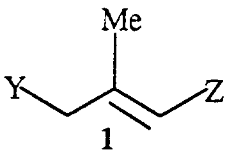
EVOLUTION IN THE CONSTRUCTION OF FUNCTIONALIZED BUILDING BLOCKS *'via'* METALLOMETALATION OF HETEROSUBSTITUTED ALKYNES

The importance of stereodefined and polysubstituted carbon-carbon double bonds in organic synthesis cannot be overemphasized. Among the others, trisubstituted olefins with two proximal groups such as **1-4** are potentialy useful synthons for the synthesis of a variety of natural products of terpenoid origin.



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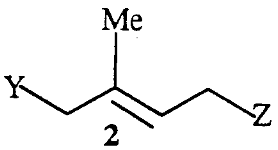

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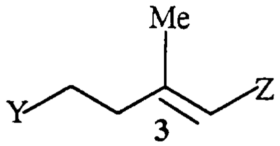

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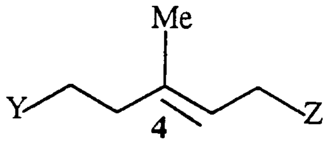


4

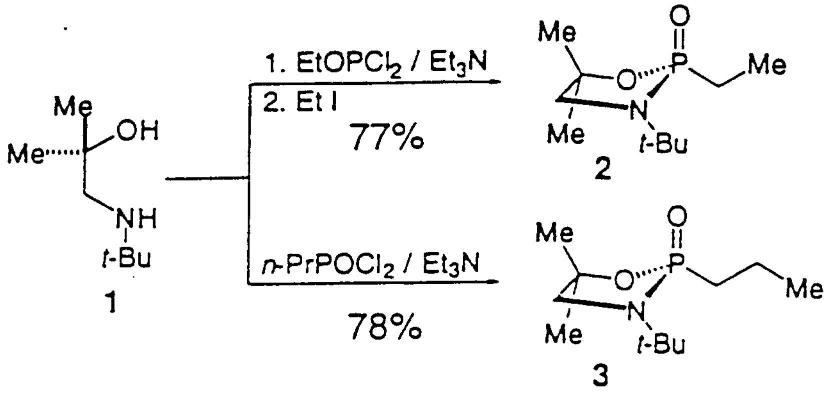
In recognition of the importance of this central functional group, many ingenious and selective methods have been devised over the years:

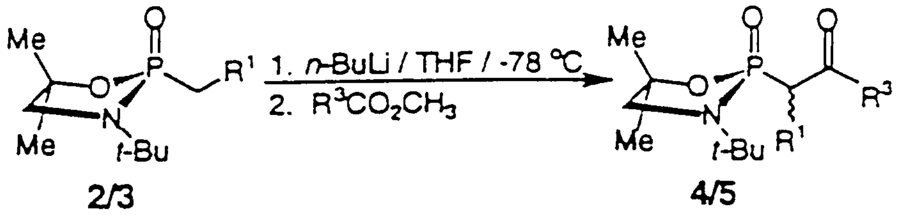
For reviews see: a)- Kelly, S.E. in *Comprehensive Organic Synthesis, Additions to C-X double bond,* Part 1; Schreiber, S.L.; Ed. Pergamon Press, Oxford, **1991**; Vol. 1, Chapter 3.
b)- Julia, M *Pure Appl. Chem.* **1985**, *57*, 763.

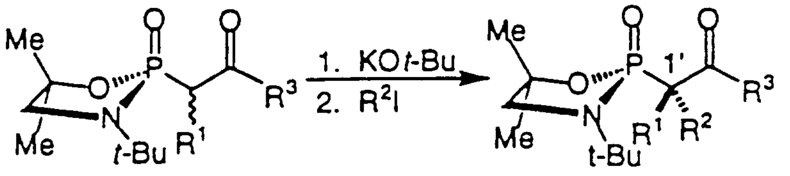
Nervertheless, the need for a general and highly selective method for the constructive synthesis of trisubstituted alkenes remains. Besides the venerable Wittig reaction for which the problems in formation of tri- and especially tetrasubstituted alkenes are well documented, other methods are emerging.

A new, general, and stereoselective method for *the synthesis of trisubstituted alkenes*

by Scott Denmark and Jack Amburgery







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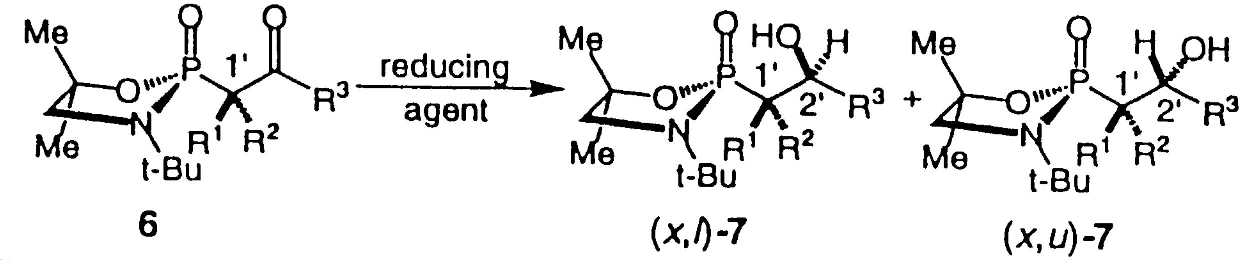
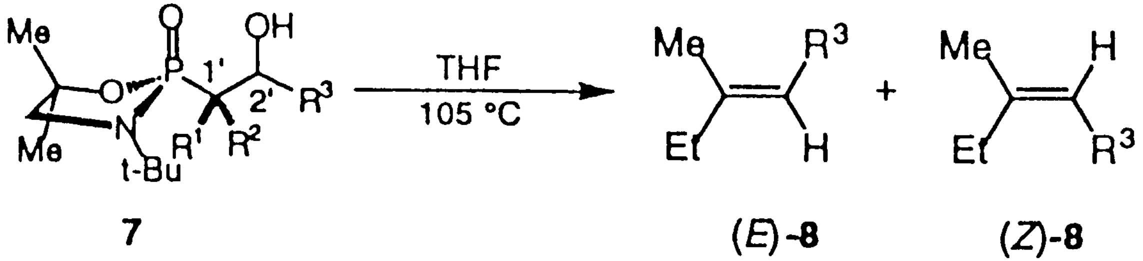
l-**6**: R^1 = Me, R^2 = Et
u-**6**: R^1 = Et, R^2 = Me





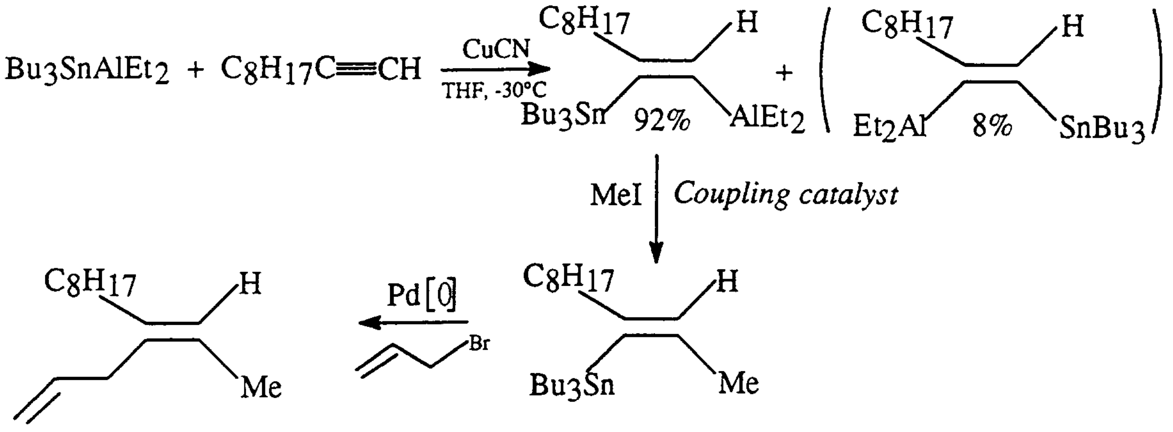
J. Am. Chem. Soc., Vol. 115, No. 22, 1993 10387

OTHER VIABLE ROUTES TO TRISUBSTITUTED OLEFINS ARE

METALLO-METALATION REACTIONS OF 1-ALKYNES

Terminal acetylenes react with bis-metallic reagents containing less electropositive metals such as Cu, B, Al, Si, Z, and Zr, in the presence of suitable catalysts (Cu^+, Pd^0, or Pd^{2+}) to give 1,2-dimetallo-1-alkenes in highly regio- and stereocontrolled reactions. These can be selectively functionalized at the more reactive vinyl-metal bond to provide a monometallo-alkene: this upon transmetalation and further reaction with electrophiles gives stereo- and regiodefined trisubstituted olefins.

Regioselectivity in metallometalations is influenced by the catalysts employed as well as by the metals and steric bulk of the alkyl groups in the bismetalloid.

