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Low-Valent Niobium-Catalyzed Reduction of α,α,α-Trifluorotoluenes

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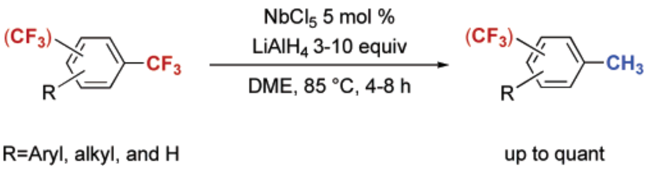
ABSTRACT



In the presence of 5 mol % of niobium(V) chloride, α,α,α-trifluorotoluene derivatives were reduced with lithium aluminum hydride to give toluene derivatives in good yields. Stepwise, partial reduction of bis(trifluoromethyl)benzene derivative was also demonstrated.

The carbon−fluorine bond is one of the most stable single bonds that constitute organic molecules.[1] Fluorine substituents in organic compounds, in general, remain intact under various vigorous conditions, and development of efficient methods to transform the C−F bonds into new C−C bonds[2] or C−X bonds[3] has therefore attracted a great deal of attention from synthetic organic chemists.

Reductions of the C−F bonds into C−H bonds are also important transformations[4] not only because of the fundamental importance on the C−F bond activation chemistry[5] but also because of the close relationship to destruction of atmospheric pollutants[6] such as chlorofluorocarbons (CFCs, ozone depletion)[7] and perfluoroalkanes (greenhouse gases).[8] Although various stoichiometric and catalytic reductions of perfluoroarenes,[9] fluoroarenes,[10] fluoroalkanes,[10a] and fluoroalkenes[9d,11] have been reported to date, efficient and widely applicable methods are still required.

It is well-recognized that α,α,α-trifluorotoluenes are one of the most inert examples among a wide range of organofluorine compounds. The trifluoromethyl groups on the

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[11] (a) Kirkham, M. S.; Mahon, M. F.; Whittlesey, M. K. *Chem. Commun.* **2001**, 813. (b) Kraft, B. M.; Jones, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 8681. (c) Noveski, D.; Braun, T.; Schulte, M.; Neumann, B.; Stammler, H.-G. *Dalton Trans.* **2003**, 4075.

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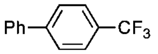
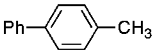
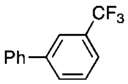
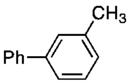
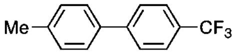
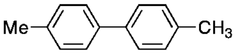
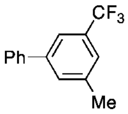
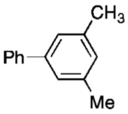
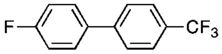
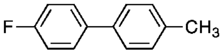
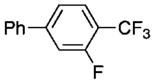
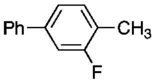
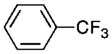
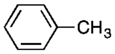
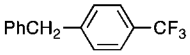
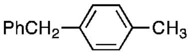
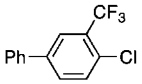
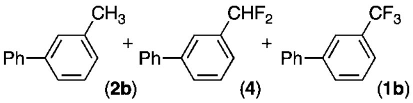
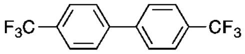
Table 1. Reduction of Trifluorotoluene Derivatives

entry	substrate	time (h)	$LiAlH_4$ (equiv)	product (s)	yield (%) [b]
1	 (**1a**)	4.0	4	 (**2a**)	96
2	 (**1b**)	6.9	4	 (**2b**)	94
3	 (**1c**)	4.0	5	 (**2c**)	85
4	 (**1d**)	4.0	5	 (**2d**)	82
5	 (**1e**)	4.0	5	 (**2e**)	82
6	 (**1f**)	4.0	3	 (**2f**)	quant
7	 (**1g**)	8.0	4	 (**2g**)	quant [c]
8 [d]	 (**1h**)	8.0	10	 (**2h**)	58
9	 (**1i**)	4.0	6	**2b**	81
10	**1i**	4.0	3	 (**2b**) (**4**) (**1b**)	33 (**2b**), 27 (**4**), 12 (**1b**)
11	 (**1j**)	4.0	10	**2c**	58

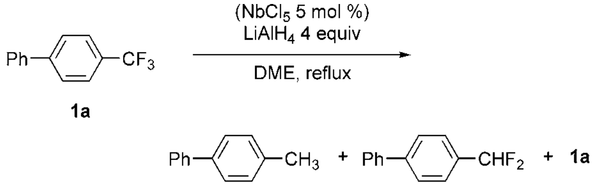
[a] Conditions: $NbCl_5$ (5 mol %), DME, reflux. [b] Starting materials were not recovered. [c] NMR yield (CH_2Br_2 was used as an internal standard). [d] $NbCl_5$ (100 mol %).

aromatic rings are scarcely affected[12] and efficient reduction of the formally benzylic C−F bonds has not been realized until very recently.[13]

We have reported niobium(V) chloride-catalyzed reduction of fluorobenzene derivatives with lithium aluminum hydride in recent years.[14] The low-valent niobium,[15] which is generated in situ, was found to be of high efficiency and the corresponding benzene derivatives were obtained in high yields. Here, we disclose reduction of α,α,α-trifluorotoluene derivatives by means of the low-valent niobium catalyst.

