Note

Cu-Catalyzed Couplings of Aryl Iodonium salts with Sodium trifluoromethanesulfinate.

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J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 03 Nov 2013

Cu-Catalyzed Couplings of Aryl Iodonium Salts with Sodium Trifluoromethanesulfinate

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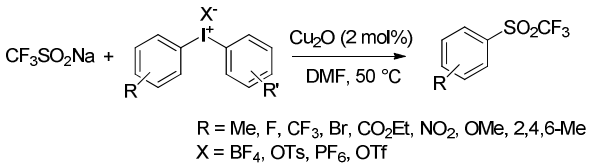
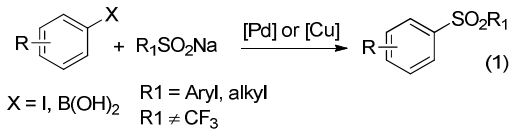


Abstract

A convenient method for the preparation of aryl trifluoromethylsulfones from the reactions of diaryl iodonium salts with sodium trifluoromethanesulfinate in the presence of copper catalysts is described. Cuprous oxide in DMF was found to be the optimal catalyst for the reaction. The reaction conditions are tolerant of various functional groups as well as of various counteranions of the iodonium salt. The synthetic utility of the process is demonstrated by performing the reaction on a preparative scale (88 g).

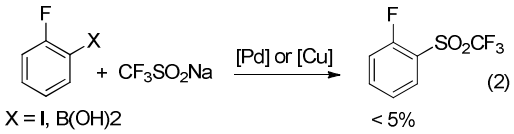
Aryl sulfones ($ArSO_2R$, R = alkyl, aryl) are common functional groups present in molecules of medicinal interest. The traditional approaches to these compounds such as oxidation of the corresponding aryl sulfides and sulfonylation of arenes are limited in scope due to limited availability of sulfides, incompatibility of many functional groups with oxidative/acidic-reaction conditions as well as the formation of isomeric products.[1-3] Pd- and Cu-catalyzed methodologies that couple aryl halides, psuedohalides, and boronic acids with sulfinic acid salts or sulfinic acid derivatives under mildly basic or neutral conditions have allowed for the synthesis of a wide variety of aryl sulfones.[4-16] Although numerous examples of the use of aryl and alkyl sulfinic acid salts as nucleophiles have been reported, the use of a trifluoromethanesulfinic acid salt as a nucleophile yielding aryltrifluoromethyl sulfones has never been reported (equation 1). Given the increasing prevalance of aryltrifluoromethanesulfones in medicinally relevant compounds[17-19] and the significant challenges in introducing the trifluoromethylsulfonyl group on aryl rings,[20-23] cross-coupling

methodologies that employ readily available and inexpensive trifluoromethanesulfinic acid salts such as CF_3SO_2Na as a nucleophile will be of synthetic value.



Several Pd- and Cu-catalyzed reactions based on the reported reaction conditions for the formation of aryl sulfones were investigated to couple sodium trifluoromethanesulfinate (CF_3SO_2Na) with 2-fluoroiodobenzene or 2-fluorophenylboronic acid (equation 2);[4-16,24,25] however, the coupled product, 2-fluorophenyl trifluoromethanesulfone, was not observed in any isolable yield (data not shown). The poor nucleophilicity of CF_3SO_2Na was hypothesized to be a likely cause for the lack of reactivity. We evaluated diaryliodonium salts as coupling partners with CF_3SO_2Na because of the former are known to react with a variety of nucleophiles, including poorly reactive nucleophiles such as fluoride.[26-37]

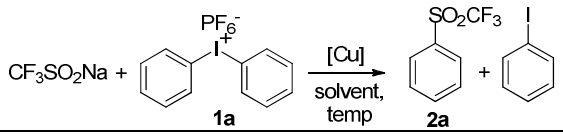
Recently, synthesis of diaryl sulfones from reactions of diaryliodonium salts with *aryl*sulfinic acid salts was reported.[34] While arylsulfinic acid salts were competent as nucleophiles, the *alkyl*sulfinic acid salt, $MeSO_2Na$, did not react.[34] In a separate report, aryltrifluoromethyl sulfones were synthesized from the reactions of arylsulfinate salts with an excess of electrophilic trifluoromethylating reagent in the presence of copper (20 mol%), ligand (40 mol%), and Bu_4NF (50 mol%) at elevated temperatures (130 °C).[23] Herein, we report a mild Cu-catalyzed method for coupling of diaryliodonium salts with CF_3SO_2Na to generate aryltrifluoromethyl sulfones in high yields.[17]