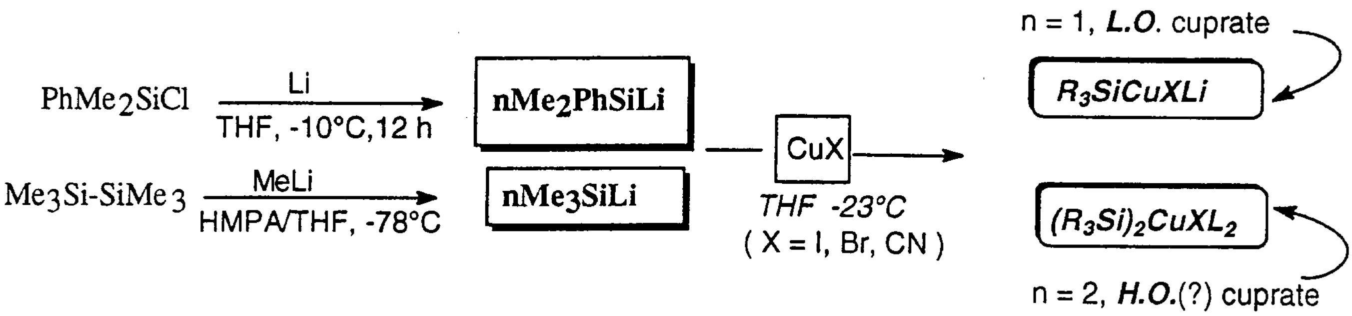


Ref.: Sharma, S.; Oehlschlager, A.C. *J. Org. Chem.* **1989**, *54*, 5064.

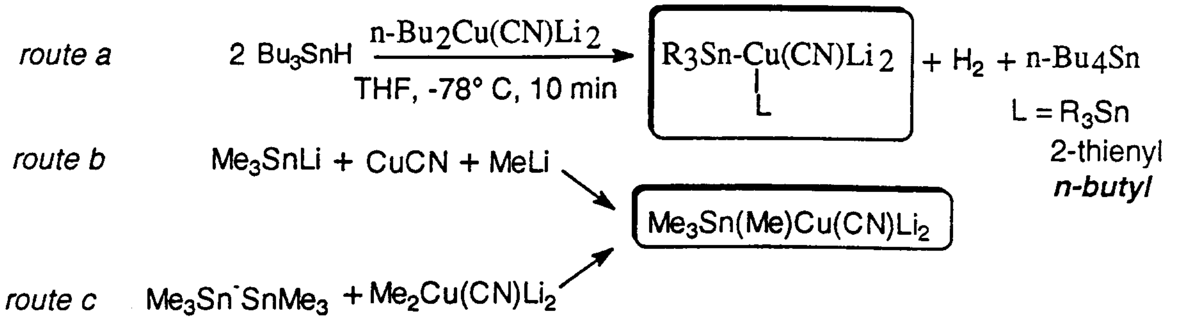
The most recent trends in the application of metallometalation as a synthetic tool, focus on metallocuprations and in particular on the application of silyl- and stannylcupration reagents. The reasons for the rising popularity of the use of Group 14-Cu reagents stems from several factors:

a)- Most of the metallometalations occur in the presence of a Cu^+ catalyst, suggesting that the true species is a metallocuprate.
b)- The differential reactivity between the C-Cu and C- *Group14* bonds, allows for the stepwise functionalization of the organometallic adduct with electrophiles.
c)- Reliable procedures are available for the generation of silylcupration and stannylcupration reagents.
d)- Possibility of tuning of the reactivity moving from monoanionic (L.O.) to bisanionic (H.O ?) metallocuprates.

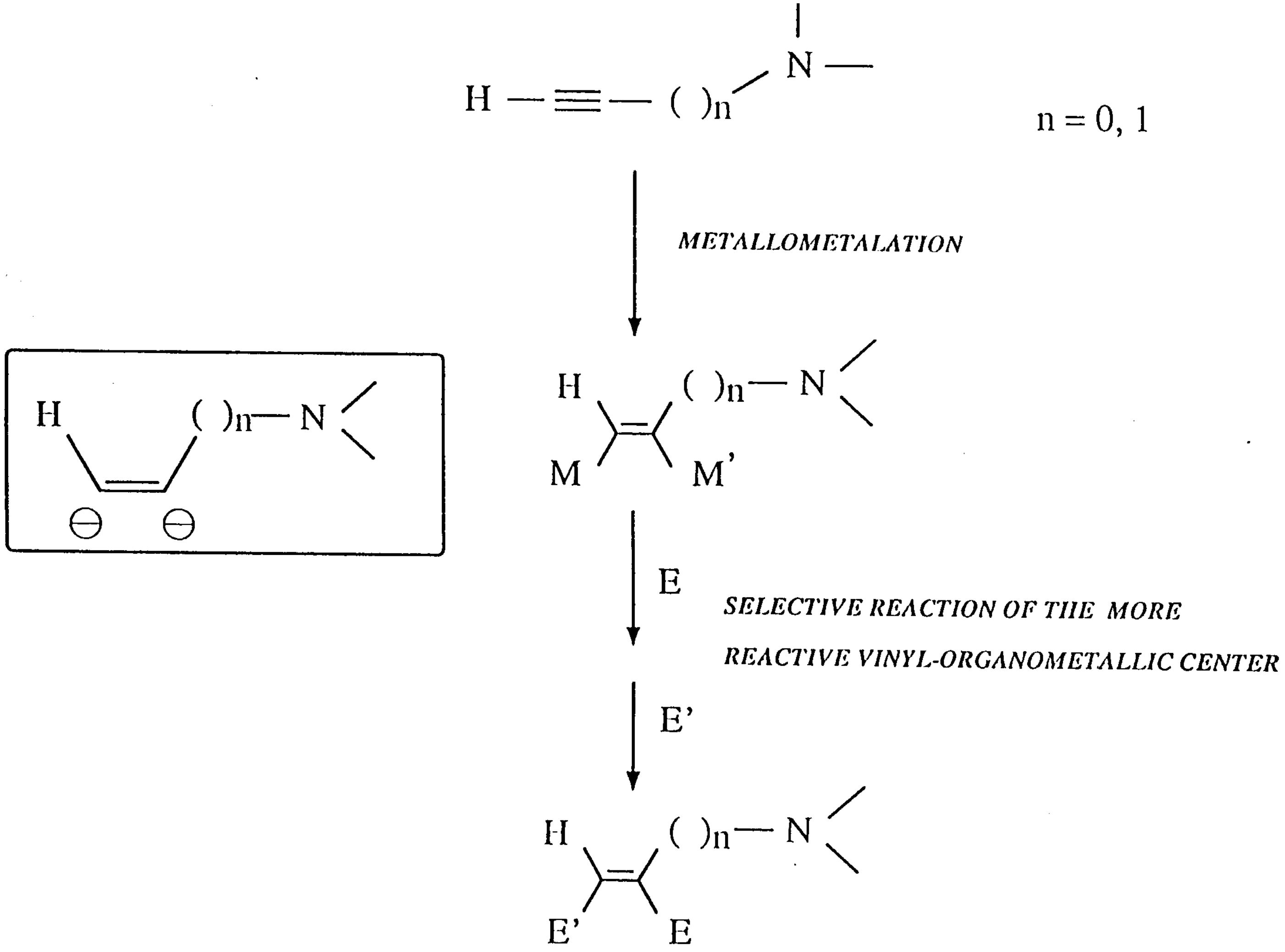
Preparation of silyl- and stannyl-cupration reagents



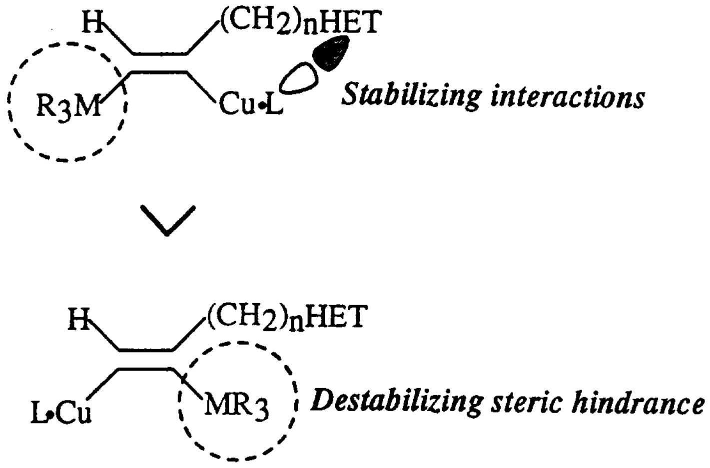
Fleming, I.; Newton, T.W. *J. Chem. Soc. Perkin Trans. I* **1984**, 1805.



Lipshutz, B.H.; Ellsworth E.L.; Dimock, S.H.; Reuter, D.C. *Tetrahedron Lett.* **1989**, *30*, 2065.

