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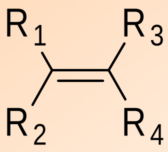
Stereocontrolled Synthesis of Tetrasubstituted Olefins

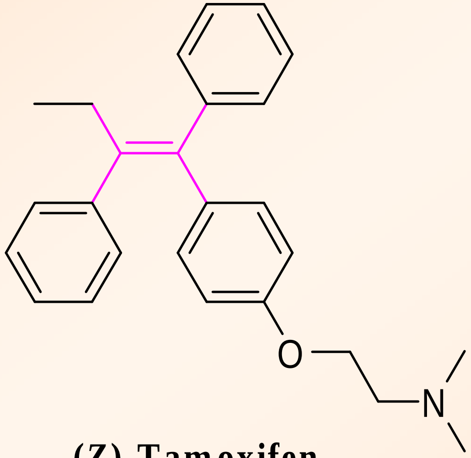
Alexandra Bartoli

StéRéO

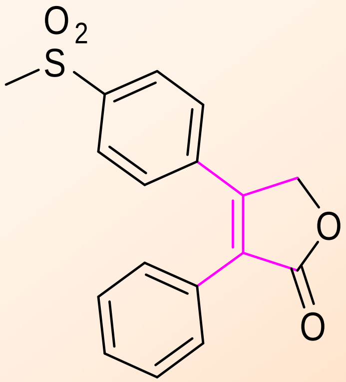
I. Introduction



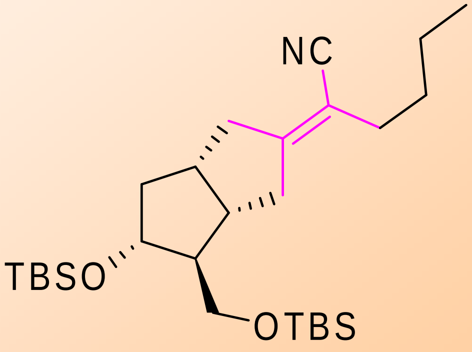
- Particular challenge in organic synthesis
- Key starting materials for various asymmetric transformations
- Presence in a lot of drugs, natural products and other biologically active substances



(*Z*)-Tamoxifen



Vioxx



Nileprost

I. Introduction

- Several processes of synthesis :

a) Carbometallation of alkynes

b) Carbonyl Olefination

c) Elimination reactions

d) Olefin metathesis

e) Ynolates

f) Cycloaddition and sigmatropic reactions

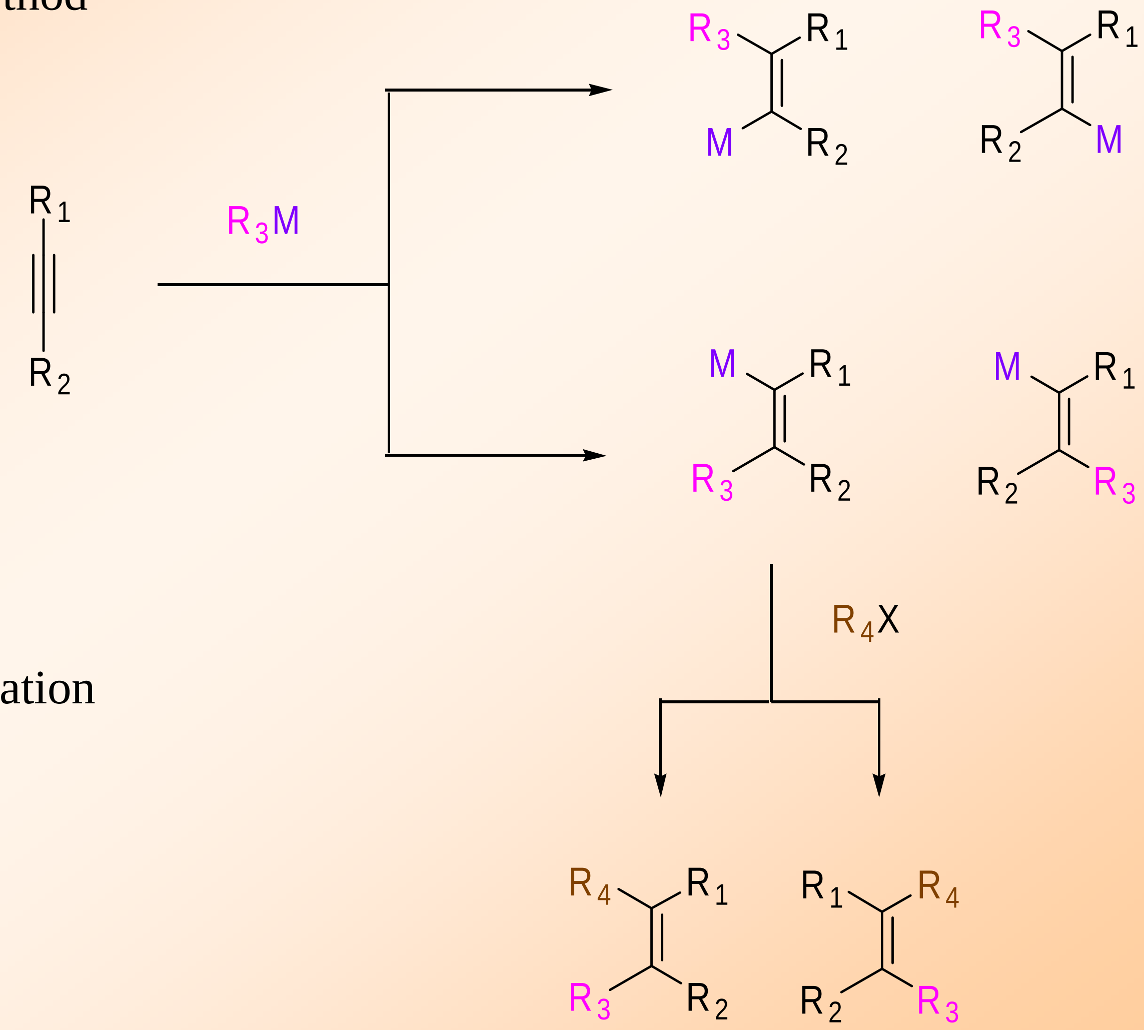
g) Radical cyclizations

h) Manipulation of existing olefins

II. Carbometallation of alkynes

1. General process :

- The most widely used method



- Significant structural variation

II. Carbometallation of alkynes

1. General process :

Problem of regioselectivity resolved by : • using directing groups

• employing symmetrical alkynes

Stereoselectivity depends on : • the metal used

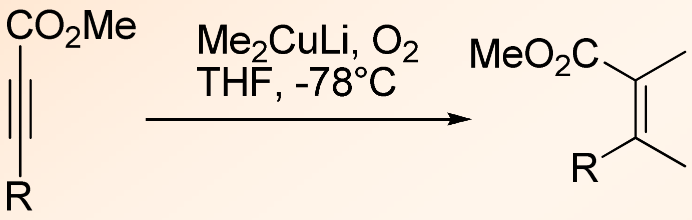
• the catalyst used

High degree of control is possible

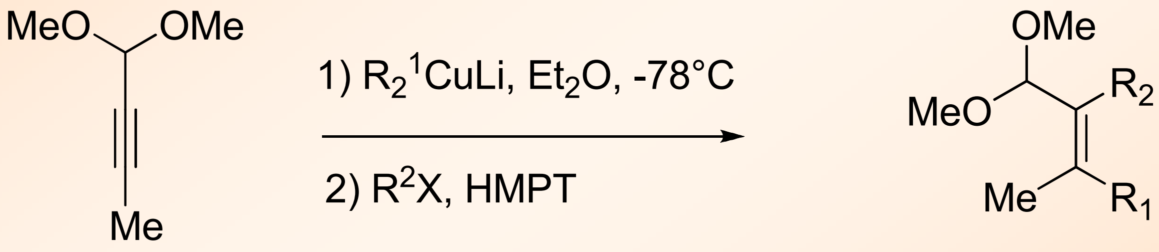
II. Carbometallation of alkynes

2. Copper :

a) Carbocupration of alkynoates



b) Carbocupration of alkynyl acetals



R_1 = *n*-Bu, R_2 = Me, 87 %

R_1 = Et, R_2 = *n*-Bu, 78%

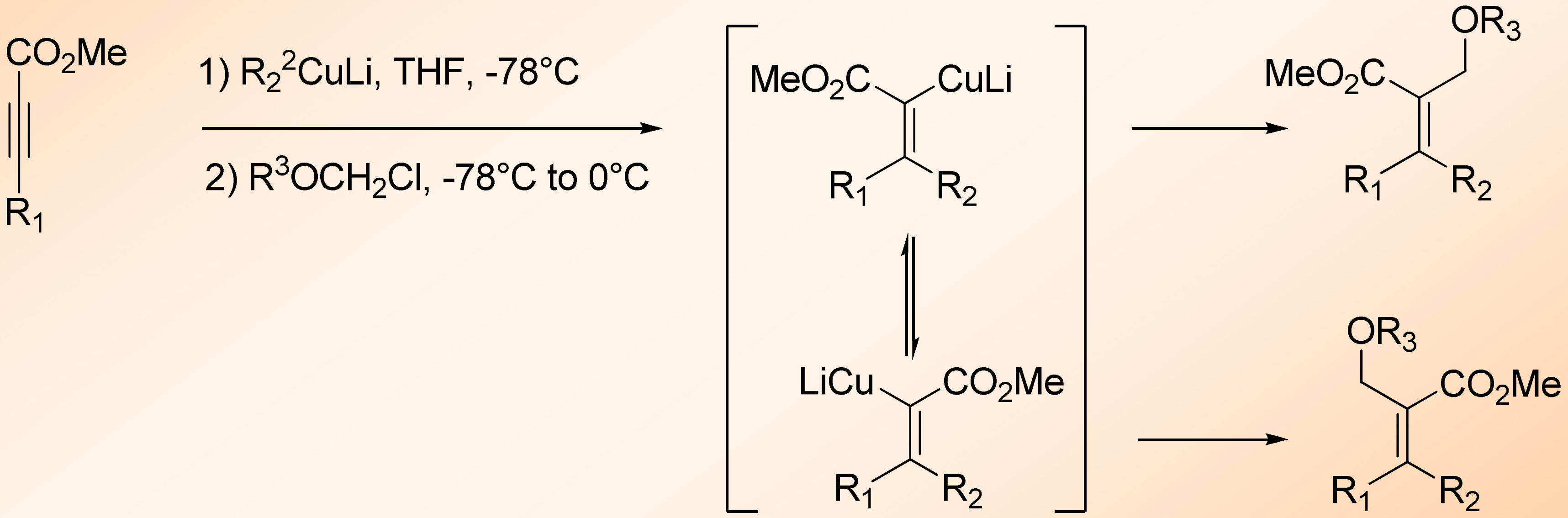
R_1 = Et, R_2 = $CH{=}CHCH_3$, 80 %

Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969,** *91,*1851.
Alexakis, A.; Commercüon, A.; Coulentianos, C.; Normant, J. F. *Tetrahedron* **1984,** *40,* 715**.**