Commercially available diphenyliodonium hexafluorophosphate (**1a**) was choosen as the coupling partner for CF_3SO_2Na during the initial identification of reaction conditions (Table 1). No appreciable amount of the coupled product (**2a**) was obtained when the reactants were heated upto 80 °C in solvents of varying polarity (entries 1-5). The use of a catalytic amount of CuI (10 mol%) afforded **2a** in 83% yield in DMF (entry 6). In addition to the expected coupled product, the formation of small amounts of 2-fluorophenol and 2,2'-difluorobiphenyl were also observed. Although **2a** was formed in acceptable yield in the presence of all the copper salts that were evaluated as catalysts (entries 6-9), the highest yields were

obtained in the presence of Cu_2O (entry 9). Equally high yields of **2a** were also obtained in the presence of only 2 mol% of Cu_2O at a lower temperature of 50 °C in either DMF or THF (entries 10 & 11). While 1,4-dioxane was also found to be an acceptable solvent for the reaction (entry 12), toluene and acetonitrile were unsuitable as solvents (entries 13 and 14). Cupric oxide (CuO) was not as effective of a catalyst as cuprous oxide (Cu_2O) (entry 14), however, to our surprise, an excellent yield of **2a** was obtained in the presence of copper metal (entries 16 & 17). Although both Cu_2O and copper metal proved to be highly effective catalysts and are inexpensive sources of copper, Cu_2O was chosen for further explorations.

Table 1: Evaluations of reaction parameters[a]

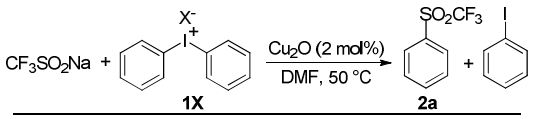


entry	[Cu] (mol %)	Solvent	Temp (°C)	Reaction Time (h)	**2a** (%)[b]
1	NA	DMF	80	24	<1
2	NA	THF	80	24	0
3	NA	toluene	80	24	0
4	NA	1,4-dioxane	80	24	2
5	NA	MeCN	80	24	0
6	CuI (10)	DMF	80	17	83
7	CuCl (10)	DMF	80	17	79
8	CuOAc (10)	DMF	80	17	83
9	Cu_2O (10)	DMF	80	15	91
10	Cu_2O (2)	DMF	50	10	92
11	Cu_2O (2)	THF	50	16	95
12	Cu_2O (2)	1,4-dioxane	50	16	84
13	Cu_2O (2)	toluene	50	16	33
14	Cu_2O (2)	acetonitrile	50	16	<2
15	CuO (2)	DMF	50	16	24
16	Cu[c] (2)	DMF	50	16	98
17	Cu[c] (2)	THF	50	16	72

(a) All reactions were performed with **1a** (1 equivalent), CF_3SO_2Na (1.1 equivalents) in solvent (0.21 M). (b) Assay yield based on HPLC analysis at 210 nm. (c) Copper powder, complexometric purity ≥99.5%

The yield of the Cu-catalyzed reaction of diphenyliodonium salts with CF_3SO_2Na was found to be essentially independent of the nature of the counteranion (Table 2). This is an important observation and bodes well for the generality of the reaction as the synthesis, yield and stability of diaryliodonium salts are known to be dependent on the nature of the counteranion.[26,38]

Table 2: Effect of counteranion on the yield of phenyltrifluoromethyl sulfone[a]



Entry	X^-	**2a** (%)[b]
1	PF_6	92
2	OTs	88
3	BF_4	96
4	CF_3SO_3	96

(a) All reactions were performed with **1X** (1 equivalent), CF_3SO_2Na (1.1 equivalents) in DMF (0.21 M). (b) Assay yield based on HPLC analysis at 210 nm.

