Silicon Grignard Reagents as Nucleophiles in Transition-Metal-Catalyzed Allylic Substitution

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Allylic silanes are an often-used class of silicon reagents and continue to be widely applied in synthesis.1 Several methods are available that provide reliable access to these compounds.2–4 One established methodology is by transition-metal-catalyzed allylic substitution of allylic precursors with silicon (pro)nucleophiles such as Si–Si2 and Si–B3 compounds as well as zinc4 reagents. Examples with copper complexes as catalysts pertinent to the present study are summarized in Scheme 1 (top). The reverse approach, that is, the nucleophilic displacement at silicon electrophiles, is far less general.5

We recently developed a robust method for the preparation of bench-stable solutions of silicon Grignard reagents 1 (Scheme 1, bottom).7 These had essentially been not available previously,8 and we decided to assess their suitability for various transition-metal catalysts with emphasis on the influence of the leaving group for primary allylic precursors, favoring α over γ. The stereochemical course of this allylic transposition was probed with a cyclic system, and anti-diastereoselectivity was obtained.

Key words allylic substitution, copper, Grignard reagents, silicon

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Abstract A broad range of transition-metal catalysts is shown to promote allylic substitution reactions of allylic electrophiles with silicon Grignard reagents. The procedure was further elaborated for CuI as catalyst. The regioselectively is independent of the leaving group for primary allylic precursors, favoring α over γ. The stereochemical course of this allylic transposition was probed with a cyclic system, and anti-diastereoselectivity was obtained.

Copper-catalyzed allylic substitution with R3SiBpin or (R3Si)2Zn

Our approach to the preparation of silicon Grignard reagents

Scheme 1 Copper-catalyzed allylic substitution with silicon (pro)nucleophiles (top; LG: leaving group) and preparation of silicon Grignard reagents (bottom)

without additional ligands (Table 1, entries 1–6). Any of these catalysts enabled the reaction, affording the linear allylic silane α-α-3a in near-quantitative yields using NiBr2·glyme, Cul, and CuCN; however, MnBr2, FeCl3, and CoCl2 furnished the desired product in somewhat lower yields. Also, (E)-2a underwent silylation in the presence of PdCl2 (entry 7). In all these reactions, the thermodynamically favored α-regioisomer was formed with high α/γ ratio. The yield remained high when 2 mol% of Cul were employed. A blank experiment without catalyst gave no conversion (entry 8).

With the ligand-free, copper-catalyzed procedure in hand, we probed the effect of various leaving groups [(E)-2a–i → α-α-3a and γ-3a, Table 2]. Next to model substrate (E)-2a, E-cinnamyl alcohols activated as carboxylate [as in (E)-2b], carbonates [as in (E)-2c and (E)-2d], carbamate [as in (E)-2e], and phosphate [as in (E)-2f] participated well in
This silylation (Table 2, entries 1–6); yields were generally high and α/γ ratios and E/Z selectivities were good. Cinnamyl halides (E)-2γ and (E)-2h were also included into the survey (entries 7 and 8), again leading to high yields but to slightly diminished regioselectivities. This outcome, that is α-selectivity for all tested leaving groups, stands in stark contrast to earlier findings in copper-catalyzed allylic substitution with Si–B compounds and silicon zinc reagents (see Scheme 1, top). As expected, the allylic substitution did not occur with free cinnamyl alcohol [(E)-2i] (entry 9).

