

A practical *ortho*-rearrangement of silyl group of *ortho*-bromophenyl silyl ethers using magnesium(0)

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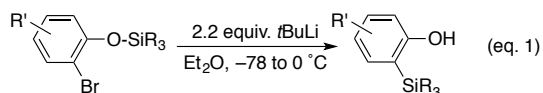
salen

ABSTRACT

A practical synthesis of *ortho*-silyl-substituted phenol from *ortho*-bromophenyl silyl ethers without using RLi is described. Various *ortho*-bromophenyl silyl ethers are treated with commercially available Mg turnings, which are easy to handle in air, and transfer of the silyl group to the *ortho*-position occurs in good to high yields. Selective mono-magnesiumation of 2,6-dibromophenyl silyl ether is observed even in the presence of excess Mg, and *ortho*-bromo-6-silylphenol is obtained as the predominant product. The obtained *ortho*-silyl-substituted phenol is formylated with (CH₂O)_n/MgCl₂/Et₃N, and then condensation with a diamine leads to a silyl-substituted salen-type ligand in a good yield. This scheme is suitable for the large scale synthesis of silyl-substituted salen-type ligands bearing imine groups.

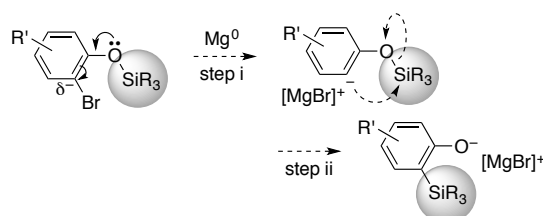
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Development of useful catalysts for novel and selective transformations has been an important topic over the past several decades, and one of the most successful prototypes is a family of salen-metal complexes. A variety of efficient processes by them including Al,¹ Cr,² Mn,³ Ru,⁴ Co,⁵ Ti,⁶ Fe,⁷ Zr,⁸ etc., has been developed. Bulky substituents on aromatic rings are required in some cases to secure desirable functions such as controlled reactivity, regio-, stereo-, and enantioselectivities, and some reports introduced bulky silyl-substituents on salen ligands.⁹ Phenols with an *ortho*-silyl-substituent are precursors for the synthesis of silyl-substituted salen ligands and are efficiently synthesized from *ortho*-bromophenyl silyl ether by *ortho*-lithiation generally using RLi via the *retro*-Brook rearrangement.¹⁰ *n*BuLi (~1.1 equiv.) at 0 °C is used in some cases, but the most general procedure is using *t*BuLi (~2.2 equiv.) from -78 to 0 °C because of its high applicability of the substrates (eq. 1). Although the method is clean, convenient, and suitable for lab-scale synthesis, it is not practical to apply to scale-up syntheses due to the high costs of the expensive reagents and also of the harsh reaction conditions at -78 °C as well as the pyrophoric nature of *t*BuLi. Na⁰ was also used for this purpose,¹¹ while Na⁰ is still reactive toward moisture and O₂ in air. We now report a practical *ortho*-silyl-rearrangement of *ortho*-bromophenyl silyl ethers using commercially available and generally air-stable Mg at/over rt.



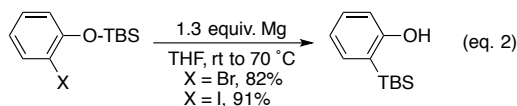
Mg is rather inexpensive and generally easy to handle in air due to a thin layer of impermeable MgO.¹² The Grignard reagent obtained from the reaction of Mg⁰ with R-X or Ar-X (X = Cl, Br, I) has arguably been one of the most useful and versatile

anionic reagents over the past century. However, there are no reports in which the *retro*-Brook rearrangement of *ortho*-halophenyl silyl ethers was systematically examined via Grignard reagent-formation to the best of our knowledge.¹³ Considering the values of the standard electrode potentials (SEPs) of Li⁺/Li⁰, Na⁺/Na⁰ and Mg²⁺/Mg⁰ ($E_{Li}^0 = -3.04$ V; $E_{Na}^0 = -2.71$ V; $E_{Mg}^0 = -2.37$ V),¹⁴ we expected that the *ortho*-silyl rearrangement could proceed via the *ortho*-magnesiumation of the *ortho*-halophenyl silyl ethers. At this point, there are two issues to be considered (Scheme 1): (i) the higher SEP value of Mg⁰ may be insufficient for reduction of the electron-rich Ar-Br to form Ar⁻ [MgBr]⁺,¹⁵ especially with a bulky and electron-donating *ortho*-R₃SiO-substituent (step i) and (ii) the lower nucleophilicity of RMgX than that of RLi may cause a poor yield for the R₃Si-transfer reaction (step ii).



