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

Weichao Xue
Martin Oestreich*

Institut für Chemie, Technische Universität Berlin, Strasse des 17. Juni 115, 10623 Berlin, Germany
martin.oestreich@tu-berlin.de

Published as part of the 50 Years SYNTHESIS – Golden Anniversary Issue

Received: 24.09.2018
Accepted: 28.09.2018
Published online: 22.10.2018

License terms: (C) 2018 Thieme

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 regioselectivity is independent of the leaving group for primary allylic precursors, favoring α over γ. The stereocentrical course of this allylic transposition was probed with a cyclic system, and anti-diastereoselectivity was obtained.

Key words allylic substitution, copper, Grignard reagents, silicon

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 as silicon nucleophiles in allylic substitution reactions, particularly with emphasis on the influence of the leaving group on the regioselectivity. Herein, we describe the application of silicon Grignard reagents to allylic substitution reactions catalyzed by manganese, iron, cobalt, nickel, copper, and palladium salts.

We started our investigation by exploring the coupling reaction of commercially available E-cinnamyl acetate [(E)-2a] and Me2PhSiMgX 1a (Table 1). At the beginning, several first-row metal salts were employed as catalysts (5 mol%) without additional ligands (Table 1, entries 1–6). Any of these catalysts enabled the reaction, affording the linear allylic silane α-(E)-3a in near-quantitative yields using NiBr2⋅glyme, CuI, 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 CuI 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] to α-(E)-3a and γ-3a, Table 2]. Next to model substrate (E)-2a, E-cinnamyl alcohols activated as carbonylate [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/3 ratios and E/Z selectivities were good. Cinnamyl halides (E)-2g 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.

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)-2i reacted cleanly to produce allylic silanes 3a, respectively, with exclusive preservation of the double bond geometry and excellent α/γ selectivity. Allylic bromide (E)-5 reacted cleanly to produce allylic silanes 3a, respectively, with exclusive preservation of the double bond geometry and excellent α/γ selectivity. Allylic bromide (E)-5 reacted cleanly to produce allylic silanes 3a, respectively, with exclusive preservation of the double bond geometry and excellent α/γ selectivity.

**Table 1** Selected Examples of the Catalyst Screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>E/Z of α-3a</th>
<th>α/γ</th>
<th>Yield (%)</th>
<th>Regioselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MnBr₂</td>
<td>99:1</td>
<td>96:4</td>
<td>67</td>
<td>95:5, 95:5</td>
</tr>
<tr>
<td>2</td>
<td>FeCl₃</td>
<td>99:1</td>
<td>98:2</td>
<td>79</td>
<td>99:1, 99:1</td>
</tr>
<tr>
<td>3</td>
<td>CoCl₂</td>
<td>99:1</td>
<td>99:1</td>
<td>81</td>
<td>99:1, 99:1</td>
</tr>
<tr>
<td>4</td>
<td>NiBr₂·glyme</td>
<td>99:1</td>
<td>98:2</td>
<td>94</td>
<td>99:1, 99:1</td>
</tr>
<tr>
<td>5</td>
<td>Cu</td>
<td>99:1</td>
<td>99:1</td>
<td>95 (95)</td>
<td>95:5, 95:5</td>
</tr>
<tr>
<td>6</td>
<td>CuCN</td>
<td>99:1</td>
<td>99:1</td>
<td>95</td>
<td>99:1, 99:1</td>
</tr>
<tr>
<td>7</td>
<td>PdCl₂</td>
<td>97:3</td>
<td>95:5</td>
<td>80</td>
<td>97:3, 97:3</td>
</tr>
<tr>
<td>8</td>
<td>none</td>
<td>–</td>
<td>–</td>
<td>trace</td>
<td></td>
</tr>
</tbody>
</table>

*Reactions performed on a 0.50 mmol scale. Yield is for the mixture of isomers and was determined by GLC analysis with tetracosane as an internal standard.

**Biographical Sketches**

**Weichao Xue** (born in 1989 in Pingdingshan/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.

\[ \text{Cul (2 mol%), } \text{MePh}_2\text{SiMgX 1a (1.2 equiv)} \]

\[ \text{THF} \]

\[ 0^\circ \text{C for 1 h} \]

\[ \text{R}^1 \]

\[ \text{R}^2 \]

\[ \text{LG} \]

\[ \text{3-7} \]

\[ \text{MePh}_2\text{SiMe}_2\text{Ph} \]

\[ \text{Si} \]

\[ \text{SiR}_3 \]

\[ \text{SiMe}_2\text{Ph} \]

\[ \text{Me}_2\text{PhSi} \]

\[ \text{Si} \]