This allylic substitution was then applied to a variety of primary allylic precursors using Me₂PhSiMgX 1a (Scheme 2). In accordance with the previous observations (Tables 1 and 2), isomerically pure geranyl acetate (E)-4a and neryl acetate (Z)-4a reacted cleanly to produce allylic silanes α-3a and α-3a, respectively, with exclusive preservation of the double bond geometry and excellent α/γ selectivity. Allylic bromide (E)-5h underwent silylation equally well, however, with reduced regio- and diastereoselectivi-

### Biographical Sketches

**Weichao Xue** (born in 1989 in Pingdingshen/China) studied Chemistry at Henan University (2008–2012) and Shanghai University (2012–2015). He obtained his bachelor’s degree with Feng Shi (Kaifeng, 2012) and master’s degree with Hegui Gong (Shanghai, 2015). He then moved to Berlin to pursue doctoral research funded by the China Scholarship Council (2015–2019). Currently, he is a Ph.D. candidate in the group of Martin Oestreich at the Technische Universität Berlin. He is also a member of the Berlin Graduate School of Natural Sciences and Engineering (BIG-NSE) of the Cluster of Excellence Unifying Concepts in Catalysis of the Deutsche Forschungsgemeinschaft.

**Martin Oestreich** (born in 1971 in Pforzheim/Germany) is Professor of Organic Chemistry at the Technische Universität Berlin. He received his diploma degree with Paul Knochel (Marburg, 1996) and his doctoral degree with Dieter Hoppe (Münster, 1999). After a two-year postdoctoral stint with Larry E. Overman (Irvine, 1999–2001), he completed his habilitation with Reinhard Brückner (Freiburg, 2001–2005) and was appointed as Professor of Organic Chemistry at the Westfälische Wilhelms-Universität Münster (2006–2011). He also held visiting positions at Cardiff University in Wales (2005), The Australian National University in Canberra (2010), and Kyoto University (2018).
ties. As expected, simple primary allylic electrophiles such as 6a and 7h were converted into corresponding silylated products in good yields.

\[ \text{Scheme 2} \] Copper-catalyzed allylic substitution of primary allylic precursors with silicon Grignard reagents. Yields are for the mixture of isomers, and regiochemical and diastereomeric ratios were confirmed by \(^1\)H NMR analysis.

Unlike primary allylic sources that engage in an \(S_N\) pathway with high regiocontrol, the regiochemical situation is different for secondary substrates. Cyclic 13a was obtained in high yield starting from the secondary bromide 12h (Scheme 3, eq 1). Acyclic 14b was transformed into \(\gamma\)-(Z)-15a with excellent \(\gamma\)-selectivity, corresponding to an \(S_N'\) mechanism (Scheme 3, eq 2). Interestingly, the Z-isomer was formed predominantly, which is different from literature precedence.\(^4a,9\) To further distinguish between \(anti-S_N'\) and \(syn-S_N'\) mechanisms, cyclic allylic carboxylate syn-16a was synthesized and subjected to the standard condition (Scheme 3, eq 3).\(^10\) Indeed, syn-16a was converted into \(anti-17a\) with complete inversion of the stereochemical information. This result is consistent with related copper-promoted allylic substitutions.\(^3f,4a,11\)

Continuing with allyl methyl carbonate (18c), different silicon Grignard reagents 1 were subjected to the standard setup (Scheme 4). Similar to Me\(_2\)PhSiMgX 1a, yields are generally excellent for regularly used Me\(_2\)Si (from 1b) and Ph\(_2\)Si (from 1c) as well as more hindered t-BuPh\(_2\)Si (from 1d) and t-Bu(Me)PhSi (from 1e). The same result was obtained with heteroatom-substituted silicon nucleophile 1f, containing Tamao’s silicon anion.\(^12\)

Considering the challenges associated with the construction of silicon-stereogenic silanes,\(^13\) we attempted an enantioselective version of this allylic substitution in the presence of chiral ligands (Scheme 5). The reaction of racemic t-Bu(Me)PhSiMgX 1e and allylic precursor 18c was chosen as a model reaction. Several catalytic systems were tested but neither led to the asymmetric induction at the silicon atom.
To summarize, we have disclosed here a practical method for the synthesis of allylic silanes from readily accessible allylic precursors and easy-to-handle silicon Grignard reagents. Several metal salts can promote this transformation in moderate to excellent yields without the need of added ligand. The leaving-group scope is broad, comprising the usual oxygen leaving groups as well as halides.

