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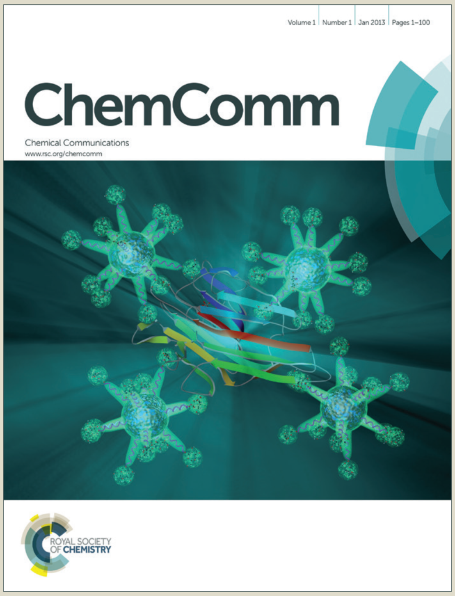

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# Silver-Catalyzed Meerwein Arylation: Intermolecular and Intramolecular Fluoroarylation of Styrenes

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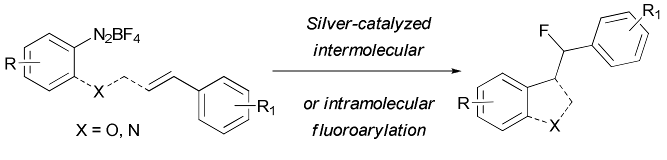
**The first example of a silver-catalyzed intermolecular and intramolecular meerwein fluoroarylation of styrenes with aryl diazonium salts has been developed. This reaction is operationally simple, scalable and proceeds under mild conditions. Furthermore, fluorinated dihydrobenzofurans and indolines were easily accessed using this method.**

Fluorinated molecules are of particular interest in the pharmaceutical, agrochemical and materials.[1] As a result, the development of new methods for fluorination under mild conditions has received increasing attention in the past few years.[2] Among numerous approaches to fluorinated compounds, transition-metal-catalyzed difunctionalization of C-C double bonds have recently received significant attention, because it enables the introduction of both fluorine and other functional groups to organic molecules in one synthetic operation, and provides facile access to functionalized fluorinated compound.[3] However, fluoroarylation of alkenes remains largely unexplored. In this communication, we report the first example of a silver-catalyzed intermolecular and intramolecular Meerwein fluoroarylation of styrenes with aryl diazonium salts under mild conditions (Scheme 1).

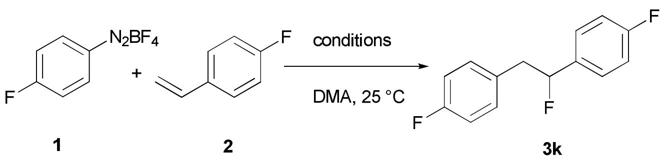


**Scheme 1**. Silver-catalyzed intermolecular or intramolecular fluoroarylation of styrenes.

Aryl diazonium salts have attracted chemists as an important source of aryl radicals.[4] It has several advantages such as easily prepared from aniline derivatives in large quantities, $N_2$ as the leaving group, and the reactions proceed with high chemoselectivity. In 1939, Meerwein reported the arylation of olefins with aryl diazonim salts catalyzed by copper salts.[5] Although the original meerwein arylation has disadvantages, such as a limited substrate scope and side products, it is a valuable synthetic transformation based on aryl radical chemistry, which has recently become an even more powerful tool for the functionalization of alkenes.[6] However, to the best of our knowledge, no examples of transition-metal catalyzed meerwein fluoroarylation with aryl diazonium salts have been reported. Recently, Ma group reported a copper catalyzed tandem Nazarov cyclization/electrophilic fluorination transformation for the preparation of fluorinated indanone derivatives.[7] Gouverneur group reported an asymmetric metal-free electrophilic intramolecular fluorocyclization for synthesis of various tetracyclic molecules.[8] Toste group reported an asymmetric palladium-catalyzed intermolecular fluoroarylation of styrenes with aryl boronic acid in the presence of the amide-based directing groups.[9] Heinrich reported the first intermolecular meerwein-type fluoroarylation of non-activated alkenes from arylhydrazines without metal. The yield of this reaction was moderate (up to 57%), and only 11% fluoroarylation yield was observed with styrenes.[10] Despite the advances of these methods, the development of a more general and practical method for fluoroarylation of alkenes is highly desirable.

