Practical Synthesis of Allylic Silanes from Allylic Esters and Carbamates by Stereoselective Copper-Catalyzed Allylic Substitution Reactions

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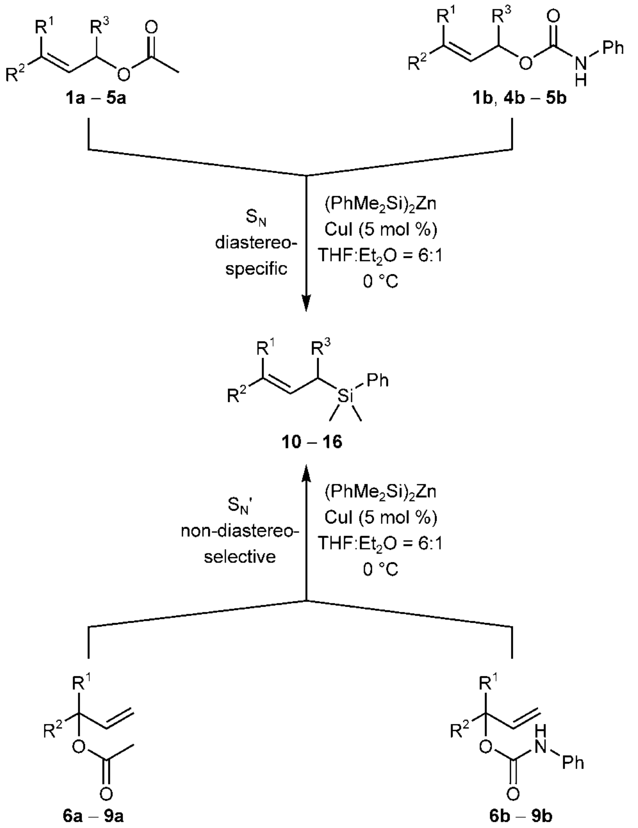
Abstract: The first copper-catalyzed allylic substitution reactions of allylic acetates and carbamates employing a bis(triorganosilyl)zinc reagent are reported. This novel procedure avoids the use of stoichiometric amounts of copper salts which are usually mandatory with this chemistry. Application of this methodology to standard model substrates substantiates a high diastereoselectivity for the double bond geometry (E:Z) as well as the relative configuration (*syn*:*anti*).

Keywords: allylic compounds; copper; cuprates; silicon; zinc

Allylic silanes are important silicon-based reagents, which have found broadest application in synthetic methodology as well as numerous complex molecule syntheses.[1–3] Several reliable reaction protocols have been developed for the preparation of allylic silanes.[3] Among these, the allylic substitution of allylic esters and carbamates employing silyl cuprates is well established.[4–8] Even so, the generation of silicon-copper reagents such as $(PhMe_2Si)_2Cu(CN)Li_2$ requires stoichiometric amounts of copper as they are accessed from the requisite silyllithium (2.0 equivs.) and a copper salt (1.0 equiv.). This quantitative transmetallation from lithium to copper appears indispensable since the silyllithium alone is a hard and basic nucleophile.

Based on an almost unnoticed report by Nozaki,[9] we have recently introduced soft bis(triorganosilyl)zinc species, such as $(PhMe_2Si)_2Zn$, which display decreased nucleophilicity and basicity when compared with the corresponding silyllithium.[10] Therefore, these mild zinc reagents are well suited for copper-catalyzed reactions. In this context, we have realized a facile copper-catalyzed conjugate addition of $(PhMe_2Si)_2Zn$ to α,β-unsaturated carbonyl compounds.[10] In this communication, we report that bis(triorganosilyl)zinc species are also applicable to allylic substitution reactions of esters **1a**–**9a** and carbamates **1b**, **4b**–**9b** under copper catalysis (Scheme 1). Our novel procedure avoids the use of equimolar amounts of copper (based on transferred silyl moiety) while showing similar diastereoselectivities and yields as the stoichiometric process developed by Fleming.[5]

Acetates **1a**–**9a**[11a] as well as carbamates **1b**, **4b**–**9b**[11b] investigated in this survey were synthesized in good yields from the corresponding alcohols using standard procedures except for cyclic acetates **2a** and **3a**, which were directly prepared from alkenes according to a procedure by Åkermark.[11c]



Scheme 1. Copper-catalyzed allylic substitution (S_N or S_N').

