Selective Fluorination

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Efficient Synthesis of Aryl Fluorides**

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Dedicated to Professor Michael Dröscher on the occasion of his 60th birthday

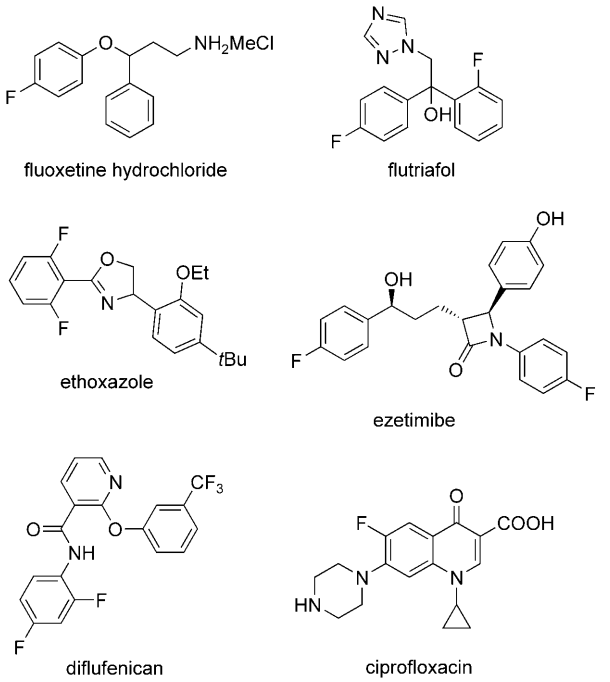
Selective functionalization reactions of aromatic and heteroaromatic halides with carbon, oxygen, and nitrogen nucleophiles have attracted much attention in the last decades.[1] In addition to typical metal-catalyzed coupling reactions, direct functionalization of aryl halides through the formation of Grignard reagents offer new ways for the efficient construction of biologically interesting carbo- and heterocycles.[2,3] Recent elegant examples include the development of LiCl-mediated preparation of Grignard reagents by Knochel and co-workers.[4] Inspired by their work and our interest in functionalization reactions of aryl halides,[5] we have been fascinated in the direct synthesis of aryl fluoride compounds from aryl Grignard reagents.

Although a large number of known pharmaceutical and agrochemical products contain fluorinated arenes (Scheme 1), which enhance solubility, bioavailability, and metabolic stability compared with non-fluorinated analogues,[6,7] there is no convenient and general synthetic method available for their synthesis. Commonly known methods for the introduction of a fluorine atom to arenes require relatively harsh reaction conditions.

Typical examples include the direct fluorination of arenes,[8] the Balz–Schiemann reaction of aryldiazonium salts with HBF_4,[9] and the so-called Halex exchange reaction of activated aryl halides with metal fluorides.[10] In addition, transition-metal-promoted fluorinations have been achieved through the use of electrophilic N–F reagents such as Selectfluor or *N*-fluoropyridinium salts.[11] Unfortunately, in most of these reactions stoichiometric amounts of the transition metal must be used or specific directing groups on the substrate are required.[12] Most recently, Buchwald and co-workers developed an elegant palladium-catalyzed fluorination of aryl triflates using AgF or CsF.[13,14]

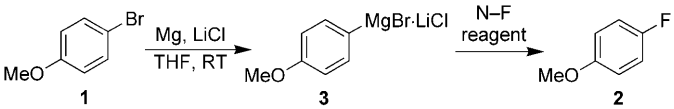
Our initial investigations aimed at the fluorination of 4-bromoanisole (**1**), which is a particularly challenging substrate for nucleophilic fluorination, to give 4-fluoroanisole (**2**; Table 1).

In our model reaction we converted **1** into the corresponding aryl Grignard **3** mediated by LiCl, according to the procedure developed by Krasovskiy and Knochel.[4a] We



Scheme 1. Selected examples of therapeutically important aryl fluoride compounds.

