Tetrahedron Letters 54 (2013) 1285–1289

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Copper-catalyzed cross-coupling of arenediazonium tetrafluoroborates with polyfluoroarenes

Xingyi Zhu, Feng Li, Weike Su *

College of Pharmaceutical Sciences, Zhejiang University of Technology, Key Laboratory of Pharmaceutical Engineering of Ministry of Education, Hangzhou 310014, China

ARTICLE INFO

Article history:
Received 6 November 2012
Revised 17 December 2012
Accepted 25 December 2012
Available online 3 January 2013

Keywords:
Arenediazonium tetrafluoroborate
Cross-coupling
Polyfluoroarene
Biaryl

ABSTRACT

A novel cross-coupling reaction of arenediazonium tetrafluoroborates with polyfluoroarenes is briefly described. It has advantages of high reaction efficiency, excellent functional group compatibility, mild reaction conditions, short reaction time, and inexpensive ligand. This reaction also can be performed as a one-pot process from anilines omitting isolation of arenediazonium tetrafluoroborates. It has been extended to the preparation of biaryls containing polyfluoroarene structural moiety.

Multiple fluorine substituted biaryls are very important compounds in our daily lives.[1] In particular, these compounds play a key role in medicinal chemistry[2] and functional materials.[3] In the past decade, in order to synthesize these compounds, significant progress has been made in the transition-metal-catalyzed direct formation of C–C bonds between polyfluoro-arenes and arylhalides/arenes/arylboronic acids.[4–6] Although arenediazonium salts have been widely applied in this type of chemistry, they have not been employed in the synthesis of multiple fluorine substituted biaryls yet. Arenediazonium salts represent an attractive alternative due to their high reactivity and easy availability from substituted aniline derivatives.[7] Over the past few decades, arenediazonium salts have been used in the transition-metal-catalyzed cross-coupling reactions as electrophiles like Heck, Suzuki–Monaural, and Sonogashira reactions.[8–10] In this study, the feasibility of a transition-metal-catalyzed approach to biaryls containing polyfluoroarene structural moiety from arenediazonium salts was investigated.

The study was begun with examining the reaction of 4-fluorobenzenediazonium tetrafluoroborate **1a** with pentafluoro-benzene **2a** in DMF at 130 °C. An initial screening showed that, **3a** could be isolated in a low yield without transition-metal-catalysts (Pd or Cu), ligands (Phen or PPh_3), or bases (K_3PO_4, Cs_2CO_3, or *t*-BuOLi) (Table 1, entry 1). Besides, the reaction could not be improved by only lowering or elevating temperatures (Table 1, entries 2–4). In order to improve the yield of **3a**, transition-metal-catalysts were employed in this reaction. But no cross-coupling product **3a** was obtained when using CuI or $Pd(OAc)_2$ with Phen or PPh_3 in the presence of bases. Then, a screening of different solvents (MeOH, THF, DME, DMF) was performed, in the presence or absence of bases (Na_2CO_3, K_2CO_3, *t*-BuOLi) at temperatures ranging from 30 to 140 °C, but there was also no cross-coupling product. In all cases, the homo-coupling product **4a** was always the main product.

In order to overcome the limit of this reaction, a strategy was proposed, in which the cross-coupling product **3a** was formed by an iododediazoniation reaction, followed by the formation of C–C bonds between arenediazonium tetrafluoroborates and polyfluoroarenes. After some experimentations, **3a** could be isolated in 35% yield in the presence of Phen, CuI, KI, and K_3PO_4 in DMF at 130 °C and no homo-coupling product **4a** was obtained (Table 1, entry 7). Then, the reaction conditions were further optimized. The type and amount of additive were changed (Table 1, entries 7–10). Results showed that, **3a** could be isolated in 55% yield in the presence of Bu_4NI (1.5 equiv, Table 1, entry 9). Next, different solvents were investigated and DMSO/MeCN afforded the yield of 67% (Table 1, entries 11–13). Increased amount of CuI and 1,10-phenanthroline lead to a higher yield (Table 1, entries 14 and 15). Finally, the reaction time was shortened, and the best yield of 81% was obtained when the reaction time was 4 h (Table 1, entries 16–19).

