Angewandte Chemie International Edition

DOI: 10.1002/anie.201004658

Allylic Substitution

Copper-Catalyzed Si–B Bond Activation in Branched-Selective Allylic Substitution of Linear Allylic Chlorides[**]

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The transmetalation of interelement linkages with Cu^I–Oalkyl complexes provides a facile entry into nucleophilic main group element/copper(I) compounds. An intriguing σ-bond metathesis is believed to be the activating step, thus building a conceptual bridge between the emerging areas of Cu^I–H,[1a] Cu^I–*B*,[1b] and Cu^I–*Si*[1c] chemistry (**I–III**; Figure 1). Both conjugate addition[2–4] and allylic or propargylic substitutions[5–7] with these reagents are currently attracting tremendous attention.

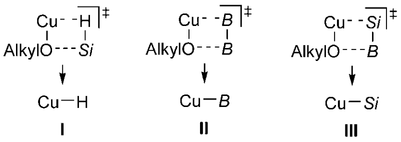
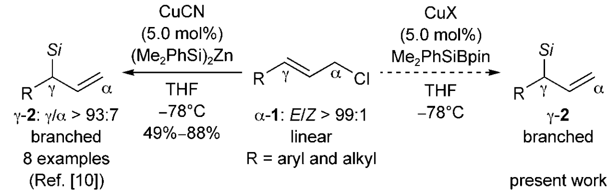


Figure 1. Transmetalation of interelement linkages through σ-bond metathesis as the common denominator (*Si* = $SiMe_2Ph$ and *B* = Bpin with pin = pinacolato).

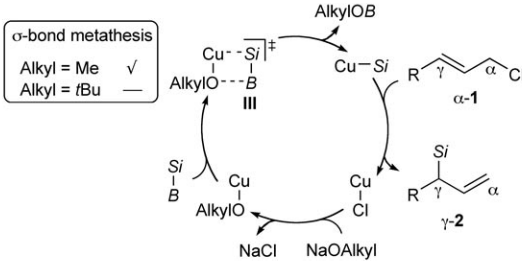


Scheme 1. Branched-selective allylic substitution of allylic chlorides. THF = tetrahydrofuran.

As part of our continuing focus on selective C–Si bond-forming reactions, we have developed a broadly applicable method for the catalytic generation of Cu^I–*Si* reagents from $(Me_2PhSi)_2Zn$ and CuX (X = I or CN).[8] The thus-generated silicon-based cuprate reagents were particularly useful for the preparation of branched allylic silanes, either by enantiospecific allylic substitution of α-chiral allylic precursors with an oxygen leaving group (carboxylate or carbamate)[9] or by regioselective allylic transposition of linear allylic halides (α-**1**→γ-**2**; Scheme 1, left).[10] An alternative way of accessing a Cu^I–*Si* reagent is the above-mentioned activation of a Si–B bond with a copper(I) alkoxide (**III**; Figure 1).[4,11] Treatment of readily prepared $Me_2PhSiBpin$[12] with CuX (X = O*t*Bu[4] or OAc[11]) is expected to yield $Me_2PhSiCu$, the same copper(I) complex as generated from $(Me_2PhSi)_2Zn$ and CuX (X = I or CN). These Cu^I–*Si* reagents only seem to be identical (neglecting different counteranions), as the latter is contaminated with excess lithium chloride introduced with the zinc reagent.[8] The lithium chloride is an issue in asymmetric variants, and we verified experimentally the detrimental effect of lithium cations on enantioselective conjugate additions.[13] The role of chloride anions still remains to be elucidated. It is therefore desirable to devise a method for the generation of Cu^I–*Si* reagents[14] not burdened with excess lithium chloride. Herein, we report an unprecedented allylic substitution of linear allylic chlorides to produce branched allylic silanes by utilizing the copper-catalyzed activation of a Si–B bond (α-**1**→γ-**2**; Scheme 1, right).

Our previous studies on the γ-selective allylic transposition of linear allylic precursors by using the $(Me_2PhSi)_2Zn$-derived copper(I) reagent had shown that allylic chlorides α-**1** were superior (*rs* > 93:7; see Scheme 1).[10] We therefore started to survey $Me_2PhSiBpin$–CuCN combinations with and without additives in that reaction (α-**1a**→γ-**2a** and α-**2a**; Table 1). CuCN alone was unable to promote this allylic displacement (Table 1, entry 1). Unexpectedly, no conversion was seen despite the addition of NaO*t*Bu to form air- and moisture-sensitive CuO*t*Bu (Table 1, entry 2). NaO*t*Bu is a common base in such copper(I) catalyses,[2–6] and our result stands in contrast to the report by Lee and Hoveyda (see Scheme 2).[4] The use of NaOMe instead of bulkier NaO*t*Bu was, however, successful (Table 1, entry 3), thus agreeing with findings by Chatani and co-workers (CuOAc/MeOH).[11]

The moderate level of regiocontrol (γ/α = 90:10) was improved to excellent regioselectivity (γ/α = 98:2) by lowering the reaction temperature from 0 °C to –78 °C (Table 1,



Scheme 2. Proposed catalytic cycle.