All reactions were performed in flame-dried glassware using conventional Schlenk techniques under a static pressure of N₂, unless otherwise stated. Liquids and solutions were transferred with syringes. Cu (anhyd Cu, 98%, ABCR), other metal salts, and chiral ligands were purchased from commercial suppliers and used as received. Allylic precursors 2a, 2g, 2h, 2l, (E)-4a, (Z)-4a, 6a, 7h, 12h, and 18c are commercially available. Compounds 2b, 2c, 2e, 2f, (E)-5h, 14b, and syn-16a were synthesized according to the reported procedure, and all spectroscopic data matched those reported. THF was dried over Na or K/benzophenone and distilled prior to use. Technical grade methanol (Methanol, Merck) was used from Grace using the indicated solvents. 1H, 13C, and 29Si NMR spectra were recorded in CDCl₃ on Bruker AV400 and AV500 instruments. Chemical shifts are reported in parts per million (ppm) and are referenced to the residual solvent resonance as the internal standard (CHCl₃: δ = 7.26 for 1H NMR and CDCl₃: δ = 77.0 for 13C NMR). 29Si NMR spectra were recorded in CDCl₃ on Bruker AV400 and AV500 instruments. Chemical shifts are reported in parts per million (ppm) and are referenced to the residual solvent resonance as the internal standard (CHCl₃: δ = 7.26 for 1H NMR and CDCl₃: δ = 77.0 for 13C NMR). 

Copper-Catalyzed Allylic Substitution with R₃SiMgX; General Procedure 2 (GP 2)

A flame-dried Schlenk flask equipped with a stir bar was charged with Cu (1.9 mg, 0.010 mmol; 2.0 mol%) and CuI (1.9 mg, 0.010 mmol, 2.0 mol%). The flask was evacuated and backfilled with N₂ (3 ×) followed by the addition of THF (1 mL). After stirring for 10 min at r.t., the indicated allylic precursor (0.50 mmol, 1.0 equiv) was added, and the solution was brought to 0 °C. Then, the corresponding R₃SiMgX (0.60 mmol, 1.2 equiv) was added over 1 min. After 1 h, the reaction was quenched with sat. aq NH₄Cl (5 mL). 

1H NMR (500 MHz, CDCl₃): δ = 0.31 (s, 6 H), 1.90 (d, J = 6.5 Hz, 2 H), 6.16–6.26 (m, 2 H), 7.12–7.17 (m, 1 H), 7.24–7.26 (m, 4 H), 7.35–7.38 (m, 3 H), 7.49–7.55 (m, 2 H).

13C NMR (125 MHz, CDCl₃): δ = 40.0, 119.6, 124.6, 127.7, 128.8, 131.2, 133.1, 133.6, 139.3.


The spectroscopic data are in accordance with those reported. 

(E)-Cinnamyl[dimethyl(phenyl)silane] ([α-(E)-3a])

Prepared from (E)-cinnamyl acetate [(E)-2a: 88 mg, 0.50 mmol] according to GP 2 with Me₂PhSiMgX 1a at 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded α-(E)-3a as a colorless oil; yield: 120 mg (95%, contaminated with 1,1,2,2-tetramethyl-1,2-diphenyldisilane); νₛᵣ,νₐₗ (light green), νₛᵣ,νₐₗ (light purple), νₛᵣ,νₐₗ (light green), νₛᵣ,νₐₗ (light purple), νₛᵣ,νₐₗ (light green).