Scheme 1. Two possible issues for *ortho*-R₃Si rearrangement using Mg⁰

We examined a typical reaction of *ortho*-halophenyl *tert*-butyldimethylsilyl (TBS) ether with Mg⁰ (1.3 equiv.) in THF. To our delight, the reaction proceeded in good yield in either case as expected (eq 2).



Success of the preliminary reaction of eq 2 prompted us to examine the reactions of *ortho*-bromoaryl TBS ethers with various substituents on the aromatic ring (Table 1). The alkyl substituents ($R^1 = \text{Me}$; $R^1 = R^2 = \text{Me}$) slightly increased the yield of the reactions (Entries 1 and 2). When the aromatic ring had both electron-donating and -withdrawing substituents ($R^1 = \text{Me}$, $R^2 = \text{Cl}$), the highest yield was obtained (Entry 3). The *para*-electron-withdrawing substituent ($R^1 = \text{Cl}$) gave a high yield (Entry 4), but introduction of an alkyl substituent ($R^2 = \text{Me}$) slightly decreased the yield (Entry 5). Chloro-substituents at the *para*- and *ortho*-positions somewhat decreased the yield (Entry 6), while a strong electron-withdrawing group at the *para*-position ($R^1 = \text{F}$) afforded the desired product in good yield (Entry 7), which showed a tendency similar to that of Entry 4. Interestingly, the electron-donating group at the *para*-position ($R^1 = \text{OMe}$) afforded a good yield comparable to that of $R^1 = \text{F}$. The electronic effects on this reaction were rather confusing. It may be caused by contradictory electronic effects; the electron-donating substituents slow down the reduction of ArX by Mg^0 , but increase the nucleophilicity of the Ar^- toward the R_3Si -group, while the electron-withdrawing substituents enhanced the reduction of ArX to form Ar^- , but decreased its nucleophilicity. All the reactions proceeded in good to high yields (80–91%) in the presence of various substituents on the aromatic ring. The silyl-transfer reactions of some representative silyl groups were then examined (Entries 9–11). Not only a smaller triethylsilyl (TES) group, but the bulkier tri-*iso*-propylsilyl (TIPS) than TBS afforded the desired products in good yields (Entries 9 and 10). However, transfer of *tert*-butyldiphenylsilyl (TBDPS) group was somewhat troublesome, and we obtained the desired *ortho*-TBDPS-phenol (70%) in addition to a by-product (~20%). We then found that diluted conditions improved the yield (Entry 11).

Table 1. R_3Si -transfer reaction of R_3Si aromatic ethers^a

Entry	R_3Si^b	R^1	R^2	Yield, % ^c
1	TBS	Me	H	86
2		Me	Me	89
3		Me	Cl	91
4		Cl	H	90
5		Cl	Me	86
6		Cl	Cl	80
7		F	H	87
8		OMe	H	85
9	TES	H	H	82
10	TIPS	H	H	80
11 ^d	TBDPS	H	H	83

^a R_3Si ether, 2.0 mmol; Mg turnings, 64 mg (2.6 mmol); THF, 4 mL; 1,2-dibromoethane, 10 μL (0.12 mmol); N_2 .

^b R_3Si : TBS = *t*BuMe₂Si; TES = Et₃Si; TIPS = *i*Pr₃Si; TBDPS = *t*BuPh₂Si.

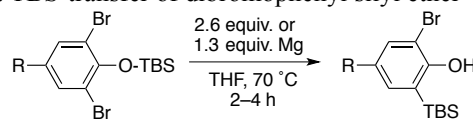
^c Isolated yield.

^d A large amount of THF (30 mL) was used to improve the chemical yield.

