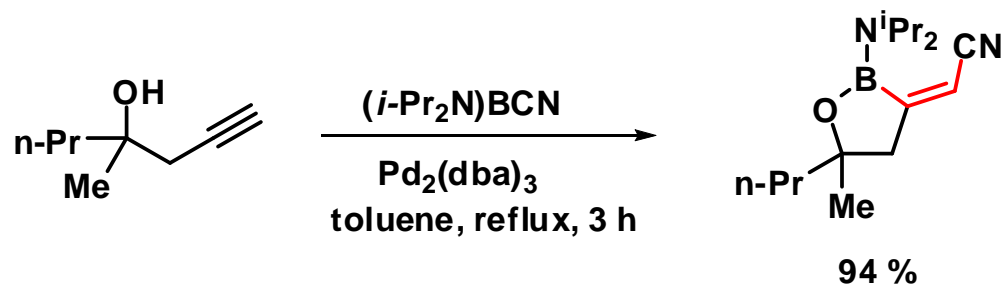
Cyclopropanation reaction



Carboration reactions

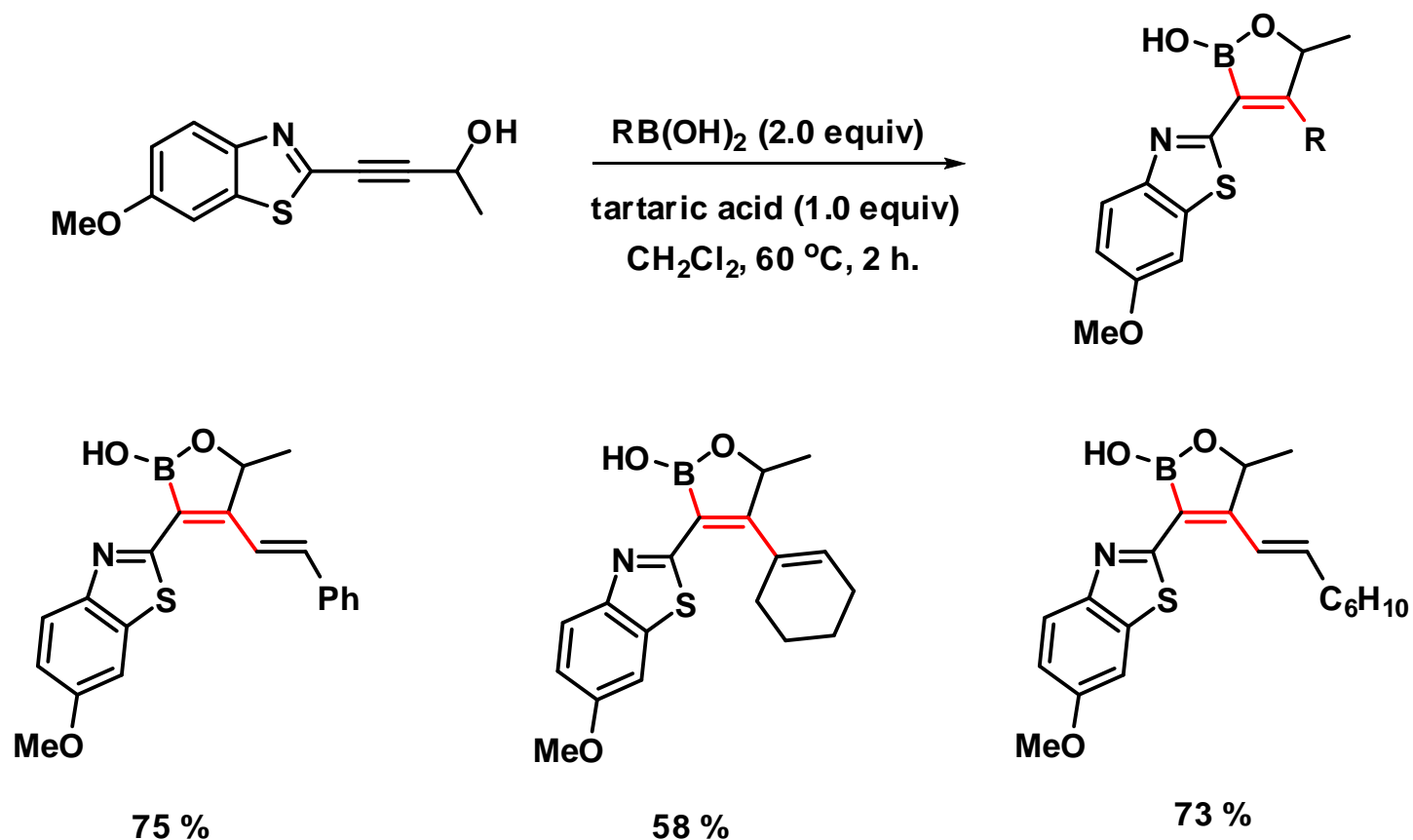