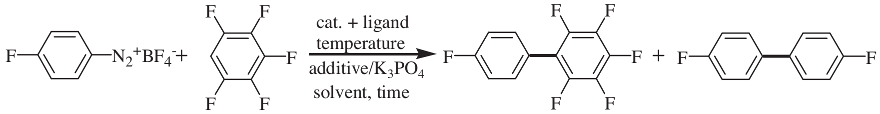
Using the optimized condition (Table 1, entry 20), the scope of the iododediazoniation/coupling reaction was examined with a series of arenediazonium tetrafluoroborates **1a–o** and pentafluoro-benzene **2a**. Results are summarized in Table 2. The electron-rich and electron-poor arenediazonium tetrafluoroborates could react with pentafluorobenzene to obtain the corresponding

---

* Corresponding author.
E-mail address: pharmlab@zjut.edu.cn (W. Su).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.12.110

Table 1
Optimization study of cross-coupling of 4-benzenefluorodiazonium tetrafluoroborate **1a** with pentafluorobenzene **2a**[a]



1a **2a** **3a** **4a**

Entry	Cat (mol %)	Ligand (mol %)	Additive (equiv)	Temperature (°C)	Time (h)	Solvent	Yield[b] of **3a** (%)	Yield of **4a** (%)
1	–	–	–	130	24	DMF	10[c]	0
2	–	–	–	70	24	DMF	8[c]	0
3	–	–	–	110	24	DMF	9[c]	0
4	–	–	–	150	24	DMF	9[c]	0
5	CuI(10)	Phen(10)	–	130	24	DMF	0	50
6	$Pd(OAc)_2$(5)	$P(Ph)_3$(10)	–	130	24	DMF	0	65
7	CuI(10)	Phen(10)	KI(1.5)	130	24	DMF	35	0
8	CuI(10)	Phen(10)	NaI(1.5)	130	24	DMF	40	0
9	CuI(10)	Phen(10)	TBAI(1.5)	130	24	DMF	55	0
10	CuI(10)	Phen(10)	TBAI(2.5)	130	24	DMF	50	0
11	CuI(10)	Phen(10)	TBAI(1.5)	130	24	DMSO	60	0
12	CuI(10)	Phen(10)	TBAI(1.5)	130	24	DMSO/MeCN	67[d]	0
13	CuI(10)	Phen(10)	TBAI(1.5)	130	24	DME	58	0
14	CuI(20)	Phen(20)	TBAI(1.5)	130	24	DMSO/MeCN	75	0
15	CuI(40)	Phen(40)	TBAI(1.5)	130	24	DMSO/MeCN	70	0
16	CuI(20)	Phen(20)	TBAI(1.5)	130	12	DMSO/MeCN	72	0
17	CuI(20)	Phen(20)	TBAI(1.5)	130	6	DMSO/MeCN	78	0
18	CuI(20)	Phen(20)	TBAI(1.5)	130	4	DMSO/MeCN	81	0
19	CuI(20)	Phen(20)	TBAI(1.5)	130	2	DMSO/MeCN	54	0

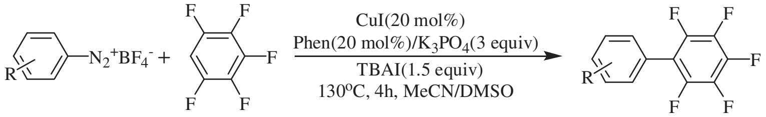
[a] Reaction conditions: substrate **1a** (1 mmol); **1a**:**2a**:K_3PO_4 = 1:3:3; solvent 1.5 mL; under N_2; Phen: 1,10-phenanthroline; TBAI: Bu_4NI.

[b] Yields are isolated yields.

[c] Without base.

[d] Solvent: 1.5 mL MeCN/1.5 mL DMSO.

Table 2
Scope of the cross-coupling of arenediazonium tetrafluoroborates with pentafluorobenzene[a]