Herein we report the first example of a silver-catalyzed intermolecular and intramolecular fluoroarylation of styrenes with aryl diazonium salts under mild conditions. As briefly illustrated in Table 1, our initial studies began with the attempted reaction of 4-fluorobenzenediazonium tetrafluoroborate **1** with 4-fluorostyrene **2** using Selectfluor as fluorinating reagent in DMA at 25 °C for 10 h under inert atmosphere, the desired product **3k** was obtained in 56% yield (entry 1). We then examined the influence of silver salt, fluorinating reagent, solvent and the number of equivalents of styrene (see the Supporting Information for more details). To our delight, the reaction yields of **3k** were increased by the use of catalytic silver salts, and AgOTf gave the highest yield (entries 2-7). Solvents affect was dramatic with DMA being the solvent of choice; no fluorinated products were formed in toluene, EtOAc, acetone, DCM and lower yield (54%) was observed in DMF. The amount of styrene significantly affected the reaction yield and 5 equivalents of styrene were used to achieve the highest yield (entries 7-9) due to less protonation byproduct of diazonium salts observed. Various fluorinating reagents were evaluated and Selectfluor gave the best results (entries 10-13). Under the optimized reaction conditions, the silver-catalyzed fluoroarylation of 4-fluorostyrene **2** with 4-fluorobenzenediazonium tetrafluoroborate **1** using Selectfluor as fluorinating reagent in DMA at 25 °C for 10 h under inert atmosphere led to formation of fluoride **3k** in 69% NMR yield (entry 7).

**Table 1**. Optimizing reaction conditions.



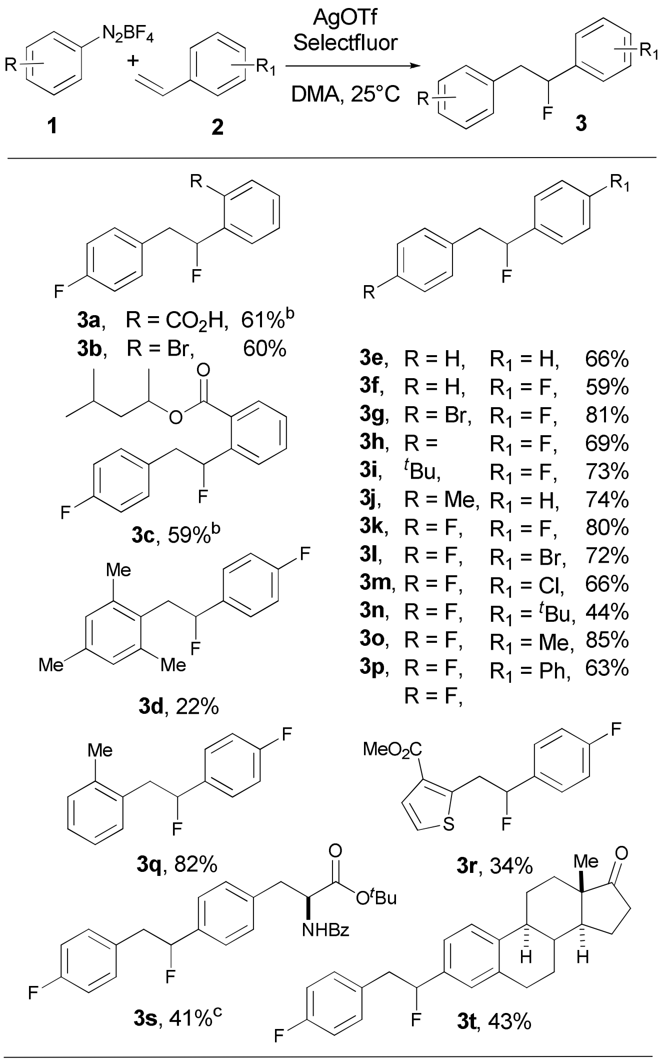
| entry | Conditions[a] | Yield(%)[b] |
|---|---|---|
| 1 | No silver salts, Selectfluor, **2** (5 equiv) | 56 |
| 2 | $AgNO_3$, Selectfluor, **2** (5 equiv) | 63 |
| 3 | $Ag_2CO_3$, Selectfluor, **2** (5 equiv) | 65 |
| 4 | $Ag_2O$, Selectfluor, **2** (5 equiv) | 68 |
| 5 | $AgBF_4$, Selectfluor, **2** (5 equiv) | 65 |
| 6 | AgSCN, Selectfluor, **2** (5 equiv) | 55 |
| 7 | AgOTf, Selectfluor, **2** (5 equiv) | **69** |
| 8 | AgOTf, Selectfluor, **2** (3 equiv) | 60 |
| 9 | AgOTf, Selectfluor, **2** (1 equiv) | 43 |
| 10 | AgOTf, Selectfluor($PF_6$), **2** (5 equiv) | 50 |
| 11 | AgOTf, NFSI, **2** (5 equiv) | 0 |
| 12 | AgOTf, NFPY, **2** (5 equiv) | 0 |
| 13 | AgOTf, AgF, **2** (5 equiv) | 0 |

