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Tunable Cascade Reaction of Aryl Diazonium Salts and Trialkylamine: Synthesis of Monofluorinated Arylhydrazones and *gem*-Difluorinated Azo Compounds

Rui Guo,[†] Zhengjuan Zhang,[‡] Feng Shi,[‡] and Pingping Tang*[,†,§]

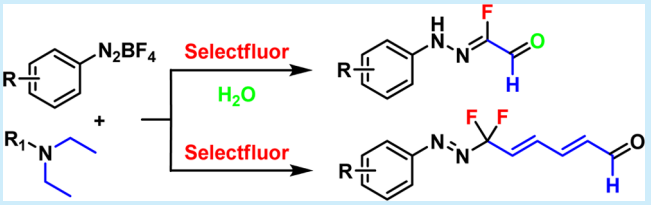
[†]State Key Laboratory and Institute of Elemento-Organic Chemistry, Nankai Unviersity, Tianjin 300071, China

[‡]Key Laboratory of Natural Medicine and Immuno-Engineering of Henan Province, Henan University, Kaifeng 475004, China

[§]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, China

Supporting Information

ABSTRACT: The first example of a mild and tunable cascade reaction of aryl diazonium salts and trialkylamine in the presence of Selectfluor to prepare monofluorinated arylhydrazones and *gem*-difluorinated azo compounds without metal has been explored. In the presence of H_2O, the monofluorinated arylhydrazones were observed in moderate to good yield. In the absence of H_2O, the *gem*-difluorinated azo compounds were obtained. The fluorinated arylhydrazones were utilized to synthesize fluorinated pyrazoles and other nitrogen-containing compounds.



The importance of fluorinated compounds in pharmaceuticals, agrochemicals, and materials has spurred vigorous research into the development of new methods for the synthesis of such compounds.[1] However, methods for direct synthesis of fluorinated arylhydrazones are comparatively scarce.[2] Since arylhydrazones have become widely used as versatile intermediates from organic synthesis,[3] such as in the construction of indoles,[4] carbazoles,[5] pyrazoles,[6] and other heterocylclic compounds,[7] and medicinal chemistry[8] to supramolecular chemistry,[9] the development of general methods for the direct synthesis of fluorinated arylhydrazones is highly desirable. Herein, we present the first example of a mild and tunable cascade reaction of aryl diazonium salts and trialkylamine in the presence of Selectfluor to prepare monofluorinated arylhydrazones and *gem*-difluorinated azo compounds without metal.

Traditionally, fluorinated arylhydrazones are synthesized via the condensation of arylhydrazines[10] or aryldiazonium salts (Japp−Klingemann reaction) with carbonyl compounds.[11] For example, Reichardt reported the coupling of fluorine-containing carbonyl compounds with aryldiazonium chlorides to prepare fluorinated arylhydazones.[12] Additionally, palladium-catalyzed coupling of hydrazones with fluorinated aryl halides has been reported for the preparation of fluorinated arylhydrazones.[13] Recently, a visible-light photoredox-catalyzed C−H activation to prepare difluorinated hydrazones has been developed by Zhu and co-workers.[14] Monteiro and co-workers reported a palladium-catalyzed C−H difluoromethylation of aldehyde-derived hydrazones.[15] To the best of our knowledge, no examples of the direct synthesis of fluorinated arylhydrazones have been reported with aryldiazonium salts and trialkylamine in the presence of fluorinating reagents. We reasoned that if F^+ reagents were used as oxidant and fluorinating reagents, trialkylamine could be oxidized to generate the enamine *in situ*, which could then react with aryldiazonium salts and F^+ reagents to prepare fluorinated arylhydrazones.