Table 1: Fluorination of 4-$MeOC_6H_4MgBr{\cdot}LiCl$: Variation of temperature and additives.[a]



Entry	N–F reagent	*T* [°C]	Additive	Yield of **2** [%][b]	Anisole [%][b]
1	Selectfluor	0	–	0[c]	–[d]
2	F-TMP-BF_4	0	–	0[c]	–[d]
3	Selectfluor	0	–	32[e]	4
4	F-TMP-BF_4	0	–	51[e]	19
5	F-TMP-BF_4	RT	–	13[f]	16
6	F-TMP-BF_4	−25	–	40	21
7	Selectfluor	0	pyridine[g]	9[h]	12
8	F-TMP-BF_4	0	pyridine[g]	18[h]	10
9	F-TMP-BF_4	0	PBu_3[g]	47	39

[a] Reaction conditions: **3** (0.5 mmol), N–F reagent (0.75 mmol), THF (2 mL), 1.5 h. [b] Determined by GC analysis with hexadecane as the internal standard; the yield is based on Grignard reagent. [c] Fluoronium source was added to the Grignard reagent. [d] Yield was not calculated. [e] Inverse addition of reagents. [f] Formation of 4,4′-dimethoxybiphenyl and **1** was observed. [g] 1 equivalent of additive was used. [h] **1** was the major product.

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envisioned that subsequent addition of electrophilic fluorination reagents should result in the desired fluorinated product **2**. Initially both Selectfluor and *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (F-TMP-BF_4) were tested as fluorinating reagents.[15] As shown in Table 1, the addition of the fluoronium source to **3** at 0 °C gave no fluorination, but 4,4′-dimethoxybiphenyl and other side products were observed (Table 1, entries 1 and 2). On the other hand, slow introduction of the Grignard reagent **3** to the fluorinating reagent at the same temperature smoothly produced the desired fluorinated arene **2** (Table 1, entries 3 and 4). In addition to the desired product, hydrolysis to the dehalogenated arene was observed. The best result (51 % yield) was obtained at 0 °C with F-TMP-BF_4. Variation of the temperature did not improve the fluorination, instead the yield decreased (Table 1, entries 5 and 6). Likewise, additives were not effective (Table 1, entries 7–9).

Next, the influence of various cosolvents was investigated in more detail. For this purpose the Grignard reagent was added to a solution of fluorination reagent in various solvents (Table 2). Notably, the cosolvent had a significant effect on the conversion and selectivity of the electrophilic fluorination. Improved yields of up to 81 % and good selectivities were obtained with heptane or commercially available methoxyperfluorobutane ($CH_3OC_4F_9$) as solvents (Table 2, entries 7 and 8). To the best of our knowledge such high yields for selective fluorination of electron-rich arenes have not been reported before.

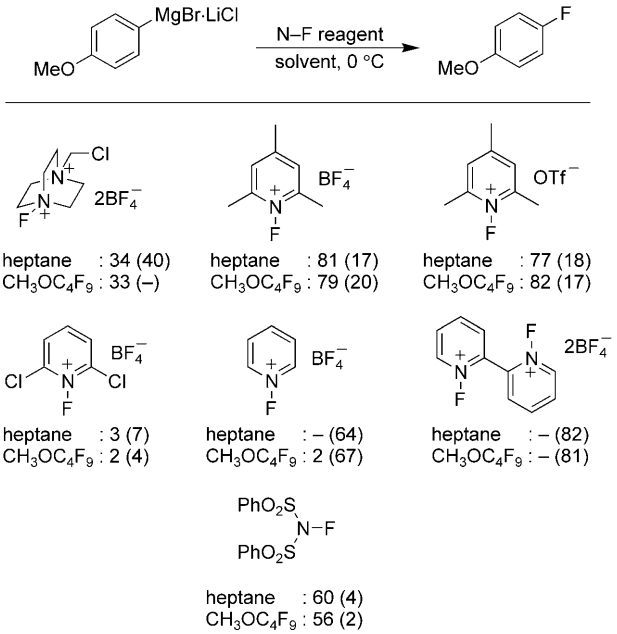
Table 2: Fluorination of 4-$MeOC_6H_4MgBr$·LiCl: Variation of solvent.[a]

