

A New Approach to 4-Aryl-1,3-butanediols by Cobalt-Catalyzed Sequential Radical Cyclization–Arylation Reaction of Silicon-Tethered 6-Iodo-1-hexene Derivatives

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Dedicated to Professor Richard Heck

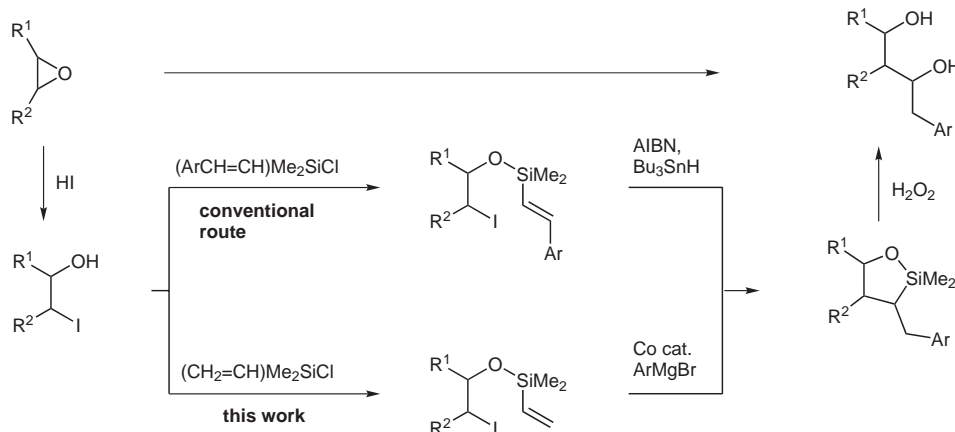
Abstract: Treatment of 6-iodo-4-oxa-3-sila-1-hexene derivatives with arylmagnesium bromide in the presence of a catalytic amount of a cobalt–diamine complex in THF afforded the corresponding benzyl-substituted oxasilacyclopentanes in good yield. The products were converted to 4-aryl-1,3-diols after Tamao–Fleming oxidation.

Key words: 1,3-diols, cobalt, arylation, radical reaction, silicon

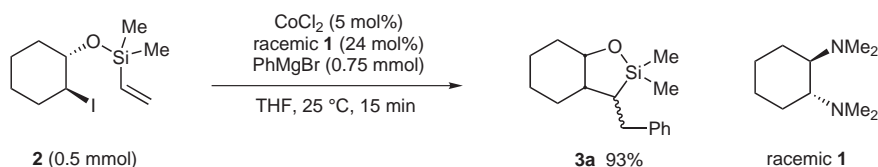
1,3-Diol units are often observed in natural products, and can be oxidized into 1,3-diketones or naturally occurring polyketides. The synthesis of 1,3-diols is thus widely investigated.¹ In light of the importance of the 1,3-diols, here we disclose a new approach to 4-aryl-1,3-butanediols starting from epoxides. As outlined in Scheme 1, ring opening of epoxides with iodide followed by silylation with chlorodimethylvinylsilane provides silicon-tethered² 6-iodo-1-hexene derivatives. Our cobalt-catalyzed radical

cyclization–arylation protocol³ yields oxasilacyclopentanes. Finally, Tamao–Fleming oxidation⁴ affords 4-aryl-1,3-butanediols. Without our cobalt-catalyzed protocol, synthesis of 4-aryl-1,3-diols via the conventional silicon-tethered strategy using the tin-based radical reaction^{2a,c} necessitates (2-arylethenyl)chlorodimethylsilanes that are not readily available. The present route admits variety in the aryl groups by simply changing the aryl Grignard reagents used.

We first chose cyclohexene oxide as the starting material. Cyclohexene oxide underwent ring opening by the action of lithium iodide and acetic acid in THF to give 2-iodo-1-cyclohexanol.⁵ Treatment of the crude *vic*-iodohydrin with chlorodimethylvinylsilane in the presence of triethylamine in dichloromethane provided silicon-tethered substrate **2** in 100% overall yield. Phenylative cyclization of **2** under the catalysis of [CoCl₂ (**1**)] afforded **3a** in excellent yield (Scheme 2).