To test this hypothesis, initial investigations focused on the reaction of 4-fluorobenzenediazonium tetrafluoroborate (**1a**) with various amines in the presence of Selectfluor and H_2O in DMA/toluene (v/v 3/1) at 25 °C under a N_2 atmosphere. As briefly illustrated in Table 1 (see the Supporting Information for more details), when triethylamine was used, the desired fluorinated arylhydrazone **2a**, whose structure was confirmed by single-crystal X-ray diffraction analysis, was obtained in 56% yield (entry 1). Lower yields were observed with diisopropylethylamine (DIPEA) and diethylmethylamine (entries 2, 7). No desired products were obtained with tributylamine, diethylamine, dimethylethylamine, and *N*,*N*-diethylaniline (entries 3−5). Then, various *N*,*N*-diethylbenzenemethanamines were evaluated (entries 8−10); to our delight, *N*,*N*-diethyl-2-trifluoromethyl-benzenemethanamine (**E**) gave the best results. In addition, different fluorinating reagents were examined, and Selectfluor gave the highest yield (entries 10−12). Water also proved to be essential for product **2a**, since less than 2% yield of product **2a** was observed in anhydrous DMA/toluene. Instead, *gem*-difluorinated azo compound **3a** was observed in 26% yield when triethylamine was used (entry 13). Single-crystal X-ray diffraction analysis of product **3a** confirmed the structure. The slightly higher yield was obtained with DMA/MeCN as the solvent (entry 14), and lower yields were observed with *N*,*N*-diethyl-2-trifluoromethyl-benzenemethanamine (**E**) and *N*,*N*-diethyl-4-*tert*-butyl-benzenemethanamine (**F**) (entries 15, 16).

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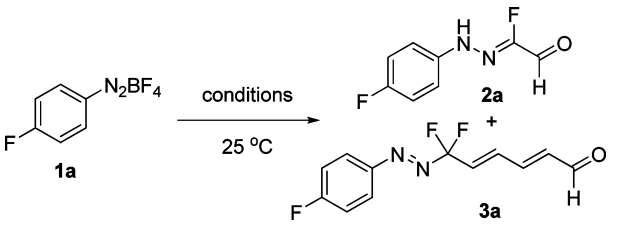
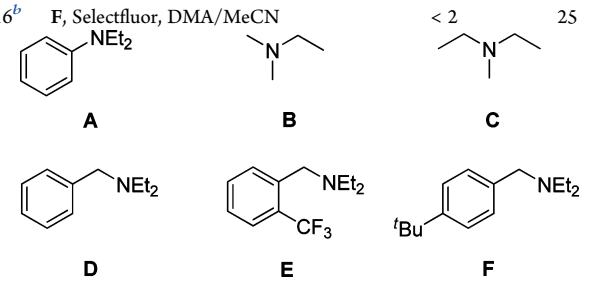
Table 1. Optimization of the Reactions[a]



entry	conditions[a]	yield (%) of 2a[c]	yield (%) of 3a[c]
1	Et_3N, Selectfluor, H_2O, DMA/toluene	56	0
2	DIPEA, Selectfluor, H_2O, DMA/toluene	40	0
3	$^nBu_3N$, Selectfluor, H_2O, DMA/toluene	0	0
4	Diethylamine, Selectfluor, H_2O, DMA/toluene	0	0
5	**A**, Selectfluor, H_2O, DMA/toluene	0	0
6	**B**, Selectfluor, H_2O, DMA/toluene	0	0
7	**C**, Selectfluor, H_2O, DMA/toluene	30	0
8	**D**, Selectfluor, H_2O, DMA/toluene	59	0
9	**E**, Selectfluor, H_2O, DMA/toluene	70	0
10	**F**, Selectfluor[d], H_2O, DMA/toluene	57	0
11	**E**, NFSI[d], H_2O, DMA/toluene	0	0
12	**E**, NFPy[d], H_2O, DMA/toluene	0	0
13[b]	Et_3N, Selectfluor, DMA/toluene	< 2	26
14[b]	Et_3N, Selectfluor, DMA/MeCN	< 2	30
15[b]	**E**, Selectfluor, DMA/MeCN	< 2	9
16[b]	**F**, Selectfluor, DMA/MeCN	< 2	25

