Niobium-Catalyzed Reduction of Monofluoroarenes with $LiAlH_4$

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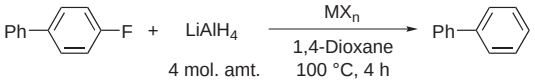
Abstract: It was found that monofluoroarenes were reduced to the corresponding hydrodefluorinated arenes by the treatment of 5 mol% of $NbCl_5$ and $LiAlH_4$. Based on the substituent effect observed, an aromatic nucleophilic substitution mechanism is proposed.

Key words: fluorine, reductions, nucleophilic aromatic substitutions, niobium, hydrodefluorination catalyst

The carbon-fluorine bond is one of the strongest bonds that constitutes organic molecules and reductive cleavage of the C-F bond is a significant problem not only from a viewpoint of organic chemistry but also from a viewpoint of environmental chemistry in relation to dehalogenation of organic compounds.[1] Polyfluoroarenes such as perfluorobenzene or perfluoronaphthalene are readily reduced by a variety of methods utilizing transition metals,[2] but reduction of simple and more stable monofluoroarenes remains to be explored.[3]

We have recently found that monofluoroarenes are readily reduced by the use of catalytic amounts of group 5 metal halides and $LiAlH_4$.

Table 1 Reduction of *p*-Fluorobiphenyl with Group 5 Metal Halides and $LiAlH_4$



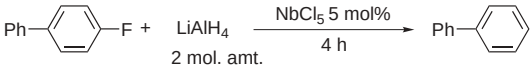
Entry	MX*n*	Loading (mol%)	Yield of biphenyl (%)[a]
1	None	–	28 (57)
2	VCl_3	20	54 (37)
3	$TaBr_5$	20	56 (29)
4	$TaCl_5$	20	60 (34)
5	$NbBr_5$	20	60 (26)
6	$NbCl_5$	20	94 (–)
7		10	93 (–)
8		5	94 (–)
9		2	41 (47)

[a] Recoveries of *p*-fluorobiphenyl are indicated in parentheses (%).

As shown in Table 1, $LiAlH_4$ alone reduced *p*-fluorobiphenyl into biphenyl in 28% yield after 4 hours reflux in 1,4-dioxane, but use of 20 mol% of VCl_3 increased the yield up to 54% (entries 1 and 2). Examination of other group 5 metal halides revealed that $NbCl_5$ was the most active catalyst (entries 2–6) and the catalyst loading could be reduced to 5 mol% (entries 6–9).[4]

Use of ethereal solvent was crucial for this reaction. Reactions in refluxing 1,4-dioxane, 1,2-dimethoxyethane (DME), and THF gave moderate to good yields of biphenyl, but reaction in toluene gave a disappointing result (Table 2). These results suggest that coordination of a solvent molecule to the metal center is essential.[5] Among the solvents examined, we concluded that DME was the most suitable for reaction under less vigorous conditions.

Table 2 Solvent Effect



Entry	Solvent	Bp (°C)	Yield of biphenyl (%)[a]
1	1,4-Dioxane	100	94 (–)
2	DME	85	91 (–)
3	THF	65	73 (18)
4	Toluene	111	10 (82)

[a] Recoveries of *p*-fluorobiphenyl are indicated in parentheses (%).

The scope and limitations of this reaction are shown in Table 3.[6] All of *o*-, *m*-, and *p*-fluorobiphenyls were reduced in the optimized system described in Table 3 to give biphenyl in good yields (entries 1, 6, 9). Not only simple fluorobiphenyls but also electron-rich methyl- or ethoxy-substituted fluorobiphenyls worked well to afford the corresponding products although prolonged time was required (entries 2, 3, 8). Chloride and bromide in fluorobiphenyl substrates were reduced prior to fluoride under the reaction conditions and complete reduction afforded biphenyl in good yields (entries 4, 5, 10). Trifluorobiphenyl also gave 91% yield of biphenyl after 6 hours reflux with 10 mol% of the catalyst (entry 12).

From Table 3, we could also learn two characteristic properties of this reaction. 1) A *meta*-isomer had a lower reactivity compared to the *para*- and *ortho*-isomers: after 4 hours reflux, *m*-fluorobiphenyl gave only 64% yield of biphenyl although *p*- and *o*-fluorobiphenyl gave 91% and 93% yields of the products, respectively (entries 1, 7, 9);

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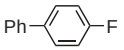
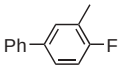
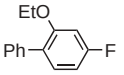
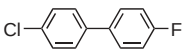
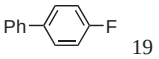
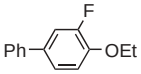
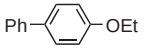
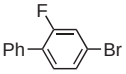
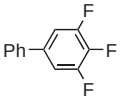
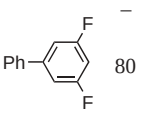
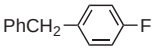
Table 3 Scope and Limitations