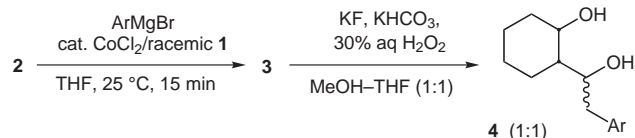


Scheme 1



Scheme 2

A variety of aryl Grignard reagents were employed for the coupling reaction (Scheme 3). All the corresponding products could be easily transformed to diols **4** after oxidation with alkaline hydrogen peroxide. Not only phenylmagnesium bromide but also 4-methoxy- and 3-trifluoromethylphenylmagnesium bromides participated in the reaction. Methyl substitution at the 2-position did not retard the reaction. The cyclization–arylation with 2-naphthyl Grignard reagent proceeded smoothly. Employing mesityl Grignard reagent did not give a satisfactory result. The products were always 1:1 mixtures of diastereomers, which originate from the relationship between the *cis*-fused bicyclic system and arylmethyl group.

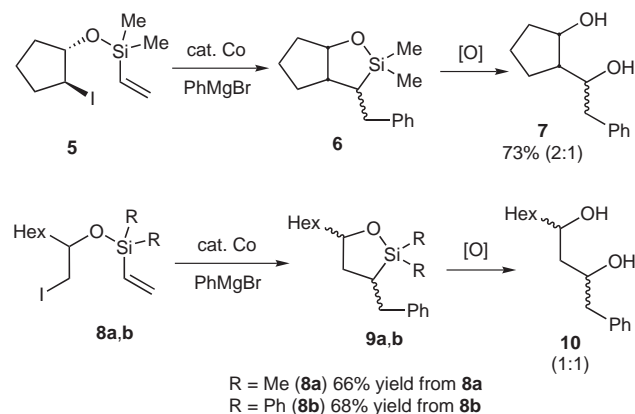


- a: Ar = Ph, 74% yield
 b: Ar = 2-naphthyl, 61% yield
 c: Ar = 2-MeC₆H₄, 73% yield
 d: Ar = 4-MeOC₆H₄, 41% yield
 e: Ar = 3-CF₃C₆H₄, 44% yield

Scheme 3

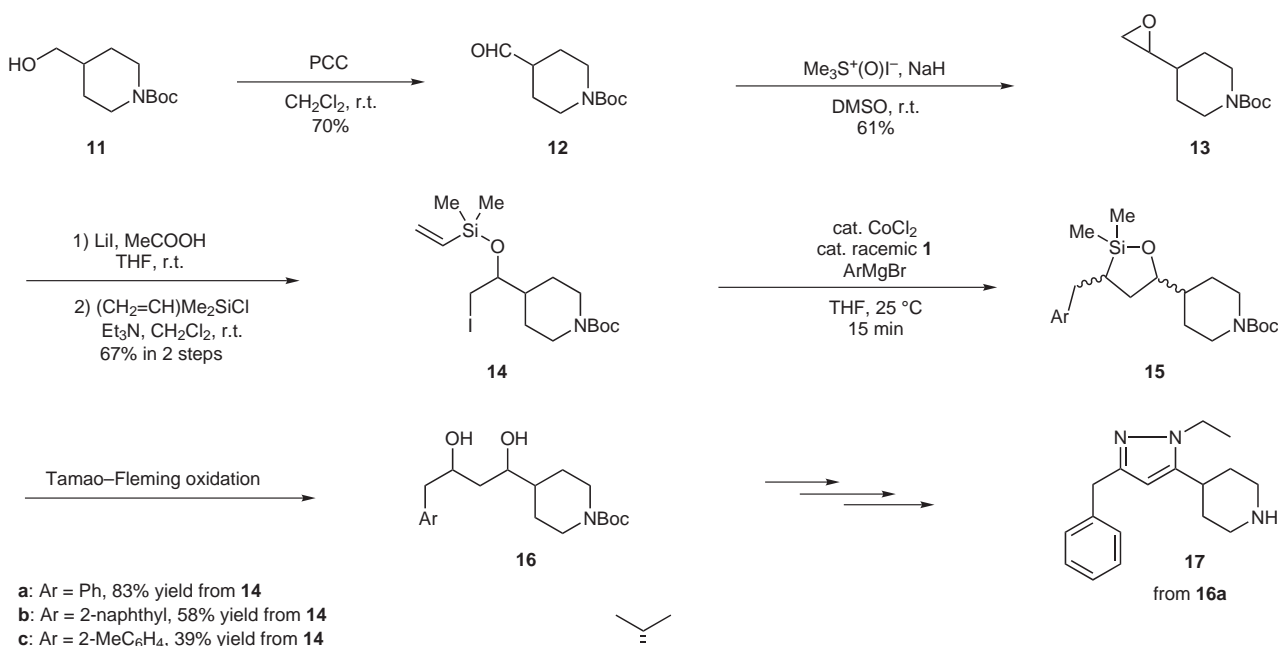
Other silicon-tethered substrates, similarly prepared from the corresponding epoxides, were examined (Scheme 4). The reaction of iodide **5** with five-membered ring showed higher diastereoselectivity than that of **2**. The primary

