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Copper-catalyzed intermolecular and regioselective aminofluorination of styrenes: facile access to β-fluoro-*N*-protected phenethylamines†

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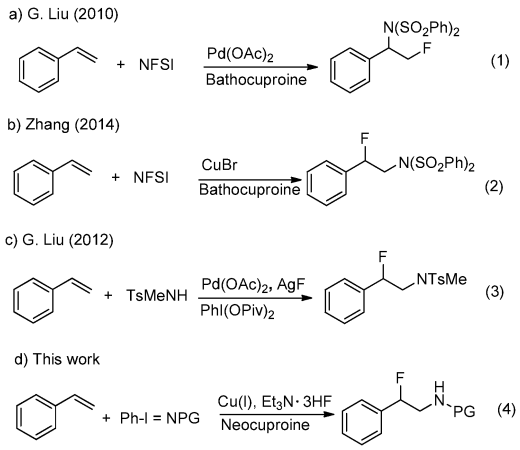
A copper-catalyzed regio- and intermolecular aminofluorination of styrenes has been developed. In this reaction Ph-I=*N*-Ts and $Et_3N\cdot 3HF$ act as nitrogen and fluorine sources, respectively. The obtained β-fluoro-*N*-Ts-phenethylamines can be *N*-alkylated with subsequent deprotection affording the corresponding β-fluoro-*N*-alkylated phenethylamines, which are interesting building blocks for compounds acting on neuronal targets.

Compounds containing the 1,2-aminofluoro moiety are valuable as building blocks because they are used in the synthesis of anticholinergic, anticancer and anti-inflammatory drugs, as well as therapeutic β-peptides.[1] Molecules bearing fluorine atoms present improved solubility, hydrophobicity and metabolic stability, explaining why 30% of all agrochemicals and 20% of all pharmaceuticals contain at least one fluorine atom.[2] In addition, the C–F bond dramatically affects the acid–base properties of fluorine-containing molecules.

1,2-Fluoroamines are not usually obtained directly, but rather using multistep procedures.[3] However, in recent years some methodologies for the direct aminofluorination of alkenes have been reported, including intramolecular amination-intermolecular fluorination and intermolecular aminofluorination, by different mechanisms.[4] Recently, Liu[5] and Zhang[6] reported palladium- and copper-catalyzed aminofluorination of styrenes using *N*-fluorobenzenesulfonimide (NFSI) as both an amino and a fluorine source, obtaining products with opposite regiochemistry (eqn (1) and (2), Scheme 1). Conversely, the removal of one or both benzenesulfonyl groups from the nitrogen atom has been shown to be difficult and harsh conditions are necessary.[7] In addition, Liu[8] reported another palladium-catalyzed oxidative aminofluorination of styrenes using *N*-methyl-*p*-toluenesulfonamide (TsMeNH) and AgF as nitrogen and fluorine sources respectively (eqn (3), Scheme 1).



Scheme 1 Metal-catalyzed vicinal aminofluorination of styrenes.

Copper-catalyzed vicinal difunctionalization of alkenes is a very active field because of its low cost and toxicity as well as the variety of reactions that can be carried out.[9]

Here we describe the successful development of a regioselective aminofluorination of styrenes which affords *N*-protected β-fluorophenethylamines, potential building blocks in the synthesis of many bioactive compounds.

In our initial attempt we investigated the copper-catalyzed aminofluorination of styrene using *N*-*p*-toluenesulfonyliminophenyliodinane (Ph-I=*N*-Ts)[10] and $Et_3N\cdot 3HF$[11] as *N*-Ts group and fluorine atom sources, respectively. No reaction was observed using 10 mol% $Cu(MeCN)_4BF_4$-neocuproine as the catalyst and 1,2-dichloroethane as solvent, either at room temperature or at 70 °C (Table 1, entries 1 and 2). Nevertheless, the addition of $Mo(CO)_6$ and heating at 70 °C led to the desired fluorosulfonamide product **2a** in 71% yield (Table 1, entry 3).

Different copper salts were tried but only $Cu(MeCN)_4PF_6$ and $Cu(BF_4)_2\cdot H_2O$ showed similar results to $Cu(MeCN)_4BF_4$ and no reaction occurred in the absence of a Cu salt (Table 1, entries 4–10).