The scope of this reaction was then examined through the experiments using 2,6-dibromophenyl silyl ether (Table 2). The

general procedure for the di-metallation of this compound was reported by Rawal, in which *t*BuLi (4 equiv.) was utilized at $-78 \sim 0^\circ\text{C}$, and the successive formylation reaction was achieved in one pot.¹⁶ Although the first magnesiation by Mg^0 proceeded to afford the *ortho*-TBS-substituted phenol, the second one did not proceed at all under the general conditions with 2.6 equiv. of Mg^0 (Entry 1). It was somewhat improved by using the corresponding diiodo-compound with excess Mg, and the protonated product via di-magnesiation was obtained in a low yield (13%, eq 3). In other words, the selective mono-magnesiation of 2,6-dibromophenyl silyl ether was achieved even in the presence of excess Mg^0 . The equivalent of Mg^0 was reduced, but the chemical yield did not practically change (Entry 2). The substituents in the *para*-position, such as Me and Cl, did not change the results very much (Entries 3 and 4). On the other hand, the CF_3 -substituent strongly disturbed the reaction (Entry 5), and no reaction was observed.

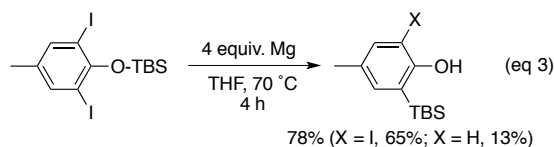
Table 2. TBS-transfer of dibromophenyl silyl ether^a



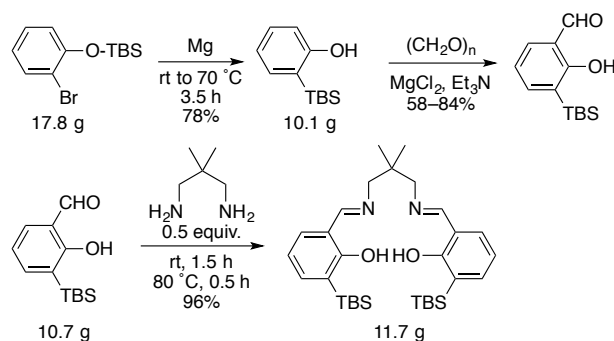
Entry	R	Yield, % ^b
1	H	85
2	H	83
3	Me	87
4	Cl	81
5	CF_3	0

^a TBS ether, 2.0 mmol; Mg turnings, 64 mg (2.6 mmol) except for Entry 1; 1,2-dibromoethane, 10 μL (0.1 mmol); THF, 4 mL; N_2 . In Entry 1, 2.6 equiv. of Mg turnings (130 mg, 5.2 mmol) were used.

^b Isolated yield.



The reason for the unsuccessful second magnesiation should be the insufficient potential of Mg^0 to reduce the highly electron-rich phenolate anion which is produced by the R_3Si -transfer to the *ortho*-position.¹³



Scheme 2. Synthesis of TBS-substituted homosalen ligand over 10 g

The reaction was then applied to the synthesis of the TBS-substituted homosalen ligand (Scheme 2), which was an excellent ligand of the Al-catalyst for the stereoselective polymerization of the racemic lactide and related polymerizations.¹⁷ The TBS-group transfer of *ortho*-bromophenyl TBS ether (17.8 g, 61.9 mmol)

was successful, and *ortho*-TBS-phenol (10.1 g, 48.6 mmol) was obtained in a reasonable yield. The yields of the *ortho*-formylation reaction according to the literature¹⁸ varied in our hands, probably due to contamination by H₂O from the hygroscopic nature of MgCl₂. The condensation reaction of the TBS-substituted salicylaldehyde (10.7 g, 45.2 mmol) and 2,2-dimethylpropane-1,3-diamine (2.70 mL, 22.6 mmol) afforded the desired homosalen ligand in nearly quantitative yield (11.7 g, 21.7 mmol, 96%). The total yield was 43–63%.

In conclusion, we have reported the practical synthetic method of the silyl-group transfer reaction using commercially available Mg turnings, which are rather inexpensive and easy to handle in air. The reaction system was general for the mono-magnesium reaction, while it was not applicable for the di-magnesium reaction due to the higher SEP of Mg²⁺, in other words, a lower reducing potential of Mg⁰. This system was suitable for scale-up synthesis, and over 10 g of *ortho*-TBS-phenol was prepared in a good yield.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found in the online version, at <http://dx.doi.org/10.1016/j.tetlet.xxxx>.