[a] 20 mol% of silver salts and 2.0 equiv of fluorinating reagents were used. [b]Yields were determined by $^{19}$F NMR with 1-fluoro-3-nitrobenzene as a standard.

With the optimized conditions in hand, we then investigated the substrate scope for intermolecular fluoroarylation of styrenes as displayed in Table 2. Aryl diazonium salts or styrenes bearing electron-withdrawing, -neutral, and -donating substituents reacted smoothly and afforded the corresponding products in moderate to good yields. Several functional groups including ester, carboxylic acid, bromide, chloride, and alkyl groups are tolerated in the reaction. For styrenes **2a** and **2c**, 3 equivalents of aryl diazonium salts were used to give the corresponding fluorinated products in moderate yield. Heteroaryl diazonium salt **1r** was also successfully employed to provide corresponding fluorinated product **3r** in 34% yield. Notably, sterically hindered aryl diazonium salt **1d** reacted smoothly to give the desired product **3d**, albeit in lower yield (22%). The reaction also worked with more complex styrenes, for example, fluoroarylation of tyrosine derivative (**2s**) and estrone derivative (**2t**) gave the corresponding products **3s** and **3t** in good yields. Less than 10% desired product yield was observed with unactivated alkenes and heterocyclic alkenes. To prove both practicality and effectiveness of this method for large-scale synthesis, **3k** was prepared on a gram scale under the reaction conditions in 62% isolated yield.

As an extension of the above fluoroarylation of styrenes, intramolecular cyclization reaction was then successfully implemented as displayed in Table 3. The fluorinated dihydrobenzofurans and indolines were obtained from various aryl diazonium salts with isolated yields ranging from 41% to 81%. The formation of trans-fluorinated dihydrobenzofurans was the major product with high diastereoselectivity, which was confirmed by X-ray analysis of compound **5d**, while lower diastereoselectivity was found in the formation of fluorinated indolines. For the reactions with substrates bearing nitrogen tethers (**4l** to **4t**), no fluorinated products were observed in the absence of protecting group on nitrogen. Other protecting group for nitrogen such as Ac (44%), Ms (56%) also worked and Ts gave the best yields (71% for **5l**). It is worth mentioning that this is the first report of intramolecular meerwein fluoroarylation to form the fluorinated dihydrobenzofurans and indolines.

