



Selective aromatic carbon–oxygen bond cleavage of trifluoromethoxyarenes: a trifluoromethoxy group as a convertible directing group

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ARTICLE INFO

Article history:

Received 11 June 2008

Revised 24 July 2008

Accepted 1 August 2008

Available online 7 August 2008

ABSTRACT

An efficient method for selective activation of aromatic C–O bonds in trifluoromethoxyarenes is developed. Upon treatment with a metallic sodium/chlorotrimethylsilane system, trifluoromethoxyarenes undergo reductive dealkoxylation to provide the corresponding arylsilanes. Also the synthetic applications of the present reactions combined with *ortho*-metallation are described.

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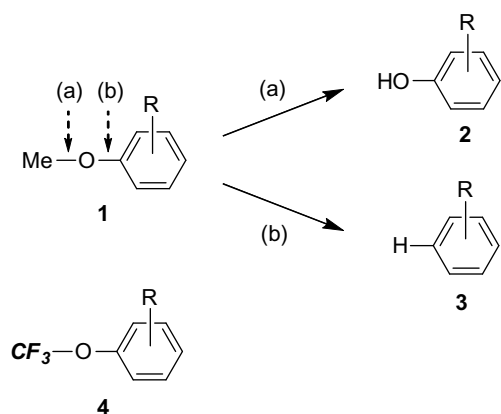
Selective activation of carbon–oxygen bonds has received increasing attention because of its fundamental scientific interest and its potential utility in organic synthesis.¹ Generally, the cleavage of aryl C–O bonds in aryl ethers is not easy due to their large bond energies (ca. 420 kJ/mol).² However, several late transition metal complexes were found to be effective to activate aryl C–O bonds,³ and recently anisole derivatives have been utilized for C–C bond formation as a cross-coupling partner.⁴ Besides transition metal catalyses, reductive breakage of C–O bonds in aryl ethers has been widely investigated so far.

Anisole derivatives **1** possess two kinds of C–O bonds (a and b) possibly susceptible to fission (Scheme 1). Alkali metal-induced reactions of **1** afford the different products, depending on which bonds are cleaved; the breakage of the alkyl–oxygen bonds (a)

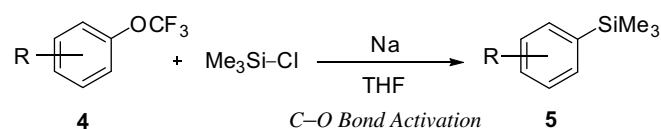
leads to phenols **2**,⁵ whereas that of aryl–oxygen bonds (b) delivers aromatic hydrocarbons **3**.⁶ In these reductive transformations, the fates of anisoles **1** (dealkylation or dealkoxylation) are dictated by reaction conditions such as solvents and low-valent metals.⁷

Among alkoxy functionalities, a trifluoromethoxy substituent is spotlighted in the fields of medicinal, agricultural, and material sciences.⁸ Introducing a trifluoromethoxy group into organic molecules holds a considerable promise for the fine-tuning of technical and biological properties. Trifluoromethoxyarenes **4** are per se stable compounds whose Ar–OCF₃ bonds are generally unreactive. However, to the best of our knowledge, there exists one report on electrochemical behaviors of aryl C–O bonds in trifluoromethoxyarenes under reductive conditions.⁹ From the viewpoint of synthetic organic chemistry, herein we report new useful transformations of trifluoromethoxyarenes **4** by virtue of their aryl carbon–oxygen bonds (Scheme 2).

First, we examined a variety of low-valent metals to evaluate their ability on C–O bond fission of trifluoromethoxybenzene. Metallic lithium, magnesium, and zinc were totally inactive due to their low reduction potentials. However, when trifluoromethoxybenzene (**4a**) was treated with metallic sodium and chlorotrimethylsilane in THF at 80 °C, the reductive dealkoxy-silylation reaction proceeded smoothly to give phenyltrimethylsilane (**5a**) in 92% NMR yield (Table 1, entry 1).¹⁰ In the present reaction, the cleavage of the aryl C–O bond in **4a** occurred predominantly over that of the CF₃–O bond; the formation of phenol (the dealkylated product) was not detected.



