Electrophilic Fluorination

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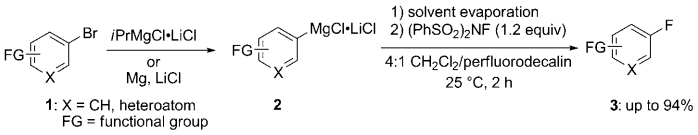
Convenient Electrophilic Fluorination of Functionalized Aryl and Heteroaryl Magnesium Reagents**

*Shigeyuki Yamada, Andrei Gavryushin, and Paul Knochel**

Dedicated to Professor Hiroki Yamanaka on the occasion of his 70th birthday

Fluorine-substituted aromatic and heterocyclic compounds are important target molecules due their useful physical and biological properties.[1] Fluorinated arenes and especially heteroarenes are prepared mostly starting from precursors already bearing fluorine substituents[2] or in the case of heterocycles from acyclic precursors.[3] Methods of direct fluorination of aromatic compounds, for example using electrolysis,[4] are usually not highly selective, and nucleophilic substitution of an aromatic halogen by fluorine is mostly limited to electron-poor aromatics.[5] However, very recently, Buchwald and co-workers[6] reported a general Pd-catalyzed conversion of aryl triflates into fluorides. In the field of electrophilic fluorination, major progress has been made by Ritter and co-workers, who have reported a fluorination of boronic acids[7] and stannanes[8] using palladium or silver catalysis. Olah and co-workers[9] and very recently the Lemaire group[10] published a direct conversion of electron-rich arylboronic acids and aryl trifluoroborates into fluoroarenes. Sanford and co-workers[11] described an electrophilic fluorination by palladium-mediated C–H activation. However, a general method for a direct conversion of organometallic reagents into the corresponding fluoroarenes is still highly desirable. Readily available bromo- or iodoarenes and heteroarenes of type **1** (Scheme 1) are attractive starting materials for the preparation of the corresponding fluorine analogues. Recently, we have developed general methods for preparing functionalized unsaturated Grignard reagents either using a halogen–magnesium exchange reaction[12] or by a direct insertion of Mg in the presence of LiCl.[13] The electrophilic fluorination of aryl magnesium compounds has been reported for simple Grignard reagents; however, it proceeds with moderate to poor yields.[14] Herein, we report an efficient conversion of aryl and heteroaryl Grignard reagents of type **2** into the corresponding fluorinated products



1: X = CH, heteroatom
FG = functional group

2

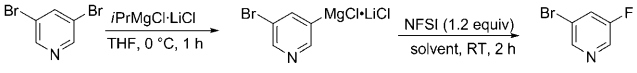
3: up to 94%

Scheme 1. One-pot method for converting aryl or heteroaryl bromides into the corresponding fluorides by Hal–Mg exchange and electrophilic fluorination of organomagnesium reagents with NFSI.

(**3**) using a Br–Mg or I–Mg exchange and a subsequent new convenient electrophilic fluorination procedure (Scheme 1).

After the screening of commercially available fluorinating reagents, we found that *N*-fluorobenzenesulfonimide (NFSI) is the most suitable reagent for the fluorination of organomagnesium compounds.[15] 3,5-Dibromopyridine (**1a**) was used as a test substrate for the one-pot Br–Mg exchange-fluorination sequence optimization. Its treatment with *i*PrMgCl·LiCl (THF, 0 °C, 1 h) afforded the corresponding Grignard reagent **2a**. However, the reaction with NFSI in THF led to 3-bromo-5-fluoropyridine (**3a**) in only 19% yield, as determined by GC. Altering the relative amounts of reagents and the reaction temperature did not lead to a significant improvement. However, the substitution of THF by other solvents dramatically influenced the reaction outcome (Table 1). Of various ethereal solvents tested, only diethyl ether gave satisfactory results (Table 1, entries 1–4). Because of solubility problems, further solvents were tested. Halogenated solvents proved to give the best results. While $PhCF_3$ led to a very low yield, both CH_2Cl_2 and 1,2-dichloroethane gave improved yields (60–68%; Table 1, entries 5, 6,

Table 1: Solvent optimization of the fluorination with NFSI.