Scheme 2 Copper-catalyzed allylic substitution of primary allylic precursors with silicon Grignard reagents. Yields are for the mixture of isomers, and regiochemical and diasteromeric 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 \(S_N^\prime\) mechanism (Scheme 3, eq 2). Interestingly, the \(Z\)-isomer was formed predominantly, which is different from literature precedence.\(^4\),\(^5\) To further distinguish between \(anti-S_N^\prime\) and \(syn-S_N^\prime\) mechanisms, cyclic allylic carbonate 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.\(^6\),\(^4\),\(^11\)

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 MePh\(_2\)Si (from 1b) and Ph\(_2\)Si (from 1c) as well as more hindered \(t\)-BuPh\(_2\)Si (from 1d) and \(t\)-Bu(\(Me\)Ph)Si (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(\(Me\)Ph)SiMgX 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. Cul (anhyd Cul, 98%, ABCR), other metal salts, and chiral ligands were purchased from commercial suppliers and used as received. Allylic precursors 2a, 2g, 2h, 2i, (E)-4a, (Z)-4a, 6a, 7a, 12h, and 18c are commercially available. Compounds 2b–k, 2c–l, 2f–l (E)-5h, 14b, 14c, and syn-16a,b,c,d,e,f,g,h,i,j,k,l were synthesized according to the reported procedure, and all spectroscopic data matched those reported. THF was dried (anhyd Na₂SO₄), filtered, and the solvents were evaporated under reduced pressure. Purification of the residue by flash chromatography on silica gel with indicated solvent as eluent afforded the silylated product. Over reduction was performed on silica gel 60 F254 glass plates from Merck. Flash column chromatography was performed on silica gel 60 (40–63 μm) over Na or K/benzophenone and distilled prior to use. Technical grade solvents for extraction or chromatography (cyclohexane, CH₂Cl₂, CH₃CO₂Et, and all spectroscopic data matched those reported. THF was dried (anhyd Na₂SO₄), filtered, and the solvents were evaporated under reduced pressure. Purification of the residue by flash chromatography on silica gel with indicated solvent as eluent afforded the silylated product.

**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 diphenylacetic 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: Me₃PPhSiMe₂X·2LiX 1a (purple), Me₂PhSiMe₂X·2LiX 1b (light purple), Ph₂SiMe₂X·2LiX 1c (brown), f-BuPh₂SiMe₂X·2LiX 1d (light green), f-BuMePhSiMe₂X·2LiX 1e (light purple), (Et₂N)₂Ph₂SiMgBr·2LiX 1f (gray).

**Copper-Catalyzed Allylic Substitution with R₃SiMgX 1; General Procedure 2 (GP 2)**

A flame-dried Schlenk flask equipped with a stir bar was charged with Cul (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 1 (0.60 mmol, 1.2 equiv) was added over 10 min. After 1 h, the reaction was quenched with sat. aq NH₄Cl (5 mL). CH₃Cl (20 mL) was added for extraction, and the CH₂Cl₂ layer was washed with brine (20 mL) and H₂O (20 mL). The aqueous phase was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic phases were dried (anhyd Na₂SO₄), filtered, and the solvents were evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel with indicated solvent as eluent afforded the silylated product.

**(-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 Me₃PPhSiMe₂X 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); δ = 0.60 ppm (n-pentane).

**HRMS (EI):** m/z [M]+ calcd for C₁₇H₂₀Si: 252.1334; found: 252.1332.

**(-E)-Geranyl(dimethyl(phenyl)silane [α-E]-8a)**

Prepared from (E)-geranyl acetate [(E)-4a; 98 mg, 0.50 mmol] according to GP 2 with Me₃PPhSiMe₂X 1a at 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded α-E-8a as a colorless oil; yield: 192 mg (87%); Rf = 0.65 (n-pentane).


The spectroscopic data are in accordance with those reported.
(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%); R₇ = 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.


The spectroscopic data are in accordance with those reported.⁹

(3-Cyclohexylallyl)dimethyl(phenyl)silane (9a)
Prepared from (E)-3-bromoprop-1-en-1-yl)cyclohexane [(E)-5h; 102 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 9a as a colorless oil; yield: 116 mg (90%, mixture of all isomers). The ratio of different isomers was confirmed by 1H NMR analysis.

α-[(E)-9a]
R₇ = 0.70 (n-pentane).

1H NMR (500 MHz, CDCl₃): δ = 0.26 (s, 6 H), 1.03–1.25 (m, 5 H), 1.61–1.71 (m, 8 H), 5.19–5.25 (m, 1 H), 5.29–5.38 (m, 1 H), 7.33–7.37 (m, 3 H), 7.49–7.54 (m, 2 H).

13C NMR (125 MHz, CDCl₃): δ = −3.4, 21.6, 26.1, 26.2, 33.5, 41.0, 122.7, 127.6, 128.8, 133.7, 136.0, 139.1.