Scheme 1.



Scheme 2.

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Table 1
Sodium-promoted dealkoxy-silylation of trifluoromethylarenes **4a–d**

Entry	R	Product	Yield ^a (%)
1	H	5a	76 (92) ^b
2	MeO	5b	59 (67)
3	Ph	5c	30 (38) ^c
4	<i>t</i> -Bu	5d	64 (71)

^a Isolated yields.

^b The numbers in parentheses are NMR yields calculated by ¹H NMR integration of products **5** relative to trioxane internal standard.

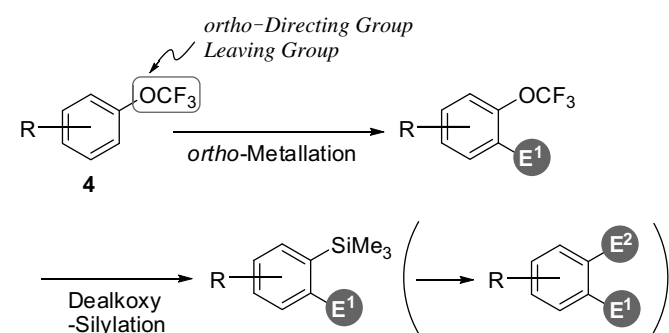
^c 35% of biphenyl was obtained as a by-product.

The reactions of *para*-substituted trifluoromethoxyarenes **4b–d** also afforded the corresponding arylsilylanes **5b–d** in moderate yields (Table 1, entries 2–4). In each case, C–O bond cleavage took place in a chemoselective manner; it is noteworthy that the methoxy grouping (OMe) in **4b** was compatible with the present reduction system (entry 2). This chemoselectivity would be attributed to the poorer leaving group ability of a methoxy group compared with that of a trifluoromethoxy group which bears electron-withdrawing fluorine atoms. In entry 3, the aromatic C–O bond cleavage of 4-trifluoromethoxybiphenyl (**4c**) with sodium afforded the desired arylsilylane **5c** in 30% isolated yield, accompanied by biphenyl (Ph-Ph) in 35% yield.

The reductive cleavage of C–O bonds in **4** using metallic sodium can be explained by assuming the pathway. Initially, one-electron transfer to Ar–OCF₃ (**4**) gives the radical anion intermediates, which participate in decomposition to aryl radicals with release of a CF₃O anion.¹¹ Next, further one-electron reduction of the radical intermediates (Ar[•]) provides the aryl anion species (Ar[−]), which are trapped by Me₃SiCl leading to the corresponding arylsilylanes **5**.¹²

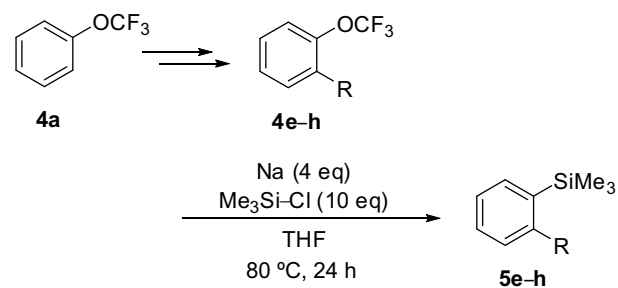
Thus, sodium-promoted selective C–O bond activation of trifluoromethoxyarenes **4** supplies a route to arylsilylanes **5**. Next, we show new reaction sequences involving the dealkoxy-silylation of trifluoromethoxyarenes **4**, in which the trifluoromethoxy substituents fulfill a dual role in imparting both an *ortho*-directing group and a leaving group (Scheme 3).

An alkoxy group attached to an aryl ring acts as a neighboring group which controls *ortho*-selective metallation and the subsequent electrophilic substitution of the aromatic ring.¹³ In 2001, Castagnetti and Schlosser reported the neighboring group-assisted hydrogen/metal permutation of trifluoromethoxybenzene (**4a**) by the action of *sec*-butyllithium.¹⁴ Using the Schlosser's methodology, diverse substituents were introduced into 2-position of **4a**



Scheme 3.