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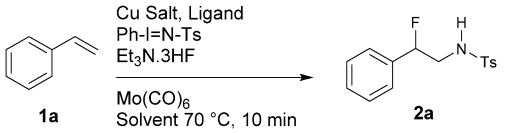
Table 1 Optimization of the reaction conditions[a]



Entry	Copper salt 10%	Ligand 10%	Solvent	Yield[b,c] [%]
1[d]	$Cu(MeCN)_4BF_4$	Neocuproine	DCE	0
2[e]	$Cu(MeCN)_4BF_4$	Neocuproine	DCE	0
3	$Cu(MeCN)_4BF_4$	Neocuproine	DCE	71 (78)
4	$Cu(MeCN)_4PF_6$	Neocuproine	DCE	67 (72)
5	$Cu(BF_4)_2{\cdot}H_2O$	Neocuproine	DCE	70 (75)
6	CuOAc	Neocuproine	DCE	(45)
7	$CuBr_2$	Neocuproine	DCE	(33)
8	CuCl	Neocuproine	DCE	(39)
9	$Cu(OSO_2CF_3)_2$	Neocuproine	DCE	(30)
10	—	Neocuproine	DCE	0
11	$Cu(MeCN)_4BF_4$	Neocuproine	$MeNO_2$	66 (69)
12	$Cu(MeCN)_4BF_4$	Neocuproine	EtOAc	(15)
13	$Cu(MeCN)_4BF_4$	Neocuproine	1,4-Dioxane	(24)
14	$Cu(MeCN)_4BF_4$	Bipyridyl	DCE	(33)
15	$Cu(MeCN)_4BF_4$	Phenanthroline	DCE	(42)
16	$Cu(MeCN)_4BF_4$	Bathocuproine	DCE	(33)
17[f]	$Cu(MeCN)_4BF_4$	Neocuproine	DCE	(15)
18[g]	$Cu(MeCN)_4BF_4$	Neocuproine	DCE	(24)
19[h]	$Cu(MeCN)_4BF_4$	Neocuproine	DCE	55 (63)
20[i]	$Cu(MeCN)_4BF_4$	Neocuproine	DCE	44 (51)

[a] Reactions were carried out with **1a** (1.0 mmol) in 3.0 mL of solvent, Ph-I=*N*-Ts (1.5 equiv.), $Et_3N{\cdot}3HF$ (6 equiv.), $Mo(CO)_6$ (0.25 equiv.) in an open tube, unless otherwise noted. [b] Isolated yields. [c] NMR-determined yields using **1a** (0.2 mmol) in 0.6 mL of solvent and $PhCF_3$ as internal standard are shown in parentheses. [d] Reaction at rt without $Mo(CO)_6$. [e] Reaction at 70 °C without $Mo(CO)_6$. [f] Catalyst (5%). [g] $Et_3N{\cdot}3HF$ (3 equiv.). [h] Ph-I=*N*-Ts (1.3 equiv.). [i] Ph-I=*N*-Ts (1.3 equiv.).

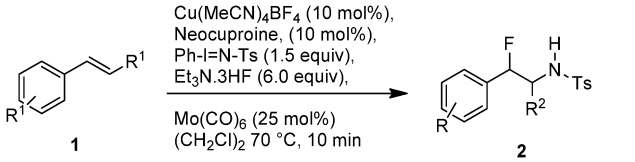
Among the different solvents tested, only $MeNO_2$ showed comparable results to DCE (Table 1, entries 10–12). Ligands other than neocuproine (Table 1, entries 13–15) were found to be less effective. Decreasing the quantity of copper salt or $Et_3N{\cdot}3HF$ resulted in a significant decrease in the chemical yield (Table 1, entries 16 and 17). Finally, when 1.3 or 1.0 equivalents of Ph-I=*N*-Ts were used, the isolated yields were reduced to 55 and 44%, respectively (Table 1, entries 18 and 19).

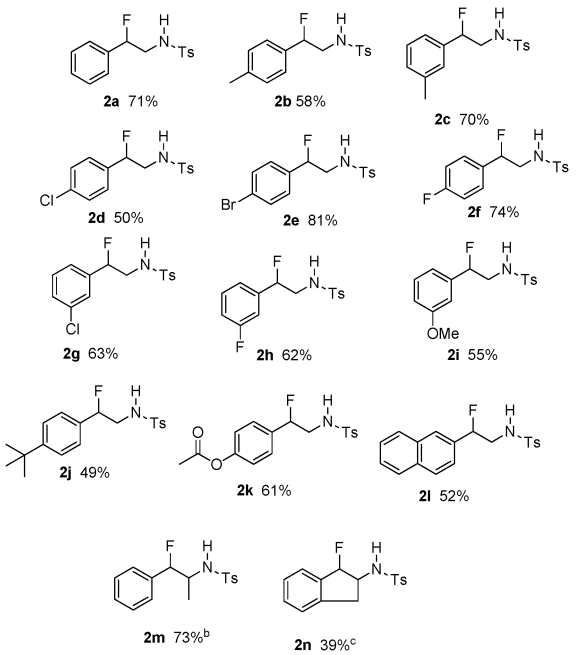
Using the optimized conditions, a number of substituted styrenes were transformed into the corresponding fluorosulfonamides **2a–n** in yields ranging from 39 to 81% (Table 2). These reactions all proceeded with complete regioselectivity. Thus, *para*- and *meta*-methylstyrenes produced the corresponding **2b** (58%) and **2c** (70%).

