CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.201000288

A New and Practical Grignard-Coupling–Fluorination Sequence: Synthesis of 2-Aryl Fluoroarenes

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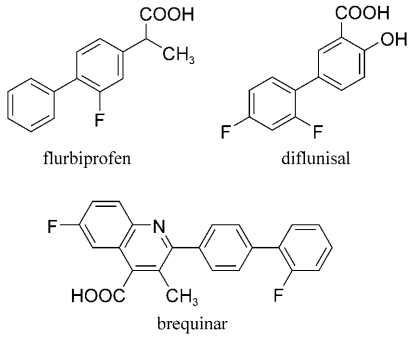
The introduction of fluorine atoms into therapeutically important molecules increases the bioavailability, solubility, and metabolic stability compared with their non-fluorinated analogues.[1–2] As a result, numerous efforts have been directed to the efficient fluorination of organic molecules in recent years. In particular, aryl fluorides attracted significant attention because of their presence in a number of pharmaceuticals and agrochemicals. Among the different aryl fluorides, 2-fluorobiaryls constitute an interesting sub-class, which is found in current drugs, such as Flurbiprofen and Diflunisal (Scheme 1).



Scheme 1. Selected examples of 2-fluorobiaryl-containing pharmaceuticals.

No convenient and general synthesis for this class of compounds has so far been reported. Clearly, modern palladium-catalyzed coupling reactions can be used for this transformation; however, substrates such as 2-fluorobromobenzenes and 2-chlorofluorobenzenes often react sluggishly. Traditionally known aromatic fluorination methods, such as the direct fluorination of arenes,[3] the Balz–Schiemann reaction of aryldiazonium salts with HBF_4,[4] and Halex exchange reactions of activated aryl halides with metal fluorides[5] require harsh reaction conditions and/or toxic reagents.

More recently, palladium-catalyzed fluorination of specific substrates by C–H activation[6] as well as fluorination of aryl boronic acids employing stoichiometric amounts of palladium[7] and silver salts[8] have been accomplished with the aid of electrophilic fluorination reagents, such as *N*-fluoropyridinium salts and Selectfluor. Similarly, silver-mediated electrophilic fluorinations of aryl stannanes were described.[9] However, the use of stoichiometric amounts of expensive metals is a drawback of these strategies. In this respect, the recent palladium-catalyzed fluorination of aryl triflates with AgF/CsF is remarkable.[10]

On the other hand, electrophilic fluorination of easily accessible aryl nucleophiles, such as aryl lithium and aryl Grignard reagents, have been scarcely studied before.[11–13] Most recently, Knochel and co-workers as well as our group have independently developed a general methodology for the electrophilic fluorination of aryl and heteroaryl Grignard reagents using NFSI (*N*-fluorobenzenesulfonimide) and *N*-fluoropyridinium salts, respectively.[14] Based on these results, herein we describe the first synthesis of 2-fluorobiaryls starting from simple aryl bromides.

As 2-bromobiaryls are not readily available, we envisioned a synthesis of 2-fluorobiaryls through an intermolecular domino reaction,[15–16] starting from aryl bromides and 1,2-dihaloarenes. Formation of the corresponding Grignard reagent, followed by coupling with an in-situ-generated benzyne[17] and subsequent electrophilic fluorination was expected to yield the desired 2-fluorobiaryl products (Scheme 2). To the best of our knowledge, such a strategy has not been applied for this class of compounds.

At the start of our investigation, we studied the electrophilic fluorination of **4**; thus, 4-bromotoluene **1** was converted into Grignard reagent **2** as described by Knochel and coworkers.[18] Unfortunately, reaction of **2** with magnesium and

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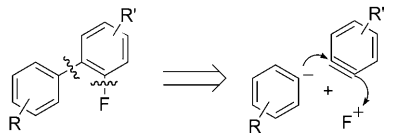
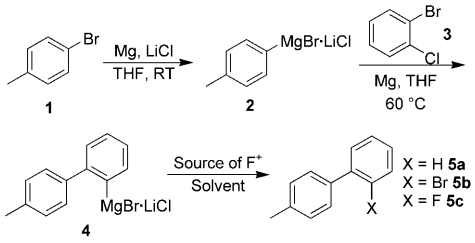
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201000288.