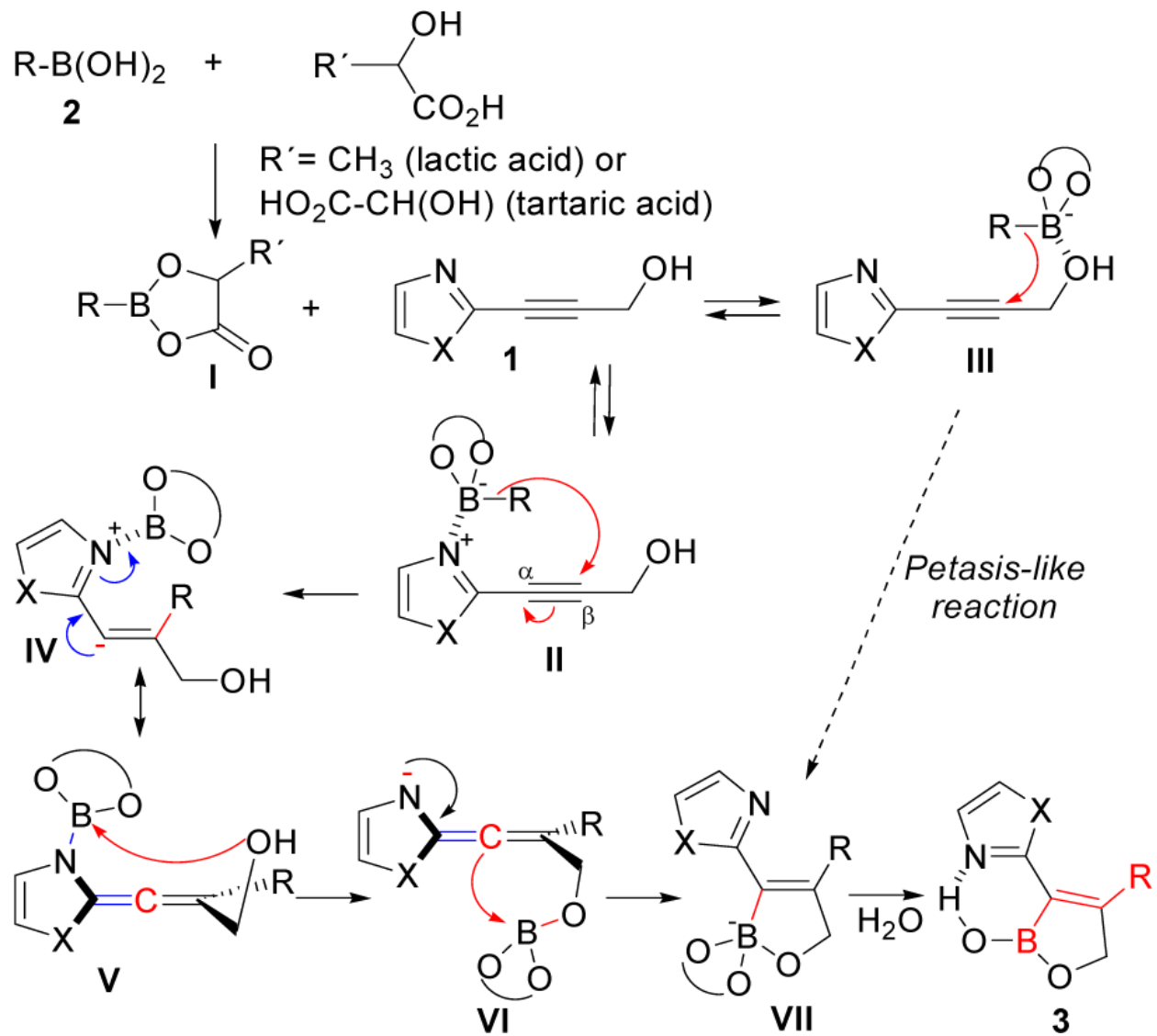
Palladium- and Nickel-Catalyzed Intramolecular Cyanoboration of Alkynes