A DME (1,2-dimethoxyethane) solution of 4-phenyl-α,α,α-trifluorotoluene **1a** and 4 molar amounts of lithium aluminum hydride was refluxed in the presence of 5 mol % of niobium(V) chloride for 4 h. The reaction was quenched with water at 0 °C and the desired 4-phenyltoluene **2a** was obtained in 96% yield (Scheme 1). Without niobium(V)

Scheme 1



1a

	2a	**3**	
with $NbCl_5$, 4 h	96%	0%	0%
without $NbCl_5$, 8 h	21%	53%	15%

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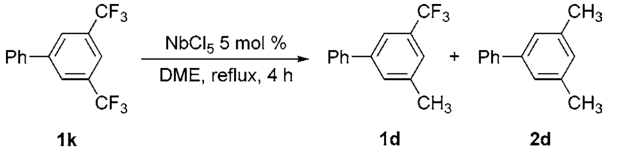
chloride, the reduction did not proceed to completion and partially reduced product **3** was obtained in 53% yield.

The low-valent niobium-catalyzed reduction could be applied to various α,α,α-trifluorotoluene derivatives and the corresponding toluene derivatives were obtained in good yields (Table 1).[16] Phenyl trifluorotoluenes bearing substituents such as methyl and fluorine gave the corresponding products **2a−f** in high yields (entries 1−6). It is noteworthy that the aromatic C−F bonds remained intact under the reaction conditions (entries 5 and 6). Not only phenyl trifluorotoluenes but also the parent trifluorotoluene **1g** and benzyl trifluorotoluene **1h** also gave the corresponding products **2g** and **2h**, respectively (entries 7 and 8). When chlorotrifluorotoluene **1i** was subjected to the conditions, both the C−F bonds and the C−Cl bond were reduced to give *m*-phenyltoluene **2b** in 81% yield (entry 9). On the other hand, when the reduction of **1i** was performed with a reduced amount of lithium aluminum hydride (6 versus 3 molar amounts), partial reduction products **4** and **1b**, in which no chlorine atom survived, were obtained (entry 10). The C−Cl bond in **1i** was found to be reduced prior to the C−F bonds. Reduction of 4,4′-bis(trifluoromethyl)biphenyl **1j** also proceeded successfully and **2c** was obtained in 58% yield (entry 11).

Selective, stepwise reduction of bis(trifluoromethyl)benzene **1k** was also accomplished (Scheme 2). With large excess amounts of lithium aluminum hydride, **1k** gave completely reduced product **2d** in 78% yield. In contrast, **1k** gave a partial reduction product **1d** in 77% yield with 3 molar amounts of the reducing agent. One of the most general methods to prepare α,α,α-trifluorotoluene derivatives is fluorine−chlorine exchange of α,α,α-trichlorotoluenes,[17,18] which are prepared by chlorination of the corresponding toluenes.[19] The low-valent niobium-catalyzed partial reduction is thus a potentially useful method to produce aromatic compounds that possess both the CH_3 group and the CF_3 group.

Scheme 2



	1d	2d
$LiAlH_4$ 10 equiv	0%	78%
$LiAlH_4$ 3 equiv	77%	4%

In conclusion, a variety of α,α,α-trifluorotoluenes could be reduced by the combined use of 5 mol % of niobium(V) chloride and lithium aluminum hydride. The corresponding toluenes were obtained in good yields. Both complete and partial reduction of bis(trifluoromethyl)benzene derivative was also demonstrated.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **2** and **1d**, and chracterization data of **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) **Typical Procedure.** To a DME solution of **1a** (308 mg, 1.39 mmol) and $NbCl_5$ (18 mg, 0.068 mmol) was added solid lithium aluminum hydride (208 mg, 5.47 mmol) carefully. The mixture was magnetically stirred and allowed to reflux for 4 h. The reaction was quenched with water at 0 °C and a small amount of sodium tartrate (ca. 200 mg) was added for ease of extraction. Products were extracted with ethyl acetate three times and the combined organic layers were dried over anhydrous sodium sulfate. The organic solvents were removed under reduced pressure and purification by column chromatography (SiO_2, hexane) gave **2a** (218 mg, 1.33 mmol, 96% yield) as a colorless crystal. The ^1H and ^{13}C NMR spectra were in complete agreement with those in the literature (Tao, B.; Boykin, D. W. *J. Org. Chem.* **2004**, *69*, 4330).

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