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 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

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] → 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
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 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).

**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.

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.\textsuperscript{4a,9} To further distinguish between anti-$S_N'$ and syn-$S_N'$ mechanisms, cyclic allylcarboxylate syn-16a was synthesized and subjected to the standard condition (Scheme 3, eq 3).\textsuperscript{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.\textsuperscript{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$_2$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.\textsuperscript{12}

Considering the challenges associated with the construction of silicon-stereogenic silanes,\textsuperscript{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. Cul (anhyd Cul, 98%, ACR), 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, 12b, 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 solvents for extraction or chromatography (cyclohexane, CH₂Cl₂, ETOAc, and n-pentane) were distilled prior to use. Analytical TLC was performed on silica gel 60 F254 glass plates from Merck.

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 rt. The concentration of R₃SiMgX–2LiX (~0.5 M in THF, full conversion) was determined by titration against I₂ (Knoevenagel’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 (purple), Me₃PMeSiX (light purple), Ph₂SiMgX (brown), t-BuPh₂SiMgX (light green), t-BuMes₂SiMgBr (light purple), (Et₂N)Ph₂SiMgBr (light purple).

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 rt., 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 1 min. After 1 h, the reaction was quenched with sat. aq NH₄Cl (5 mL). The organic phase 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)-Cinnamylidimethyl(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-diphenylsilane); R₆ = 0.60 (n-pentane).

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 = –3.3, 23.0, 125.6, 126.3, 127.1, 127.8, 128.4, 128.9, 129.1, 133.6, 138.4, 138.5.

29Si DEPT NMR (99 MHz, CDCl₃): δ = –4.1.


The spectroscopic data are in accordance with those reported.

(E)-Geranylidimethyl(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: 119 mg (87%); R₆ = 0.65 (n-pentane).

1H NMR (500 MHz, CDCl₃): δ = 0.26 (s, 6 H), 1.50 (s, 3 H), 1.61 (s, 3 H), 1.64 (d, J = 8.6 Hz, 2 H), 1.69 (s, 3 H), 1.97–2.02 (m, 2 H), 2.03–2.10 (m, 2 H), 5.09 (tt, J = 6.7, 1.4 Hz, 1 H), 5.17 (tt, J = 8.8, 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 = –3.8.


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 Me₃SiPhMgX 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%); Rₖ = 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.18

(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 Me₃SiPhMgX 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
Rₖ = 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, 139.9, 139.1.

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

HRMS (EI): m/z [M]+ calcd for C₁₇H₂₆Si: 258.1789; found: 258.1786.

Preynyl(dimethyl(phenyl)silane (α-10a)
Prepared from preynyl acetate (6a; 64 mg, 0.50 mmol) according to GP 2 with Me₃SiPhMgX 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%); Rₖ = 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, 139.3.

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

HRMS (EI): m/z [M]+ calcd for C₁₇H₂₆Si: 258.1329; found: 258.1329.

The spectroscopic data are in accordance with those reported.9

anti-Dimethyl(5-methylcyclohexyl-2-en-1-yl)(phenyl)silane (anti-17a)
Prepared from syn-5-methylcyclohexyl-2-en-1-yl acetate (syn-16a; 77 mg, 0.50 mmol) according to GP 2 with Me₃SiPhMgX 1a at 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded anti-17a as a colorless oil; yield: 109 mg (95%; mixture of all isomers). The ratio of different isomers was confirmed by 1H NMR analysis; Rₖ = 0.50 (n-pentane).

1H NMR (500 MHz, CDCl₃): δ = 0.29 (s, 6 H), 1.61–1.68 (m, 5 H), 5.25–5.46 (m, 2 H), 7.33–7.38 (m, 3 m, 1 H), 7.46–7.57 (m, 2 H).

29Si DEPT NMR (99 MHz, CDCl₃): δ = –4.6.

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 Me₃SiPhMgX 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%); Rₖ = 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 m, 1 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.
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%); mp 90.0–90.8 °C; [M]+ calcd for C₁₉H₂₂Si: 280.1642; found: 280.1636.


Allyl(tert-butyl)(methyl)(phenyl)silane (19e)
Prepared from allyl methyl carbonate (18c; 58 mg, 0.50 mmol) according to GP 2 with t-BuMeSiMgX 1e at 0 °C. Purification by flash column chromatography on silica gel using n-pentane afforded 19e as a colorless oil; yield: 99 mg (91%); [M]+ = 0.65 (n-pentane).


References

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