II. Carbometallation of alkynes

2. Copper :

c) Addition of organocuprates and α-halo ethers to acetylenic esters



Hall, D. G.; Chapdelaine, D.; Preville, P.; Deslongchamps, P. *Synlett* **1994,** *660*.

II. Carbometallation of alkynes

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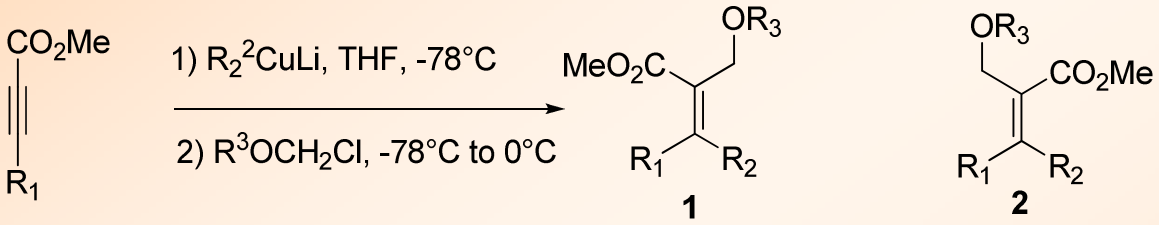
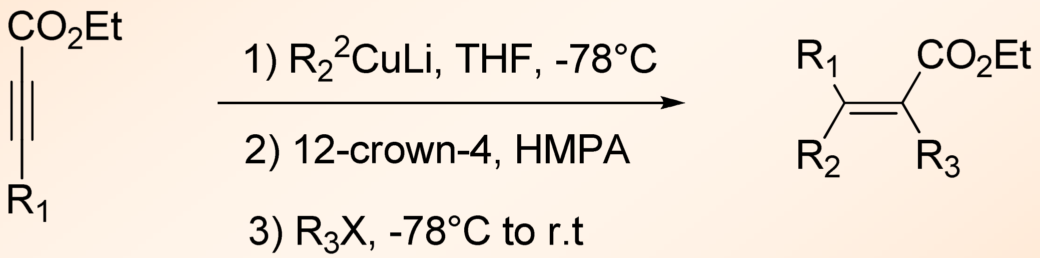


R1	R2	R3	yield (%) (1 : 2)
TBDPSO$(CH_2)_2$	Me	$BnOCH_2$	59 (24 : 1)
TBDPSO$(CH_2)_2$	Me	4-$MeOC_6H_4OCH_2$	66 (6 :1)
TBDPSO$(CH_2)_2$	Me	$Me_3Si(CH_2)_2OCH_2$	68 (>25 : 1)
TBDPSO$(CH_2)_2$	Me	$MeOCH_2$	87 (25 : 1)
TBDPSO$(CH_2)_2$	Bu	$Me_3Si(CH_2)_2OCH_2$	61 (4.5 : 1)
TBDPSO$(CH_2)_3$	Me	4-$MeOC_6H_4OCH_2$	72 (6 : 1)
Et	Me	$BnOCH_2$	70 (10 : 1)

II. Carbometallation of alkynes

2. Copper :

d) Addition of organocuprates and halo alkyls to acetylenic esters



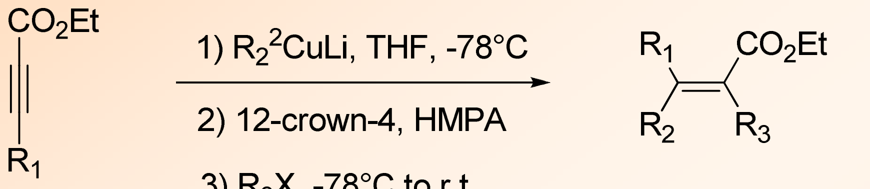
> 19 : 1 cis addition

(a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002,** *124*, 898. (b) Zhu, N.; Hall, D. G. *J. Org. Chem.* **2003,** *68*, **6066.**

II. Carbometallation of alkynes

2. Copper :

d) Addition of organocuprates and α-halo alkyls to acetylenic esters

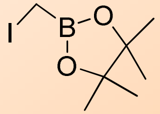


1) R_2^2CuLi, THF, -78°C

2) 12-crown-4, HMPA

3) R_3X, -78°C to r.t

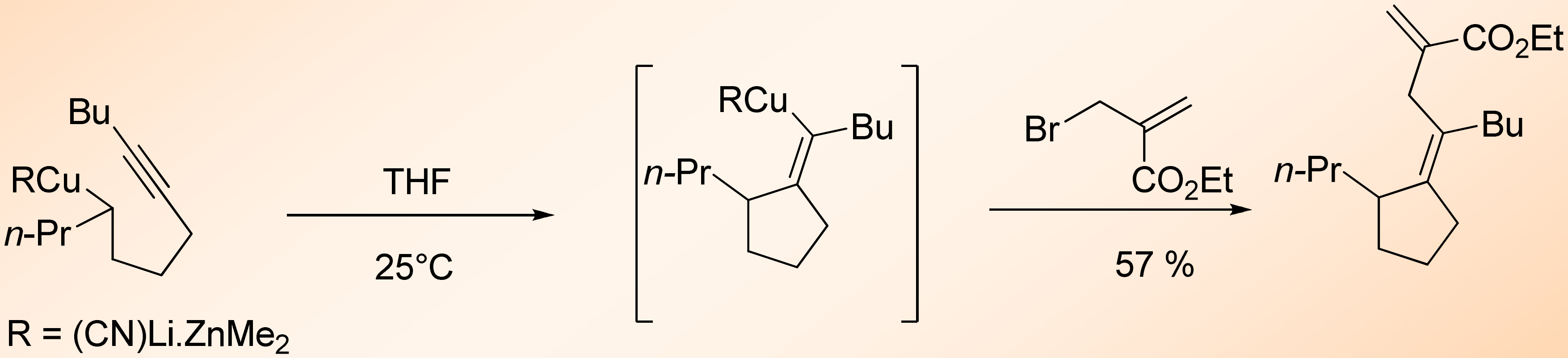
> 19 : 1 cis addition

R1	R2	R3	yield (%)
Et	Me	ICH_2SnBu_3	80
Et	Me	ICH_2SiMe_3	30
Et	Me	$BrCH_2Ph$	40
Et	Me	$BrCH_2CH=CH_2$	76
Et	Me	$BrCH_2C(Br)=CH_2$	57
Et	Me	$BrCH_2CH=CMe_2$	78
Et	*s*-Bu	$BrCH_2CH=CH_2$	72
$TBDPSOCH_2$	Me	$BrHCH3CH=CH_2$	85
Et	Me		66