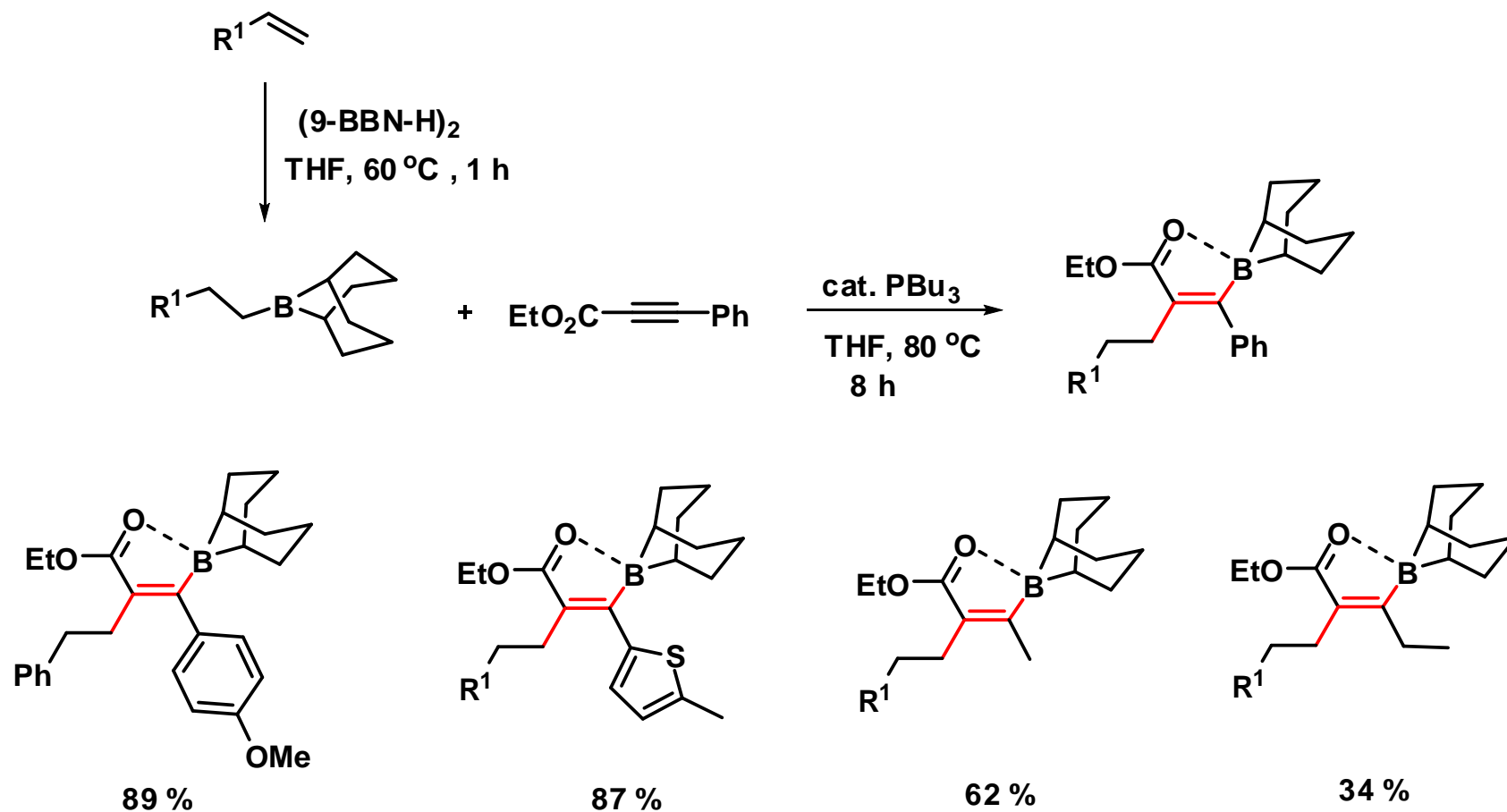
$\text{Ni}(\text{COD})_2$ also works as efficiently as Pd catalyst