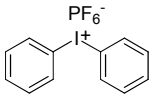
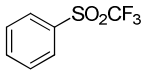
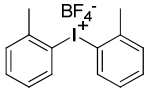
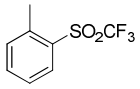
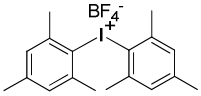
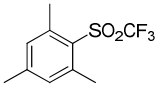
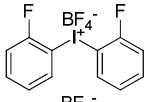
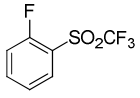
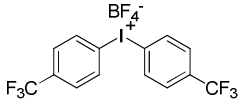
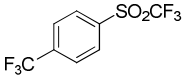
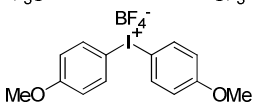
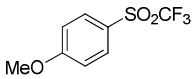
The substrate scope of the Cu-catalyzed reactions of sodium trifluoromethanesulfinate with a variety of diaryliodonium salts was explored (Table 3). The coupled product **2a** was isolated in 86% yield (entry 1). No effect on the efficiency of the reaction was observed when sterically hindered di-*ortho*-tolyliodonium tetrafluoroborate was used as the electrophile (entry 2). However, a further increase in the steric bulk led to a significantly lower yield of the coupled product (entry 3). The coupled product **2c** was isolated in only 20% yield despite conducting the reaction with 20 mol% of Cu_2O. Mesitol and mesitylene were observed as side products. The reactions of electron-poor (entries 4 and 5) as well as electron-rich (entry 6) diaryliodonium salts afforded the corresponding coupled products in high yield. Functional groups such as fluoride (entry 4), bromide (entry 7), ester (entry 8), and nitro (entry 11) were well tolerated under the reaction conditions. The heterocyclic iodonium salt **1i** was evaluated as coupling partner and was found to form the desired product **2i** in acceptable yield (entry 10).

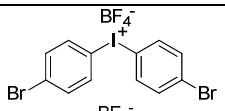
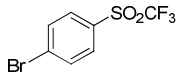
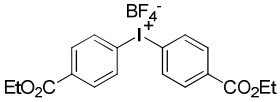
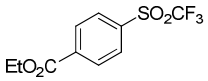
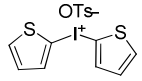
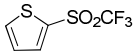
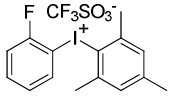
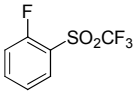
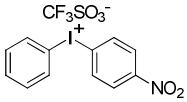
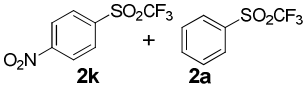
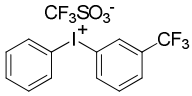
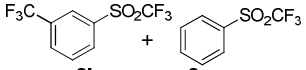
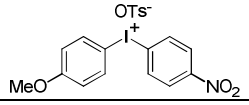
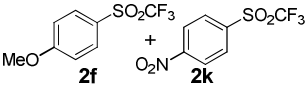
Next, the reactivity and selectivity of unsymmetrical diaryliodonium salts were investigated. Unsymmetrical iodonium salt **1j,** containing sterically differentiated aryl groups, was found to be a suitable substrate (entry 11). The coupled product **2d** that arises from the reaction of the less sterically hindered aryl group was observed in 60% yield while product **2c** that could arise from the reaction of the more sterically hindered aryl group was observed in less than 2% yield (30:1 ratio). The preferred reactivity of less sterically hindered aryl groups with CF_3SO_2Na is consistent with reported Cu-catalyzed reactions of diaryliodonium salts with several other nucleophiles[26,37,39] but is in contrast to the preferential reaction of bulkier aryl group with phosphorous nucleophiles in the presence of copper chloride as catalyst.[33] The metal-catalyzed reactions of unsymmetrical diaryliodonium salts containing an electron-rich and an

electron-poor aryl group generally shows significant preference for transfer of the more electron-rich aryl group,[26,40] but some exceptions have been observed.[33,40] Interestingly, we observed only a modest preference for transfer of the *less* electron-donating aryl group in the reactions of unsymmetrical diaryliodonium salts as reactions of **1k** [(4-$NO_2C_6H_4$)I(C_6H_5)OTf], **1l** [(3-$CF_3C_6H_4$)I(C_6H_5)OTf], and **1m** [(4-$NO_2C_6H_4$)I(4-$OMeC_6H_4$)OTs] with CF_3SO_2Na in the presence of Cu_2O as catalyst (entries 11-13) gave 1.5:1, 1.2:1, and 1.6:1 product ratios, respectively.