II. Carbometallation of alkynes

2. Copper :

d) Intramolecular carbocupration

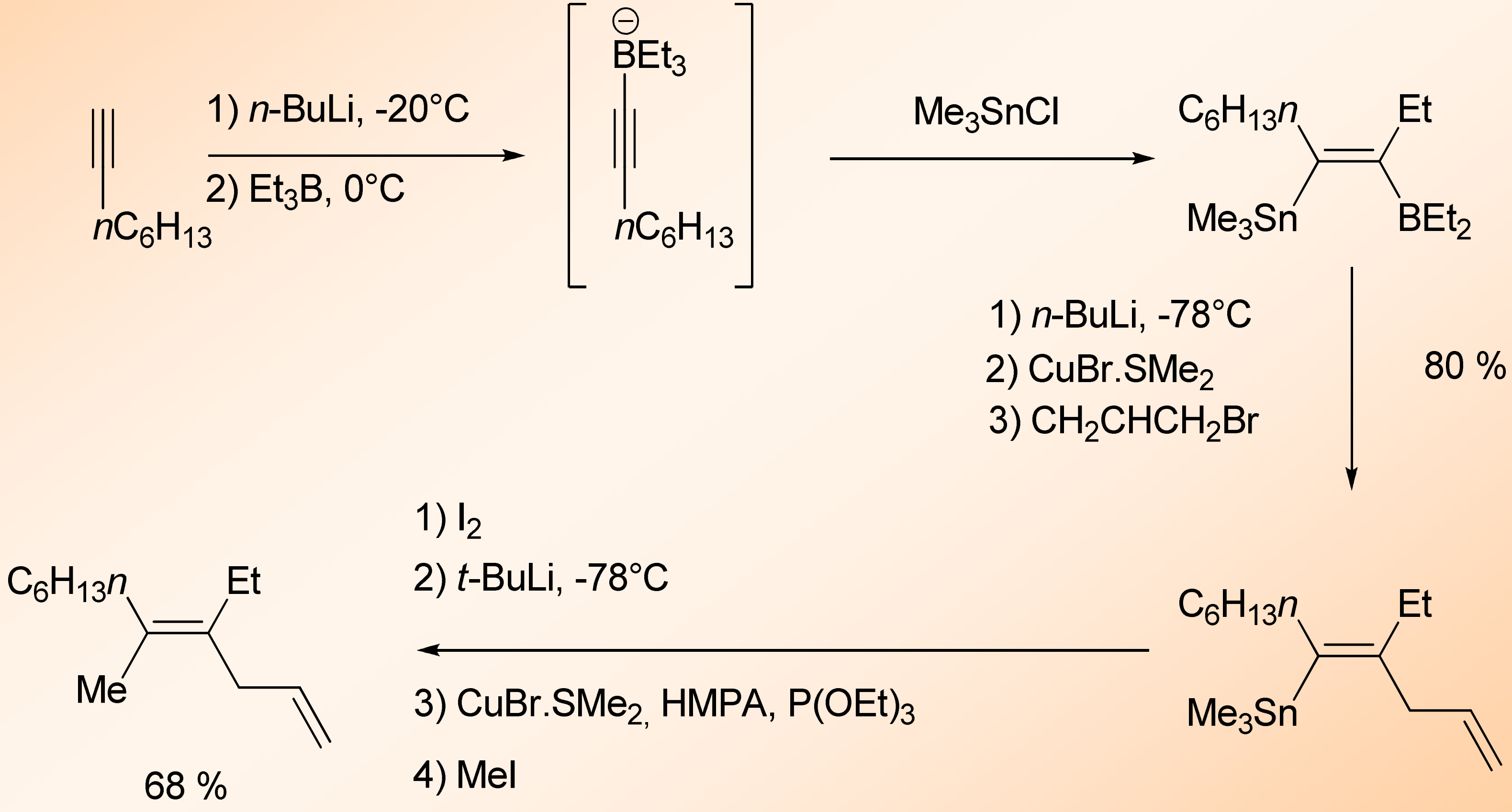


Rao, S. A.; Knochel, P. *J. Am. Chem. Soc.* **1991,** *113*, 5735.

II. Carbometallation of alkynes

3. Boron :

a) Rearrangement of Boron Ate-Complexes to give tetrasubsituted olefins

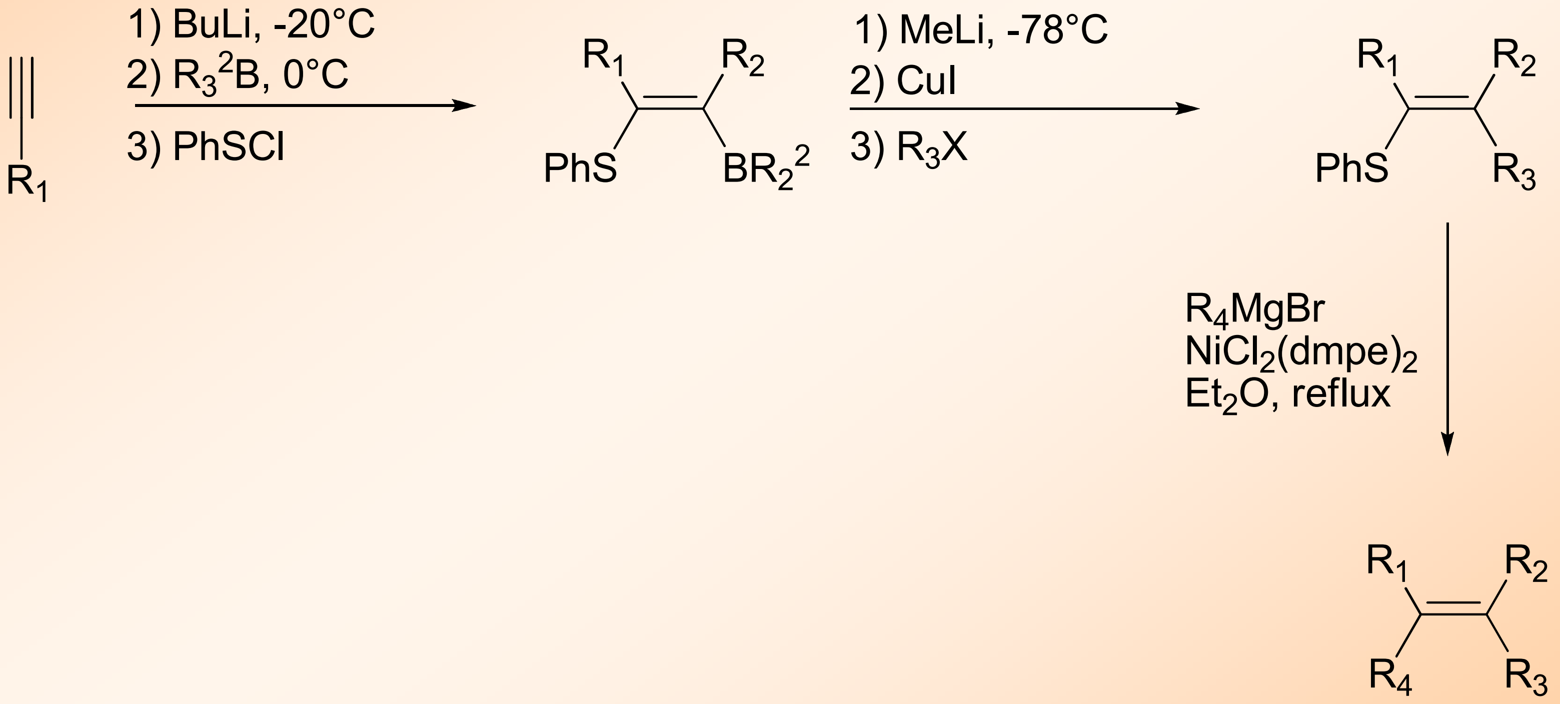


(a) Chu, K.-H.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 767. ***(b)*** Wang**,** K. K.; Chu, K.-H.; Lin, Y.; Chen, J.-H. *Tetrahedron* **1989**, *45*, 1105

II. Carbometallation of alkynes

3. Boron :

b) Rearrangement of Boron Ate-Complexes in the presence of PhSCl



Gerard, J.; Bietlot, E.; Hevesi, L. *Tetrahedron Lett.* **1998,** 8735.
Gerard, J.; Hevesi, L. *Tetrahedron* **2004,** *60,* 367.

II. Carbometallation of alkynes

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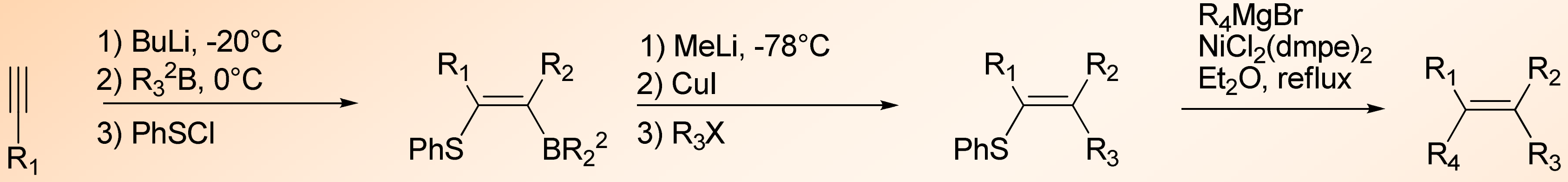
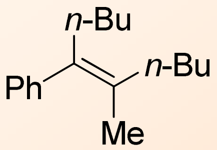
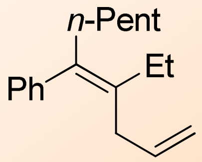
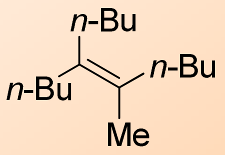
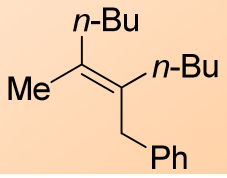
b) Rearrangement of Boron Ate-Complexes in the presence of PhSCl

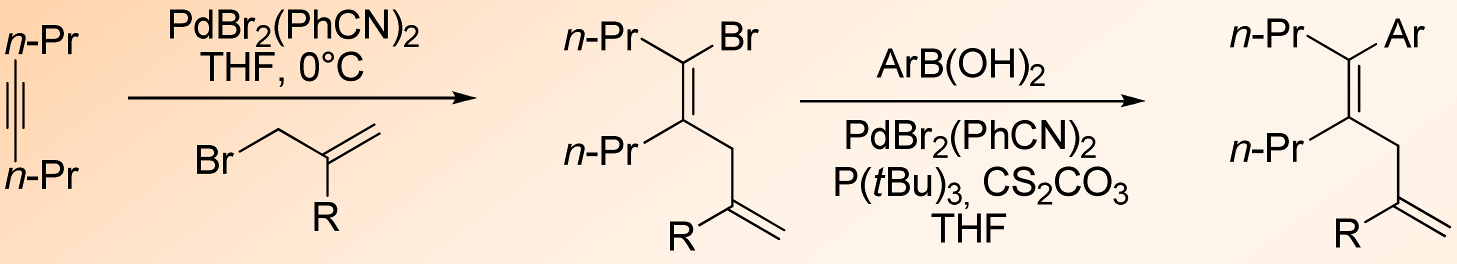


R_1	R_2	R_3	R_4	Product	*E*/*Z*	yield (%)
n-Bu	*n*-Bu	Me	Ph		>99:1	82
n-Pent	Et	allyl	Ph		<1:99	38
n-Bu	*n*-Bu	Me	*n*-Bu		-	70
n-Bu	*n*-Bu	CH_2Ph	Me		>99:1	24