**Table 2**. Silver-catalyzed intermolecular fluoroarylation of styrenes.[a]



[a] The reaction was performed with aryl diazonium salts **1** (0.30 mmol), styrene **2** (1.50 mmol), AgOTf (20 mmol%), Selectfluor (0.600 mmol) in 1.2 mL DMA for 10 h at 25°C unless otherwise noted. The ratio of isomers was determined by $^{19}$F NMR. Yields refer to isolated product. [b] Aryl diazonium salts **1** (0.90 mmol) and styrene **2** (0.30 mmol) were used. [c] Aryl diazonium salts **1** (0.15 mmol) and styrene **2** (0.45 mmol) were used.

Although a detailed mechanism of this reaction is currently unclear, some preliminary studies were conducted to gain mechanistic insight into this process. Less than 5% yields of fluorinated products were formed when 1.0 equivalent of the radical inhibitor butylated hydroxytoluene (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the intermolecular and intramolecular reactions. In addition, yields in the absence of $O_2$ are higher than in its presence.[11] The aryl diazonium salt **4** was converted in the presence of 2.5 equiv of TEMPO to the dihydrobenzofuran 6 by a 5-exo cyclization (Scheme 2),[12] which is consistent with a free radical mechanism. Furthermore, no fluoroarylated products were found when CsF, TBAF or AgF was used as the fluorinating

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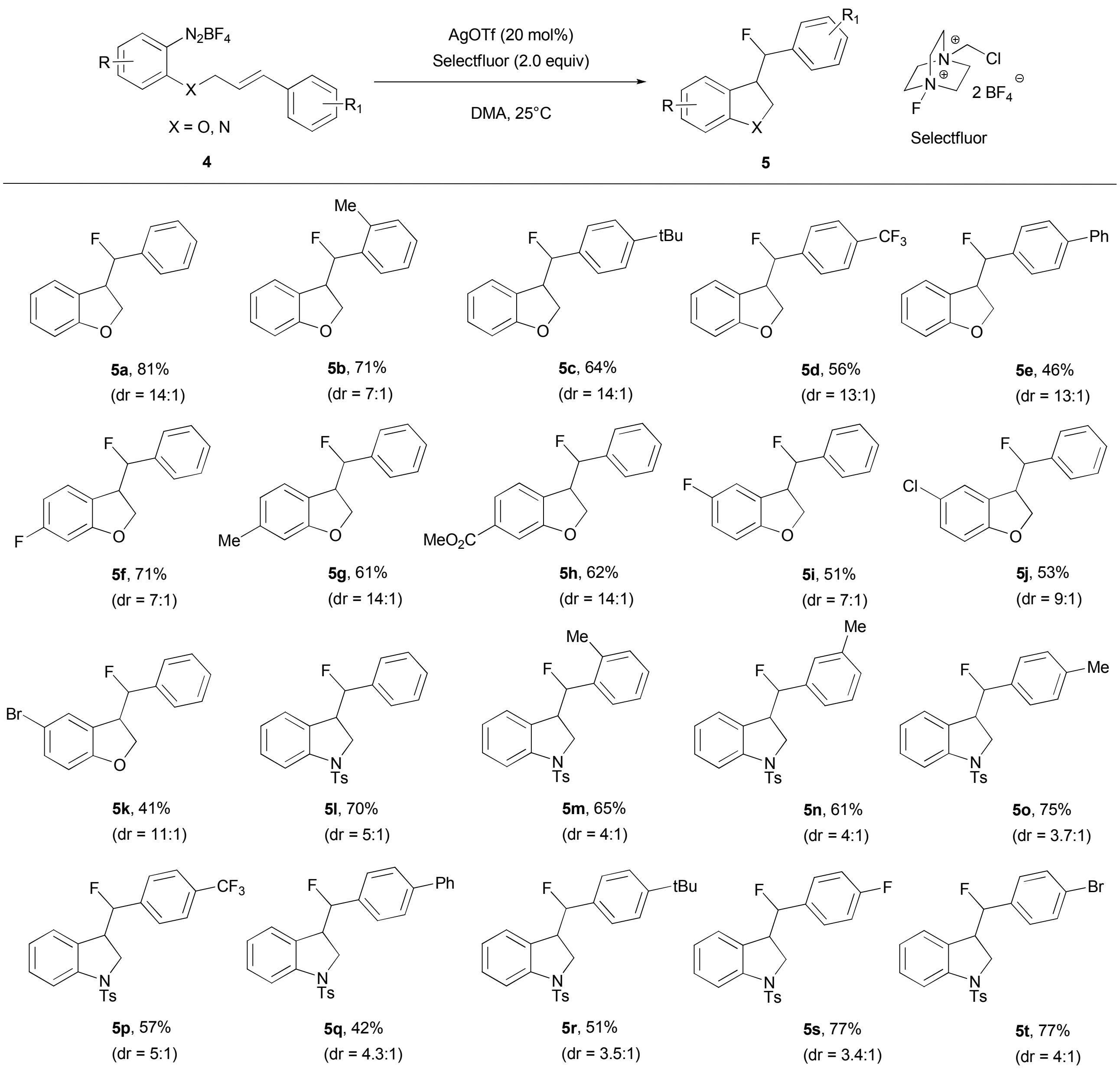
**Table 3.** Silver-catalyzed intramolecular fluoroarylation of styrenes[a]