Preparation of R₃SiMgX 1; General Procedure 1 (GP 1)

At 0 °C, the required chlorosilane (24.0 mmol, 1.0 equiv) was added to a flame-dried Schlenk flask charged with activated Li chunks (666 mg, 96.0 mmol, 4.0 equiv) suspended in THF (20 mL), and the resulting suspension was stirred at this temperature overnight under N₂ atmosphere to give R₃SiLi. The concentration of R₃SiLi (~1.0 M in THF, approximately 80–90% conversion) was determined by titration against diphenylecyanid acid (Kofron’s method). A flame-dried two-necked round-bottomed flask charged with a magnetic stir bar and equipped with a water condenser is connected to a Schlenk line and purged with N₂. The flask was charged with Mg turnings (292 mg, 12.0 mmol, 1.2 equiv) followed by the addition of THF (10 mL) and was then heated to 66 °C. 1,2-Dibromoethane (1.88 g, 10.0 mmol, 1.0 equiv) was quickly added via syringe, and the reaction mixture was heated at reflux for 3 h at high water-flow rate to afford MgBr₂ (1.0 M in THF at 66 °C). Then, the corresponding R₃SiLi solution (10 mmol, 1.0 equiv) was subsequently added dropwise to the MgBr₂ solution over 10 min at this temperature. R₃SiMgX·2LiX solution formed was cooled to r.t. The concentration of R₃SiMgX·2LiX (~0.5 M in THF, full conversion) was determined by titration against I₂ (Knochel’s method). The homogeneous R₃SiMgX·2LiX solution could be stored in a Schlenk flask purged with N₂ at 2–8 °C in a fridge.

The color of the R₃SiMgX·2LiX solution depends on the substitution at the silicon atom: Me₃PhSiMgX·2LiX 1a (purple), MePh₂SiMgX·2LiX 1b (light purple), Ph₂SiMgX·2LiX 1c (brown), t-BuPh₂SiMgX·2LiX 1d (light green), t-BuMePhSiMgX·2LiX 1e (light purple), (Et₂N)Ph₃SiMgBr·2LiX 1f (gray).
(Z)-Neryl(dimethyl(phenyl)silane [α-Z-8a]
Prepared from (Z)-neryl acetate ([Z]-4a; 98 mg, 0.50 mmol) according to GP 2 with Me₃PhSiMgX 1a at 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded α-Z-8a as a colorless oil; yield: 124 mg (91%); Rf = 0.65 (n-pentane).

1H NMR (500 MHz, CDCl₃): δ = 0.26 (s, 6 H), 1.60 (s, 3 H), 1.65 (d, J = 8.6 Hz, 2 H), 1.69 (s, 6 H), 1.94–2.02 (m, 4 H), 5.07–5.13 (m, 1 H), 5.17 (t, J = 8.6 Hz, 1 H), 7.33–7.38 (m, 3 m, 1 H), 7.49–7.54 (m, 2 H).

13C NMR (125 MHz, CDCl₃): δ = –3.2, 17.3, 17.6, 23.4, 25.7, 26.4, 31.7, 119.7, 124.6, 127.7, 128.8, 131.4, 133.6, 133.9, 139.3.

29Si DEPT NMR (99 MHz, CDCl₃): δ = –4.2.

HRMS (EI): m/z [M]+ calcd for C₁₄H₂₀Si: 204.1329; found: 204.1329.

The spectroscopic data are in accordance with those reported.4a

Dimethyl(cyclohex-2-en-1-yl)(phenyl)silane (13a)
Prepared from 3-bromocyclohexene (12h; 81 mg, 0.50 mmol) according to GP 2 with Me₃PhSiMgX 1a at 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded 13a as a colorless oil; yield: 91 mg (84%); Rf = 0.75 (n-pentane).

1H NMR (500 MHz, CDCl₃): δ = 0.28 (s, 3 H), 0.29 (s, 3 H), 1.43–1.53 (m, 2 H), 1.63–1.70 (m, 1 H), 1.74–1.82 (m, 2 H), 1.88–2.03 (m, 2 H), 5.60–5.69 (m, 2 H), 7.31–7.39 (m, 3 H), 7.50–7.56 (m, 2 H).

13C NMR (125 MHz, CDCl₃): δ = –3.8 (SiCH₃), –4.6 (SiCH₃), 22.5, 23.8, 25.0, 25.6, 125.9, 127.5, 128.9, 133.9, 138.3.