1a **2a** **3a**

Entry	Solvent	Yield of **3a** [%][a]
1	THF	19
2	Et_2O	54
3	DME[b]	<10
4	1,4-dioxane	28
5	$PhCF_3$	<10
6	$ClCH_2CH_2Cl$	60
7	CH_2Cl_2	68
8	**CH_2Cl_2/perfluorodecalin (4:1)**	**92**

[a] Yield of hydrolyzed reaction aliquots as determined by GC using an internal standard. [b] DME = dimethoxyethane.

[*] Dr. S. Yamada, Dr. A. Gavryushin, Prof. Dr. P. Knochel
Ludwig Maximilians-Universität München
Department Chemie & Biochemie
Butenandtstrasse 5–13, Haus F, 81377 München (Germany)
Fax: (+49) 89-2180-77680
E-mail: paul.knochel@cup.uni-muenchen.de

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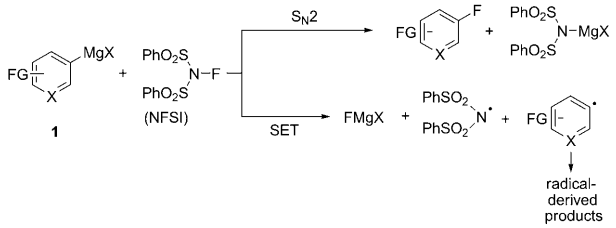
and 7). Unfortunately, the Grignard reagent (**2a**) undergoes a fast decomposition in 1,2-dichloroethane, precluding the use of this solvent. Dichloromethane was found to be the solvent of choice, as it leads to almost homogeneous reaction mixtures and provides the best reaction yields. The only side reaction in the fluorination step is the formation of protonated product.

The electrophilic fluorination[16] of Grignard reagents is believed to proceed by a nucleophilic substitution on the fluorine atom of NFSI (S_N2 mechanism), which competes with a single electron transfer, leading to radical intermediates (Scheme 2).[17] Thus, the formation of the protonated arene as a side product can be attributed to the formation of a radical intermediate, which abstracts a hydrogen atom from the solvent.



Scheme 2. Reaction pathways of unsaturated magnesium reagents with NFSI.

We presumed that the introduction of a fluorinated cosolvent may improve the reaction outcome, since the formed aryl radical may be able to abstract a fluorine atom from this cosolvent. Indeed, addition of hexafluorobenzene (20 vol%) increased the yield of **3a** from 68% to 84%. After the screening of various fluorinated additives, we found that perfluorodecalin gives the best results, leading to the minimum amount of the side product (arene). In a 4:1 mixture of CH_2Cl_2/perfluorodecalin, 3-bromo-5-fluoropyridine (**3a**) was obtained in 92% yield (determined by GC; Table 1, entry 8).

Using the new fluorination protocol, we have prepared, starting from aryl bromides (**1b–k**) and heteroaryl bromides and iodides (**1a**, **1l–s**), various fluorinated arenes and heteroarenes (Table 2 and Table 3). The Grignard reagents were obtained either a by Br–Mg exchange reaction (method A)[12a] or by the direct insertion of Mg into an aromatic bromide in the presence of LiCl (method B).[13] The solvent was then removed in vacuo and replaced by a 4:1 CH_2Cl_2/perfluorodecalin mixture. Addition of NFSI and reaction for 2 h at room temperature gave the corresponding aryl fluorides of type **3** in satisfactory yields. Electron-rich bromoarenes **1b**, **1c**, **1d**, **1f** (entries 1–3 and 5 of Table 2) and electron-poor bromoarenes **1h, 1i, 1k** (entries 7, 8, and 10) can be readily converted into the corresponding fluorides of type **3** using this new protocol. Highly sterically hindered substrates such as 2,4,6-trimethylphenylmagnesium bromide (**2b**) or even 2,4,6-triisopropylphenylmagnesium bromide (**2d**; Table 2, entries 1 and 3) react especially smoothly and afford the best yields of the fluorinated products. Functional groups like an ester (Table 2, entry 2) or an amide (entry 4) are well-tolerated. Noticeably, *o*-fluoro-*N*,*N*-dimethylaniline (**3f**), prone to radical oxidation, was obtained in 64% yield (Table 2, entry 5). Also, halogenated aryl bromides **1g–k** were converted into the corresponding Grignard reagents using *i*PrMgCl·LiCl in THF and led to the fluorinated products (**3g–k**) in 34–55% yield of isolated product (Table 2, entries 6–10).

