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

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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 regioselectivity is independent of the leaving group for primary allylic precursors, favoring α over γ. The stereocchemical 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. Several methods are available that provide reliable access to these compounds. 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, 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 (Scheme 1, bottom). These had essentially been not available previously, 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-regiosomer 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]→α-(E)-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

Scheme 1 Copper-catalyzed allylic substitution with R3SiBpin or (R3Si)2Zn

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

1. This is a research paper discussing the use of silicon Grignard reagents as nucleophiles in transition-metal-catalyzed allylic substitution reactions. The authors describe the development of a robust method for the preparation of bench-stable solutions of silicon Grignard reagents and assess their suitability as silicon nucleophiles in allylic substitution reactions.

2. 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 stereocchemical course of this allylic transposition was probed with a cyclic system, and anti-diastereoselectivity was obtained.

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this silylation (Table 2, entries 1–6); yields were generally high and α/γ 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.

Table 1 Selected Examples of the Catalyst Screening

| Entry | Catalyst | E/Z of α-3a<sup>b</sup> | α/γ<sup>b</sup> | Yield (%)<sup>b</sup> of 3a
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>MnBr&lt;sub&gt;2&lt;/sub&gt;</td>
<td>99:1</td>
<td>96:4</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>FeCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>99:1</td>
<td>98:2</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>CoCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>99:1</td>
<td>99:1</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>NiBr&lt;sub&gt;2&lt;/sub&gt;-glyme</td>
<td>99:1</td>
<td>98:2</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>CuCl</td>
<td>99:1</td>
<td>99:1</td>
<td>95 (95)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>CuCN</td>
<td>99:1</td>
<td>99:1</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>PdCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>97:3</td>
<td>95:5</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>none</td>
<td>-</td>
<td>-</td>
<td>trace</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions performed on a 0.50 mmol scale.
<sup>b</sup> Yield is for the mixture of isomers and was determined by GLC analysis with tetracosane as an internal standard.
<sup>c</sup> With CuI (2 mol%).

This allylic substitution was then applied to a variety of primary allylic precursors using Me<sub>2</sub>PhSiMgX 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-(E)-8a and α-(Z)-8a, 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 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.

![Scheme 2](image)

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 $S_N^*$ mechanism (Scheme 3, eq 2). Interestingly, the Z-isomer was formed predominantly, which is different from literature precedence.$^4a,b$ To further distinguish between anti-$S_N^*$ and syn-$S_N^*$ mechanisms, cyclic allyl 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 MePh$_2$Si (from 1b) and Ph$_3$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.$^{12}$

![Scheme 4](image)

Scheme 4 Copper-catalyzed allylic substitution of allylic precursor 18c with silicon Grignard reagents. Yields are for the mixture of isomers, and ratios were determined by $^1$H NMR analysis. *EtOH/NH$_4$Cl added after reaction.

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.

![Scheme 5](image)

Scheme 5 Attempted enantioselective allylic substitution of allylic carbonate 18c with t-Bu(Me)PhSiMgX (1e)
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. 

Preparation of R₃SiMgX | 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 Schlenk flask purged with N₂ at 2–8 °C in a fridge. The color of the R₃SiMgX solution depends on the substitution at the silicon atom: Me₃SiMgX | (light purple), Ph₂SiMgX | (purple), t-BuPh₂SiMgX | (light green), 4b-tBu(Me)PhSiMgX | (light purple), (Et₂N)Ph₂SiMg-Br | (gray).

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%). 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 10 min at this temperature. R₃SiMgX solution formed was cooled to r.t. The concentration of R₃SiMgX·LiX (0.5 M in THF, full conversion) was determined by titration against i₂ (Knoevenagel’s method). The homogeneous R₃SiMgX·LiX solution could be stored in a Schlenk flask purged with N₂ at 2–8 °C in a fridge. Over 10 min at this temperature, R₃SiMgX·LiX solution formed was cooled to r.t. The concentration of R₃SiMgX·LiX (0.5 M in THF, full conversion) was determined by titration against i₂ (Knoevenagel’s method). The homogeneous R₃SiMgX·LiX solution could be stored in a Schlenk flask purged with N₂ at 2–8 °C in a fridge. The color of the R₃SiMgX solution depends on the substitution at the silicon atom: Me₃SiMgX | (light purple), Ph₂SiMgX | (purple), t-BuPh₂SiMgX | (light green), 4b-tBu(Me)PhSiMgX | (light purple), (Et₂N)Ph₂SiMg-Br | (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%); δR = 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.¹⁶

(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 (93%, mixture of all isomers). The ratio of different isomers was confirmed by 1H NMR analysis.