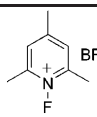
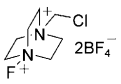


Scheme 2. Approach to the synthesis of 2-fluorobiaryls.

1-bromo-2-chlorobenzene **3** at 60 °C,[17] followed by direct fluorination of the resultant Grignard **4** gave a mixture of products, which was difficult to purify. As shown in Table 1, fluorination of **4** with *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate in tetrahydrofuran at 0 °C afforded the reduced product **5a**, the brominated product **5b**, and the expected fluorinated product 2-fluoro-4′-methylbiphenyl **5c**.[19] The ratio of these three products was found to be **5a**/**5b**/**5c** = 1:3:6 (Table 1, entry 1).[20]

Table 1. Domino Grignard-coupling–fluorination: Variation of solvents and fluorination reagents.[a]



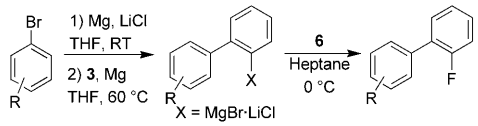
Entry	Source of F^+		Solvent	Ratio of 5a/5b/5c[b]	Yield [%][c]
1		**6**	THF	1:3:6	66
2			heptane	1:0:15	73
3			$CH_3OC_4F_9$	1:0:16	71
4		**7**	heptane	6:3:1	61
5		**8**	heptane	1:5:6	65
6		**9**	heptane	28:1:5	59

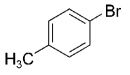
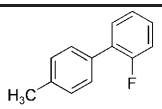
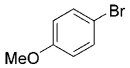
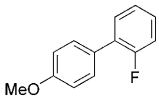
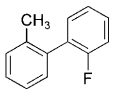
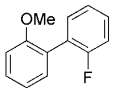
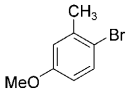
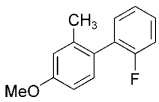
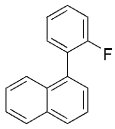
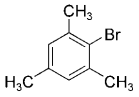
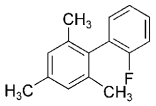
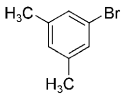
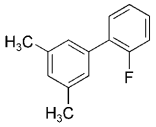
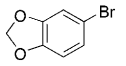
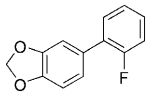
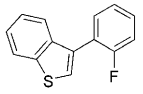
[a] Reaction conditions: Grignard reagent (0.5 mmol), N–F reagent (0.75 mmol), solvent (2 mL), 0 °C, 2 h. Grignard reagent was added slowly over 1 h; [b] Ratio of the products was estimated by ^{1}H NMR analysis; [c] Combined yield of the isolated mixture of **5a**, **5b**, and **5c**. THF = tetrahydrofuran.

To improve the selectivity, we varied both solvent and fluorination reagent. Heptane and methoxyperfluorobutane ($CH_3OC_4F_9$) as solvents gave improved product ratios of 1:0:15 and 1:0:16, respectively (Table 1, entries 2 and 3). However, fluorination with other N–F reagents, such as Selectfluor **7**, NFSI **8**, and *N*-fluoropyridinium tetrafluoroborate **9** were not as effective as *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate **6**, yielding **5a** and **5b** as the major products (Table 1, entries 4–6).[21]

After having found suitable reaction conditions for this intermolecular fluorination sequence, we explored the substrate scope in more detail. Inexpensive aryl bromides, such as *para*-tolyl and *para*-anisyl bromides, are readily converted into their corresponding 2-fluorobiaryls in 73 % and 59 % yield, respectively (Table 2, entries 1 and 2).