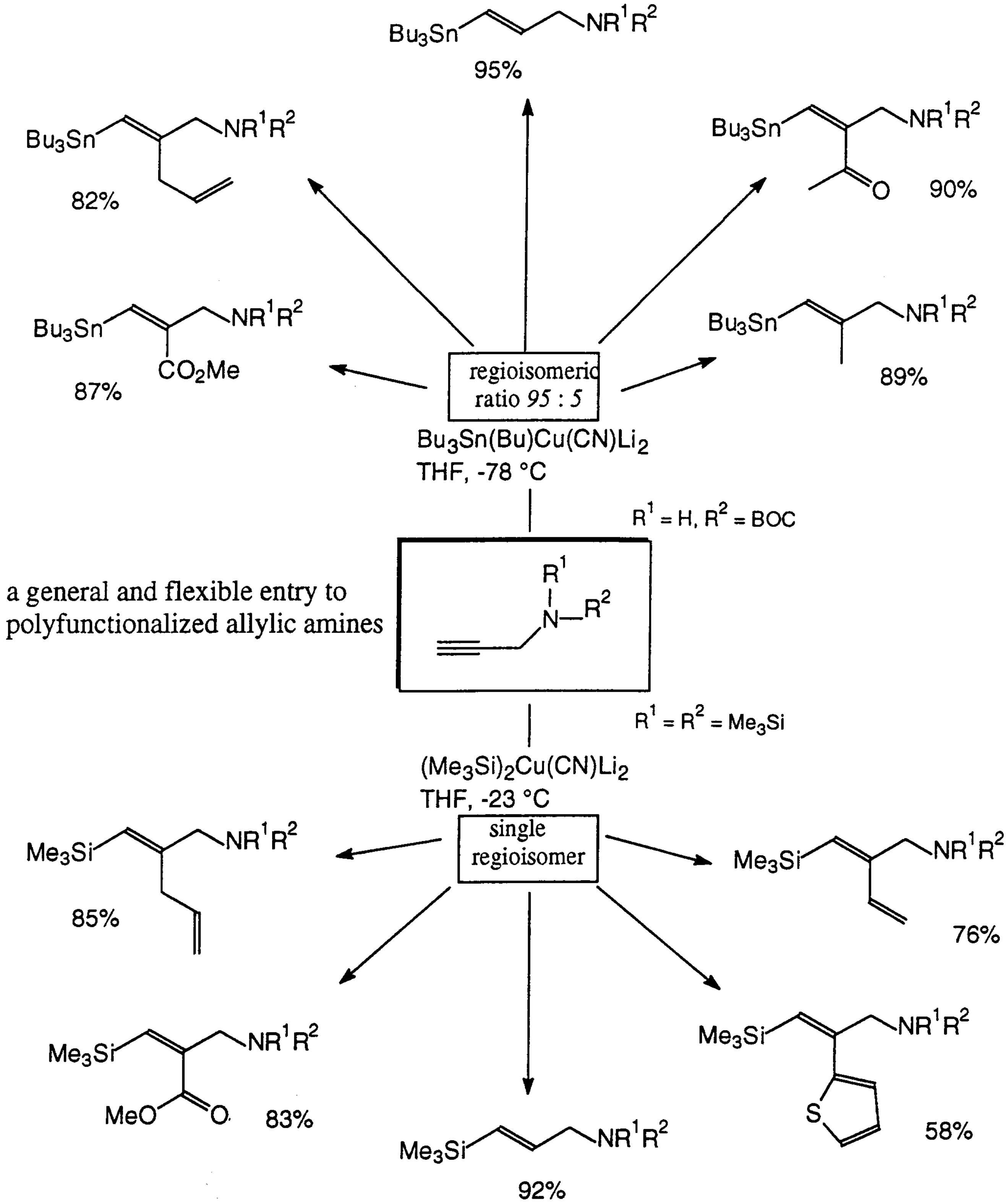


Regio- and stereodefined selectively polyfunctionalized olefins



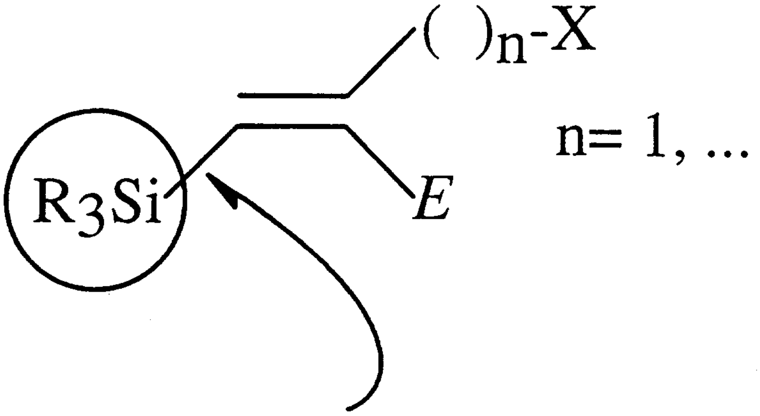
n = 0, 1
HET = NHP, NPP, SR
P = BOC, Me_3Si.

Capella, L.; Degl' Innocenti, A.; Mordini, A.; Reginato, G.; Ricci, A.; Seconi, G.
Synthesis, **1991**, 1201.

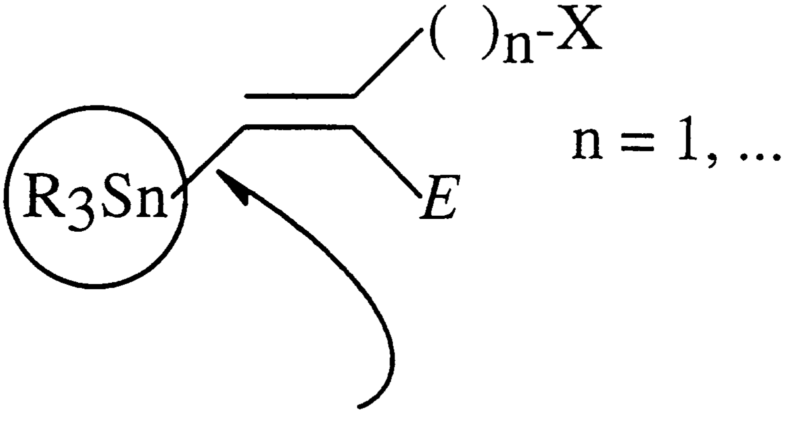


a general and flexible entry to polyfunctionalized allylic amines

Capella, L; Degl' Innocenti, A.; Reginato G.; Ricci, A.; Taddei, M.; Seconi, G.
J. Org. Chem. **1989**, *54*. 1473.

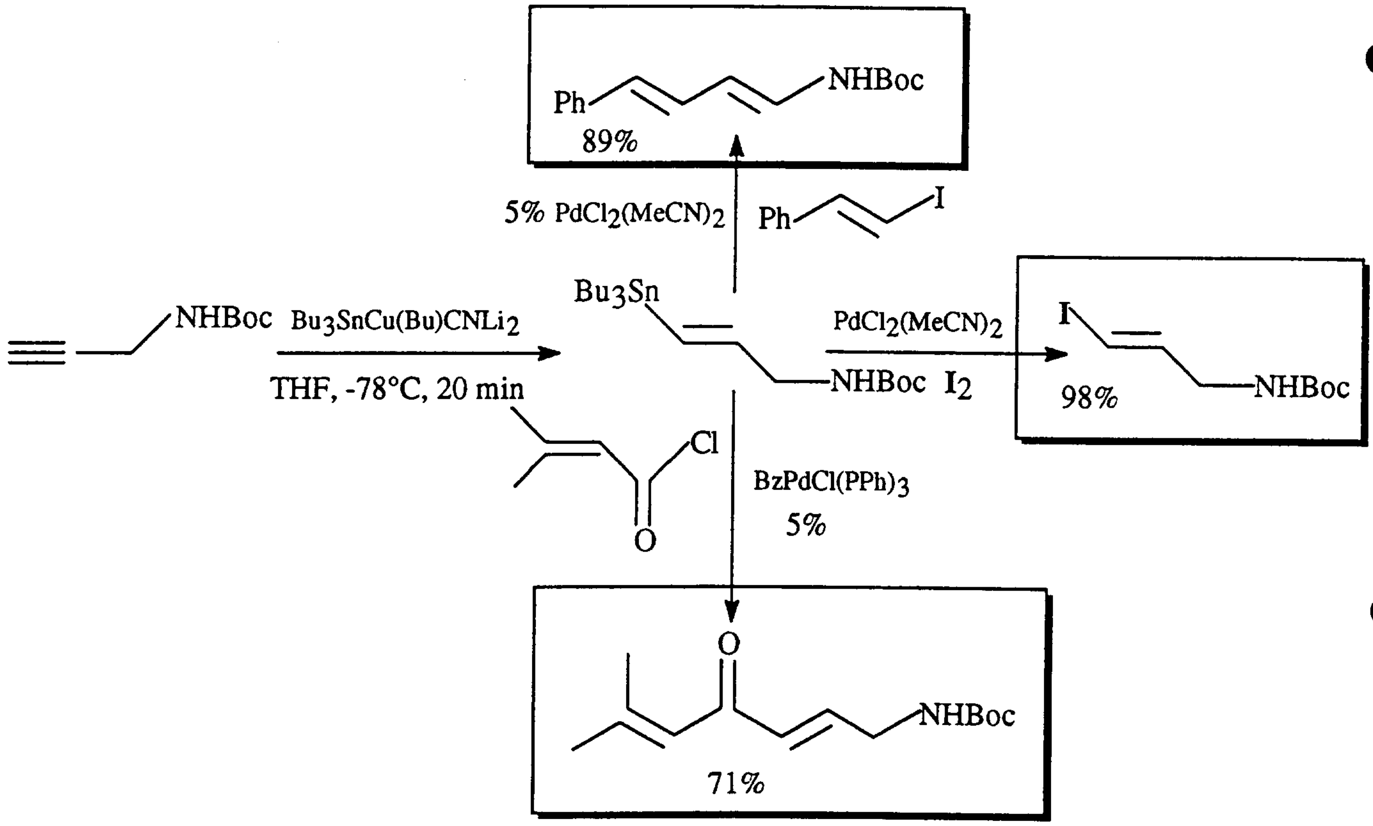


Cleavage methodologies based on F⁻ or strong Lewis acids: possible incompatibility with acidic hydrogens or with heteroatom-based functions.