Transition-Metal-Free Direct *anti*- Carboboration of Alkynes with Boronic Acids

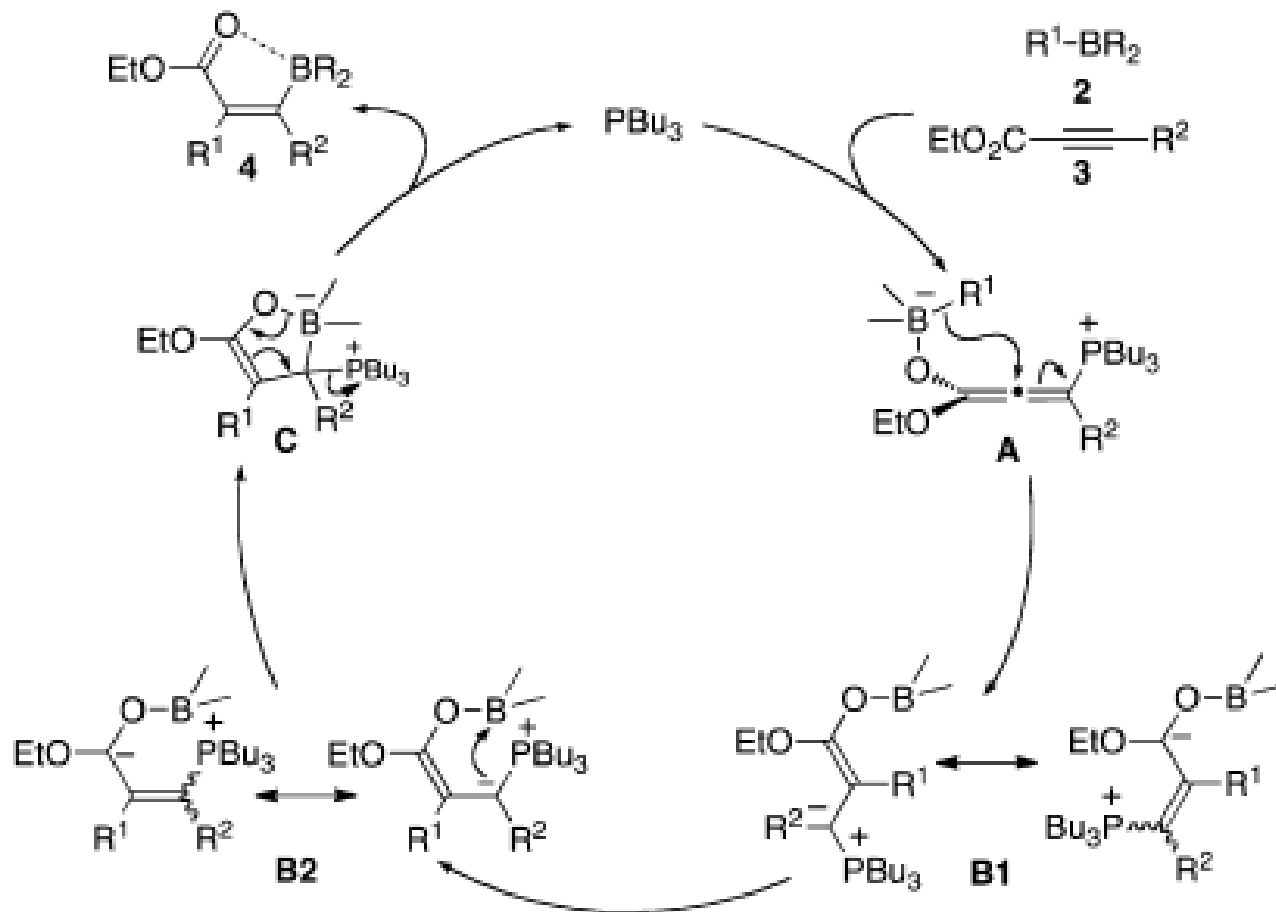




Phosphine-Catalyzed Anti-Carboboration of Alkynoates

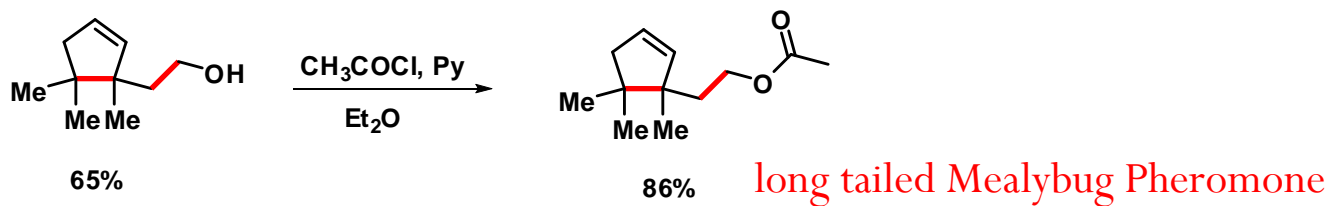