1a-o(1 equiv) **2a(3 equiv)** **3a-o**

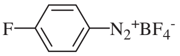
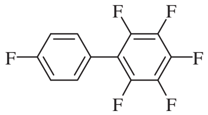
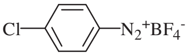
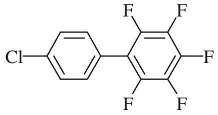
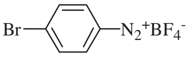
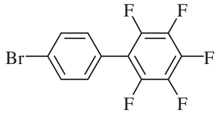
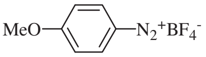
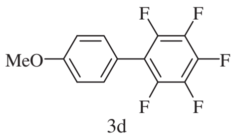
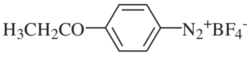
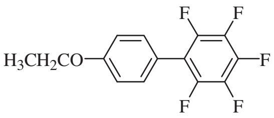
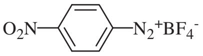
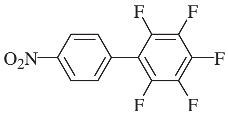
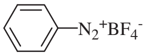
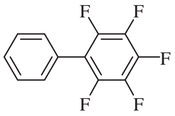
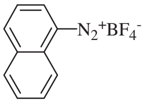
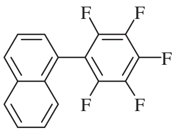
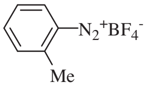
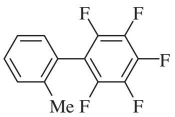
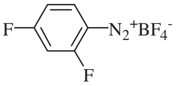
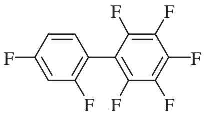
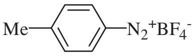
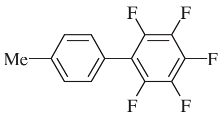
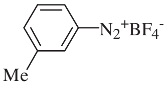
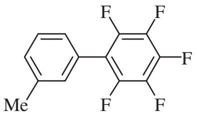
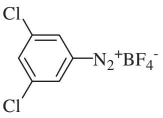
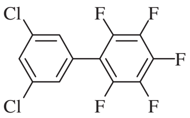
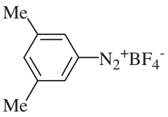
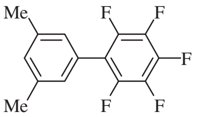
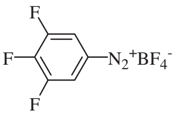
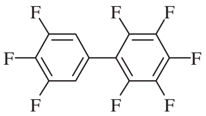
Entry	Arenediazonium tetrafluoroborates **1a–o**	Products **3a–o**	Yield[b] (%)
1	 1a	 3a	82
2	 1b	 3b	66
3	 1c	 3c	78
4	 1d	 3d	85

Table 2 (*continued*)

Entry	Arenediazonium tetrafluoroborates **1a**–**o**	Products **3a**–**o**	Yield[b] (%)
5	 1e	 3e	88
6	 1f	 3f	84
7	 1g	 3g	84
8	 1h	 3h	89
9	 1i	 3i	60
10	 1j	 3j	62
11	 1k	 3k	72
12	 1l	 3l	75
13	 1m	 3m	55
14	 1n	 3n	80
15	 1o	 3o	64

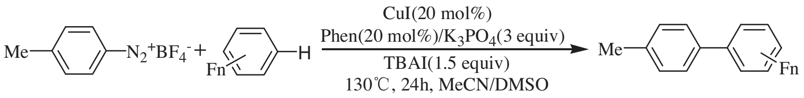
---

[a] Reactions were carried out in 1 mmol scale; 1.5 mL DMSO/1.5 MeCN; under N_2 atmosphere.

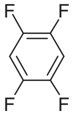
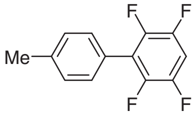
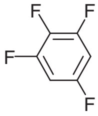
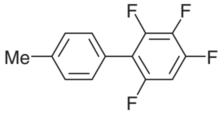
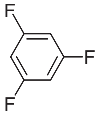
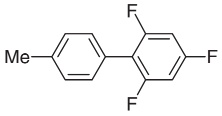
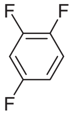
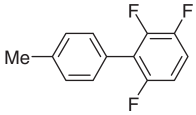
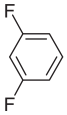
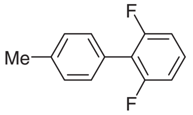
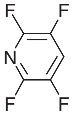
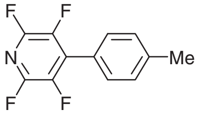
[b] Isolated yields.

cross-coupling products **3a–o** in moderate to excellent yields. The reaction tolerated a variety of substituents including fluoro, chloro, bromo, alkoxy, methyl, and nitro groups. It was noted that, when using ortho substituents as substrates, the yields were significantly decreased due to the steric hindrance (Table 2, entries 9 and 10).