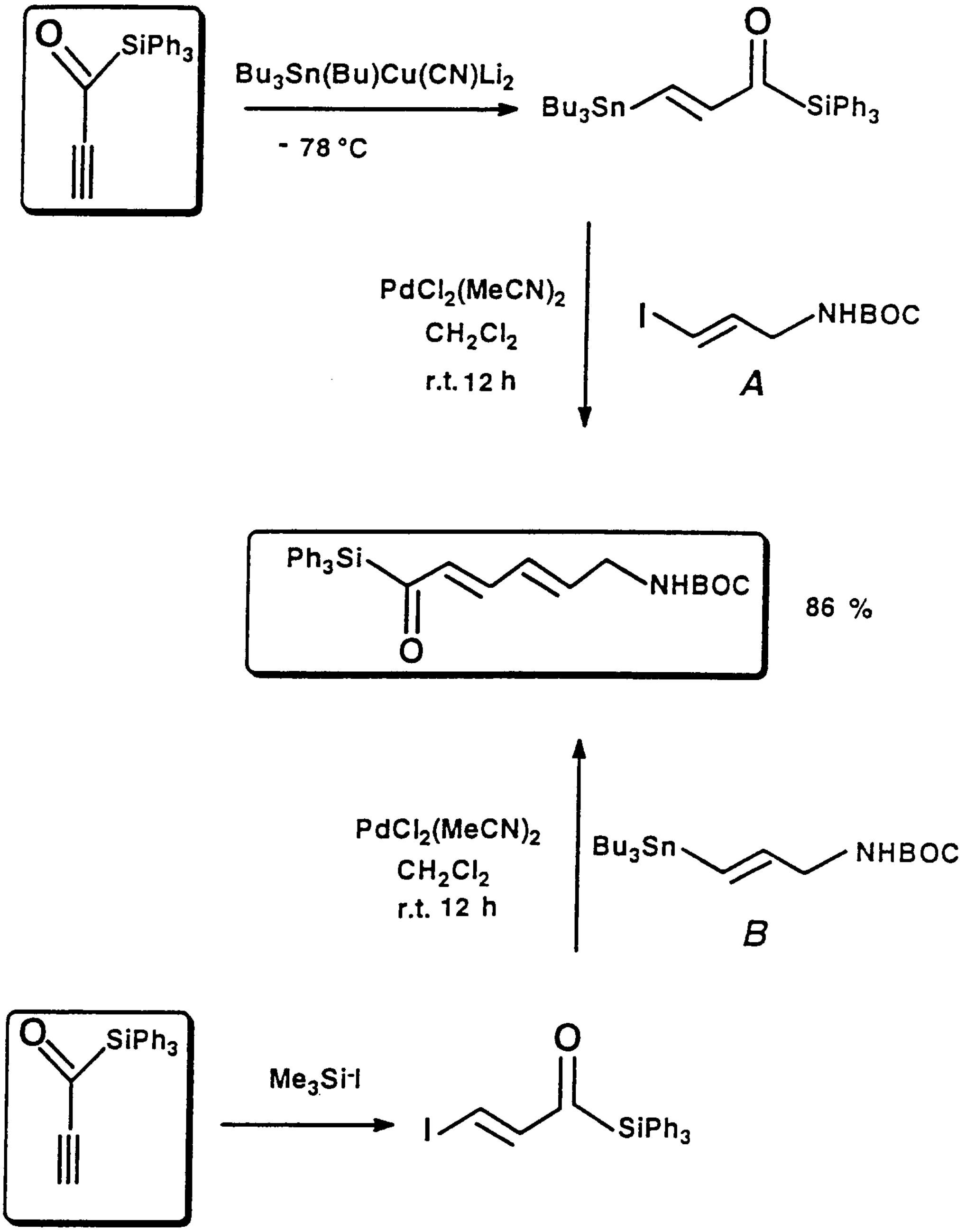


Pd(0)-catalyzed coupling of halides with vinylstannanes: a particularly attractive feature of this method is the toleration of a variety of substituents.

Scott, W.J.; Stille, J.K. *J. Am. Chem. Soc.* **1986**,*108*, 3033.

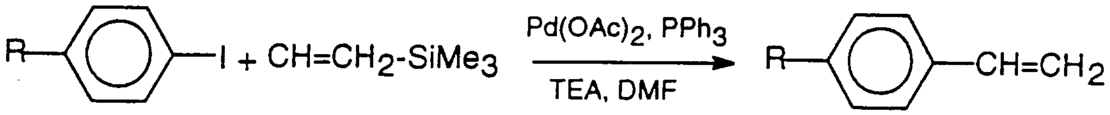


Ricci, A.; Degl' Innocenti, A.; Reginato, G.; et al. *Synlett* **1992**, 329 and 332.



A. Ricci. A. Degl'Innocenti, G. Reginato et al., Synlett, 1992, 329 and 332

Pd Catalyzed Cross-Coupling of Organosilanes with Organic Halides



Hallberg, A.; Westerlund, C. *Chem. Lett.* **1982**, 1993

$$R^1\text{-}X \;+\; R^2SiMe_3 \xrightarrow[(\eta^3\text{–}C_3H_5PdCl)_2]{\text{TASF or TBAF}} R^1\text{-}R^2$$

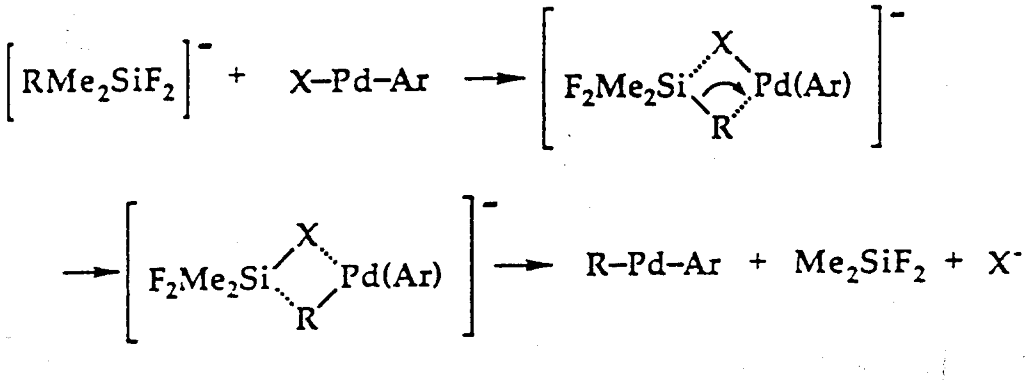
R^1 = Aryl, Alkenyl, Allyl
R^2 = Alkenyl, Allyl, Alkynyl

TASF = $(Et_2N)_3S^+\,Me_3SiF_2^-$

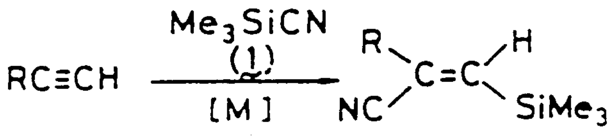
Hiyama, T.; Hatanaka, Y. *J. Org. Chem.* **1988**, *53*, 918
Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 605.
Hatanaka, Y.; Ebina, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 7075
Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845

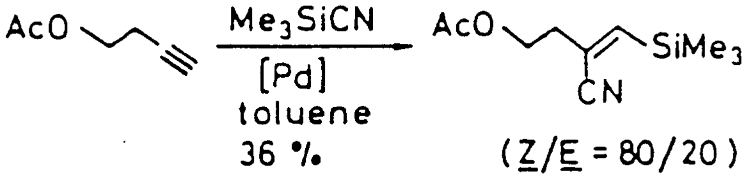
$\boxed{R\text{-}SiMe_{3\text{-}n}F_n}$ $\quad FMe_2Si > F_2MeSi \gg F_3Si,\ Me_3Si$

$\boxed{R\text{-}SiMe_{3\text{-}n}(OR)_n}$

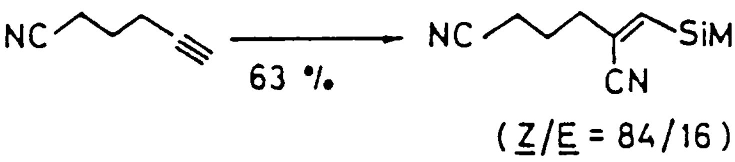


Pd- and Ni-Catalyzed Reaction of Me_3SiCN with Acetylenes

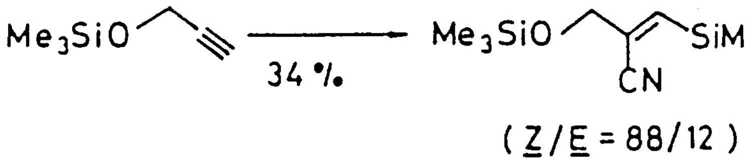




(8)



(9)



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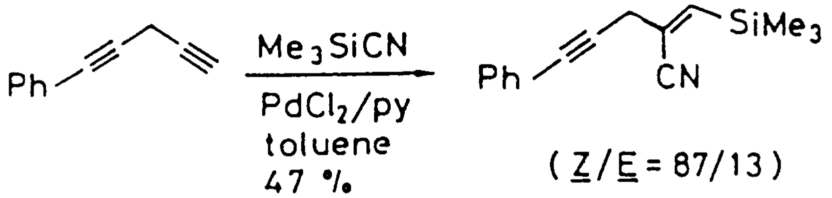
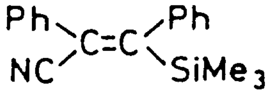
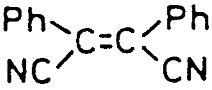



34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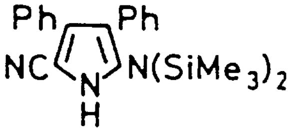
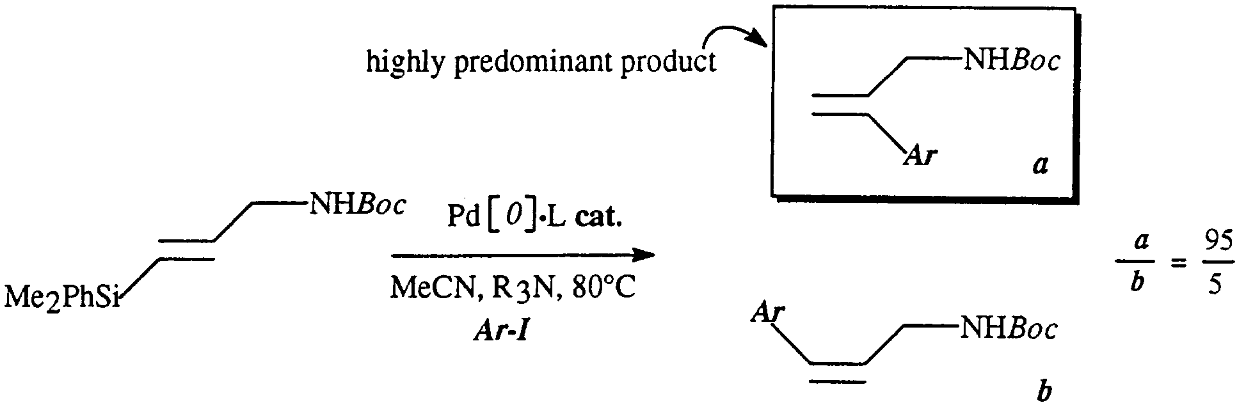