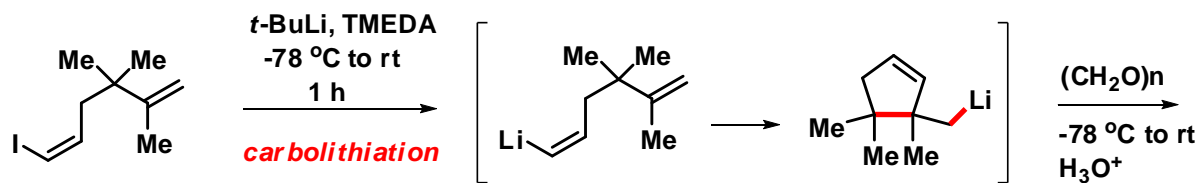


Mechanism

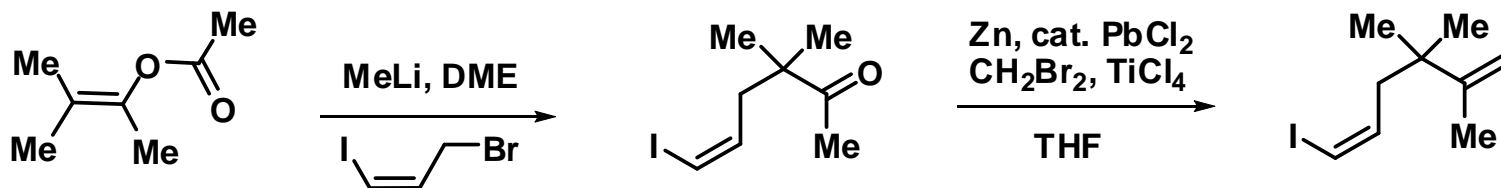


Corrolithiation reactions

Carbolithiation reaction



Starting material synthesis



Still, Many More Reactions.....

Thanks for your attention