Different halo-substituted styrenes were compatible with the reaction conditions and afforded the corresponding products **2d**, **2e**, **2f**, **2g** and **2h** in moderate to good yields. While *para*-methoxy styrene failed to give the aminofluorination product, *ortho*-methoxy styrene afforded **2i** in 55% yield. Other styrenes with electron donating groups at the *para* position such as *tert*-butyl and OAc led to the corresponding fluoroamine products **2j** and **2k** in 49 and 61% yields, respectively. 2-Vinylnaphthalene afforded **2l** in 52% yield. Interestingly, internal alkenes such as *trans*-β-methylstyrene and indene also afforded **2m** and **2n** in 73 and 39% yields, respectively.

The structure of **2e** was unequivocally assigned by X-ray diffraction analysis.[12]

Table 2 Scope of the aminofluorination[a]





[a] Yields of isolated products after column chromatography of reactions on a 1 mmol scale. [b] 5 : 1 *threo* : *erythro* ratio of diastereomers determined by ^{19}F NMR of the crude product. [c] Isolated yield of the predominant *anti*-diastereomer.

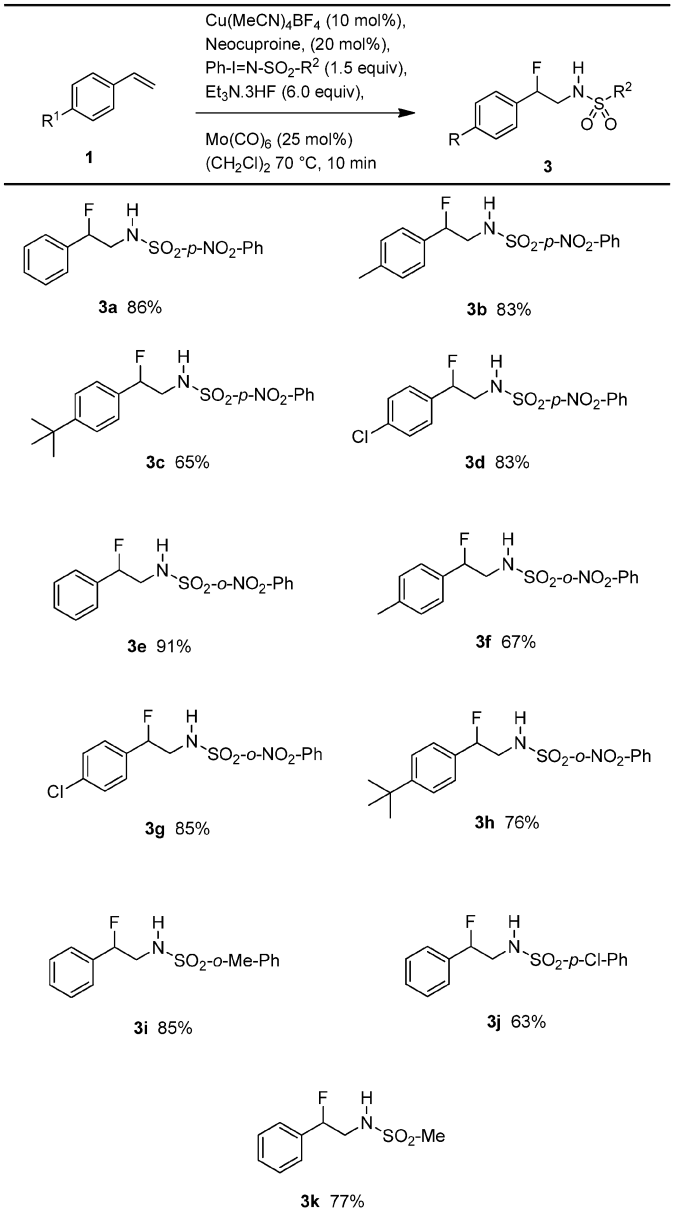
Unfortunately, with unactivated olefins, including 1-octene and cyclohexene, the desired β-fluorosulfonamides were not obtained and the corresponding aziridines were the principal products.[13]

The successful combination of fluorination with other sulfonamides as nitrogen sources was demonstrated with some styrenes (Table 3). Thus, *para*-nitrobenzenesulfonamide (H_2N-SO_2-*p*-NO_2-Ph) and *ortho*-nitrobenzenesulfonamides, (H_2N-SO_2-*o*-NO_2-Ph), as well as *ortho*-methylbenzenesulfonamide (H_2N-SO_2-*o*-Me-Ph), *para*-chlorobenzenesulfonamide (H_2N-SO_2-*p*-Cl-Ph) and methanesulfonamide (H_2N-SO_2Me) were used as nitrogen sources. These reactions produced the desired fluorosulfonamides **3a–k** in yields ranging from 63 to 91%.