Table 2. Domino Grignard-coupling–fluorination: Synthesis of 2-(heteroaryl)arylfluorobenzenes.[a]



Entry	Aryl bromide	Product	Yield [%][b]
1			73
2			59
3			61
4			67
5			56
6			63
7			88
8			68
9			54
10			49

[a] All reaction were carried out with 1.2 equiv of aryl bromide, 1 equiv of **3**, and 1.5 equiv of **6**. [b] Combined yield of the isolated mixture of fluorinated and reduced product in a ca. 15:1 ratio.

Reaction with mesityl bromide, a more hindered substrate, provided 2-fluorophenyl mesitylene in excellent yield (Table 2, entry 7). Similarly, less hindered (*ortho*-tolyl and 1-naphthyl) and non-hindered (3-xylyl) aryl bromides were also transformed into the desired products in good yield

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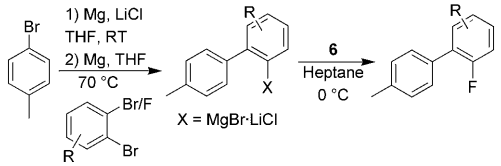
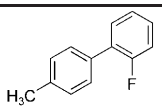
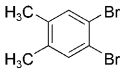
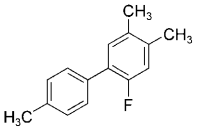
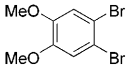
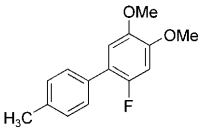
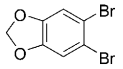
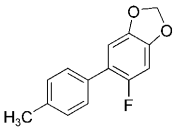
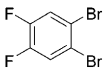
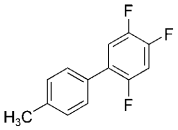
(Table 2, entries 3, 6, and 8). Moreover, electron-rich 2-fluorobiaryl compounds were obtained in moderate to good yield (Table 2, entries 4, 5, and 9). Finally, a heteroaryl bromide (3-bromobenzothiophene) was also an effective substrate for this domino reaction, producing 2-fluorophenyl-3-benzothiophene in moderate yield (Table 2, entry 10).

Next, to expand the scope of the aryne, various 1,2-dihaloarenes were examined. Therefore, *para*-tolylmagnesium bromide was coupled with different 1,2-dihaloarenes and the resultant Grignard reagent was fluorinated with **6** to obtain diverse 2-fluorobiaryls. 1-Bromo-2-fluorobenzene, a complementary dihaloarene to 1-bromo-2-chlorobenzene **3**, smoothly afforded the 2-fluorobiaryl in good yield (Table 3,

Table 3. Domino Grignard-coupling–fluorination: Synthesis of 2-(*para*-tolyl)fluoroarenes.[a]

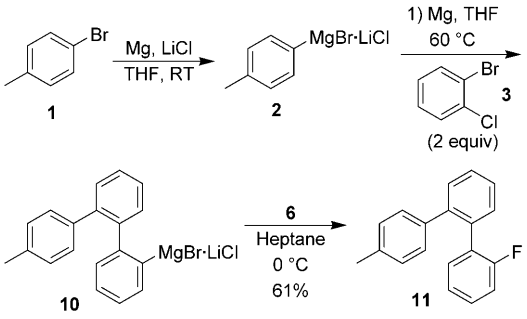


Entry	1,2-Dihaloarene	Product	Yield [%][b]
1			78[c]
2			52
3			65
4			59
5			64

[a] All reaction were carried out with 1.2 equiv of 4-bromotoluene, 1 equiv of 1,2-dihaloarene, and 1.5 equiv of **6**. [b] Combined yield of the isolated mixture of fluorinated and reduced product in a ca. 15:1 ratio. [c] 60 °C.

entry 1). Reaction with the substituted aryne that was generated from 4,5-dibromo-*ortho*-xylene underwent efficient coupling, followed by fluorination with **6** (Table 3, entry 2). Additionally, an electron rich aryne (generated from 4,5-dibromoveratrole and 4,5-(methylenedioxy)-1,2-dibromobenzene) as well as an electron poor aryne (generated from 1,2-dibromo-4,5-difluorobenzene) were also readily converted into their corresponding 2-fluorobiaryls in good yield (Table 3, entries 3–5).