**4**

**5**

**5a**, 81% (dr = 14:1)

**5b**, 71% (dr = 7:1)

**5c**, 64% (dr = 14:1)

**5d**, 56% (dr = 13:1)

**5e**, 46% (dr = 13:1)

**5f**, 71% (dr = 7:1)

**5g**, 61% (dr = 14:1)

**5h**, 62% (dr = 14:1)

**5i**, 51% (dr = 7:1)

**5j**, 53% (dr = 9:1)

**5k**, 41% (dr = 11:1)

**5l**, 70% (dr = 5:1)

**5m**, 65% (dr = 4:1)

**5n**, 61% (dr = 4:1)

**5o**, 75% (dr = 3.7:1)

**5p**, 57% (dr = 5:1)

**5q**, 42% (dr = 4.3:1)

**5r**, 51% (dr = 3.5:1)

**5s**, 77% (dr = 3.4:1)

**5t**, 77% (dr = 4:1)

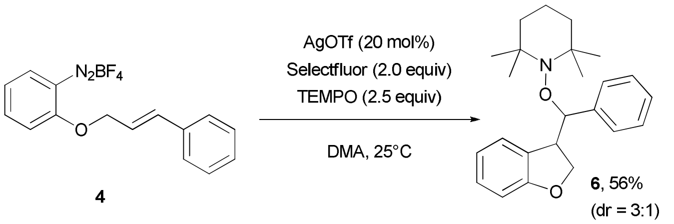
[a] The reaction was performed with **4** (0.30 mmol), AgOTf (20 mmol%), Selectfluor (0.600 mmol) in 2.0 mL DMA for 20 h at 25°C. The ratio of isomers was determined by $^{19}F$ NMR. Yields refer to isolated product.

reagent in the presence of silver salts (see the Supporting Information for more details), which indicates that the reaction may not proceed through a carbocationic intermediate. To get further insights into the reaction mechanism, EPR (electron paramagnetic resonance) experiments were performed with the addition of free radical spin trapping agent DMPO (5,5-dimethyl-1-pyrroline N-oxide). Some signals of unknown organic radicals were observed. Together, these observations indicated that a radial chain mechanism or single-electron transfer (SET) may be involved in this transformation.

## Conclusions

In conclusion, we have reported the first example of a silver-catalyzed intermolecular and intramolecular meerwein fluoroarylation of styrenes with aryl diazonium salts under mild conditions. The new reaction offers a complementary method for difunctionalization of alkenes to form fluorinated compounds and extends the scope of the meerwein arylation.

Additionally, the reaction is amenable to gram-scale synthesis and fluorinated dihydrobenzofurans and indolines were easily prepared through this method. Mechanism studies suggested that the reaction proceeded through a free-radical process. With its operational simplicity this method could find practical applications in pharmaceutical and agrochemical research and development for the synthesis of fluorinated compounds.



**Scheme 2.** Mechanism study

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## Notes and references

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† Electronic Supplementary Information (ESI) available: Data for new compounds and experimental procedures. See DOI: 10.1039/c000000x/

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