To show the applicability of the new compounds as building blocks in organic synthesis and taking advantage of the acidity of the Ts–N–H bond, we decided to use **2a**, **2c**, **3a**, **3d**, **3e** and **3g** to synthesize *N*-alkyl derivatives **4a–j** using basic alkylation or Mitsunobu conditions. **4a–j** were obtained in yields in the 17–92% range (Table 4).

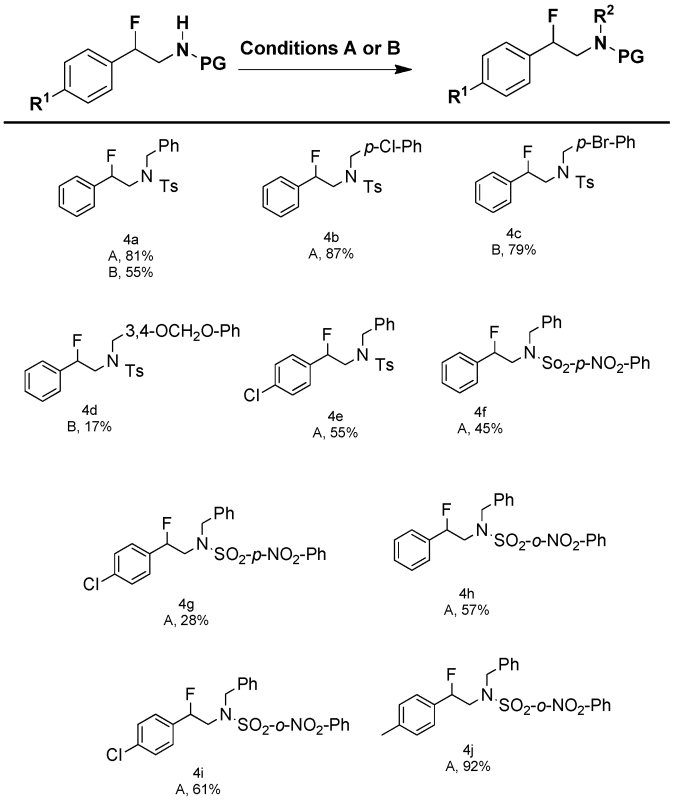
Finally, compounds **4a** and **4j** were subsequently deprotected. Thus, the Ts group was removed using Mg in methanol with ultrasound[14] activation, and *o*-Ns was removed using 2-mercaptoethanol and DBU in DMF[15] affording the secondary phenethylamines **5a–5b** (Scheme 2).

Table 3 Regioselective aminofluorination of styrenes with different sulfonimides as the nitrogen source[a]

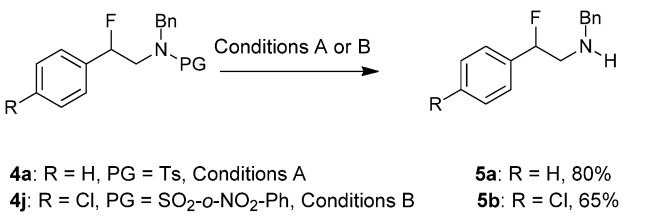


[a] Yields of isolated products after column chromatography of reactions on a 1 mmol scale.

Table 4 *N*-Alkylation of fluorosulfonamides[a]



[a] Yields of isolated products after column chromatography of reactions on a 0.5 mmol scale. Conditions: (A) fluorosulfonamide (1.0 equiv.), NaH (1.1 equiv.), DMF, benzyl halide (1.1 equiv.), 0 °C to rt, 12 h. (B) fluorosulfonamide (1.0 equiv.), triphenylphosphine (1.4 equiv.), benzyl alcohol (1.4 equiv.), DEAD (2.0 equiv.), THF, 0 °C, 12 h.



Scheme 2 Deprotection of β-fluoro-*N*-benzyl-*N*-protected phenethylamines. Conditions: (A): Mg, MeOH, ultrasound, rt, 1 h. (B): 2-mercaptoethanol, DBU, DMF, rt, 12 h. Bn: benzyl.

In summary, we have developed a new copper-catalyzed regioselective aminofluorination of styrenes. The reaction proceeds under mild conditions using $Cu(MeCN)_4BF_4$-neocuproine and $Mo(CO)_6$ as the catalytic system and Ph-I=*N*-Ts and $Et_3N{\cdot}3HF$ as nitrogen and fluorine sources respectively. The reaction employs commercially available reagents and is completed in 10 minutes. The reported reactivity should be of interest for the development of β-fluorophenethylamines. Currently, detailed mechanistic studies and the extension of this reaction to other classes of alkenes are underway.

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