Table 3
Scope of the cross-coupling of fluoroarenes with 4-methylbenzenediazonium tetrafluoroborate[a]



1k 2b–h 3p–v

Entry	Fluoroarenes **2b–h**	Products **3p–v**	Yield[b] (%)
1	 2b	 3p	80
2	 2c	 3q	73
3	 2d	 3r	60
4	 2e	 3s	25
5	 2f	 3t	55[c]
6	 2g	 3u	60

[a] Reactions were carried out in 1 mmol scale; 1.5 mL DMSO/1.5 MeCN; under N_2 atmosphere.

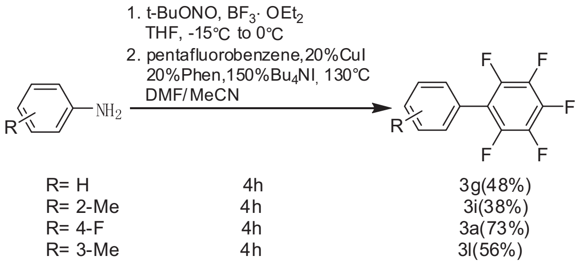
[b] Isolated yields.

[c] 2% $Pd(OAc)_2$ as catalyst and 10% PPh_3 as ligand.

Subsequently, the extension of the reaction to a variety of fluoroarenes **2b–h** was examined. Results are shown in Table 3. The compounds of 1,2,4,5-tetrafluorobenzene **2b** and 1,2,3,5-tetrafluorobenzene **2c** could be arylated with excellent yields (Table 3, entries 1 and 2). 1,3,5-Trifluorobenzene **2d** could be arylated in good yield to obtain the cross-coupling product **3r** (Table 3, entry 3). However, the arylation of 1,2,4-trifluorobenzene **2e** afforded only a low yield of the cross-coupling product **3s** (Table 3, entry 4). 1,3-Difluorobenzenes **2f** was unreactive, with the CuI/Phen catalytic system. After screening of the reaction conditions of 1,3-difluorobenzene **2f** with 4-methylbenzenediazonium tetrafluoroborate **1k**, use of the $Pd(OAc)_2/PPh_3$ catalytic system was feasible. 1,3-Difluorobenzenes **2f** reacted with 4-methylbenzenediazonium tetrafluoroborate **1k** in good yield (Table 3, entry 5). What is more, 1,2,4,5-tetrafluoropyridine **2g** could react with 4-methylbenzenediazonium tetrafluoroborate **1k** in a moderate yield (Table 3, entry 6).

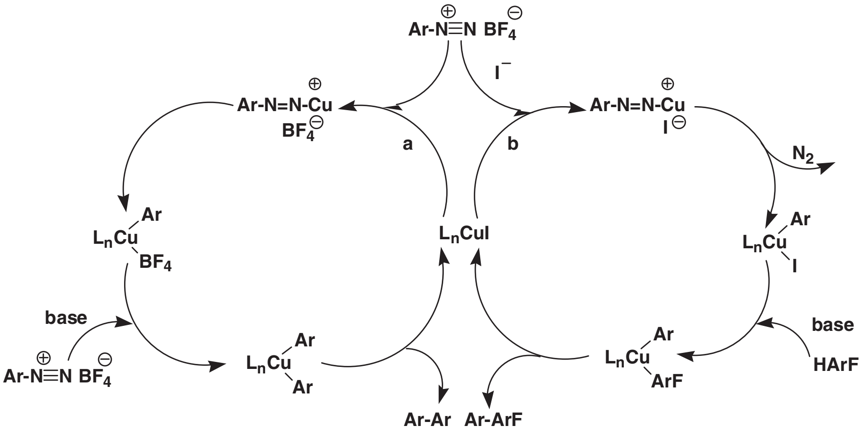
Besides, the entire diazonium salt synthesis/iodmuch dediazoniation/C–C bond forming sequence was performed as a one-pot process, without the isolation of the arenediazonium salt intermediate[11] (Scheme 1). After optimization experiments, the best result was obtained when the reagents required for the arylation step were added to a crude mixture following the preparation of the diazonium salts that had been concentrated under reduced pressure.