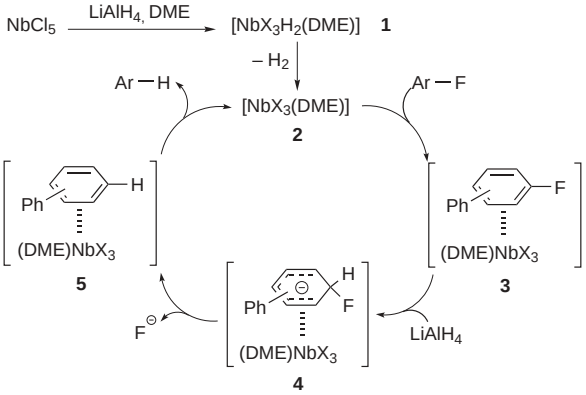
ArF + $LiAlH_4$ (2 mol. amt.) —$NbCl_5$ 5 mol%, DME, 85 °C→ ArH

Entry	ArF	Time (h)	ArH	Yield (%)[a]
1		4.0		91 (–)
2		10.0		90 (–)
3		10.2		Quant. (–)
4		4.0[b]		98 (–)
5		0.6		19 – (76)
6		6.0		91 (–)
7		4.0		64 (34)
8		8.0[c]		90 (–)
9		4.0		93 (–)
10		8.0[d]		90 (–)
11		2.2		81 (–)
12		6.0[d]		91 (–)
13		0.25[e]		80 – (6)
14		6.2	$PhCH_2Ph$	13 (76)

[a] Recoveries of starting material are indicated in parentheses (%).
[b] 3.5 molar amounts of $LiAlH_4$ was used.
[c] 10 Mol% of $NbCl_5$ and 10 mol% of Et_3N were used.
[d] 10 Mol% of $NbCl_5$ and 6 molar amounts of $LiAlH_4$ were used.
[e] 6 Molar amounts of $LiAlH_4$ was used. A few percents yield of *m*-hydrodefluorinated product was detected by GC-MS analysis.

and trifluorobiphenyl mainly gave 80% yield of a *p*-hydrodefluorinated product after 15 minutes reflux (entry 13). 2) An assistance of an extra phenyl group on fluorobenzene ring was necessary for the reaction to proceed because *p*-benzyl(fluoro)benzene afforded only 13% yield of diphenylmethane (entry 14).

Based on the substituent effect mentioned as above, we now surmise that aromatic nucleophilic substitution might take place (Scheme 1): $NbCl_5$ and $LiAlH_4$ undergo hydride-halogen exchange to give niobium(V) di- or polyhydride species **1** and subsequent reductive elimination of dihydrogen[7] forms niobium(III) species **2**.[8] Compound **2** undergoes complexation with the fluoroarene to form the 18-electron η^6-arene complex **3**[9] which contains a DME molecule as a bidentate ligand. Aromatic nucleophilic addition of $LiAlH_4$ onto the arene ligand of **3** takes place[10,11] and the resulting anionic charge is delocalized effectively when an extra phenyl group is placed *para* or *ortho* to the fluorine atom. Subsequent elimination of fluoride from the resulting intermediate **4** gives η^6-arene complex **5**. Liberation of the arene product from **5** regenerates niobium(III) species **2**, which allows the reaction to proceed catalytically.[12]



Scheme 1 Supposed reaction mechanism

In summary, we found that $NbCl_5$ catalyzes reduction of monofluoroarenes with $LiAlH_4$.

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(1) For review, see: (a) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev.* **1994**, *94*, 373. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009.

(2) For examples, see: (a) Aizenberg, M.; Milstein, D. *Science* **1994**, *265*, 359. (b) Aizenberg, M.; Milstein, D. *J. Am. Chem. Soc.* **1995**, *117*, 8674. (c) Edelbach, B. L.; Jones, W. D. *J. Am. Chem. Soc.* **1997**, *119*, 7734. (d) Braun, T.; Cronin, L.; Higgitt, C. L.; McGrady, J. E.; Perutz, R. N.; Reinhold, M. *New J. Chem.* **2001**, *25*, 19. (e) Kraft, B. M.; Jones, W. D. *J. Organomet. Chem.* **2002**, *658*, 132. (f) Laev, S. S.; Evtefeev, V. U.; Shteingarts, V. D. *J. Fluorine Chem.* **2001**, *110*, 43.