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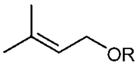
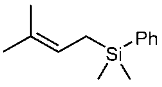
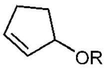
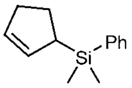
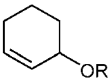
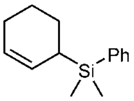
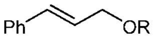
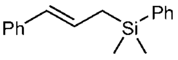
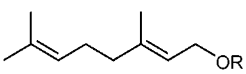
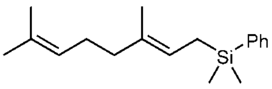
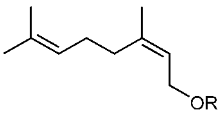
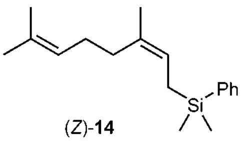
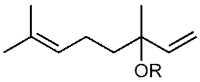
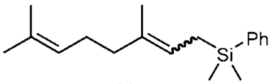
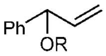
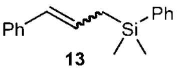
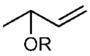
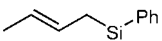
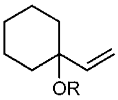
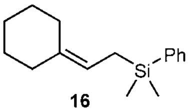
Table 1. Copper-catalyzed allylic substitution of allylic acetates **1a**–**9a** and carbamates **1b**, **4b**–**9b**.[a]

Entry	Allylic Substrate **a** (R=Ac) or **b** [R=C(O)NHPh]	*E*:*Z* of Substrate	Allylic Silane	*E*:*Z* of Silane	Yield [%] (Acetate)[b]	Yield [%] (Carbamate)[b]
1	 **1a** or **1b**	–	 **10**	–	62	95
2	 **2a**	–	 **11**	–	68	–
3	 **3a**	–	 **12**	–	82	–
4	 (*E*)-**4a** or (*E*)-**4b**	99:1[c]	 (*E*)-**13**	99:1[c]	75	70
5	 (*E*)-**5a** or (*E*)-**5b**	99:1[d]	 (*E*)-**14**	99:1[d]	83	65
6	 (*Z*)-**5a** or (*Z*)-**5b**	1:99[d]	 (*Z*)-**14**	1:99[d]	96	90
7[e]		1:99[d]		1:99[d]	98	97
8[f]		1:99[d]		1:99[d]	97	86
9	 **6a** or **6b**	–	 **14**	50:50[d]	90	82
10	 **7a** or **7b**	–	 **13**	50:50[c, g]	74	68
11	 **8a** or **8b**	–	 (*E*)-**15**	85:15[c]	66	83
12	 **9a** or **9b**	–	 **16**	–	74	83

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[a] All reactions were conducted with a substrate concentration of 0.14 M on a 1.00-mmol scale using 5.0 mol % of CuI (see Representative Procedure for details).

[b] Yield of analytically pure product after flash chromatography on silica gel.

[c] Determined from the ^{1}H NMR spectra of the crude reaction mixture by integration of baseline separated resonance signals.

[d] Determined from the ^{13}C NMR spectra of the crude reaction mixture since the ^{1}H NMR spectra of the double bond isomers are almost identical; a single isomer was detected for (*E*)-**14** and (*Z*)-**14**, respectively.

[e] Reactions were performed on a 25.0-mmol scale using 5.0 mol % of CuI.

[f] Reactions were performed on a 5.00-mmol scale using 1.0 mol % of CuI.

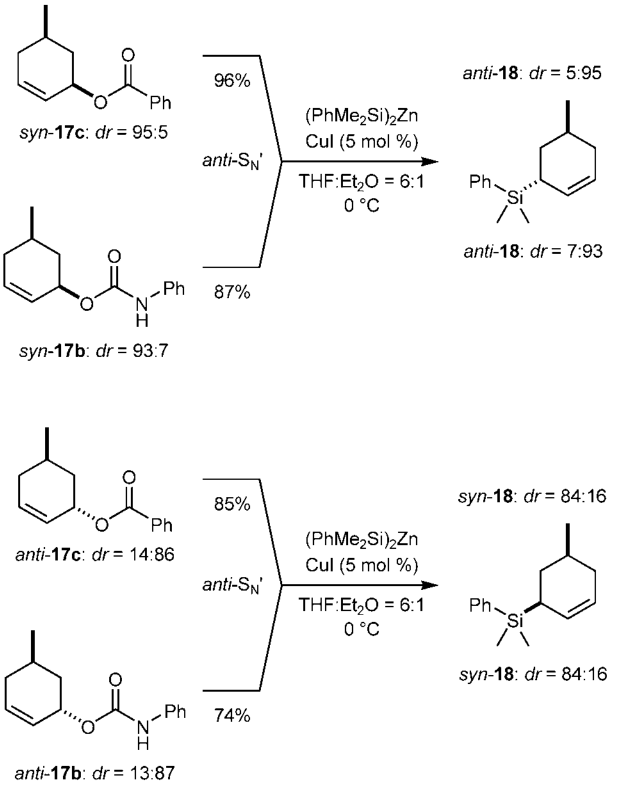
[g] Ratios ranged from 40:60 to 60:40.