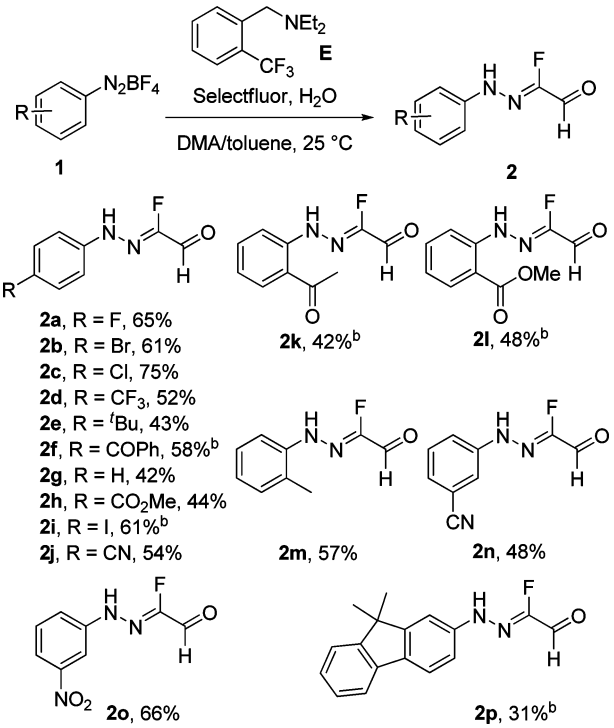


[a]Conditions: 4 equiv of amine, 4.5 equiv of Selectfluor, and 0.93 equiv of H_2O were used in the 3:1 (v:v) DMA/toluene at 25 °C for 10 min under a N_2 atmosphere. [b]Conditions: 5 equiv of amine, 5 equiv of Selectfluor were used at 25 °C for 12 h under a N_2 atmosphere. [c]Yields were determined by ^{19}F NMR with 1-fluoro-3-nitrobenzene as a standard. [d]The structures of Selectfluor, NFSI, and NFPy are displayed in the Supporting Information.

The lower yield of product **3a** was observed due to the protonation byproduct of aryl diazonium salts and other unknown fluorinated byproducts being observed. After thoroughly optimizing the reaction conditions, reactions with 4 equiv of *N*,*N*-diethyl-2-trifluoromethyl-benzenemethanamine (**E**), 4.5 equiv of Selectfluor, and 0.93 equiv of H_2O in 3:1 (v:v) DMA/toluene at 25 °C for 10 min under a N_2 atmosphere were found to produce high yields of the product **2a**. High yields of the product **3a** were obtained with 5 equiv of triethylamine and 5 equiv of Selectfluor in 3:1 (v:v) DMA/MeCN at 25 °C for 12 h under a N_2 atmosphere.

With the optimized conditions in hand, we then investigated the substrate scope to give the monofluorinated arylhydrazones displayed in Table 2. Aryldiazonium salts bearing electron-withdrawing, -neutral, and -donating substituents at the *ortho*, *meta*, or *para* position of the benzene ring gave the corresponding products in moderate to good yields. Various functional groups, such as fluoride, chloride, bromide, iodide,

Table 2. Scope of the Cascade Reaction To Give Monofluorinated Arylhydrazones.[a]



[a]Reaction conditions: aryl diazonium salts **1** (1 equiv), trialkylamine **E** (4 equiv), Selectfluor (4.5 equiv) and H_2O (0.93 equiv), DMA/toluene (v/v 3/1), 25 °C, N_2, 10 min. Yields refer to isolated product. [b]Et_3N was used.

nitrile, nitro, ketone, or ester, were tolerated in the reaction. For substrates (**1f**, **1i**, **1k**, **1l**, **1p**), high yields of the corresponding fluorinated products were observed when triethylamine was used. To prove the practicality of this method for large-scale synthesis, product **2a** was prepared on a gram scale under the standard reaction conditions in 58% isolated yield.

Next, the substrate scope to give the *gem*-difluorinated azo compounds was evaluated as displayed in Table 3. Aryldiazonium salts with various substituents, such as fluoro, bromo, chloro, or keto at the *para* position of the benzene ring gave the *gem*-difluorinated azo compounds **3** in 21% to 27% yield. Besides the desired products, the protonation byproduct of aryl diazonium salts and other unknown fluorinated byproducts were observed. Although a lower yield of *gem*-difluorinated azo compounds **3** was observed, this is the first example to synthesize the *gem*-difluorinated azo compounds **3** in one pot from aryldiazonium salts, and the transformation of this reaction is attractive, which can be further investigated.