Entry	Solvent	Yield of **2** [%][b]	Anisole [%][b]
1	THF	51	19
2	Et_2O	24	15
3	dioxane	35	24
4	$C_6H_5CH_3$	63	19
5	$C_6H_5CF_3$	59	23
6	CH_2Cl_2	30	19
7	heptane	81	17
8	$CH_3OC_4F_9$	79	20

[a] Reaction conditions: **3** (0.5 mmol), F-TMP-BF_4 (0.75 mmol), solvent (2 mL), 0 °C, 1.5 h. [b] Determined by GC analysis with hexadecane as the internal standard; the yield is based on Grignard reagent. THF = tetrahydrofuran.

As shown in Scheme 2, the fluorination reagent also showed a major influence on the model system. As a result, *N*-fluoro-2,4,6-trimethylpyridinium salt is superior to Selectfluor in both heptane and $CH_3OC_4F_9$. Interestingly, examination of various fluoropyridinium salts revealed the importance of the 2,4,6-trimethylpyridinium motif and showed no influence of the counter ion belonging to the fluorination reagent.

Finally, we were interested in the scope and limitations of the procedure using different aryl Grignard reagents. As seen in Table 3, the fluorination of aryl Grignard reagents has substantial scope. Simple aromatic substrates, such as 2-methoxy- and 2-methylphenyl magnesium bromides, reacted smoothly and provided the corresponding aryl fluorides in high yield (Table 3, entries 2 and 4).



Scheme 2. Fluorination of 4-$MeOC_6H_4MgBr$·LiCl using various fluorination reagents. Yield of fluorination in designated solvents and yield of anisole is in parenthesis. Tf = trifluoromethanesulfonyl.

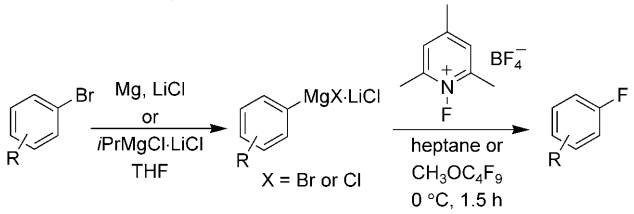
Notably, unhindered substrates such as 4-methyl- and 4-fluoro phenyl magnesium bromides are also efficiently converted into the fluorinated products without increased hydrolysis (Table 3, entries 3 and 13). What is important from a synthetic standpoint is that various functional groups such as methylthio, vinyl, and heteroarenes such as pyridines were also successfully fluorinated by using these reaction conditions (Table 3, entries 5, 6, 17, and 18). Besides being tolerant of many functional groups, this reaction accommodated sterically crowded and electron-rich Grignard reagents that were efficiently fluorinated in good yield (Table 3, entries 7–11). Moderate to good yields of fluorinated arene compounds were obtained with the electron-deficient Grignard reagents, which are substrates that react slowly (Table 3, entries 12–16).