II. Carbometallation of alkynes

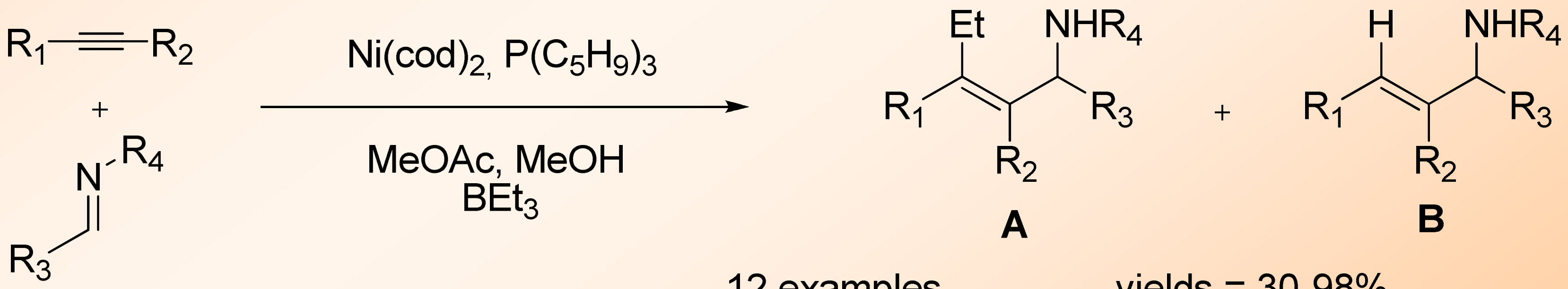
3. Boron :

c) Tetrasubstituted olefins in a skipped diene



R = H, Ar = 3-$NO_2C_6H_4$, 79 %
R = Me, Ar = *N*-tosyl-3-indoyl, 83 %

d) Multicomponent assembly of alkynes, imines and organoboron reagents



12 examples yields = 30-98%

A/B = 86/14- 96/4

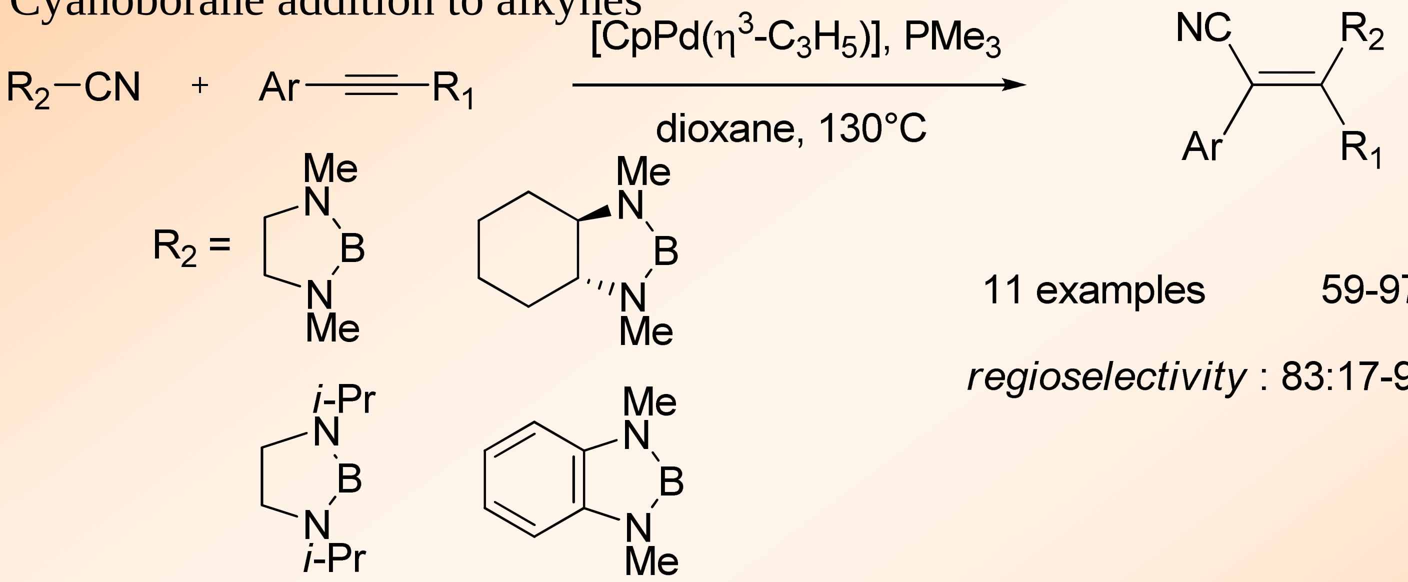
regioselectivity = 89:11-93:7

Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979,** *44,* 55.
Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003,** *42,* 1364.

II. Carbometallation of alkynes

3. Boron :

e) Cyanoborane addition to alkynes



11 examples 59-97%

regioselectivity : 83:17-98:2

→ Conclusion : • cis geometry for the initial carbometallation

• loss of stereochemical information less frequent than with organocuprates.

• using directing groups or making symmetrically substituted products achieves reliable regioselectivity

• vinyl borane intermediates are excellent partners for subsequent palladium-mediated processes.

Suginome, M.; Yamamoto, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2005,** *44,* 2380**.**

II. Carbometallation of alkynes

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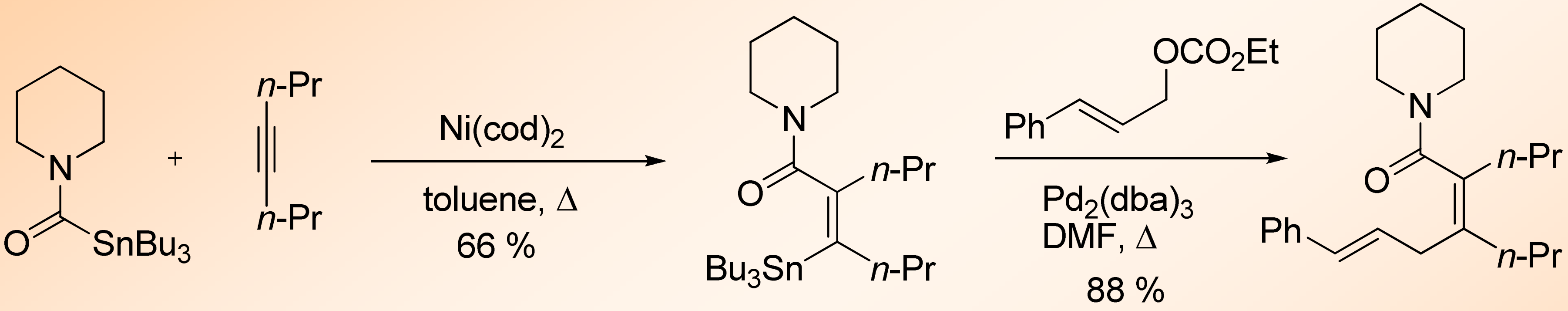
Suginome, M.; Yamamoto, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2005,** *44,* 2380**.**

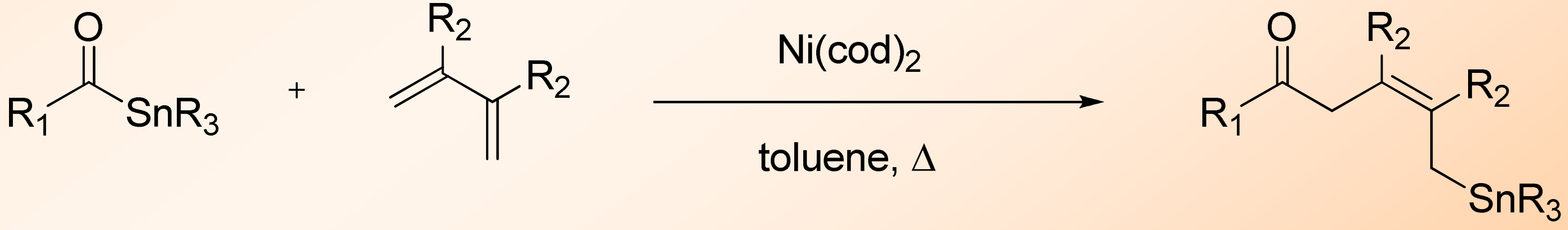
II. Carbometallation of alkynes

4. Tin :

a) Addition of acyl stannanes to alkynes



b) Addition of acyl stannanes to dienes



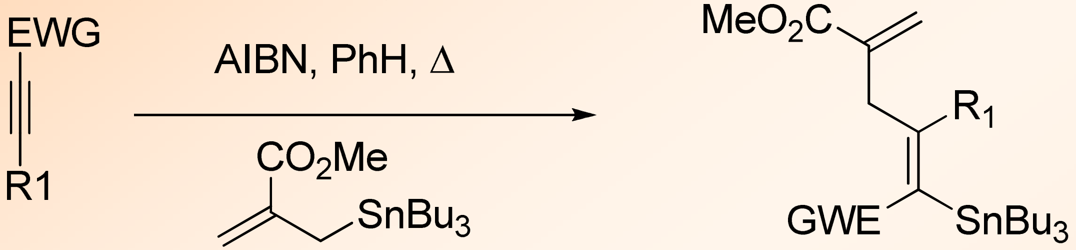
5 examples 36-73 %

Shirakawa, E.; Yamasaki, K.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **1999,** *121*, 10221.
Shirakawa, E.; Nakao, Y.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **2000,** *122*, 9030.