The possible reaction mechanism is shown in Scheme 2. When the reaction proceeded without iodide anions, it resulted in homo-coupling products of arenediazonium tetra-fluoroborates[12] (Scheme 2, path a). However, if iodide anions were applied, the



R	Time	Product
R= H	4h	3g(48%)
R= 2-Me	4h	3i(38%)
R= 4-F	4h	3a(73%)
R= 3-Me	4h	3l(56%)

Scheme 1. One-pot domino cross-coupling of anilines with pentafluorobenzene.



Scheme 2. Possible reaction mechanism.

reaction would start with an iododediazoniation step, followed by a cross-coupling reaction[4b,13] (Scheme 2, path b). Control experiment revealed that, arenediazonium salts were quickly converted into the corresponding aryl iodides in the presence of iodide anions.

In summary, a novel cross-coupling reaction of arene-diazonium tetrafluoroborates with polyfluoroarenes has been described. The reaction tolerates a variety of substituents including fluoro, chloro, bromo, alkoxy, methyl, and nitro groups. Ortho substituents such as fluoro and methyl are also tolerated. Bu_4NI plays a key role in the success of the reaction that proceeds through a domino iododediazoniation/C–C bond forming process. Further, the entire diazonium salt synthesis/iododediazoniation/C–C bond forming sequence can be performed as a one-pot process from anilines. Since arylamines are abundant and easily available, this transformation provides an efficient and economic approach for the preparation of multiple fluorine substituted biaryls.

Acknowledgment

We are grateful to the Natural Science Foundation of China (Nos. 21006097, 21076191, and 21276237) for financial help.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.110.

References and notes

1. For selected recent reviews, see: (a) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881; (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320; (c) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119.
2. Zahn, A.; Brotschi, C.; Leumann, C. *Chem. Eur. J.* **2005**, *11*, 2125.
3. For selected recent reviews and papers, see: (a) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. *Chem. Commun.* **2007**, 1003; (b) Tang, M. L.; Reichardt, A. D.; Miyaki, N.; Stoltenberg, R. M.; Bao, Z. *J. Am. Chem. Soc.* **2008**, *130*, 6064; (c) Wang, Y.; Watson, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 2536.
4. (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754; (b) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097; (c) Do, H. Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128; (d) Do, H. Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185; (e) Do, H. Q.; Daugulis, O. *Chem. Commun.* **2009**, 6433; (f) Rene, O.; Fagnou, K. *Org. Lett.* **2010**, *12*, 2116.
5. Wei, Y.; Su, W. P. *J. Am. Chem. Soc.* **2010**, *132*, 16377.
6. Wei, Y.; Kan, J.; Wang, M.; Su, W. P.; Hong, M. *Org. Lett.* **2009**, *11*, 3346.
7. (a) Nan, G.; Ren, F.; Luo, M. *Beilstein J. Org. Chem.* **2010**, *6*, 70; (b) Coy, B. E. D.; Jovanovic, L.; Sefkow, M. *Org. Lett.* **2010**, *12*, 1976; (c) Felpin, F. X.; Ibarguren, O.; Nassar, H. L.; Fouquet, E. *J. Org. Chem.* **2009**, *74*, 1349; (d) Moro, A. V.; Cardoso, F. S. P.; Correia, R. D. *Org. Lett.* **2009**, *11*, 3642; (e) Liu, C. Y.; Andrey, G.; Knochel, P. *Chem. Asian J.* **2007**, *2*, 1020; (f) Dai, M.; Liang, B.; Wang, C.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 221.
8. (a) Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1977**, 159; (b) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581; (c) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *14*, 2320; (d) Taylor, J. G.; Moro, A. V.; Correia, C. R. D. *Eur. J. Org. Chem.* **2011**, 1403.
9. Fan, Y. M.; Qiu, D.; Yu, J. *Tetrahedron Lett.* **2011**, *52*, 518.
10. (a) Anna, R.; Anna, P. Q.; Marcial, M. M. *Chem. Rev.* **2006**, *106*, 4622; (b) Felpin, F. X.; Luma, N. H.; Francois, L. C.; Fouquet, E. *Tetrahedron* **2011**, *67*, 2815.
11. Doyle, M. P.; Bryker, W. J. *J. Org. Chem.* **1979**, *44*, 1572.
12. Monique, K. R.; Vasilina, S. K.; James, M. H. *Tetrahedron Lett.* **2007**, *48*, 7687.
13. Roberta, B.; Sandro, C.; Giancarlo, F.; Antonella, G.; Paolo, S. *Org. Biomol. Chem.* **2010**, *8*, 4518.