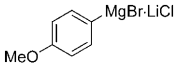
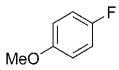
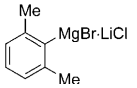
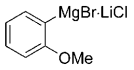
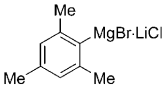
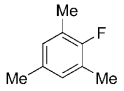
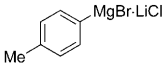
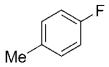
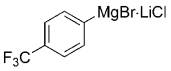
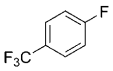
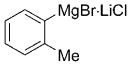
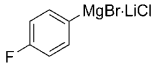
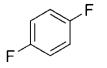
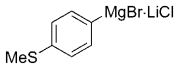
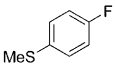
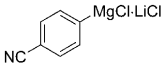
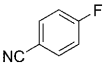
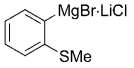
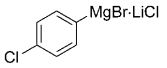
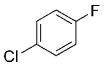
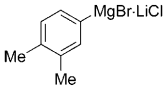
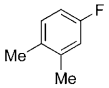
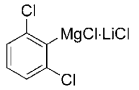
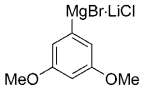
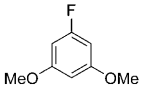
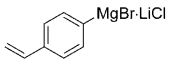
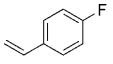
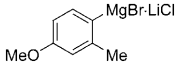
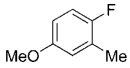
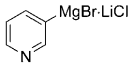
In summary, a general and convenient protocol for the electrophilic fluorination of aryl and heteroaryl Grignard reagents has been developed. Various aryl fluoride derivatives were synthesized in a straightforward manner in only two steps from readily available aryl bromides. Notable features of this novel fluorination procedure are easy handling and mild reaction conditions.

Experimental Section

General procedure for the preparation of Grignard reagents with direct Mg insertion in the presence of LiCl: To a Schlenk tube flushed with argon was added Mg (5.5 mmol), LiCl (5 mmol), and then THF (1.5 mL). To the slurry 0.2 mL of a solution of aryl bromide in THF (5 mmol was dissolved in 3.5 mL) was added and stirred vigorously. The formation of Grignard reagents was initiated in one minute (which was realized by the generation of heat), then remaining aryl bromide was added slowly by maintaining the same temperature.

Table 3: Fluorination of ArMgX·LiCl with F-TMP-BF_4: Scope and limitation.



Entry	ArMgX·LiCl[a]	Product	Yield [%][b] heptane	Yield [%][b] $CH_3OC_4F_9$	Entry	ArMgX·LiCl[a]	Product	Yield [%][b] heptane	Yield [%][b] $CH_3OC_4F_9$
1			81	79	10			71	79
2			69	78	11			73	62
3			73	83	12			–[c]	57
4			70	80	13			57	76
5			61	73	14[d]			33	30
6			61	69	15			48	66
7			68	71	16[d]			40	37
8			44	48	17			60	78
9			59	80	18			61	48

[a] Grignard reagents were prepared in two ways, Method A: Direct insertion of Mg into the C–Br bond in the presence of LiCl; Method B: Br/Mg exchange with *i*PrMgCl·LiCl. [b] Determined by GC analysis with hexadecane as the internal standard; the yield is based on Grignard reagent. [c] Solvent and product had same retention time. [d] Grignard reagent was prepared by using Method B.

After the addition of aryl bromide the reaction mixture was stirred for 15–30 min at RT. The quantitative estimation of Grignard was carried out by GC analysis with hexadecane as THE internal standard.

General procedure for the preparation of Grignard reagents via Br/Mg exchange with *i*PrMgCl·LiCl: To a Schlenk tube flushed with argon was added *i*PrMgCl·LiCl (5.5 mmol, 1.3 M solution in THF). Neat aryl bromide (5 mmol) was added in portions over 20–30 min at 0 °C. The reaction mixture was stirred for 1–3 h. Quantitative estimation of formed Grignard reaction was achieved by GC analysis with hexadecane as the internal standard.

General procedure for the fluorination of Grignard reagents with N–F reagent: To a dry Schlenk tube flushed with argon was added the N–F reagent (0.75 mmol) followed by the respective solvent (2 mL) and cooled to 0 °C (Table 3). A solution of Grignard reagent in THF (≈0.5 mmol in 0.5 mL of THF) was added very slowly over 45–50 min using the syringe pump technique. After the addition, the reaction mixture was stirred for 45 min at the same temperature and quenched by addition of saturated aq NH_4Cl. The yield of fluorinated product was determined by GC analysis of the organic phase with hexadecane as the internal standard.

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Keywords: aryl fluorides · aryl halides · electrophilic fluorination · Grignard reagents · N–F reagents

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