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Low-Valent Niobium-Mediated Double Activation of C−F/C−H Bonds: Fluorene Synthesis from *o*-Arylated α,α,α-Trifluorotoluene Derivatives

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The C−F bond is the strongest single bond connected to carbon.[1] Although several aromatic and aliphatic C−F bond activations have been reported in recent years,[2,3] the development of a novel method for C−F bond activation remains elusive. In particular, the CF_3 group attached to an aromatic ring is surprisingly stable, and the activation of these benzylic C−F bonds is quite limited.[4] The transformation of the CF_3 groups is thus a challenging task from the viewpoint of both synthetic organic chemistry and organofluorine chemistry.

We previously reported the reductive cleavage of aromatic C−F bonds by means of low-valent niobium generated in situ.[5] Under similar conditions, we recently found that the CF_3 group of *o*-phenyl-α,α,α-trifluorotoluene **1a** could also be activated, generating fluorene **2a** (Table 1, entry 1). To a DME solution of **1a** and an equimolar amount of $NbCl_5$ was added solid $LiAlH_4$ (10 mol amt) in one portion. After refluxing for 6 h, we isolated fluorene **2a** in 61% yield, together with conventional reduction product **3a** in 18% yield. Although coupling reactions via C−F bond activation remain underdeveloped,[3] we were able to accomplish the C−C coupling reaction via the double activation of C−F and C−H bonds.[6] Other metal salts, such as $TaCl_5$ or VCl_3, gave inferior results (entries 2−5). When the reaction was carried out in the absence of metal salts, partial reduction product **4** was obtained as the major product (entry 6).

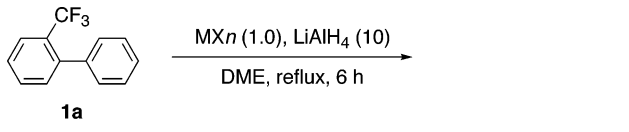
The ratio of **2a** to **3a** was dramatically improved when a DME suspension of $LiAlH_4$ was added to the medium and the reaction was allowed to proceed for 1 h (65% of **2a** and 3% of **3a**, Scheme 1). Use of 1,4-dioxane as solvent further increased the yield of **2a** up to 82%.

Unexpectedly, intermolecular C−C coupling reaction took place when the reaction was carried out in toluene (Scheme 2). 9,9-Ditolylfluorene **5** and 9-tolylfluorene **6** were obtained in 71% and 14% yields, respectively. 9,9-Difluorofluorene **7**, prepared from 9-fluorenone, gave essentially the same products under the identical conditions.

The reaction is outlined as follows in Scheme 3. *o*-Phenyl trifluorotoluene **1a** undergoes low-valent niobium-mediated formal dehydrofluorination from benzylic C−F bond and aromatic ortho C−H bond to give 9,9-difluorofluorene **7**.[7] **7** is readily reduced under the conditions to produce parent fluorene **2a**.[8] On the other hand, **1a** is competitively reduced with excess $LiAlH_4$ present in the reaction medium to give **3a** via partial reduction product **4**.[8] The slow addition of $LiAlH_4$ suppresses the latter process to give a high **2a**/**3a** ratio. When the reaction is carried out in toluene, **7** undergoes *intermolecular* formal dehydrofluorination to give **5** and **6**.

One possible mechanism for the formation of difluorofluorene **7** is that difluorobenzylic niobium species is generated from **1a** and the low-valent niobium.[9] The difluorobenzylic niobium species might undergo intramolecular coupling with ortho C−H bond to give **7**.[10]

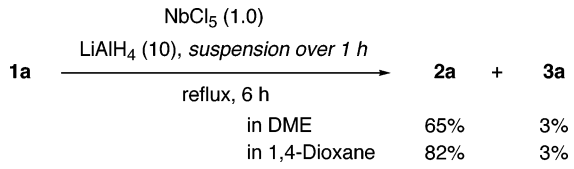
Table 1. Formation of Fluorene[a]



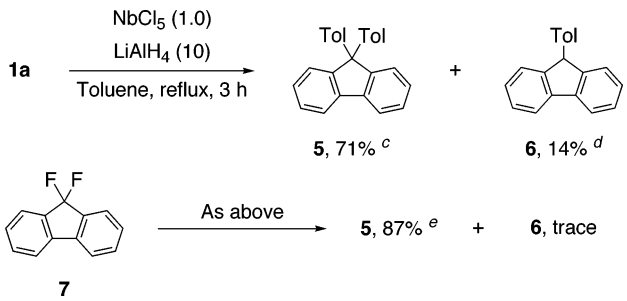
entry	MX*n*	**2a**/%	**3a**/%	**4**/%	**1a**/%
1	$NbCl_5$	61	18	−	−
2	$TaCl_5$	57	27	−	−
3	VCl_3	36	29	−	−
4	$ZrCl_4$	40	29	−	−
5	$PdCl_2$	41	44	4	−
6	none	−	11	52	33

[a] DME = 1,2-dimethoxyethane.