The synthetic utility of monofluorinated arylhydrazones was also evaluated. Fluorinated pyrazoles are an important class of compound utilized in pharmaceuticals and agrochemicals.[16] Accordingly pyrazole **4** was synthesized from the corresponding monofluorinated arylhydrazone **2a** and 2-bromoacetophenone in 61% yield (eq 1). Additionally a Wittig reaction to couple the triethylphosphonoacetate and monofluorinated arylhydrazones **2a** were performed to give the unsaturated ester **5** in 92% yield (eq 2), which can be further used to prepare fluorinated nitrogen-containing compounds.

Although detailed mechanistic studies have not been clear, some preliminary mechanistic observations were made. Deuterated product [**D**]**2a** was obtained when deuterated trialkyl-

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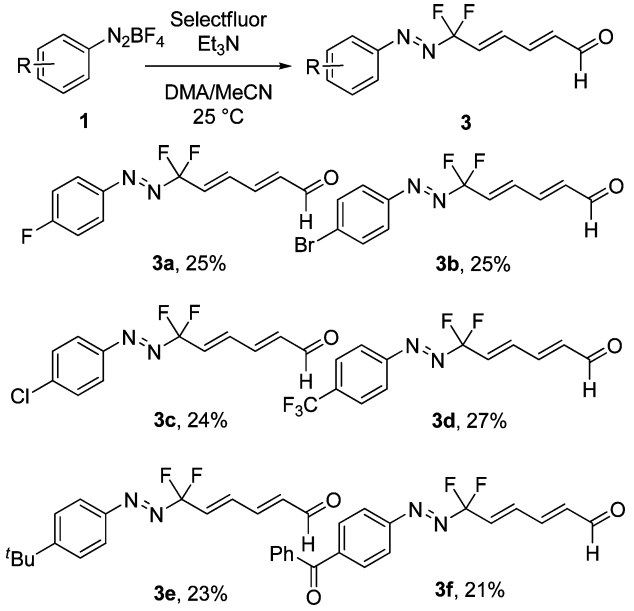
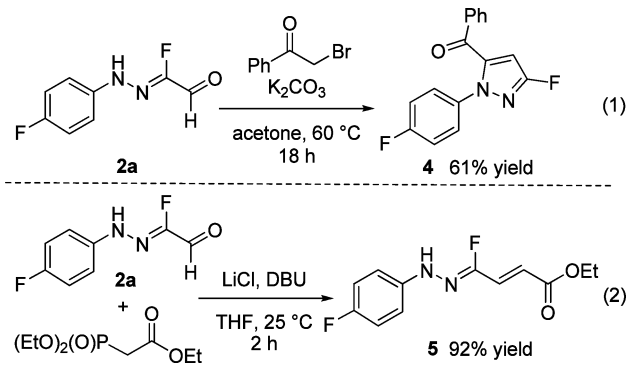
Table 3. Scope of the Cascade Reaction To Give *gem*-Difluorinated Azo Compounds[a]



[a]The reaction was performed with aryl diazonium salts **1** (1.0 equiv), triethylamine (5.0 equiv), Selectfluor (5.0 equiv) in DMA/MeCN (v/v 3/1) at 25 °C for 12 h under a N_2 atmosphere. Yields refer to isolated product.



amine **E′** was used (Figure 1, eq 3), and no deuterated product [**D**]**2a** was observed when D_2O was used under the standard reaction conditions, which indicate that the H atom of aldehyde was from the trialkylamine. Furthermore, the corresponding product [^{18}O]**2a** was detected in the presence of $H_2{}^{18}O$, with 85% ^{18}O incorporation at the position indicated (Figure 1, eq 4), which suggested that the oxygen atom in the product came from H_2O. In addition, deuterated product [**D**]**3a** was observed when deuterated **F′** was used as the trialkylamine source (Figure 1, eq 5).

On the basis of these mechanistic findings, a plausible mechanism is proposed (Figure 2). In the presence of Selectfluor, trialkylamine is oxidized to the fluorinated quaternary ammonium salt **I**, which undergoes elimination to generate the iminium ion **II**. This further forms the enamine **III**. Subsequent treatment with aryldiazonium salts produces the azo intermediate **IV**, which can generate **V** in the presence of base. Then intermediate **V** reacts with Selectfluor to obtain the fluorinated azo intermediate **VI**, which further generates the monofluorinated intermediate **VII**. In the presence of H_2O, **VII** reacts with H_2O to form the monofluorinated arylhydrazones **2**.