29Si DEPT NMR (99 MHz, CDCl₃): δ = –2.5.

HRMS (EI): m/z [M]+ calcd for C₁₇H₂₆Si: 258.1798; found: 258.1786.

The spectroscopic data are in accordance with those reported.9
**Synthesis**

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**Feature**

**Allyldimethyl(phenyl)silane (19a)**
Prepared from allyl methyl carbonate (18c; 58 mg, 0.50 mmol) according to GP 2 with Me2PhSiMgX to 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded 19a as a colorless oil; yield: 174 mg (86%); mp 91.0–91.8 °C; 133.1, 134.70, 134.73.

**Allyl(methyl)triphenylsilane (19b)**
Prepared from allyl methyl carbonate (18c; 58 mg, 0.50 mmol) according to GP 2 with MePh2SiMe3 to 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded 19b as a colorless oil; yield: 108 mg (91%); Rf = 0.65 (n-pentane). 1H NMR (500 MHz, CDCl3): δ = 0.29 (s, 3 H), 1.76 (dd, J = 8.6 Hz, 2 H), 4.82–4.92 (m, 2 H), 5.73–5.83 (m, 1 H), 7.33–7.39 (m, 3 H), 7.49–7.55 (m, 2 H).

**Allyltriphenylsilane (19c)**
Prepared from allyl methyl carbonate (18c; 58 mg, 0.50 mmol) according to GP 2 with Ph2SiMe3 to 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded 19c as a white solid; yield: 134 mg (89%); mp 135.7.

1H NMR (500 MHz, CDCl3): δ = 0.56 (s, 3 H), 2.08 (dd, J = 8.6 Hz, 2 H), 4.85–4.95 (m, 2 H), 5.75–5.85 (m, 1 H), 7.33–7.40 (m, 6 H), 7.51–7.56 (m, 4 H).

13C NMR (125 MHz, CDCl3): δ = –13.8.


**Allyl(tert-butyl)(methyl)(phenyl)silane (19e)**
Prepared from allyl methyl carbonate (18c; 58 mg, 0.50 mmol) according to GP 2 with t-BuMe2PhSiMgX to 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded 19e as a colorless oil; yield: 99 mg (91%); Rf = 0.65 (n-pentane).

HPLC-analysis: OJ-RH (Dacial), MeCN/H2O = 65:35, 0.2 mL/min, λ = 210 nm, tR = 47.9, 51.1 min.

1H NMR (500 MHz, CDCl3): δ = 0.28 (s, 3 H), 0.90 (s, 9 H), 1.81–1.87 (m, 1 H), 1.93–1.99 (m, 1 H), 4.78–4.82 (m, 1 H), 4.86–4.92 (m, 1 H), 5.71–5.82 (m, 1 H), 7.31–7.44 (m, 3 H), 7.48–7.55 (m, 2 H).

13C NMR (125 MHz, CDCl3): δ = –8.6, 17.4, 18.7, 26.8, 113.6, 127.5, 128.9, 134.7, 135.0, 136.0.

HRMS (EI): m/z [M]+ calcd for C14H19Si: 218.1485; found: 218.1482.

**Allyl(ethoxy)diphenylsilane (19f)**
Prepared from allyl methyl carbonate (18c; 58 mg, 0.50 mmol) according to GP 2 with (Et2N)Ph2SiMgX to 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded 19f as a colorless oil; yield: 115 mg (86%); Rf = 0.55 (n-pentane).

1H NMR (500 MHz, CDCl3): δ = 0.56 (s, 3 H), 2.08 (dd, J = 8.6 Hz, 2 H), 4.85–4.95 (m, 2 H), 5.75–5.85 (m, 1 H), 7.33–7.40 (m, 6 H), 7.51–7.56 (m, 4 H).

13C NMR (125 MHz, CDCl3): δ = –13.8.


The spectroscopic data are in accordance with those reported.21

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**References**