II. Carbometallation of alkynes

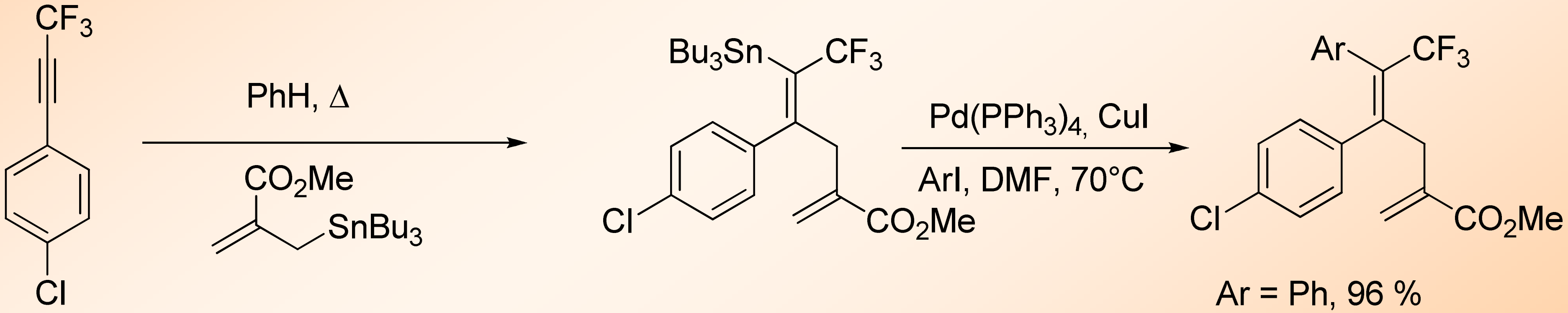
4. Tin :

c) Radical carbostannylation of alkynes



19-45 %

EWG = CO_2Et or CN



Ar = Ph, 96 %
Ar = *p*-$MeOC_6H_4$, 78 %
Ar = *p*-Cl-C_6H_4, 93 %

→ Conclusion : • highly stereoselective

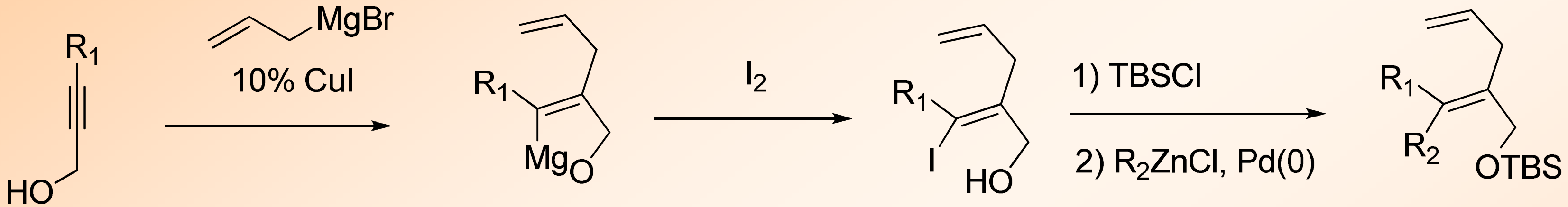
• moderately regioselective

(a) Miura, K.; Itoh, D.; Hondo, T.; Saito, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* **1996,** *37,* 8539. (b) Miura, K.; Matsuda, T.; Hondo, T.; Ito, H.; Hosomi, A. *Synlett* **1996,** 555.
Konno, T.; Takehana, T.; Chae, J.; Ishihara, T.; Yamanaka, H. *J. Org. Chem.* **2004,** *69,* 2188.

II. Carbometallation of alkynes

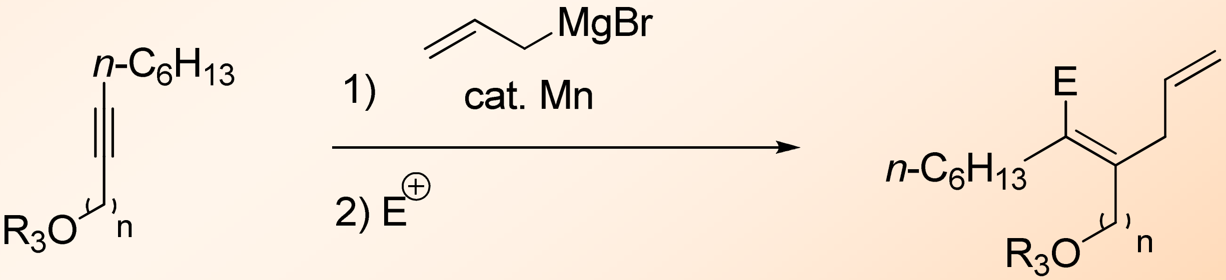
5. Magnesium :

a) Carbomagnesiation of propargylic alkynes



R_1 = Me, R_2 = *n*-Bu, 86%
R_1 = *n*-Bu, R_2 = Me, 97 %

b) Conversion of propargylic and homopropargylic ethers to tetrasubstituted olefins



6 examples 35-92 %

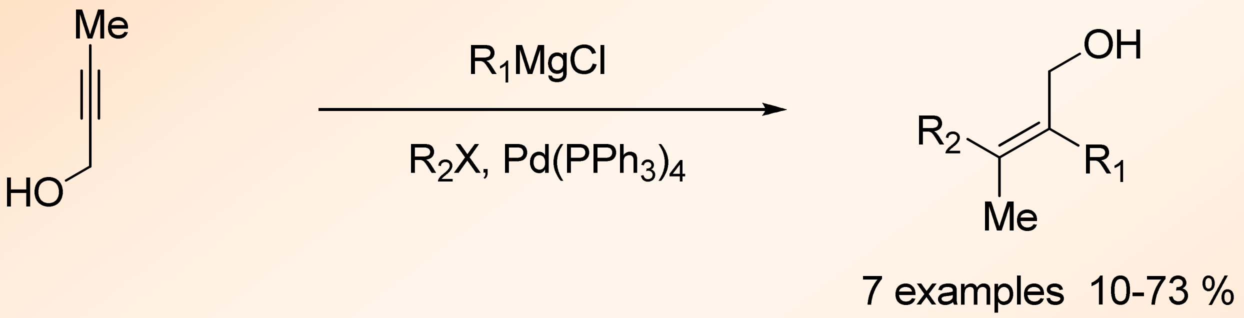
(a) Negishi, E.; Zhang, Y.; Cederbaum, F. E.; Webb, M. B. *J. Org. Chem.* **1986,** *51***,** 4080**.** (b) Anastasia, L.; Dumond, Y. R.; Negishi**,** E. *Eur. J. Org. Chem.* **2001,** 3039**.**

(a) Okada, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc***. 1996,** *118*, 6076. *(b) Tang, J.; Okada, K.; Shinokubo, H.; Oshima, K. Tetrahedron* **1997,** *53***,** 5061**.**

II. Carbometallation of alkynes

5. Magnesium :

c) Three component coupling of alkenes and dienes



7 examples 10-73 %

→ Conclusion : • trans addition

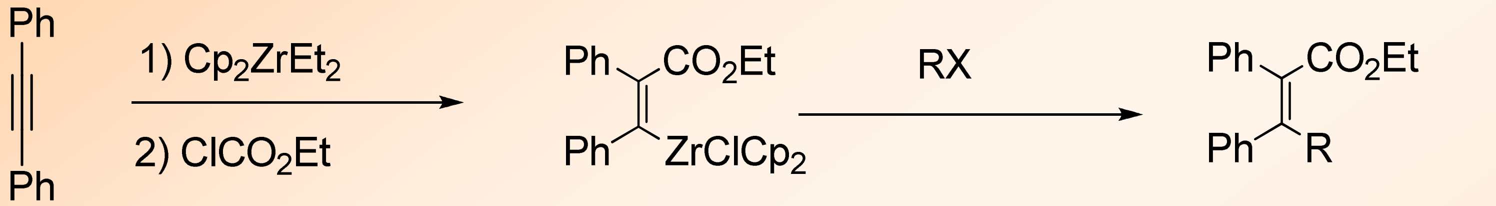
- initial stereochemistry preserved in the subsequent coupling
- using directing groups achieves reliable regioselectivity
- works only with propargylic or homopropargylic alcohols

Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett*. **2003,** *5,* 2989.

II. Carbometallation of alkynes

5. Other metals :

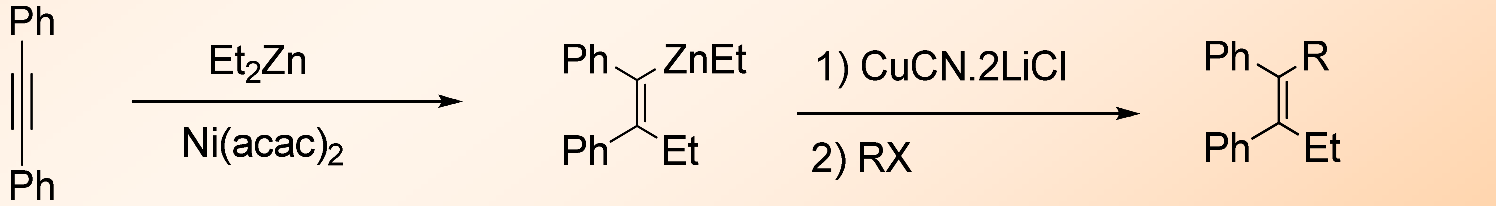
a) Carbozirconation :



4 examples : 31-65 %

→ high degree of stereoselectivity
→ syn isomers

b) Carbozincation :



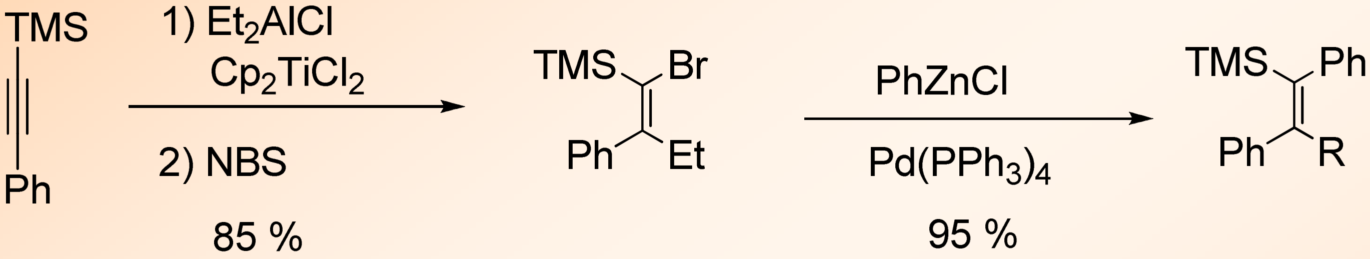
3 examples : 55-71 %

Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* **2000,***122*, 3228.
Stu¨demann, T.; Ibrahim-Ouali, M.; Knochel, P. *Tetrahedron* **1998,** *54*, 1299.