During our studies on the model reaction, we observed the formation of **11** in small quantities (8–10%). It appears that 4-tolylmagnesium bromide **2** reacts with two equivalents of benzyne, followed by fluorination (Scheme 3). To



Scheme 3. Domino Grignard-double-coupling–fluorination sequence for the synthesis of 2-(4-methylbiphenyl)-fluorobenzene.

obtain **11** as the predominant product, we simply increased the amount of 1-bromo-2-chlorobenzene **3** to two equivalents and obtained **11** in 61% yield. Obviously, other aryl Grignard reagents could be also used for this domino Grignard-double coupling–fluorination reaction.

In conclusion, the synthesis of 2-(heteroaryl)aryl-fluoroarenes was accomplished using a novel domino Grignard-coupling–fluorination sequence. This reaction utilizes simple Grignard reagents as effective nucleophiles and as a coupling partner.

Experimental Section

Synthesis of 2-arylfluoroarenes: In the glove box, a 25 mL Schlenk tube flushed with argon was charged with LiCl (2.2 mmol), a magnetic stir bar, and sealed with a septum. Mg (2.5 mmol) and 0.5 mL of THF were added under argon. To this slurry, 0.2 mL of a solution of aryl bromide in THF (2 mmol was dissolved in 1.5 mL) was added and stirred vigorously. The formation of Grignard reagents began very rapidly (1 minute; realized by the generation of heat), then the remaining aryl bromide was added slowly by maintaining the temperature around RT. After the addition of aryl bromide, the reaction mixture was stirred for 15–30 min at RT. GC analysis with hexadecane as the internal standard revealed the formation of Grignard reagent in 90–95% yield. Another 25 mL Schlenk tube flushed with argon was charged with Mg (2.2 mmol), a magnetic stir bar, and sealed with a septum, followed by THF (1 mL) and ArMgBr·LiCl (2.2 mmol, prepared as mentioned above) at room temperature. To the slurry, 0.1 mL of a solution of 1-bromo-2-chlorobenzene in THF (2 mmol dissolved in 1 mL) was added and the solution was stirred vigorously at room temperature. After the formation of the Grignard reagent was initiated, the reaction mixture was kept at 60 °C and the remaining aryl bromide was added slowly over 30 min. After the addition of aryl bromide, the reaction mixture was stirred for 1 h at the same temperature and was used for the subsequent fluorination step. To the another dry 10 mL Schlenk tube flushed with argon was added *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (1.5 mmol), and a magnetic stir bar. After sealing the Schlenk tube with a septum, heptane (4 mL) was added and the mixture was cooled to 0 °C. A solution of Grignard reagent in THF (ca. 1 mmol, prepared as mentioned above) was added slowly over

1.5 h using a syringe pump. After the addition, the reaction mixture was stirred for 1 h at same temperature before being quenched by addition of saturated aqueous NH_4Cl and extracted with diethyl ether. Evaporation of the solvent, followed by column chromatography of the crude product using pentane/diethyl ether as eluent yielded the corresponding 2-(heteroaryl)arylfluorobenzene.

Acknowledgements

This work has been funded by the Alexander-von-Humboldt-Stiftung, the State of Mecklenburg-Western Pomerania, the BMBF, and the DFG (Leibniz Prize). We thank Mrs. S. Leiminger, Drs. W. Baumann, C. Fisher, and Mrs. S. Buchholz (all LIKAT) for analytical support.

Keywords: arylfluorides · arynes · domino reactions · fluorination · Grignard reaction

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Received: April 21, 2010