An especially interesting and challenging problem is the synthesis of fluorinated heterocycles. Such compounds are quite important for modern medicinal and materials chemistry.[18] Our new procedure allows the preparation of various fluorinated derivatives of most important classes of heterocycles. Halogenated pyridines (**1a**, **1l**, **1m**), an isoquinoline (**1n**), a pyrrole (**1o**), a benzo[*b*]thiophene (**1p**), thiophenes (**1q** and **1r**), and furan (**1s**) afford satisfactory yields of the corresponding fluorinated derivatives by this simple one-pot procedure (Table 3).

Thus, the substituted pyridines (**1a**, **1l**, **1m**) are readily converted to the corresponding magnesium reagents of type **2**

Table 2: Preparation of fluoroarenes by the reaction of Grignard reagents with NFSI in 4:1 CH_2Cl_2/perfluorodecalin.

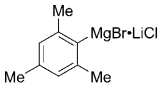
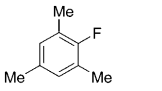
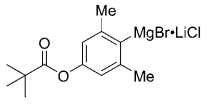
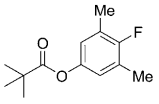
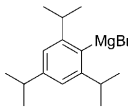
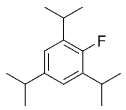
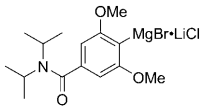
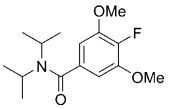
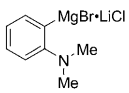
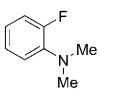
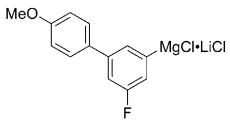
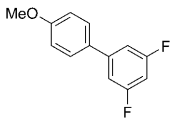
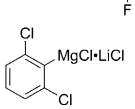
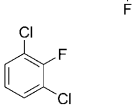
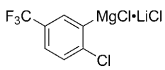
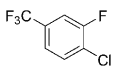
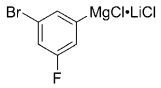
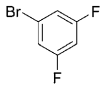
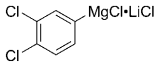
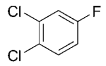
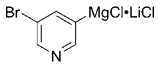
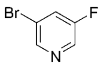
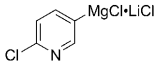
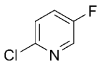
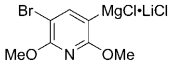
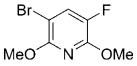
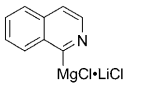
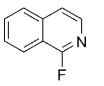
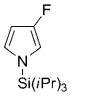
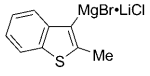
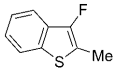
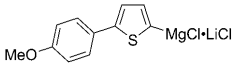
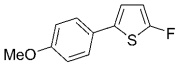
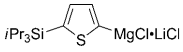
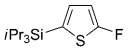
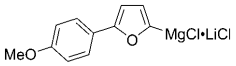
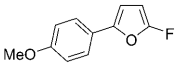
Entry	Grignard reagent	Method of magnesiation[a]	Product	Yield [%][b]
1		**2b** B, 25 °C, 15 h		**3b** 74 (91)
2		**2c** B, 25 °C, 15 h		**3c** 91[c]
3		**2d** B, 25 °C, 15 h		**3d** 90
4		**2e** B, 25 °C, 2 h		**3e** 94[c]
5		**2f** B, 25 °C, 15 h		**3f** 64
6		**2g** A, 25 °C, 1 h		**3g** 55
7		**2h** A, 0 °C, 1 h		**3h** 53
8		**2i** A, 0 °C, 0.5 h		**3i** 52 (88)

Table 2: (Continued)

Entry	Grignard reagent	Method of magnesiation[a]	Product	Yield [%][b]
9		**2j** A, 25 °C, 1 h		**3j** (66)
10		**2k** A, 25 °C, 1 h		**3k** 34 (62)

[a] Method A: Br/Mg exchange using *i*PrMgCl·LiCl. Method B: Mg insertion in the presence of LiCl. [b] Yields of isolated products more than 95% pure as determined by NMR spectroscopy. Yields in parentheses are determined by GC (comparison with an authentic sample). [c] The remaining starting material (**1**) was removed by performing a Negishi cross-coupling with 4-methoxyphenylzinc bromide on the reaction mixture.