Table 2
Dealkoxy-silylation of *ortho*-substituted trifluoromethylarenes **4e–h**



Entry	R	Product	Yield ^a (%)
1	Me	5e	84 (91) ^b
2	Ph	5f	72 (85)
3	CH ₂ –CH=CH ₂	5g	82 (92)
4	Bn	5h	91

^a Isolated yields from **4e–h**.

^b The numbers in parentheses are NMR yields calculated by ¹H NMR integration of products **5** relative to trioxane internal standard.

to furnish **4e–h**. Then, *ortho*-substituted trifluoromethoxyarenes **4e–h** were subjected to sodium-promoted reductive C–O bond cleavage (Table 2). By the use of 10 equiv of Me₃SiCl, alkoxy-silylation reactions of **4e–h** proceeded cleanly to give the corresponding *ortho*-substituted arylsilylanes **5e–h** in high yields. In the case of substrate **4g**, possessing an alkene moiety, neither intra- nor intermolecular addition of the intermediate radical species with the C–C double bond moiety,¹⁵ selective formation of allylic product **5g** was accomplished in an isolated yield of 82% (entry 3).

In conclusion, we have demonstrated the useful transformation of trifluoromethoxyarenes **4** in which trifluoromethoxy groups are able to function as convertible directing groups.^{16–18} Trifluoromethoxyarenes **4** are readily prepared from the corresponding phenols.¹⁹ Compared to sulfonate groupings, trifluoromethoxy moieties in arenes **4** partake in selective *ortho*-metallation without side reactions such as benzyne formation²⁰ or anionic thia-Fries rearrangement.²¹ The present procedure for dealkoxy-silylation is simple, and metallic sodium as a reducing agent is inexpensive. And the resultant arylsilylanes **5** are general and versatile building blocks for nucleophilic introduction of aryl groups.^{22,23} Thus, ingenuity to leverage the nature of aromatic C–O bond would ensure to achieve highly regioselective synthesis of polysubstituted aromatics.

Acknowledgments

The financial support of the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grant-in-Aid for Scientific Research (B), No. 18350054 and Grant-in-Aid for Scientific Research on Priority Areas 'Chemistry of Concerto Catalysis', No. 20037050) is gratefully acknowledged. We would like to thank Professor Masahiko Hayashi (Kobe University) for his useful suggestions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.002.

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10. A typical procedure: synthesis and characterization of (*o*-allylphenyl)-trimethylsilane (**5g**). To a mixture of chlorotrimethylsilane (0.103 g, 10 mmol) in anhydrous THF (2.0 mL) and Na (92 mg, 4.0 mmol) stirring under argon atmosphere was added 4 g (202 mg, 1.0 mmol) dropwise. The reaction mixture was stirred at 80 °C for 24 h and quenched carefully with methanol and then water. The aqueous layer was extracted with ether and the combined organic phase was dried over MgSO₄. Evaporation of solvents and Kugelrohr distillation afforded **5g** as a colorless oil (156 mg, 82%); bp 102 °C (10 mmHg); ¹H NMR (CDCl₃, 400 MHz) δ 7.48 (d, 1H, J = 7.2 Hz), 7.32 (t, 1H, J = 7.6 Hz), 7.22–7.18 (m, 2H), 5.78 (ddt, 1H, J = 17.2, 10.4, 6.4 Hz), 5.08 (dd, 1H, J = 10.4, 2.0 Hz), 7.48 (dd, 1H, J = 17.2, 2.0 Hz), 3.52 (d, 2H, J = 6.4 Hz), 0.33 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 145.5, 138.4, 137.9, 134.5, 129.2, 129.1, 125.4, 115.9, 40.1, 0.4; Anal. Calcd for C₁₂H₁₈Si: C, 75.71; H, 9.53. Found: C, 75.72; H, 9.77.
11. The fate of the trifluoromethoxy moiety was determined by ¹⁹F NMR measurement of the resulting reaction mixture. After the reaction shown in entry 1, the formation of Me₃SiF instead of CF₃OSiMe₃ was detected. Probably, decomposition of the metal trifluoromethoxide took place. See: Christe, K. O.; Hegge, J.; Hoge, B.; Haiges, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 6155–6158.
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