29Si DEPT NMR (99 MHz, CDCl₃): δ = −4.7.

HRMS (EI): m/z [M]+ calcd for C₁₄H₂₀Si: 258.1798; found: 258.1786.

Prenyldimethyl(phenyl)silane (α-10a)
Prepared from prenyl acetate (6a; 64 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-10a as a colorless oil; yield: 97 mg (95%); R₇ = 0.70 (n-pentane).

1H NMR (500 MHz, CDCl₃): δ = 0.26 (s, 6 H), 1.50 (s, 3 H), 1.63 (d, J = 8.6 Hz, 2 H), 1.69 (s, 3 H), 5.16 (t, J = 8.6, 1.4 Hz, 1 H), 7.31–7.38 (m, 3 H), 7.49–7.55 (m, 2 H).

13C NMR (125 MHz, CDCl₃): δ = −3.2, 17.6, 17.7, 25.7, 119.3, 127.6, 128.8, 129.5, 133.6, 139.3.

29Si DEPT NMR (99 MHz, CDCl₃): δ = −3.8.

HRMS (EI): m/z [M]+ calcd for C₁₃H₂₂Si: 204.1329; found: 204.1329.

The spectroscopic data are in accordance with those reported.⁹

Dimethyl(2-methylallyl)(phenyl)silane (α-11a)
Prepared from 3-bromo-2-methylpropene (7h; 68 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-11a as a colorless oil; yield: 82 mg (86%); R₇ = 0.70 (n-pentane).

1H NMR (500 MHz, CDCl₃): δ = 0.32 (s, 6 H), 1.62 (s, 3 H), 1.78 (s, 2 H), 4.47–4.50 (m, 1 H), 4.59–4.62 (m, 1 H), 7.32–7.39 (m, 3 H), 7.50–7.57 (m, 2 H).

13C NMR (125 MHz, CDCl₃): δ = −2.9, 25.2, 25.7, 108.8, 127.7, 128.9, 133.6, 139.1, 143.3.

29Si DEPT NMR (99 MHz, CDCl₃): δ = −5.0.


The spectroscopic data are in accordance with those reported.₃⁸
**Synthesis**  W. Xue, M. Oestreich

**Feature**

**Allyldimethyl(phenyl)silane (19a)**
Prepared from allyl methyl carbonate (18c; 58 mg, 0.50 mmol) according to GP 2 with Me3SiMgX 1a at 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded 19a as a colorless oil; yield: 115 mg (82%); δ = 0.29 (s, 6 H), 1.76 (dt, 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).

13C NMR (125 MHz, CDCl3): δ = –3.5, 133.1, 134.70, 134.73.


**Allyl(tert-butyldimethyl)(phenyl)silane (19d)**
Prepared from allyl methyl carbonate (18c; 58 mg, 0.50 mmol) according to GP 2 with t-BuMe2SiMgX 1d at 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded 19d as a colorless oil; yield: 115 mg (86%); δ = –4.7.

1H NMR (500 MHz, CDCl3): δ = 0.30 (t, J = 7.1 Hz, 3 H), 2.18 (dt, J = 7.8, 1.4 Hz, 2 H), 3.81 (q, J = 7.1 Hz, 2 H), 4.88–4.98 (m, 2 H, 5.80–5.90 (m, 1 H), 7.35–7.44 (m, 6 H), 7.59–7.64 (m, 4 H).

13C NMR (125 MHz, CDCl3): δ = 18.4, 21.9, 59.5, 115.0, 127.8, 129.9, 133.1, 134.70, 134.73.


The spectroscopic data are in accordance with those reported.21

**Allyl(tert-butyldimethyl)(phenyl) silane (19e)**
Prepared from allyl methyl carbonate (18c; 58 mg, 0.50 mmol) according to GP 2 with t-Bu(Me)PhSiMgX 1f at 0 °C. Afterwards, anhyd ETOH (1 mL) and NH4Cl (55 mg, 2.0 mmol) was added, and the reaction mixture was stirred overnight. Purification by flash column chromatography on silica gel using n-pentane afforded 19e as a colorless oil; yield: 115 mg (86%); δ = 0.30 (n-pentane).

1H NMR (500 MHz, CDCl3): δ = –8.6, 17.4, 18.7, 26.8, 113.6, 127.5, 128.9, 134.7, 135.0, 136.0.

13C NMR (125 MHz, CDCl3): δ = –5.2.


The spectroscopic data are in accordance with those reported.21

**Funding Information**
This research was supported by the China Scholarship Council (predoctoral fellowship to W.X., 2015–2019) and the Deutsche Forschungsgemeinschaft (Oe 249/15-1). M.O. is indebted to the Einstein Foundation Berlin for an endowed professorship.

**Supporting Information**
Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610309.

**References**