Simple prenyl acetate **1a** and carbamate **1b** underwent clean allylic substitution (S_N) when added to a solution of $(PhMe_2Si)_2Zn$ pre-treated with catalytic amounts (5 mol %) of copper iodide but with a higher yield for the latter substrate (Table 1, Entry 1); likewise, good yields were obtained for cyclic secondary acetates **2a** and **3a** (Table 1, Entries 2 and 3). As expected, allylic substitution of cinnamic ester (*E*)-**4a** and carbamate (*E*)-**4b** proceeded with complete preservation of the double bond geometry in good yields (Table 1, Entry 4). In order to further verify the stereoselectivity of the allylic substitution, we independently subjected isomerically pure geranyl acetate (*E*)-**5a** and neryl acetate (*Z*)-**5a** to these reaction conditions. We were pleased to find that allylic silanes (*E*)-**14** and (*Z*)-**14**, respectively, were formed with excellent diastereoselectivity in high yields. The corresponding carbamates (*E*)-**5b** and (*Z*)-**5b** performed equally well (Table 1, Entries 5 and 6).

In contrast, allylic substitution (S_N') of linalyl acetate **6a** and carbamate **6b** provided allylic silane **14** with no stereocontrol at all (Table 1, Entry 9). The same was observed for secondary acetate **7a** and carbamate **7b** (Table 1, Entry 10); only **8a** and **8b** showed some diastereoselectivity albeit not in synthetical useful *E*:*Z* ratios (Table 1, Entry 11). These results are in accordance with reported data.[4,5] Tertiary derivatives **9a** and **9b** furnished allylic silane **16** in high yields (Table 1, Entry 12).

As exemplified for the nerol-derived substrates (*Z*)-**5a** and (*Z*)-**5b**, the high yields remained completely unaffected on a 25.0-mmol scale (Table 1, Entry 7). Importantly, lowering the amount of catalyst from 5.0 mol % to 1.0 mol % on a 5.00-mmol scale was also met with success (Table 1, Entry 8). Both large-scale reactions and catalyst loadings as low as 1.0 mol % clearly underline the practicability of this procedure. It is noteworthy that all reactions were conducted without using an excess of the zinc reagent; these yields were achieved with equimolar quantities of $(PhMe_2Si)_2Zn$ and substrate. We routinely used copper iodide as the catalyst but other copper sources such as copper cyanide also work.

Fleming investigated the stereoselectivity of such allylic substitution reactions starting from disubstituted cyclic substrates *syn*-**17** and *anti*-**17**,[5c] which are accessible in diastereomerically enriched form by *syn*-selective reduction of the corresponding carbonyl compound[11d] and subsequent Mitsunobu inversion[5d] as an entry into the *anti* relative configuration. As previously shown using stoichiometric amounts of pre-formed silyl cuprate,[5c] allylic substitution of these substrates proceeded with high diastereoselectivity following an *anti*-S_N' mechanism. We were able to confirm these observations for our catalytic procedure (Scheme 2). Both benzoate *syn*-**17c** and carbamate *syn*-**17b** provided allylic silane *anti*-**18** with complete preservation of the (inverted) stereochemical information (*syn*-**17** → *anti*-**18**). Accordingly, substrates *anti*-**17c** and *anti*-**17b** with opposite relative configuration afforded *syn*-**18** (*anti*-**17** → *syn*-**18**).



Scheme 2. Diastereoselective copper-catalyzed allylic substitution (*anti*-S_N').

Upon quantitative deprotonation of the carbamate moiety followed by the addition of stoichiometric amounts of copper iodide and then the silyllithium, this group is transformed into a reagent-directing group[12] thereby switching the *anti*-S_N' into a *syn*-S_N' process.[5c] Not unexpectedly, this elegant diastereodivergent substitution of allylic carbamates **17b** failed for our catalysis! Again, clean *anti*-selectivity and comparable yields (78%) were detected for the deprotonated carbamate.

In summary, we have elaborated a practical reaction protocol for the first preparation of allylic silanes by a copper-catalyzed allylic substitution of allylic esters and carbamates. Apart from good to excellent yields, (1) allylic silanes are formed highly diastereoselectively (*E*:*Z*) when starting from primary allylic esters **4a**–**5a** and carbamates **4b**–**5b** (Table 1, Entries 4–8) and (2) high diastereospecifity (*anti*-S_N') is seen for the model substrates *syn*-**17** and *anti*-**17** (Scheme 2).