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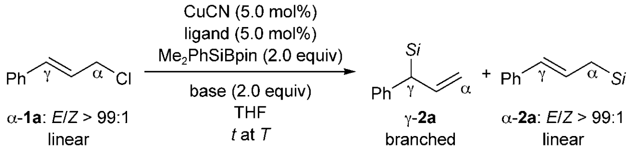
[**] D.J.V. thanks the NRW Graduate School of Chemistry for a predoctoral fellowship (2008–2011).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201004658.

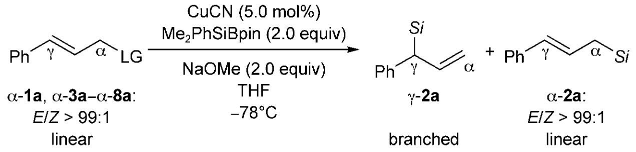
Table 1: Optimization of the reaction conditions.[a]



Entry	Base	Ligand	T [°C]	t [h]	γ/α[b]	Yield [%][c]
1	–	–	0→RT	48	–	–[d]
2	NaO*t*Bu	–	0	1	–	–[e]
3	NaOMe	–	0	1	90:10	71
4	NaOMe	–	−78	6	98:2	88
5	NaOMe	Ph_3P[f]	0→RT	24	96:4	71
6	NaOMe	dppp	0→RT	72	95:5	56
7	NaOMe	dppf	0→RT	24	98:2	71
8	NaOMe	DPEphos	0→RT	48	98:2	57

[a] All reactions were conducted according to the general procedure with addition of the indicated ligand (entries 5–8). [b] Ratio of regioisomers determined by GLC analysis prior to purification. [c] Combined yield of analytically pure regioisomers after purification by flash chromatography on silica gel. [d] No reaction. [e] No conversion of allylic chloride and decomposition of $Me_2PhSiBpin$ observed. [f] 10 mol%. dppp = 1,3-bis(diphenylphosphanyl)propane, dppf = 1,1′-bis(diphenylphosphanyl)-ferrocene, DPEphos = bis(2-diphenylphosphanylphenyl) ether.

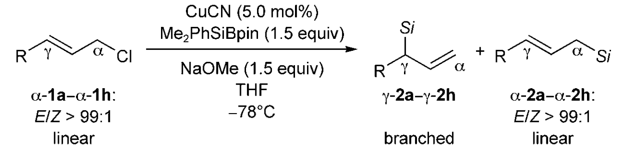
Table 2: Survey of leaving groups.[a]



Entry	Allylic precursor	Leaving group	γ/α[b]	Yield [%][c]
1	α-**1a**	Cl	98:2	88
2	α-**3a**	Br	72:28	89
3	α-**4a**	$OP(O)(OEt)_2$	91:9	85
4	α-**5a**	OC(O)OEt	16:84	79
5	α-**6a**	OC(O)NHPh	18:82	70
6	α-**7a**	OC(O)Ph	18:82	83
7	α-**8a**	OC(O)Me	19:81	74

[a] All reactions were conducted according to the general procedure, using the indicated allylic precursors α-**3a**–α-**8a**. [b] Ratio of regioisomers determined by GLC analysis prior to purification. [c] Combined yield of analytically pure regioisomers after purification by flash chromatography on silica gel. LG = leaving group.

Table 3: Copper-catalyzed, γ-selective allylic substitution of allylic chlorides.



Entry	Allylic precursor	Substituent R	Allylic silane	γ/α[a]	Yield [%][b]
1	α-**1a**	Ph	γ/α-**2a**	98:2	88
2	α-**1b**	$4\text{-}MeOC_6H_4$	γ/α-**2b**	98:2	77[c]
3	α-**1c**	$3\text{-}MeOC_6H_4$	γ/α-**2c**	99:1	94
4	α-**1d**	$4\text{-}F_3CC_6H_4$	γ/α-**2d**	98:2	83
5	α-**1e**	$4\text{-}BrC_6H_4$	γ/α-**2e**	98:2	95
6	α-**1f**	Cy	γ/α-**2f**	>99:1	81
7	α-**1g**	*i*Pr	γ/α-**2g**	>99:1	84
8	α-**1h**	Me_3Si	γ/α-**2h**	76:24	72