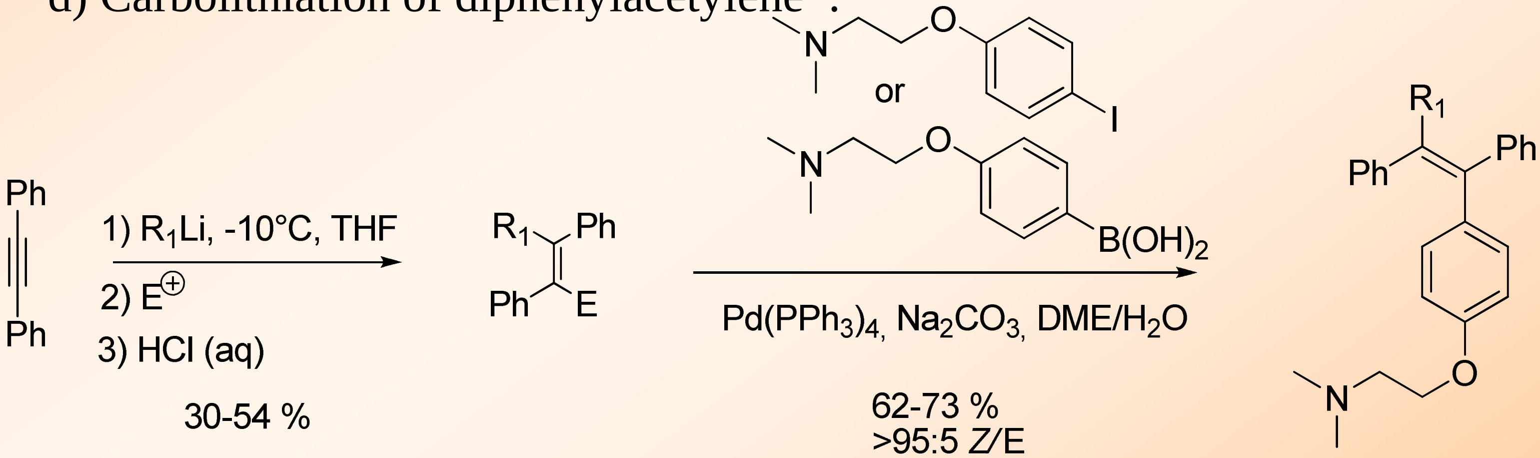
II. Carbometallation of alkynes

5. Other metals :

c) Carboalumination :



d) Carbolithiation of diphenylacetylene :



Miller, R. B.; Al-Hassan, M. I. *J. Org. Chem.* **1985,** *50,* 2121.

Treitel, N.; Eshdat, L.; Sheradsky, T.; Donovan, P. M.; Tykwinski, R. R.; Scott, L. T.; Hopf, H.; Rabinovitz, M. *J. Am. Chem. Soc.* **2006,** *128*, 4703

II. Carbometallation of alkynes

→ Conclusion : • Access to various tetrasubstituted double bonds

- High degree of control is possible

- Stereoselectivity influenced by the type of metal used and the type of catalyst used

- Regioselectivity addressed by using directing groups or by employing symmetrical alkynes.

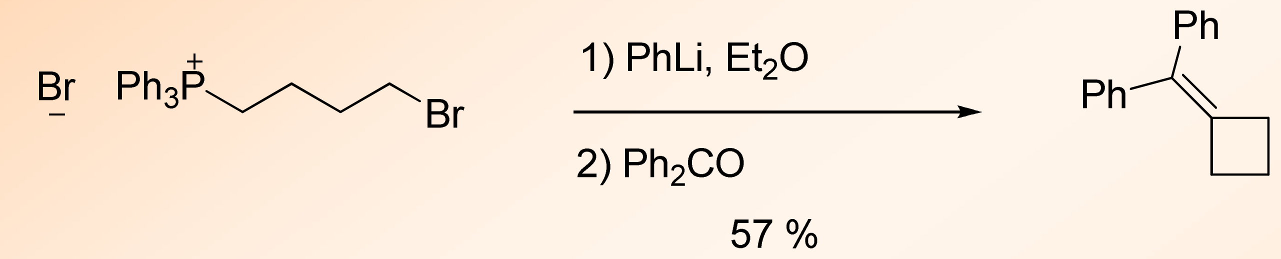
- To synthetise (*Z*) double bond, the most effective is the boron

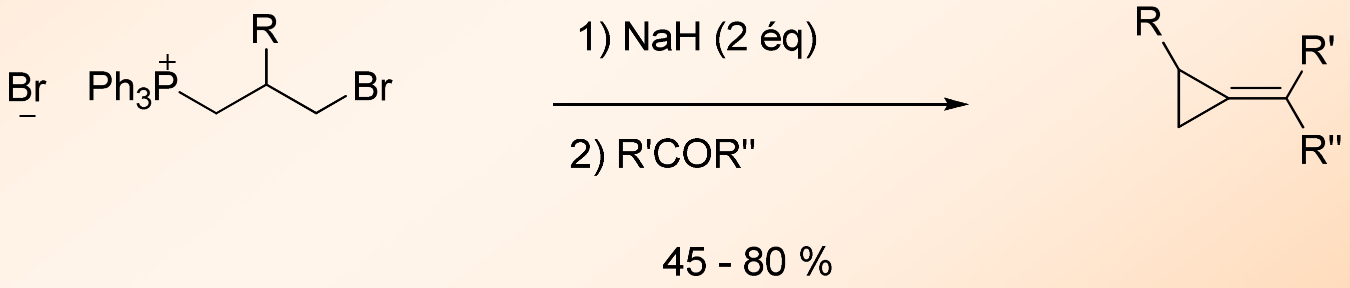
- To synthetise (E) double bond, the most effective is the magnesium.

III. Carbonyl olefination

1. Wittig and Horner-Wadsworth-Emmons :

   a) Wittig reaction :





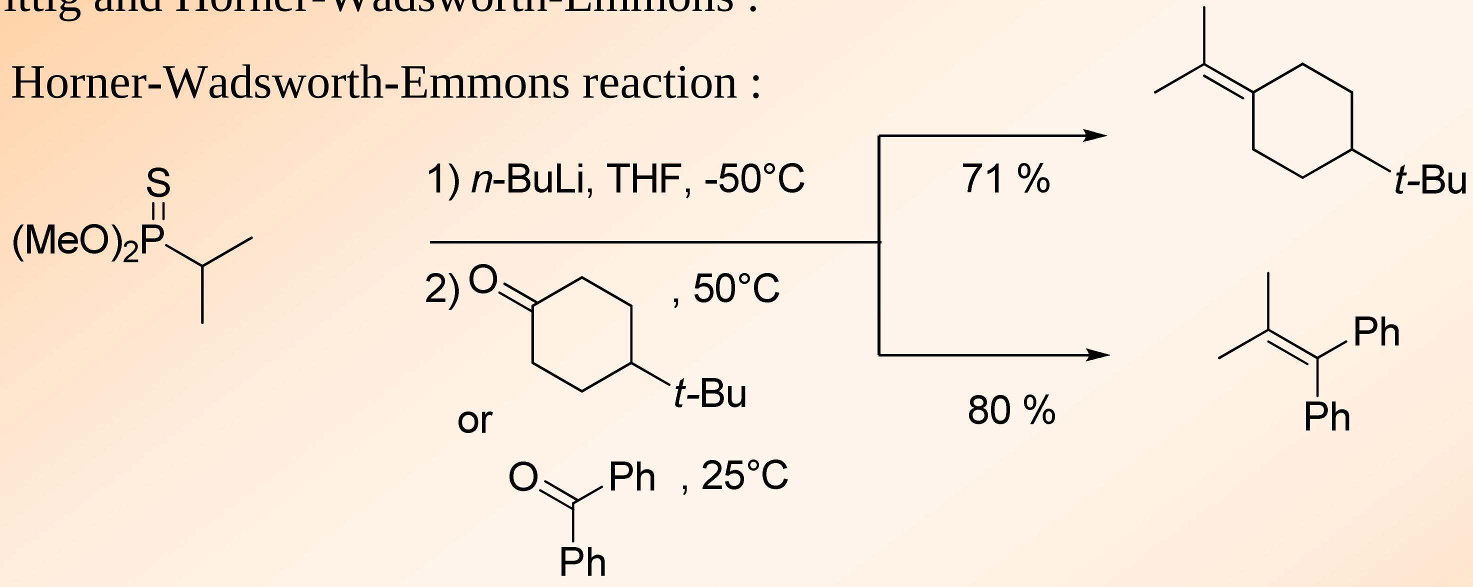
Scherer, K. V., Jr.; Lunt, R. s., III. *J. Org. Chem.* **1965**, *30*, 3215