(3) For examples of stoichiometric reductions, see: (a) Imamoto, T.; Takeyama, T.; Kusumoto, T. *Chem. Lett.* **1985**, 1491. (b) Kraft, B. M.; Lachicotte, R. J.; Jones, W. D. *J. Am. Chem. Soc.* **2001**, *123*, 10973. (c) For catalytic reductions, see: Li, H.; Liao, S.; Xu, Y. *Chem. Lett.* **1996**, 1059. (d) See further: Yang, H.; Gao, H.; Angelici, R. J. *Organometallics* **1999**, *18*, 2285. (e) Young, R. J. Jr.; Grushin, V. V. *Organometallics* **1999**, *18*, 294. (f) Kuhl, S.; Schneider, R.; Fort, Y. *Adv. Synth. Catal.* **2003**, *345*, 341. (g) Cellier, P. P.; Spindler, J.-F.; Taillefer, M.; Cristau, H.-J. *Tetrahedron Lett.* **2003**, *44*, 7191. (h) See also: Yus, M. *Synlett* **2001**, 1197.

(4) Oshima and Sato reported reduction of organic compounds employing stoichiometric amounts of low valent niobium species generated from $NbCl_5$ and $NaAlH_4$. See: Sato, M.; Oshima, K. *Chem. Lett.* **1982**, 157.

(5) *p*-Fluorobiphenyl reacted with $LiAlH_4$ alone to give 13% yield of biphenyl and 81% recovery of the starting material after 4 h reflux in DME.

(6) **Typical Procedure**: To a DME solution (3 mL) of *p*-fluorobiphenyl (217 mg, 1.26 mmol) and $NbCl_5$ (17 mg, 0.06 mmol) was added $LiAlH_4$ (96 mg, 2.52 mmol) in one

portion. The clear yellow solution turned to dark gray immediately and gas evolved exothermically. After being refluxed for 4 h, the reaction mixture was quenched with H_2O at 0 °C. Sodium tartrate (0.2 g) was added and extraction with EtOAc gave the crude mixture. Purification by silica gel column chromatography (hexane) afforded biphenyl (176 mg, 1.14 mmol, 91%).

(7) When $LiAlH_4$ was added to a DME solution of fluoroarene and $NbCl_5$, gas evolved exothermically.

(8) It was reported that treatment of $NbCl_5$ with 2 molar amounts of *n*-Bu_3SnH gave $NbCl_3$(DME) complex with gas evolution: (a) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 6551. (b) Hartung, J. B. Jr.; Pedersen, S. F. *Organometallics* **1990**, *9*, 1414. (c) See also: Tebbe, F. N.; Parshall, G. W. *J. Am. Chem. Soc.* **1971**, *93*, 3793. (d) Klabunde, U.; Parshall, G. W. *J. Am. Chem. Soc.* **1972**, *94*, 9081.

(9) A variety of η^6-arene complexes of niobium and tantalum have been reported: Morris, M. J. In *Comprehensive Organometallic Chemistry II*, Vol. 5; Abel, A. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon: New York, **1995**, 471.

(10) Use of $LiAlD_4$ instead of $LiAlH_4$ resulted in quantitative formation of *p*-deuteriobiphenyl of 79% D (5 mol% of $NbCl_5$, 2.0 equiv of $LiAlD_4$, reflux in DME, 4 h; deuterium incorporation was determined based on integrals of ^{1}H NMR spectrum).

(11) (a) Djukic and coworkers reported hydride attack to η^6-fluoro(triisopropyl)benzene chromium tricarbonyl complex. See: Djukic, J. P.; Geysermans, P.; Rose-Munch, F.; Rose, E. *Tetrahedron Lett.* **1991**, *32*, 6703. (b) Jones and coworkers proposed an aromatic nucleophilic addition mechanism for their reduction of fluorobenzene with zirconium hydride, see ref. 3b. We rejected a mechanism in which the niobium hydride species undergoes aromatic nucleophilic substitution and adopted a direct hydride attack mechanism because use of *n*-Bu_3SnH instead of $LiAlH_4$ resulted in 88% recovery of the *p*-fluorobiphenyl (5 mol% of $NbCl_5$, 2.4 molar amounts of *n*-Bu_3SnH, reflux in DME, 4 h).

(12) It is already known that some η^6-arene complexes of transition metals such as chromium, iron, and manganese undergo aromatic nucleophilic substitution, but liberation of arene ligand does not take place readily and stoichiometric amounts of the metal are required. For reviews, see: (a) Semmelhack, M. F. In *Comprehensive Organometallic Chemistry II*, Vol. 12; Abel, A. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon: New York, **1995**, 929. (b) For reactions of fluorobenzene complexes: Mahaffy, C. A. L.; Pauson, P. L. *J. Chem. Res.* **1979**, 128. (c) Baldoli, C.; DelButtero, P.; Licandro, E.; Maiorana, S. *Gazz. Chim. Ital.* **1988**, *118*, 409.