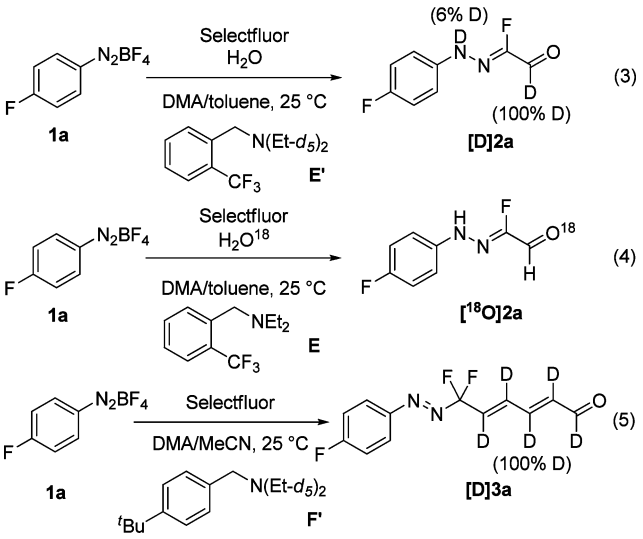


Figure 1. Mechanism study.

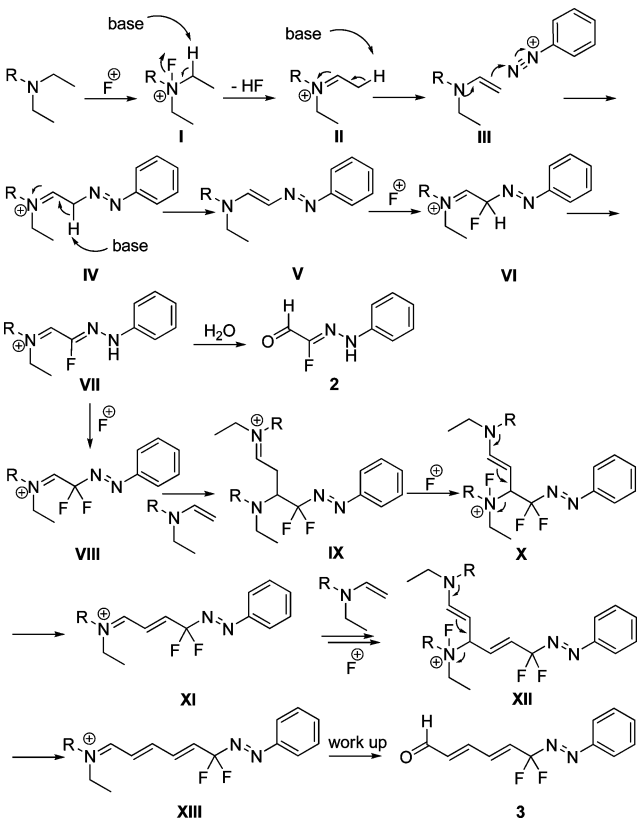


Figure 2. Plausible mechanism.

In the absence of H_2O, the monofluorined intermediate **VII** reacts with Selectfluor to form the *gem*-difluorinated azo intermediate **VIII**, which reacts with enamine **III** to give intermediate **IX**, which undergoes oxidation, and elimination to form the *gem*-difluorinated iminium ion **XI**. This forms **XIII** after a chain extension, which undergoes hydrolysis to give the *gem*-difluorinated azo compound **3**.

In conclusion, we have developed the first example of a tunable cascade reaction of aryl diazonium salts and trialkylamine in the presence of Selectfluor to prepare monofluorinated arylhydrazones and *gem*-difluorinated azo compounds without metal. The reaction is mild, operationally simple, and scalable. Furthermore,

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the fluorinated arylhydrazones were easily used to synthesize a fluorinated pyrazole and other nitrogen-containing compounds. We anticipate that this new method will find wide application in organic synthesis, medicinal chemistry, and supramolecular chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00130.

Experimental procedures and characterization of all new compounds including ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ptang@nankai.edu.cn.

Notes

The authors declare no competing financial interest.

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