Scheme 1. Slow Addition of $LiAlH_4$



Scheme 2. Formation of 9,9-Ditolylfluorene in Toluene[a,b]

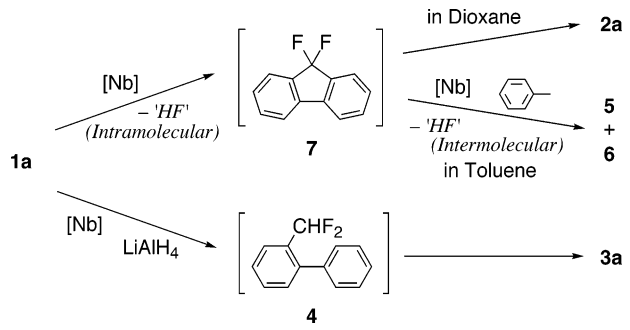


[a] Toluene suspension of $LiAlH_4$ was added over 1 h. [b] Regioisomer ratios of the tolyl groups were determined by GC analysis. [c] *m*-*m*:*m*-*p*:*p*-*p* = 13:51:36. [d] *m*:*p* = 41:59. [e] *m*-*p*:*p*-*p* = 22:78.

This reaction could be carried out with 0.3 molar amount of $NbCl_5$ and 6 molar amounts of $LiAlH_4$ (Table 2). Various *o*-arylated trifluorotoluene derivatives gave the corresponding fluorenes in good yields. In particular, it is of great interest that the CF_3 group was activated prior to C−O, C−S, C−N, and aromatic C−F bonds to give the heteroatom-substituted fluorenes in good yields (entries 4−7). The loading of $NbCl_5$ could be reduced to 0.1 molar amount with a slight decrease of the yield (entry 8).

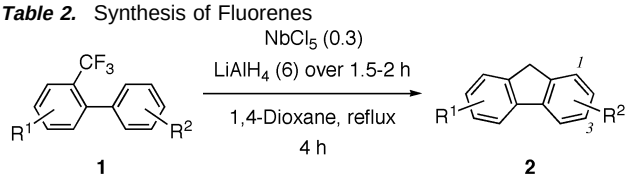
10.1021/ja0565323 CCC: $33.50

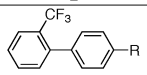
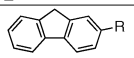
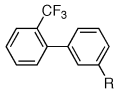
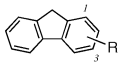
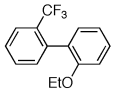
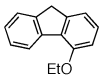
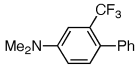
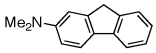
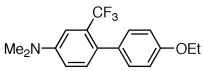
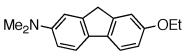
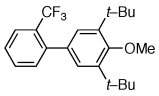
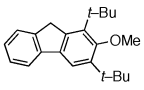
Scheme 3. Outline of the Double Activation Reaction[a]



[a] [Nb] = low valent niobium.

Table 2. Synthesis of Fluorenes



entry	1	(R)	2	2/%
1		H, **1a**		83
2		Me, **1b**		80
3		*t*–Bu, **1c**		82
4		OEt, **1d**		92
5		SMe, **1e**		89
6		NMe_2, **1f**		74 (6 h)
7		F, **1g**		85 (2 h)
8		**1a** [a]		72
9		OEt, **1h**		80 (*1*/*3*=46/54)
10		Me, **1i**		81 (*1*/*3*=43/57)
11		**1j**		52 [b]
12		**1k**		86 (6 h)
13		**1l**		62 [b]
14		**1m**		54

[a] $NbCl_5$ 0.1 mol. amt., $LiAlH_4$ 5 mol. amt. [b] $NbCl_5$ 1.0 mol. amt., $LiAlH_4$ 0.1 mol. amt.

Fluorene is the core structure of (naturally occurring) potent molecules[11] such as the MTP inhibitor,[11a] interferon inducers,[11b] antitumor compounds,[11c,d] and on the contrary, carcinogens.[11e–h] Fluorenes in polymer form have also attracted much attention as molecular devices for blue-light-emitting materials.[11i,j] The niobium-mediated cyclization described here might contribute to these areas of research by supplying these fluorene-containing materials.[12]

In summary, we have developed a double C–F/C–H bond activation protocol for *o*-arylated trifluorotoluenes. By means of this low-valent niobium-mediated system, a variety of substituted fluorenes were synthesized in good yields.

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Supporting Information Available: Supplementary data, preparation of the starting materials, typical procedures, and characterization data of the compounds **1a**–**m**, **2a**–**m**, **4**, **5**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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