α-(E)-9a
Rf = 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 m, 1 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⁺] calculated for C₁₆H₂₁Si: 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%); δR = 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 (tt, J = 8.6, 1.4 Hz, 1 H), 7.31–7.38 (m, 3 m, 1 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, 136.3.

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

HRMS (EI): m/z [M⁺] calculated for C₁₆H₂₁Si: 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%); δR = 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.⁴³
Allyl(dimethyl(phenyl)silane (19a))
Prepared from allyl methyl carbonate (18c; 58 mg, 0.50 mmol) according to GP 2 with Me$_3$SiMe$_2$ClX at 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded 19a as a colorless oil; yield: 115 mg (86%); mp 90.0–90.8 °C; 1H NMR (500 MHz, CDCl$_3$): δ = 0.29 (s, 6 H), 1.76 (d, 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, CDCl$_3$): δ = –3.5, 23.7, 113.4, 127.7, 129.0, 133.6, 134.6, 138.7.

19b Prepared from allyl methyl carbonate (18c; 58 mg, 0.50 mmol) according to GP 2 with Ph$_3$SiMgX at 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded 19b as a colorless oil; yield: 134 mg (89%); mp 90.0–90.8 °C; R$_f$ = 0.55 (n-pentane).

1H NMR (500 MHz, CDCl$_3$): δ = 0.56 (s, 3 H), 2.08 (d, 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, CDCl$_3$): δ = –4.8, 22.1, 114.2, 127.8, 129.2, 134.1, 134.5, 136.6.

29Si DEPT NMR (99 MHz, CDCl$_3$): 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, CDCl$_3$): δ = –8.6, 17.4, 18.7, 26.8, 113.6, 127.5, 128.9, 134.7, 135.0, 136.0.

29Si DEPT NMR (99 MHz, CDCl$_3$): δ = 1.5.

HRMS (EI): m/z [M]+ calcd for C$_{13}$H$_{18}$Si: 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 Ph$_3$SiMgX at 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded 19f as a colorless oil; yield: 115 mg (86%); R$_f$ = 0.55 (n-pentane).

1H NMR (500 MHz, CDCl$_3$): δ = 2.40 (d, J = 7.1 Hz, 2 H), 4.87–4.98 (m, 2 H), 5.81–5.92 (m, 1 H), 7.33–7.44 (m, 9 H), 7.50–7.55 (m, 6 H).

13C NMR (125 MHz, CDCl$_3$): δ = 18.5, 18.8, 27.9, 114.5, 127.5, 129.1, 133.4, 134.7, 136.0.

29Si DEPT NMR (99 MHz, CDCl$_3$): δ = –5.2.

HRMS (EI): m/z [M]+ calcd for C$_{13}$H$_{18}$Si: 280.1642; found: 280.1636.

The spectroscopic data are in accordance with those reported.

Allyl(tert-butyldimethyl(phenyl)silane (19e)
Prepared from allyl methyl carbonate (18c; 58 mg, 0.50 mmol) according to GP 2 with t-BuMe$_2$SiMgX at 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded 19e as a colorless oil; yield: 119 mg (86%); R$_f$ = 0.65 (n-pentane).

1H NMR (500 MHz, CDCl$_3$): δ = 0.12 (t, J = 8.6 Hz, 12 H), 1.5 (m, 2 H), 1.81–1.87 (m, 1 H), 4.85–4.98 (m, 2 H), 5.76–5.86 (m, 1 H), 7.33–7.40 (m, 9 H), 7.50–7.55 (m, 6 H).

13C NMR (125 MHz, CDCl$_3$): δ = 18.4, 21.9, 55.9, 115.0, 127.8, 129.9, 133.1, 134.7, 134.73.

29Si DEPT NMR (99 MHz, CDCl$_3$): δ = –8.6.

HRMS (EI): m/z [M – C$_3$H$_7$]+ calcd for C$_{16}$H$_{22}$Si: 227.0889; found: 227.0889.

The spectroscopic data are in accordance with those reported.

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