36

$$PhC\equiv CPh \xrightarrow[\text{PdCl}_2 \text{ no solvent}]{Me_3SiCN} \underset{\sim}{36} \quad 88\ \%$$

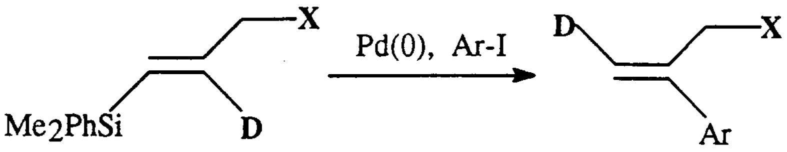
J. Org. Chem., Vol. 53, No. 15, 1988

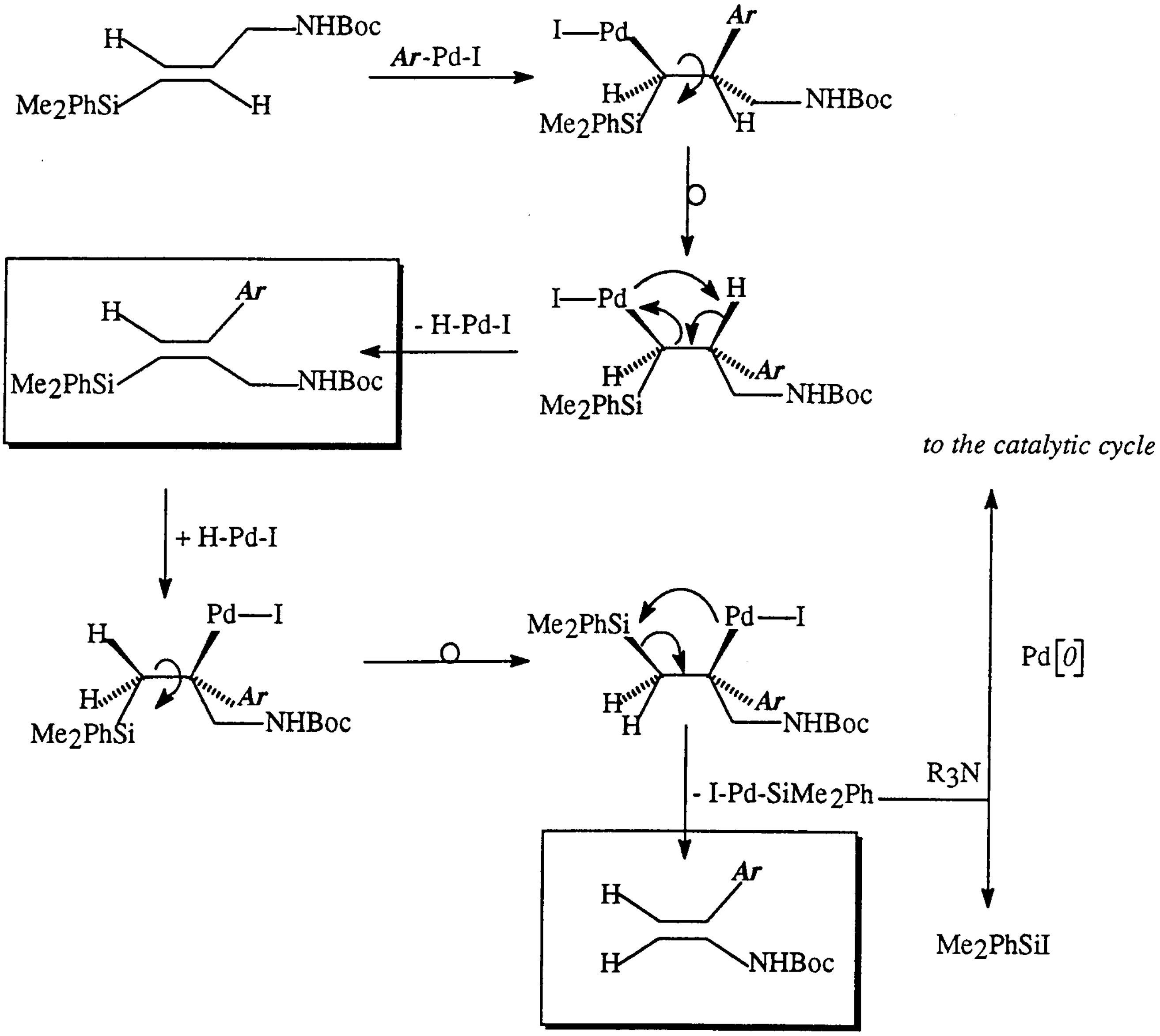


Overall yields from 60 to 75%

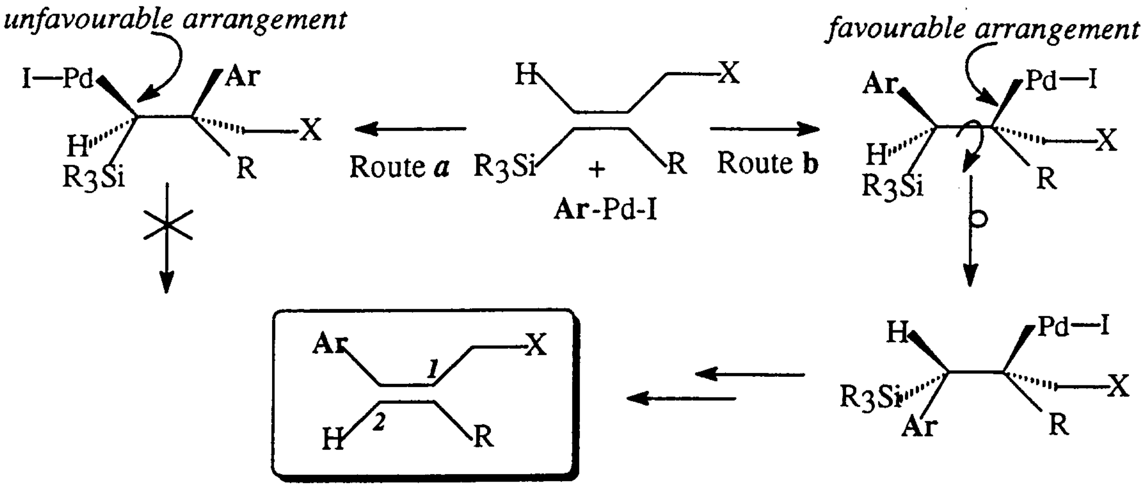
Ar = p-MeO-C_6H_4-, C_6H_5, p-Me-C_6H_4-, thenyl-

E. Blart, A. Ricci, *work in progress*

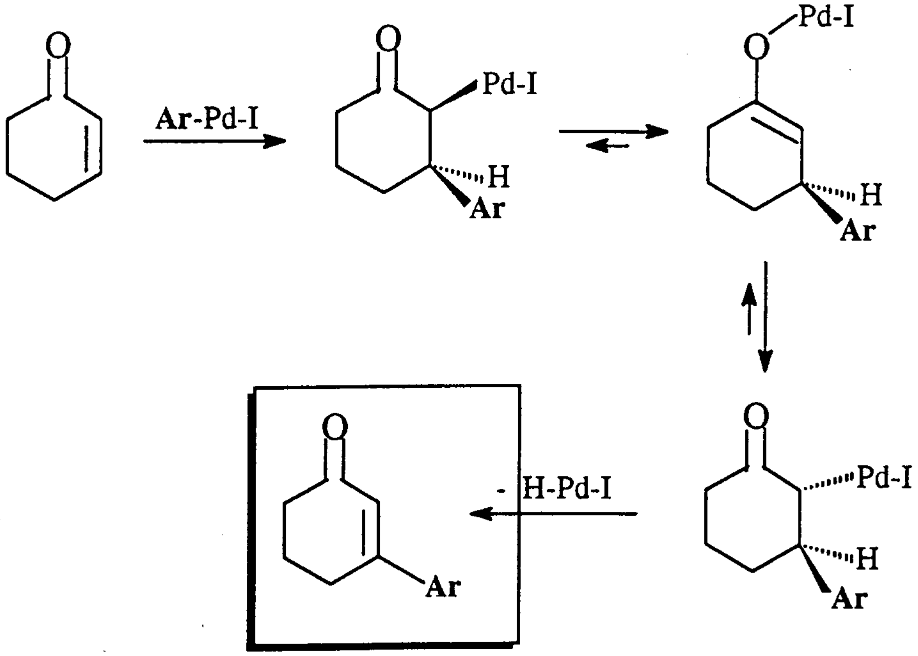

X
Me2PhSi
D
Pd(0), Ar-I
D
X
Ar


H
NHBoc
Me2PhSi
H
Ar-Pd-I
I—Pd
Ar
H
Me2PhSi
H
NHBoc
H
Ar
Me2PhSi
NHBoc
- H-Pd-I
I—Pd
H
H
Ar
Me2PhSi
NHBoc
to the catalytic cycle
+ H-Pd-I
H
Pd—I
H
Ar
Me2PhSi
NHBoc
Me2PhSi
Pd—I
H
H
Ar
NHBoc
Pd[0]
- I-Pd-SiMe2Ph
R3N
H
Ar
H
NHBoc
Me2PhSiI