Experimental Section

Bis(dimethylphenylsilyl)zinc

Dimethylphenylsilyl chloride (427 mg, 2.50 mmol, 2.50 equivs.) was maintained with freshly cut lithium (large excess) in THF (4 mL) at −8 °C under an argon atmosphere for 18 h.

In order to separate the formed dimethylphenylsilyllithium (2.00 mmol, ~80% conversion) from unreacted lithium metal, the resulting dark red solution was transferred to another flask *via* a double-ended cannula. At 0 °C, $ZnCl_2$ (1.00 mL, 1.00 mmol, 1.00 equiv., 1 M in Et_2O) was added accompanied by a color change from red to yellowish brown. The reaction mixture was maintained at this temperature for further 15 min and was then ready to use.

Representative Procedure for the Copper-Catalyzed Allylic Substitution

A suspension of CuI (9.6 mg, 0.050 mmol, 5.0 mol %) and THF (1 mL) was pre-cooled to $-78\,^{\circ}C$ and treated with bis(dimethylphenylsilyl)zinc (1.00 mmol, 1.00 equiv.) *via* syringe. The auburn reaction mixture was allowed to warm to 0 °C and maintained at this temperature for 20 min. Addition of either geranyl/neryl acetate (*E*)-**5a**/(*Z*)-**5a** (196 mg, 1.00 mmol, 1.00 equiv.) or geranyl/neryl *N*-phenyl carbamate (*E*)-**5b**/(*Z*)-**5b** (273 mg, 1.00 mmol, 1.00 equiv.) in THF (1 mL) was followed by stirring for 1 h at 0 °C. Upon completion of the reaction, the mixture was poured into saturated aqueous NH_4Cl (5 mL) and the flask was rinsed with methyl *tert*-butyl ether (10 mL). The aqueous phase was separated and extracted with methyl *tert*-butyl ether (3 × 10 mL). The combined organic phases were extracted with brine (10 mL). After drying (Na_2SO_4), the solvents were evaporated under reduced pressure and the crude product, (*E*)-**14** or (*Z*)-**14** respectively, was purified by flash chromatography on silica gel using cyclohexane as solvent.

***(E)-(3,7-Dimethyl-2,6-octadienyl)dimethylphenylsilane* [(*E*)-14] (Table 1, Entry 5):** Colorless liquid; yield: 83% [from (*E*)-**5a**] and 65% [from (*E*)-**5b**]; R_f (cyclohexane) = 0.48; IR (cuvette): $\tilde{\nu}$ = 3055 (s), 2985 (s), 2686 (w), 2361 (m), 2307 (s), 2254 (m), 1549 (w), 1427 (s), 1264 (s), 1155 (m), 1113 (m), 1019 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.26$ (s, 6H), 1.50 (s, 3H), 1.61 (s, 3H), 1.63 (d, $J = 8.6$ Hz, 2H), 1.68 (s, 3H), 1.98 (m, 4H), 5.09 (tt, $J = 6.6$ Hz, $J = 1.3$ Hz, 1H), 5.18 (tq, $J = 8.6$ Hz, $J = 1.3$ Hz, 1H), 7.34 (m, 3H), 7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = -3.2$, 15.9, 17.7, 17.8, 25.8, 27.0, 40.1, 119.7, 124.7, 127.8, 128.9, 131.2, 133.3, 133.7, 134.3, 139.5; LR-MS (CI/NH_3): $m/z = 290$ $[(M+NH_4)^+]$, 273 $[(M+H)^+]$; anal. calcd. for $C_{18}H_{28}Si$ (272.50): C 79.34, H 10.36; found: C 79.13, H 10.22.

***(Z)-(3,7-Dimethyl-2,6-octadienyl)dimethylphenylsilane* [(*Z*)-14] (Table 1, Entries 6–8):** Colorless liquid; yield: 96–98% [from (*Z*)-**5a**] and 86–97% [from (*Z*)-**5b**]; R_f (cyclohexane) = 0.48; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.28$ (s, 6H), 1.62 (s, 3H), 1.67 (d, $J = 8.6$ Hz, 2H), 1.70 (s, 6H), 1.95 (m, 4H), 5.11–5.14 (m, 1H), 5.17 (t, $J = 8.6$ Hz, 1H), 7.35 (m, 3H), 7.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = -3.1$, 17.4, 17.7, 23.4, 25.8, 26.5, 31.8, 119.9, 124.7, 127.8, 128.9, 129.2, 131.4, 133.7, 134.3, 139.4.

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