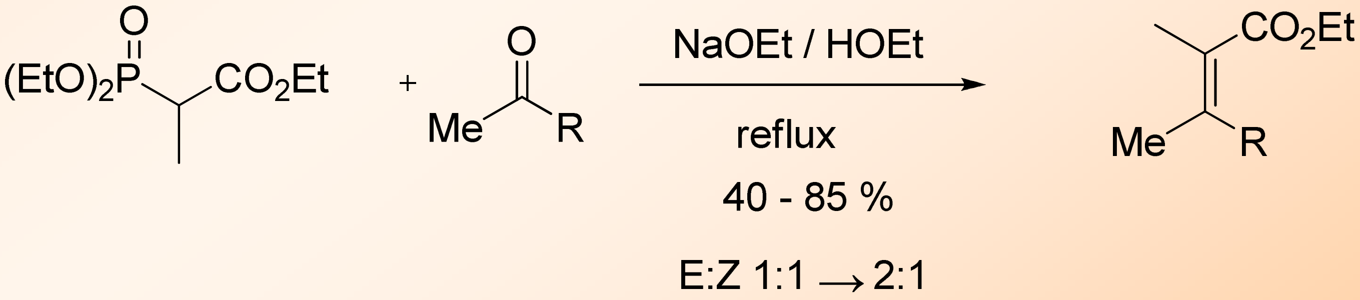
Utimoto, K.; Tamura, M.; Sisido, K. *Tetrahedron* **1973**, *29*, 1169

III. Carbonyl olefination

1. Wittig and Horner-Wadsworth-Emmons :

   b) Horner-Wadsworth-Emmons reaction :



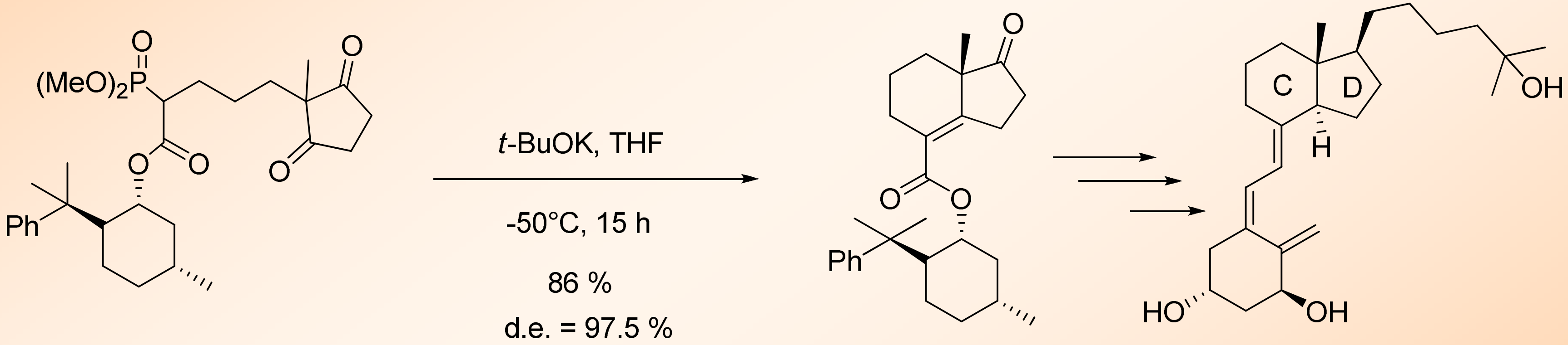


Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966,** *88,* 5654**.** Ramazani, A.; Azizian, A.; Bandpey, M.; Noshiranzadeh, N. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006,** 2731.
Gallagher, G., Jr.; Webb, R. L. *Synthesis* **1974,** 122**.**

III. Carbonyl olefination

1. Wittig and Horner-Wadsworth-Emmons :

   c) Intramolecular diastereoselective Horner-Wadsworth-Emmons reaction :

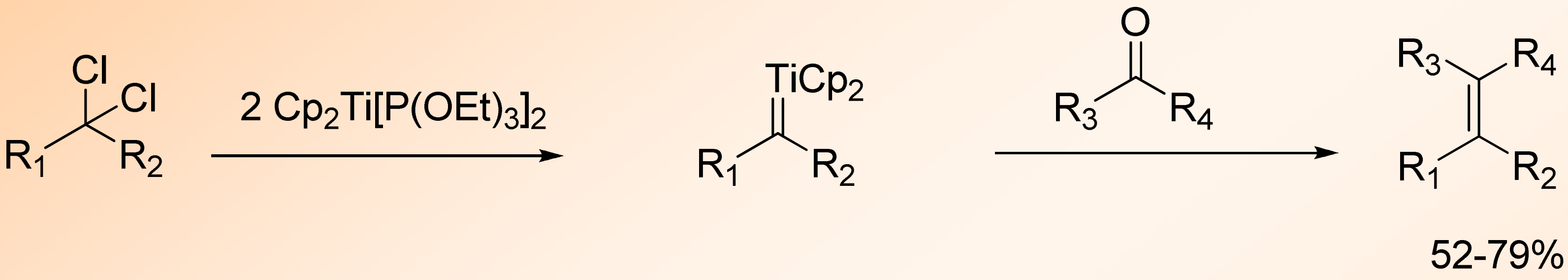


1α, 25-dihydroxyvitamin D3

Mandai, T.; Kaihara, Y.; Tsuji, J. *J. Org. Chem.* **1994,** *59*, 5847.

III. Carbonyl olefination

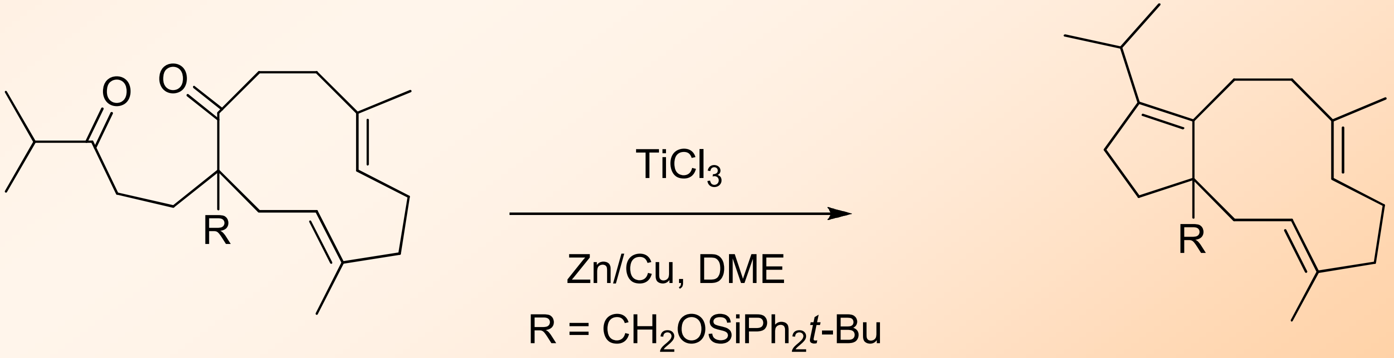
2. Olefination with Metal Carbenes :



- works only when R1 = R2 and R3=R4

- when R1≠R2 and R3≠R4, bad stereoselectivity : mixture of *E*/*Z* isomers

→ McMurry Reaction : synthesis of several terpenes

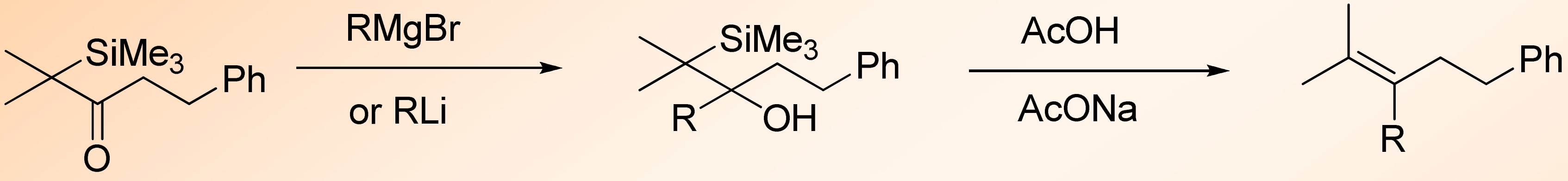


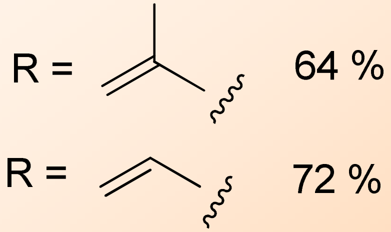
Takeda, T.; Sasaki, R.; Fujiwara, T. *J. Org. Chem.* **1998,** *63*, 7286.
Jenny, L.; Borschberg, H.-J. *HelV. Chim. Acta* **1995,** *78*, 715.