alkyl iodide **8a** serves as a substrate to provide the diol **10** in 66% yield. The substrate **8b** bearing a diphenylvinylsilyl group participated in the cyclization. Unfortunately, the use of the corresponding bromides as substrates gave the desired products in no more than 5% yield.



Scheme 4

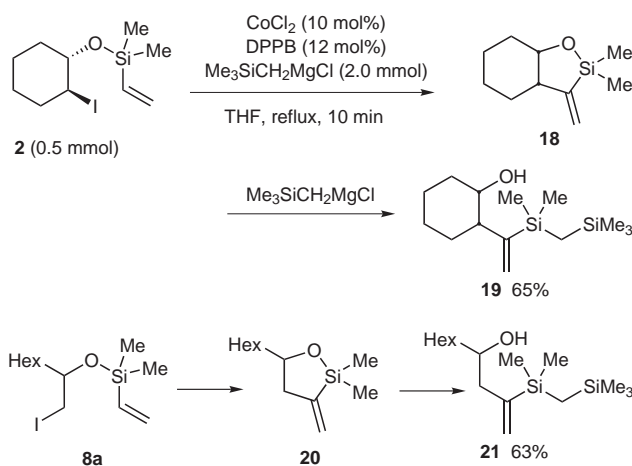
The new approach to 4-aryl-1,3-butanediols is applicable for the construction of an intermediate **16a** in the synthesis of **18**, an antagonist of human CCR5 receptor.⁶ The synthesis is outlined in Scheme 5. Construction of the epoxide group in **13** was performed from **11** in two steps. Ring opening of epoxide **13** with iodide followed by silylation with chlorodimethylvinylsilane provided silicon-



Scheme 5

tethered 6-iodo-1-hexene derivatives **14** in 67% overall yield. Treatment of **14** under the cobalt-catalyzed conditions led to sequential radical cyclization–cross-coupling reaction to afford a phenylated product **15a**. Oxidation of **15a** provided diol **16a**, which will be converted into **17**, a key intermediate of **18**. In addition, the protocol offered easy accesses to 2-naphthyl- and 2-tolyl-substituted analogues **16b** and **16c** by simply changing the aryl Grignard reagents used.

We reported cobalt-catalyzed intramolecular Heck-type reaction of 6-halo-1-hexene derivatives.^{7,8} We next turned our attention to the Heck-type reaction of the silicon-tethered substrates. Trimethylsilylmethylmagnesium chloride (2.0 mmol, 1.7 M THF solution) was added to a mixture of cobalt(II) chloride (0.05 mmol) and 1,4-bis(diphenylphosphino)butane (0.06 mmol) in THF. The resulting mixture was stirred for 5 minutes, and substrate **2** (0.5 mmol) was added at 0 °C. The mixture was heated at reflux for 10 minutes, usual work-up followed by silica gel column purification afforded the alcohol **19** in 65% yield (Scheme 6). In this process, the Heck-type reaction offered methyleneoxasilacyclopentane **18**, which was then alkylated with trimethylsilylmethyl Grignard reagent, yielding **19**. This Heck-type reaction was applicable to the primary iodide **8a** to yield **21**. We attempted the synthesis of β -hydroxyketone. However, Tamao–Fleming oxidation of **19** and **21** resulted in failure.



Scheme 6

In summary, we have developed an access to a variety of 4-aryl-1,3-diols by a combination of the silicon-tethered strategy and the cobalt-catalyzed radical arylative cyclization reaction. The silicon-tethered substrates also enjoyed intramolecular Heck-type reaction upon treatment with trimethylsilylmethylmagnesium chloride under cobalt catalysis.⁹

Acknowledgment

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- General Procedure for Sequential Cyclization–Cross-Coupling Reaction.**