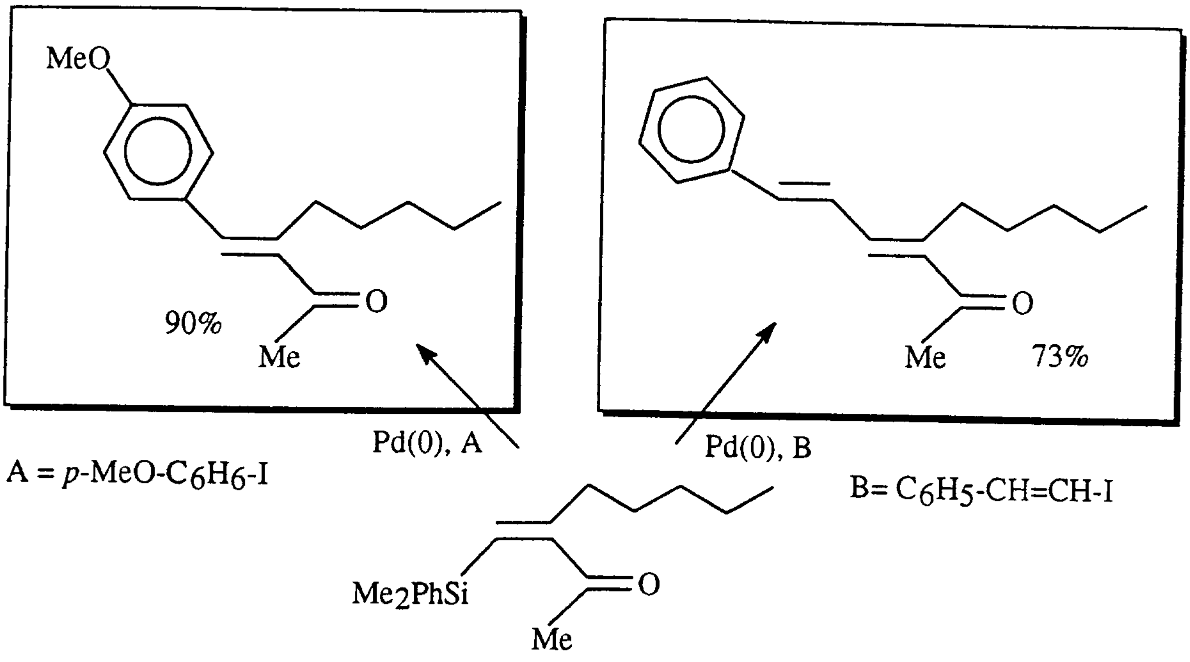
A Route to the Trisubstituted Olefins



A C-1 interaction with Pd (route **b**) can be favoured by conjugated carbonyl groups :

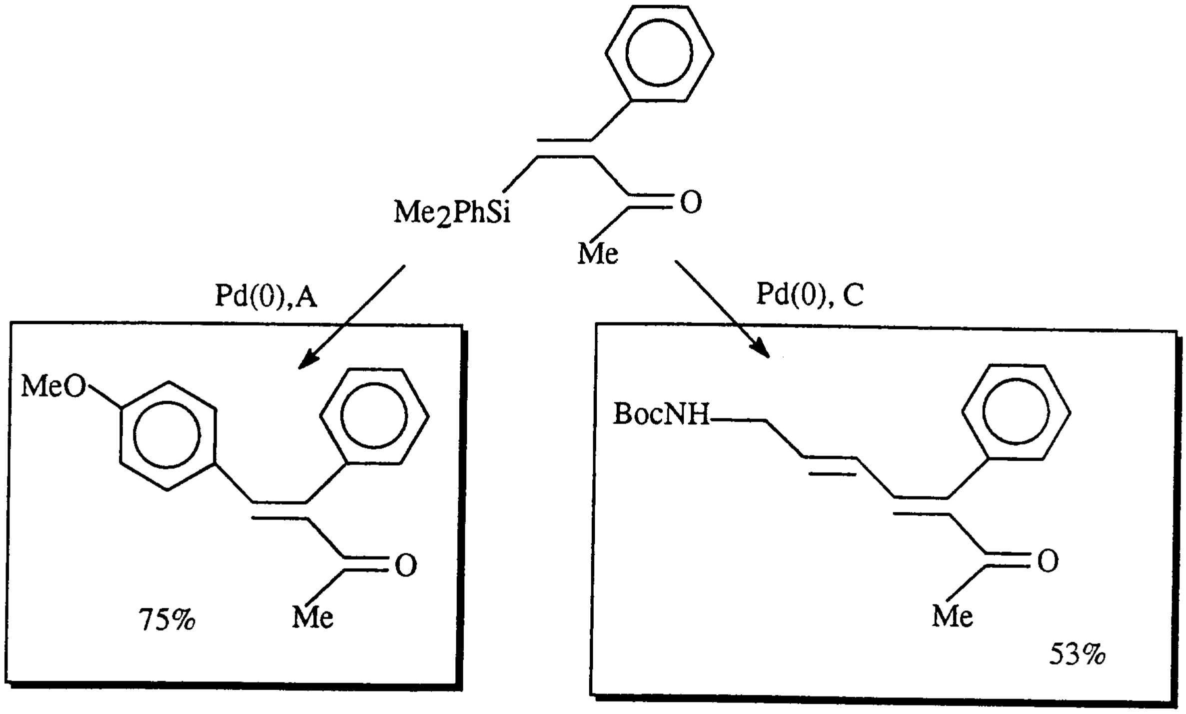


Genet, J.P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715.



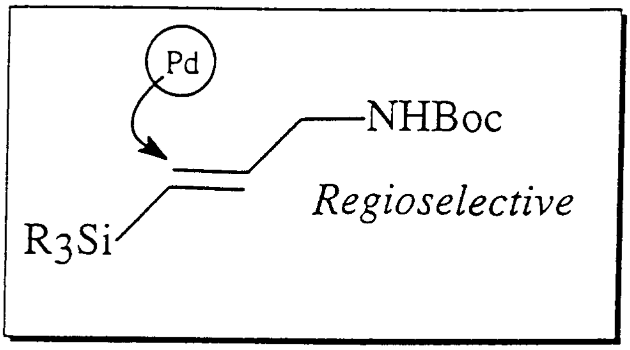
A = p-MeO-C_6H_6-I

B= C_6H_5-CH=CH-I

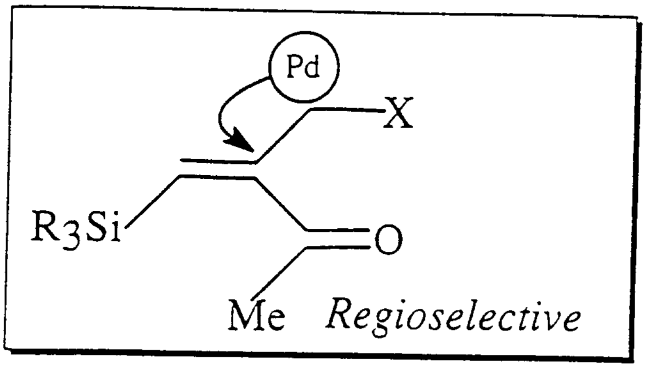


C= BocNH-CH_2-CH=CH-I (*E*)