Table 3: Fluorine-substituted heterocyclic products of type **3** obtained by electrophilic fluorination using NFSI.

Entry	Grignard reagent	Method of magnesiation[a]	Product	Yield [%][b]
1		**2a** A, 0 °C, 1 h		**3a** 58 (92)
2		**2l** A, 0 °C, 1 h		**3l** 75[c] (97)
3		**2m** A, 25 °C, 1 h		**3m** 65
4		**2n** A, 0 °C, 1 h		**3n** 63
5		**2o** B, 25 °C, 24 h		**3o** 43[d]
6		**2p** B, 25 °C, 15 h		**3p** 60[d]
7		**2q** A, 25 °C, 1 h		**3q** 57[e]
8		**2r** A, 25 °C, 1 h		**3r** 56
9		**2s** A, 25 °C, 1 h		**3s** 49

[a] Method A: Br/Mg exchange using *i*PrMgCl·LiCl. Method B: Mg insertion in the presence of LiCl. [b] Yields of isolated products more than 95% pure as determined by NMR spectroscopy. Yields in parentheses are determined by GC (comparison with an authentic sample). [c] 2.4 equiv NFSI was used. [d] The remaining starting material (**1**) was removed by performing a Negishi cross-coupling with 4-methoxyphenylzinc bromide on the reaction mixture. [e] $PhOCF_3$ was used as a cosolvent instead of perfluorodecalin.

by a Br–Mg exchange.[12] After the replacement of THF by a 4:1 mixture of CH_2Cl_2/perfluorodecalin and treatment with NFSI (1.2 equiv), the expected fluorinated pyridines **3a**, **3l** and **3m** are obtained in 58–75% yields (Table 3, entries 1–3). Interestingly, the magnesiated isoquinoline (**2n**) obtained by I–Mg exchange is smoothly fluorinated, leading to 1-fluoroisoquinoline (**3n**) in 63% yield of isolated product (Table 3, entry 4). Sensitive electron-rich pyrroles, thiophenes, and furans are readily magnesiated either by direct Mg insertion[13] (leading to **2o**, **2p**) or Br–Mg exchange[12] (leading to **2q**–**s**). Using the same procedure, those heterocyclic Grignard reagents are converted to the fluorinated 5-membered heterocycles **3o**–**s** in 43–60% yield of isolated product.

In summary, we developed a simple, convenient, and highly versatile one-pot method for converting aromatic and heteroaromatic bromides or iodides into the corresponding fluorides by choosing an optimized solvent mixture (4:1 CH_2Cl_2/perfluorodecalin). This procedure allows a direct access to fluorinated pyridines, thiophenes, pyrroles and isoquinolines as well as to sterically congested fluorine-substituted benzenes, which are otherwise difficult to prepare. Further investigations of this potentially practical synthetic method are currently underway.

Experimental Section

Typical procedure (synthesis of **3a**): A 50 mL Schlenk flask under N_2 was charged with 3,5-dibromopyridine (**1a**, 1.21 g, 5 mmol) in THF (5.0 mL). *i*PrMgCl·LiCl (5.5 mmol) in THF (1.16 M, 4.7 mL) was added at 0 °C and the mixture was stirred at this temperature for 1 h. Then the solvent was removed in vacuo (0.5 mbar, 40 °C, 0.5 h). CH_2Cl_2 (5 mL) was added, and NFSI (1.95 g, 6 mmol) in CH_2Cl_2 (15 mL) and perfluorodecalin (5 mL) was slowly added at −78 °C. The reaction mixture was stirred at 0 °C for 30 min, then at 25 °C for 2 h, and was poured into ice-cooled saturated aqueous NH_4Cl (50 mL). After extraction with CH_2Cl_2 (3 × 50 mL), the organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2) using pentane/Et_2O (20:1) as an eluent, affording **3a** (574 mg, 58% yield). The analytical data for **3a** are in accordance with those of the commercially available compound.

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