[a] Ratio of regioisomers determined by GLC analysis or by ^1H NMR spectroscopy prior to purification. [b] Combined yield of analytically pure regioisomers after purification by flash chromatography on silica gel. [c] Yield of isolated product over two steps based on the corresponding allylic alcohol. Cy = cyclohexyl.

entries 3 and 4). Both γ/α ratios are perfectly in accord with those obtained with the $(Me_2PhSi)_2Zn–CuCN$ reagent,[10] again corroborating the assumption that $Me_2PhSiCu$ is the nucleophile in these catalyses.[8d,10] We then tested Ph_3P and a series of bidentate phosphines (Table 1, entries 5–8) to see whether a prospective asymmetric variant would be potentially fruitful. Added ligands had a dramatic effect on the reaction rate, and the reactions had to be performed at 0 °C. It is remarkable though that the regioselectivities were as high as those obtained under the "ligand-free" reaction conditions at −78 °C. A control experiment without CuCN but with NaOMe gave no conversion.

With the phosphine-free protocol in hand, we next probed the effect of the leaving group on the regioselectivity (α-**3a**–α-**8a** → γ-**2a** and α-**2a**; Table 2). We were anticipating the same trend as in our previous study,[10] that is, γ selectivity for halides and phosphates (Table 2, entries 1–3) and α selectivity for carbonates, carbamates, and carboxylates (Table 2, entries 4–7). We found this to be also true for the novel catalytic system with a noteworthy deviation: α-**5a**–α-**8a** with oxygen leaving groups react with substantially eroded α selectivities of γ/α ≈ 18:82 (Table 2, entries 4–7) as opposed to flawless γ/α < 1:99 in the cuprate series.[8c,10] From this data, it appears that the $Me_2PhSiBpin–CuCN–NaOMe$ system tends to prefer the branched isomer.

Encouraged by the superb regioselectivity obtained with α-**1a**, we set out to extend the scope of the new method (α-**1b**–α-**1h** → γ-**2b**–γ-**2h** and α-**2b**–α-**2h**; Table 3). We were also able to use less $Me_2PhSiBpin$ and NaOMe, now 1.5 equivalents each. To our delight, both aryl- and alkyl-substituted precursors α-**1a**–α-**1e** and α-**1f**–α-**1g**, respectively, yielded the corresponding allylic silanes with excellent regioselectivities (Table 3, entries 1–5 as well as entries 6 and 7), exceeding previously reported ones.[10] The γ/α ratio for silyl-substituted α-**1h** was comparable to that seen with the known method[10] (Table 3, entry 8). We explain this modest γ selectivity (γ/α = 76:24) by a steric rather than an electronic effect because the *t*Bu-substituted allylic chloride (not shown) reacted with even worse selectivity (γ/α = 62:38), whereas *i*Pr-substituted α-**1g** produced the γ regioisomer with γ/α > 99:1 (Table 3, entry 7).

The tentative mechanism (Scheme 2) is based on the quantumchemical analysis of the related activation of the B–B linkage by Marder and co-workers (**II** and **III**; Figure 1).[1b] We emphasize the role of added or generated alkoxide: O*t*Bu[4] (in CuO*t*Bu) is likely to be too sterically hindered to allow for the σ-bond metathesis to occur, whereas OMe (in

CuOMe[11]) secures smooth Si–B bond activation, which agrees with our experiments (Table 1, entries 2 and 3).

This copper-catalyzed Si–B bond activation through transmetalation and its application to allylic substitution closes an important gap.[18] It is a competitive alternative to the established cuprate chemistry.[8a,10] Branched allylic silanes are now accessible with synthetically useful levels of regiocontrol. We also showed that phosphine ligands are tolerated in this catalysis, finally opening the door to asymmetric variants.[9,19–21]

Received: July 28, 2010

Keywords: allylic substitution · copper · regioselectivity · silicon · transmetalation

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[14] Our research group introduced the rhodium-catalyzed Si–B activation,[15] which is likely to follow a similar transmetalation mechanism (see **III**; Figure 1). The resultant nucleophilic Rh^{I}–*Si* reagent participates in conjugate addition[15] and propargylic substitution[16] but, in our hands, not in allylic substitution.[17] We, therefore, decided to study the related copper(I) catalysis.

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[21] A few test runs using binap ($rs = 98:2$) and josiphos ($rs = 90:10$) yielded only racemic γ-**2a**, not even reaching full conversion after several days at ambient temperature (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl and josiphos = 1-[2-(diphenylphosphanyl)ferrocenyl]ethyldicyclohexylphosphine).