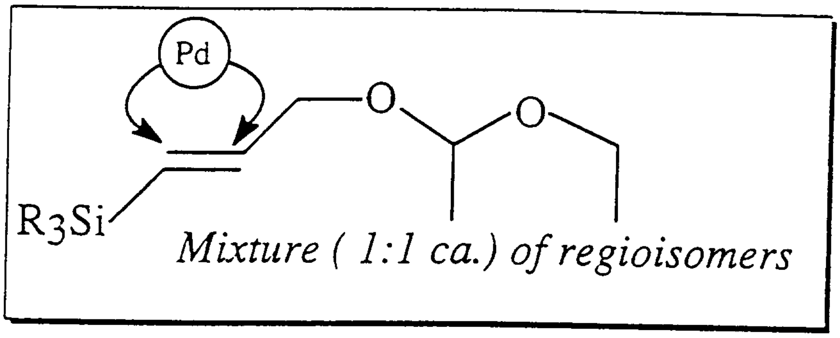
Ricci, A.; Blart, E. *work in progress*



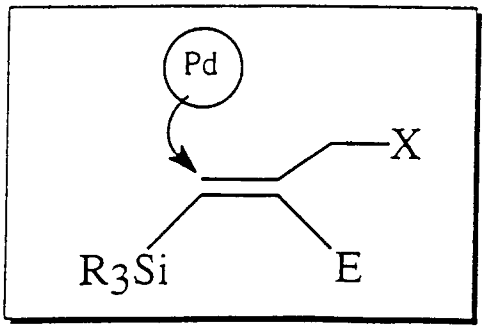
Regioselective

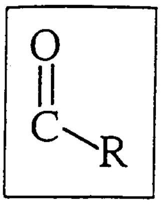


Regioselective



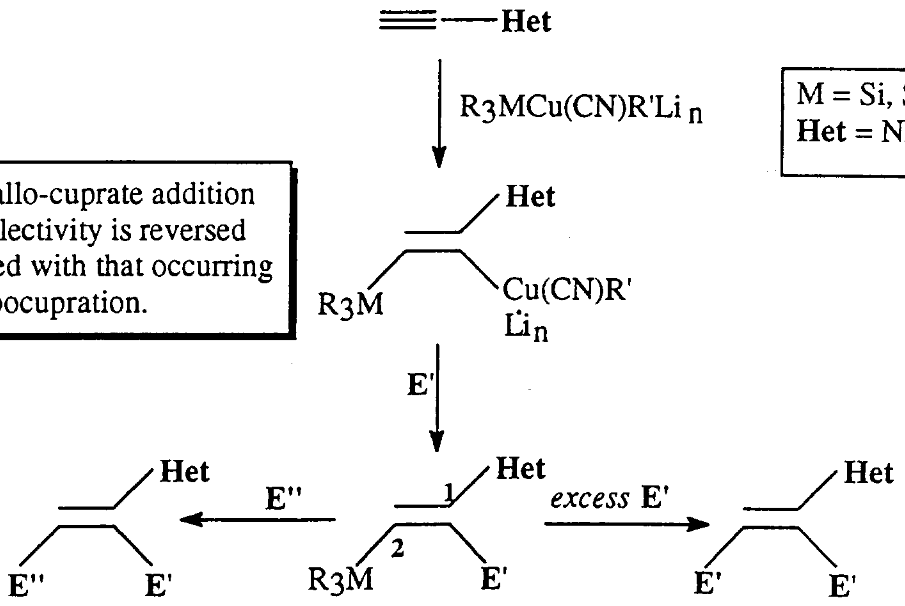
Mixture (1:1 ca.) of regioisomers



with E ≠ from  or H

$RC(=O)-$

Unfavourable situation for the reactivity



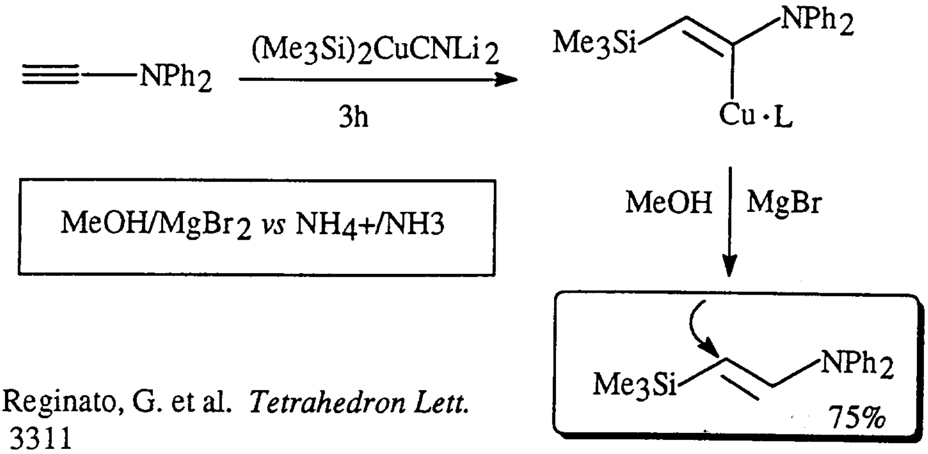
M = Si, Sn
Het = NPh$_2$, SCH(CH$_3$)$_2$

In the metallo-cuprate addition the regioselectivity is reversed as compared with that occurring in the carbocupration.

The presence of an heteroatom-based functionality (N or S) at C-1 conveys to the vinyl organometallic moiety at C-2 unusually high reactivity which allows for *functionalization with electrophiles in the absence of catalysts*.

$$Me_3Si.SiMe_3 + MeLi \xrightarrow[-78°C \to 0°C]{HMPA/THF} Me_3SiLi + Me_4Si$$

$$2Me_3SiLi + CuCN \xrightarrow[-23°C]{} (Me_3Si)_2CuCNLi_2$$

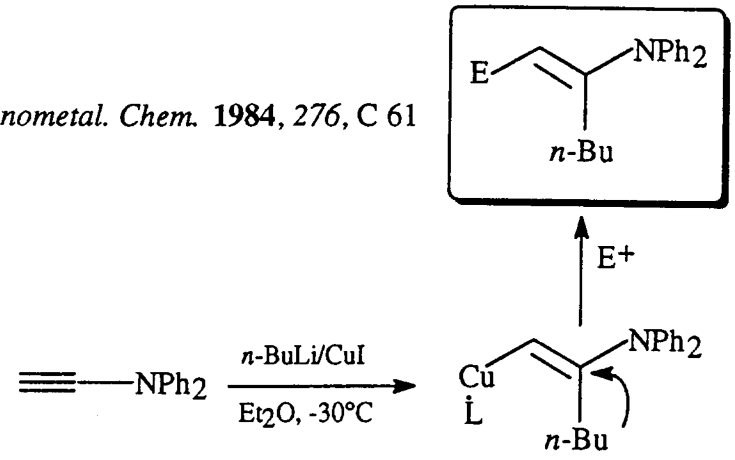


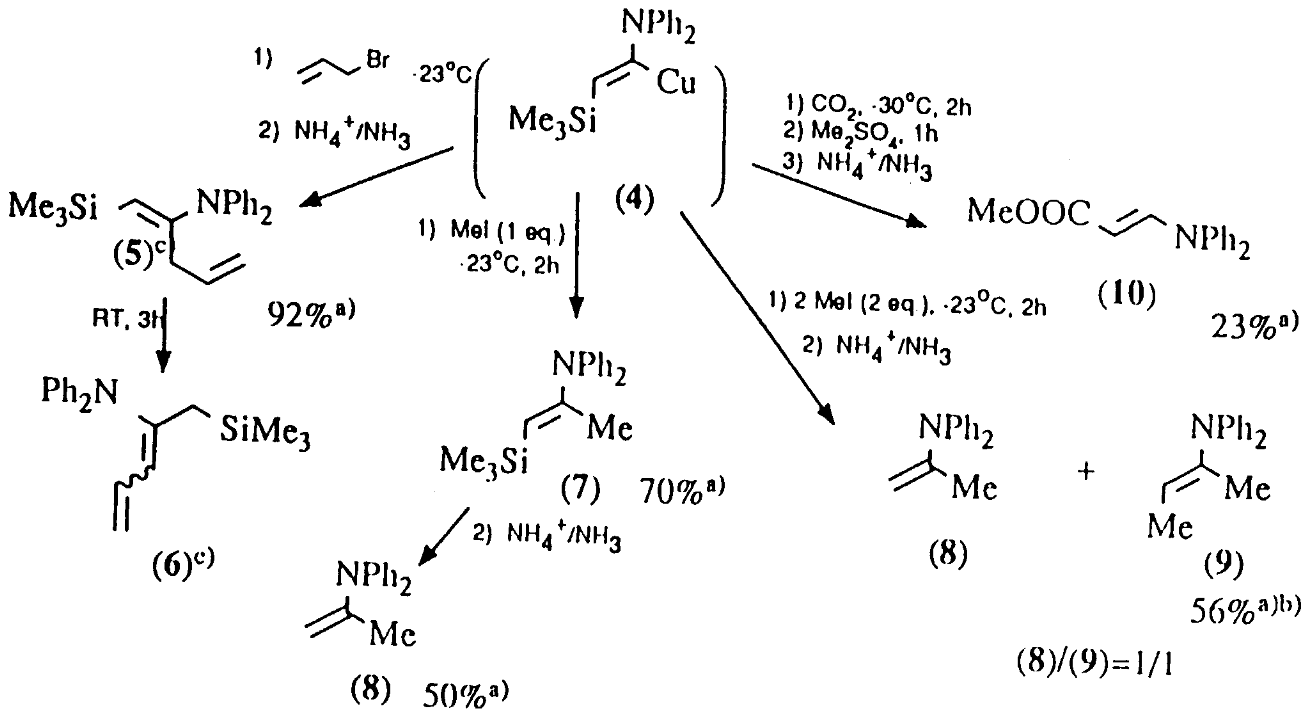
MeOH/MgBr$_2$ *vs* NH$_4$+/NH3

J *trans* = 16.6 Hz

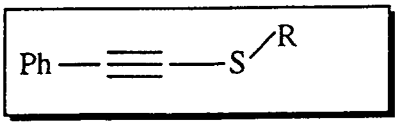
Ricci,A.; Reginato, G. et al. *Tetrahedron Lett.* **1993**, *34*, 3311

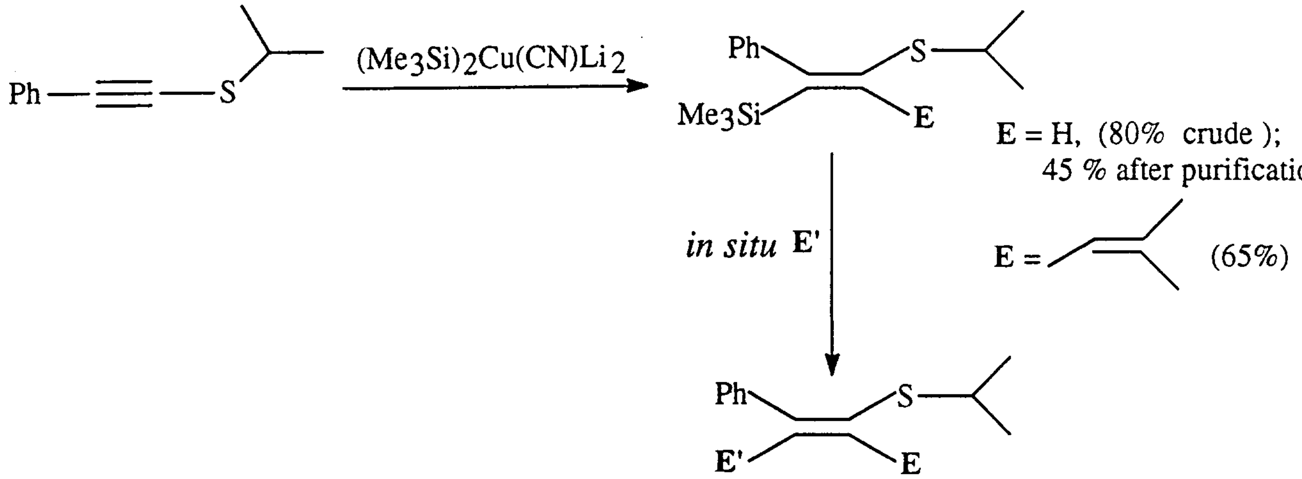
Corriu,R. et al. *J. Organometal. Chem.* **1984**, *276*, C 61