Anhyd CoCl₂ (3.2 mg, 0.025 mmol) was placed in a 20-mL reaction flask and was heated with a hair dryer in vacuo for 2 min. After the color of the cobalt salt became blue, anhyd THF (2 mL) and racemic **1** (20 mg, 0.12 mmol) were sequentially added under argon. The mixture was stirred for 3 min and 6-halo-4-oxa-3-sila-1-hexene derivative **2** (155 mg, 0.5 mmol) was added. Phenylmagnesium bromide (1.0 M THF solution, 0.75 mL, 0.75 mmol) was then added over 5 s to the reaction mixture at 25 °C. While the Grignard reagent was being added, the mixture turned brown. After being stirred for 15 min at 25 °C, the reaction mixture was poured into sat. NH₄Cl solution. The products were extracted with hexane (2 × 20 mL). The combined organic layer was dried over Na₂SO₄ and concentrated to provide a yellow oil. The ¹H NMR analysis with dibromomethane as an internal standard indicated the formation of the desired oxasilacyclopentane **3a** in 93% yield. Then, KF (58 mg, 1.0 mmol) and KHCO₃ (100 mg, 1.0 mmol) were dissolved in MeOH–THF (5 mL, 1:1 mixture). The crude product and 30% aq H₂O₂ (0.52 mL) were successively added. After being stirred at r.t. for 12 h, the reaction mixture was poured into sat. Na₂S₂O₃ solution. The product was extracted with EtOAc (2 × 20 mL). The combined organic layer was dried over Na₂SO₄ and concentrated. Purification by silica gel column chromatography (hexane–EtOAc = 2:1) provided the diol **4a** (81 mg, 0.37 mmol) in 74% isolated yield. Diol **4a** (1:1 mixture of diastereomers): white solid; mp 69–

72 °C. IR (nujol): 3345, 2924, 973, 743 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ = 1.21–1.32 (m, 1 H), 1.32–1.52 (m, 3.5 H), 1.56–1.87 (m, 4.5 H), 2.23–2.29 (br s, 2 H), 2.71–2.94 (m, 2 H), 3.86 (m, 0.5 H), 4.04–4.08 (m, 1 H), 4.40 (m, 0.5 H), 7.20–7.35 (m, 5 H). ^{13}C NMR (125.7 MHz, CDCl_3): δ = 18.63, 19.97, 20.35, 25.00, 25.83, 25.88, 33.23, 33.87, 41.38, 41.97, 44.23, 44.77, 67.40, 72.43, 76.59, 77.62, 126.66, 126.75, 128.82, 128.88, 129.44, 129.50, 138.82, 138.83.

A Typical Procedure for Heck-Type Reaction.

The CoCl_2 (6.5 mg, 0.05 mmol) was placed in a 20-mL reaction flask and was heated with a hair dryer in vacuo for 2 min. Then, DPPB (26 mg, 0.06 mmol) and anhyd THF (0.1 mL) were added under argon. After the mixture being stirred for about 5 min at r.t., trimethylsilylmethylmagnesium chloride (1.7 M THF solution, 1.2 mL, 2.0 mmol) and **2** (155 mg, 0.5 mmol) were sequentially added dropwise to the

reaction mixture at 0 °C. The resulting mixture was heated at reflux for 10 min. After the mixture was cooled to r.t., the reaction mixture was poured into sat. NH_4Cl solution. The products were extracted with EtOAc (2×20 mL). The combined organic layer was dried and concentrated in vacuo. Chromatographic purification on silica gel afforded the alcohol **19** (87 mg, 0.32 mmol) in 65% isolated yield. Alcohol **19**: oil. IR (neat): 3567, 1447, 1249, 1051, 837 cm^{-1} . ^1H NMR (300 MHz, C_6D_6): δ = -0.24 (s, 2 H), 0.05 (s, 9 H), 0.11 (s, 3 H), 0.12 (s, 3 H), 1.16–1.42 (m, 6 H), 1.74–1.95 (m, 2 H), 2.08 (m, 1 H), 2.37 (dm, J = 12.3 Hz, 1 H), 3.86 (m, 1 H), 5.45 (d, J = 2.7 Hz, 1 H), 5.64 (dd, J = 2.7, 1.2 Hz, 1 H). ^{13}C NMR (125.7 MHz, C_6D_6): δ = 0.22, 0.48, 1.87, 2.86, 20.40, 24.98, 27.11, 33.18, 47.22, 66.98, 125.68, 156.10. Anal. Calcd for $\text{C}_{14}\text{H}_{30}\text{Si}_2\text{O}$: C, 62.15; H, 11.18. Found: C, 62.39; H, 11.44.