III. Carbonyl olefination

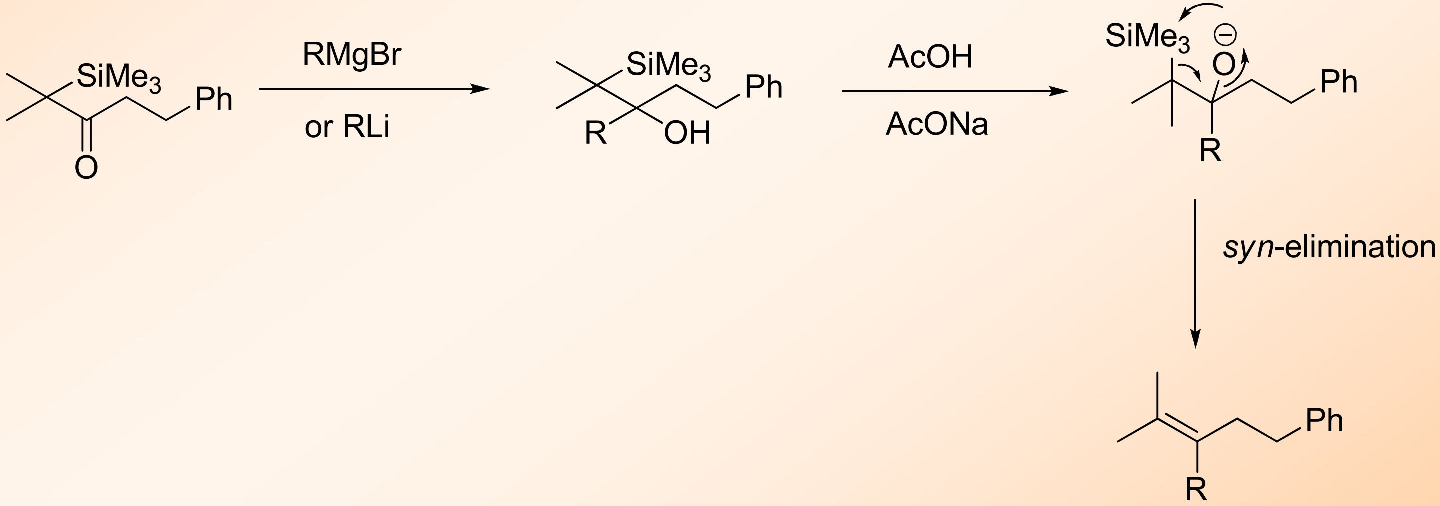
2. Peterson and Julia-Lythgoe Olefination :

a) Peterson olefination : → limited process : only one example





→ General mecanism :

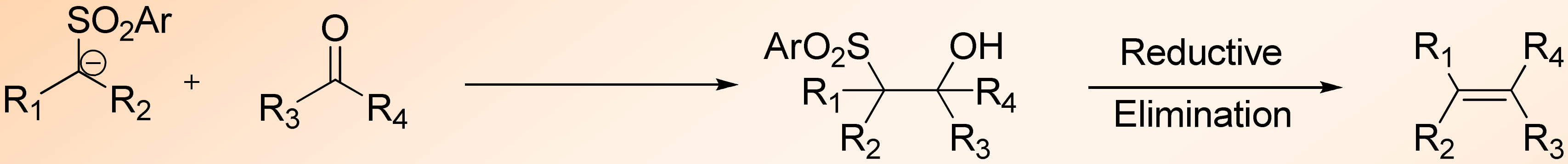


Brown, P. A.; Bonnert, R. V.; Jenkins, P. R.; Selim, M. R. *Tetrahedron Lett*. **1987,** *28*, 693.

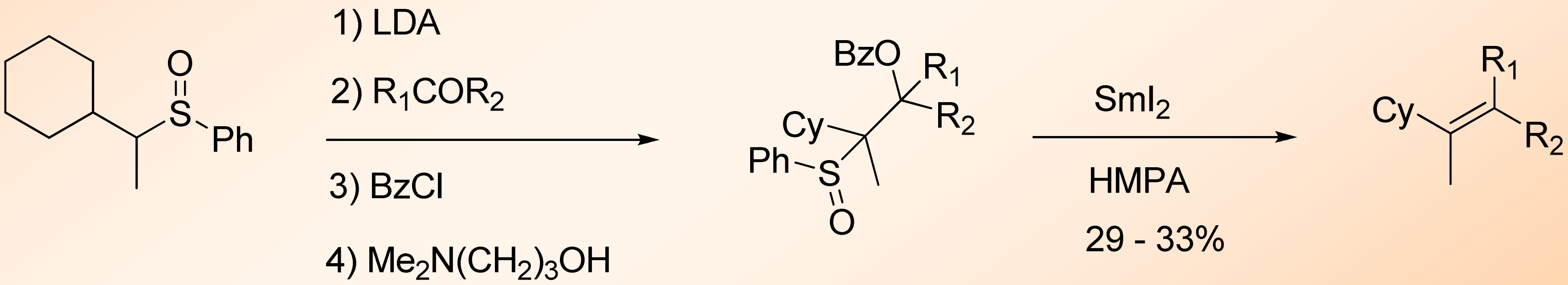
III. Carbonyl olefination

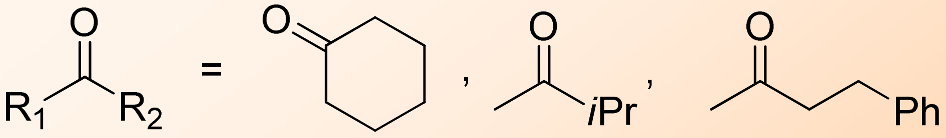
2. Peterson and Julia-Lythgoe Olefination :

b) Julia-Lythgoe olefination :



→ difficult reaction between secondary α-sulfonyl carbanions and ketones





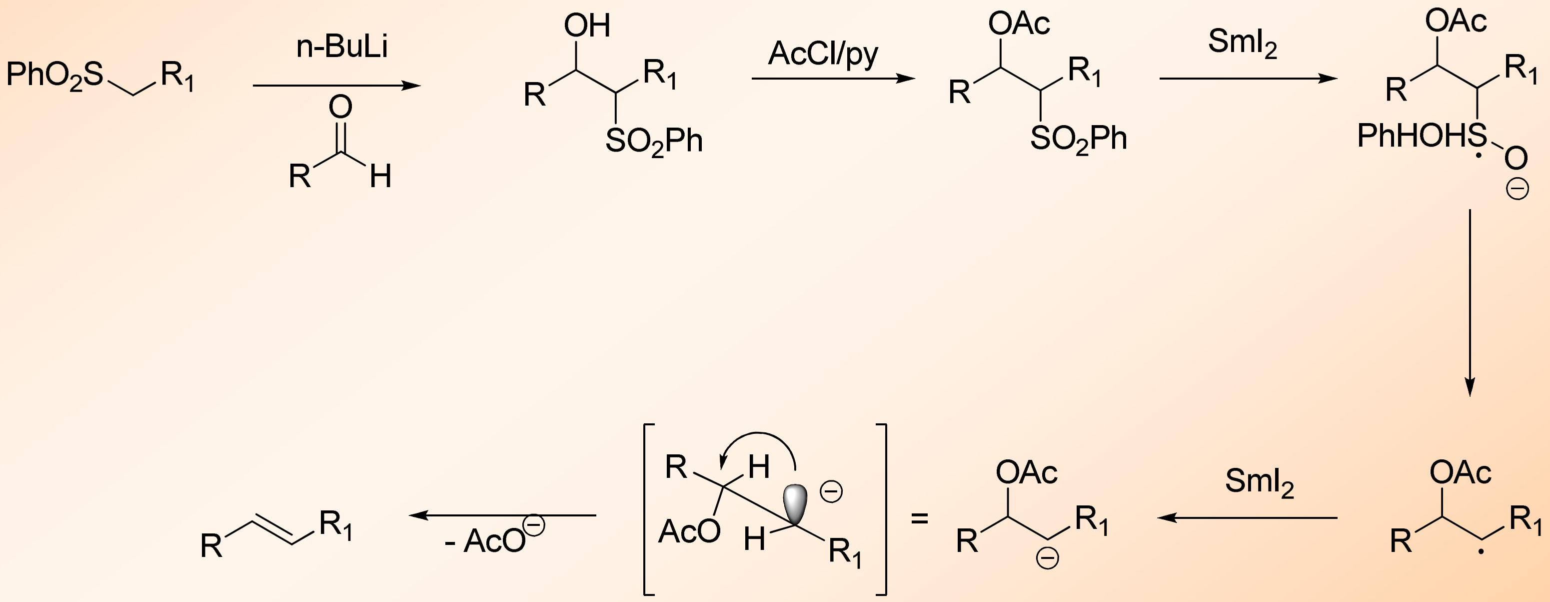
Pospısil, J.; Pospısil, T.; Marko´, I. E. *Org. Lett.* **2005,** *7*, 2373.

III. Carbonyl olefination

2. Peterson and Julia-Lythgoe Olefination :

b) Julia-Lythgoe olefination :

→ General mechanism

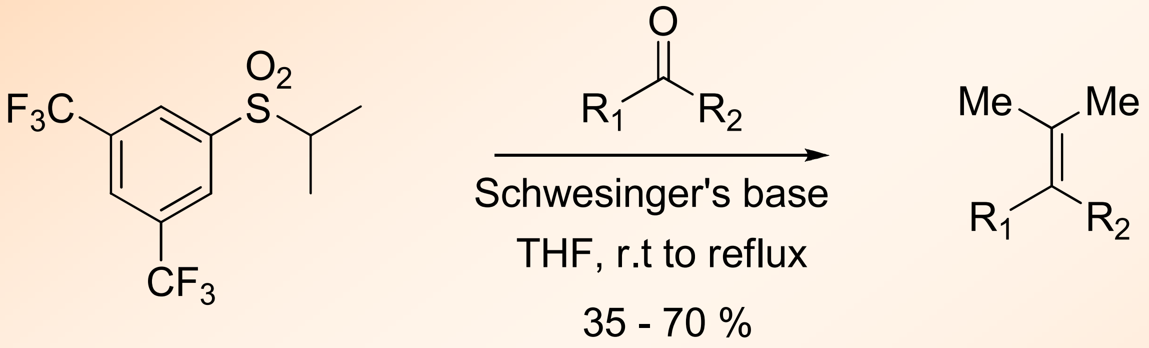


Pospısil, J.; Pospısil, T.; Marko´, I. E. *Org. Lett.* **2005,** *7*, 2373.

III. Carbonyl olefination

2. Peterson and Julia-Lythgoe Olefination :

c) Julia-Kocienski olefination of electron-deficient sulfones with ketones :



→ Conclusion : •widely used for formation of mono- and disubstituted olefins

- limited for synthesis of tetrasubstituted olefins
- the most effective is the McMurry reaction

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IV. Conclusion

→ Various processes to synthetize tetrasubstituted olefins

→ Generally, the most used processes to synthetise double bonds are the carbometallation of alkynes and the carbonyl olefination

→ In our case, the most effective is the carbometallation of alkynes.