NPh2
Cu
Me3Si
(4)
1) Br ·23°C
2) NH4+/NH3
Me3Si
NPh2
(5)c
92%a)
RT, 3h
Ph2N
SiMe3
(6)c)
1) MeI (1 eq.) ·23°C, 2h
NPh2
Me
Me3Si
(7) 70%a)
2) NH4+/NH3
NPh2
Me
(8) 50%a)
1) CO2, ·30°C, 2h
2) Me2SO4, 1h
3) NH4+/NH3
MeOOC
NPh2
(10)
23%a)
1) 2 MeI (2 eq.), ·23°C, 2h
2) NH4+/NH3
NPh2
Me
(8)
+
NPh2
Me
Me
(9)
56%a)b)
(8)/(9)=1/1

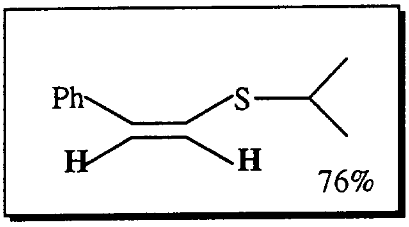
Silyl-cupration of acetylenic sulphides



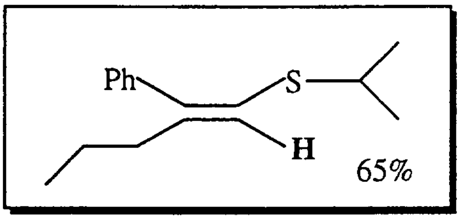


E = H, (80% crude);
45 % after purificatio

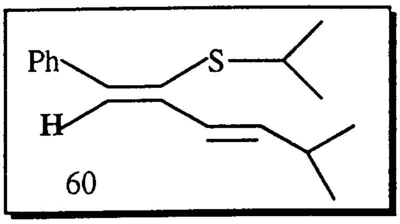
E = (65%)



76%



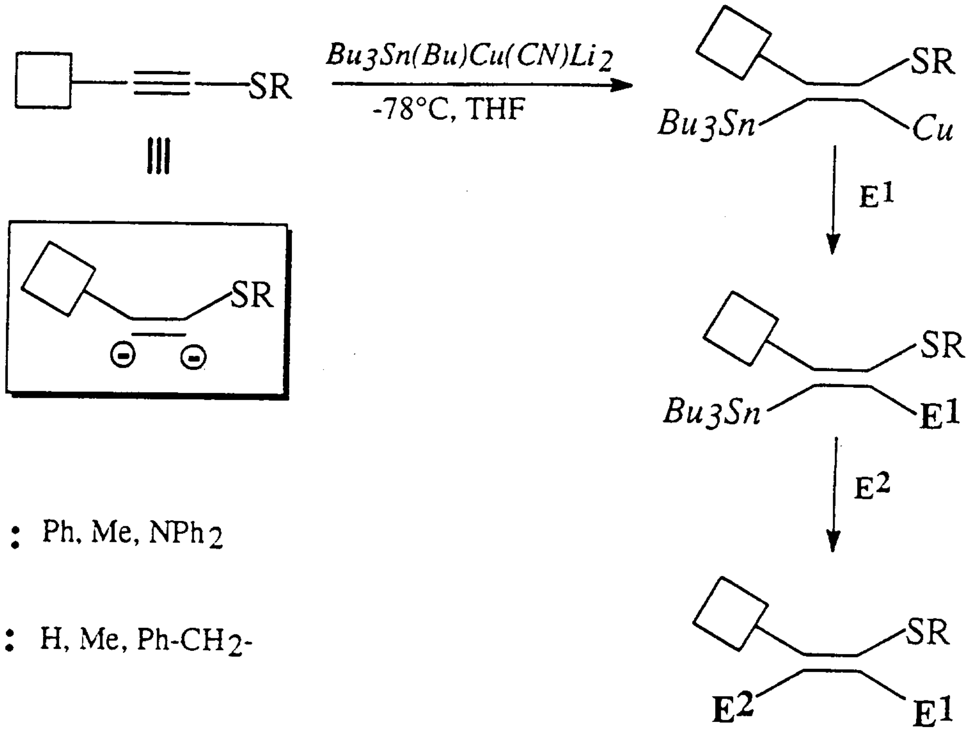
65%



60

Viable route to polysubstituted vinylic sulphides

Casarini, A.; Ricci, A. unpublihed results (*work in progress*)



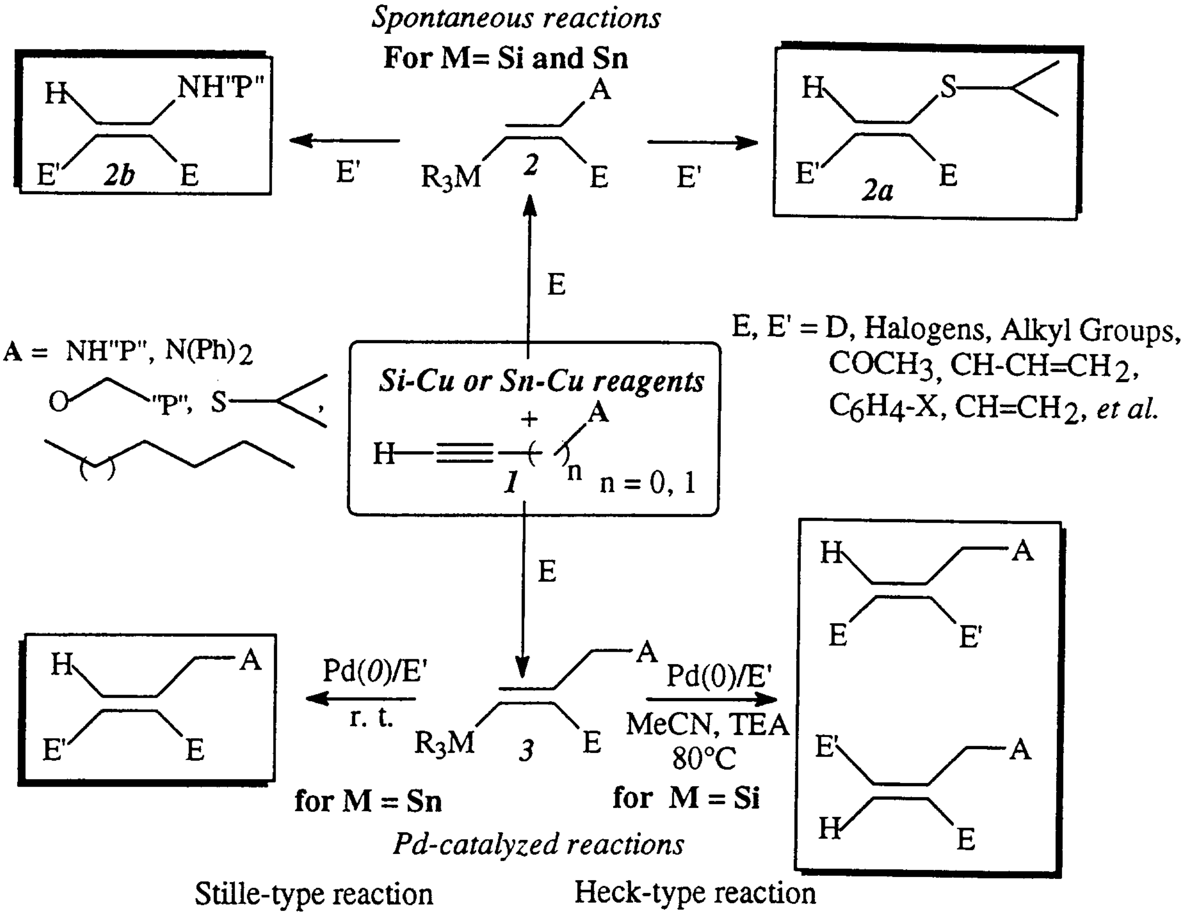
□ : Ph, Me, NPh$_2$

E^1 : H, Me, Ph-CH$_2$-

E^2 : CO$_2$/Me$_2$SO4, CH$_2$=CH-CH$_2$-

yields ranging from 35 to 75 %

Casarini, A.; Ricci, A. *submitted for publication* (1994)


Spontaneous reactions
For M= Si and Sn
H
NH"P"
E'
2b
E
E'
A
R3M
2
E
E'
H
S
E'
2a
E
E
A = NH"P", N(Ph)2
O "P", S
E, E' = D, Halogens, Alkyl Groups,
COCH3, CH-CH=CH2,
C6H4-X, CH=CH2, et al.
Si-Cu or Sn-Cu reagents
+
A
H
1
n
n = 0, 1
E
H
A
E
E'
H
A
E'
E
Pd(0)/E'
r. t.
A
R3M
3
E
Pd(0)/E'
MeCN, TEA
80°C
E'
A
H
E
for M = Sn
for M = Si
Pd-catalyzed reactions
Stille-type reaction
Heck-type reaction