One hypothesis for the lack of strong chemoselectivity in the reactions of **1k**-**m** is that two distinct reaction pathways are occuring simultaneously, each having comparable rates but with opposite chemoselectivities; for example, a catalytic reaction pathway favoring one product and a non-catalyzed background pathway favoring the other.[32] This possibility was ruled out when reactions of **1k** and **1m** with CF_3SO_2Na was attempted in the absence of catalyst and produced less than 5% product. The modest selectivity observed in the current work along with contrasting chemoselctivities reported for the reactions of electronically differentiated unsymmetrical diaryliodonium salts in the presence of transition metal catalysts point towards significantly different reaction pathways being operative under varying reaction conditions.[40]

Table 3: Substrate scope of the reaction of iodonium salts with sodium trifluoromethanesulfinate.

entry	Diaryliodonium		Product		Yield (%)
1		**1a**		**2a**	86
2		**1b**		**2b**	88
3[a]		**1c**		**2c**	20
4		**1d**		**2d**	79
5[b]		**1e**		**2e**	63
6		**1f**		**2f**	80

entry	Diaryliodonium		Product		Yield (%)
7		**1g**		**2g**	71
8		**1h**		**2h**	84
9		**1i**		**2i**	66
10		**1j**		**2d**	60[c]
11		**1k**		**2k+2a**	41[d,e]
12		**1l**		**2l+2a**	81[f,g]
13		**1m**		**2f+2k**	37+59[h]

Unless noted otherwise, all experiments were performed with diaryliodonium salt (1 equivalent), CF_3SO_2Na (1.1 equivalents), Cu_2O (0.02 equivalents) in DMF (0.21 M) at 50 °C. (a) Cu_2O (0.2 equivalents). (b) THF was used as the reaction solvent. (c) Assay yield based on HPLC analysis. (d) **2k** and **2a** were observed in 1.5:1 ratio by HPLC. (e) Yield of **2k**. (f) **2l** and **2a** were observed in a ratio of 1.2:1 by ^{1}H NMR spectroscopy. (g) Combined yield of **2l** and **2a.** We were unable to separate **2a** and **2l** by silica gel chromatography. (h) **2k** and **2f** were observed in a ratio of 1.6:1.

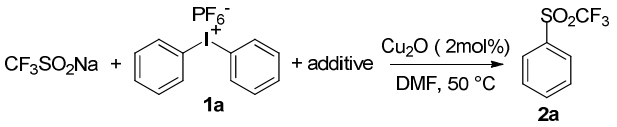
Once a reasonable scope of the reaction was established in the presence of electron-withdrawing, electron-donating, sterically hindered, and hetrocyclic functional groups (Table 3), a survey was conducted to further assess the functional group tolerance under the standard reaction conditions. The Cu-catalyzed reaction of **1a** with CF_3SO_2Na was conducted in the presence of a molar equivalent of additives containing common functional groups (Table 4). The yield of the coupled product **2a** was quantitavely determined using high pressure liquid chromatography (HPLC). If the yield of **2a** in the presence of an additive containing a functional group is comparable to the reaction performed in the absence of any additives (entry 1, Table 3), then it suggests that this particular functional group is well tolerated under the reaction conditions and it is unlikely to inhibit the reaction when present in a complex molecular structure. This rapid, complementary approach of understanding the functional group tolerance of a reaction was recently discussed by Collins and Glorius[41] and is likely to be very useful in studying new methodologies where the starting materials are not commercially available and need to be synthesized. Since the functional groups present in additives are distal to the reaction center, it is possible that in certain cases the impact of a

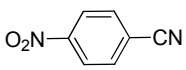
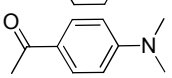
functional group on the reaction when directly attached to the reaction center may contradict the observations made in Table 4.

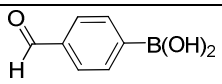
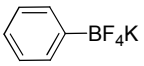
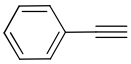
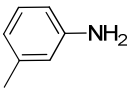
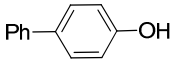
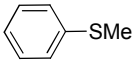
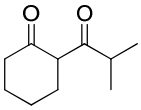
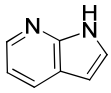
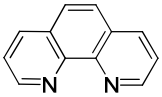
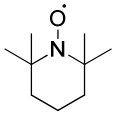
Full consumption of **1a** was observed in the presence of nitro, cyano, acetyl, dialkylamino, formyl, boronic acid, terminal alkyne, phenol, amine and pyridine (Table 4, entries 1-8). The yields of the coupled product **2a** were comparable to that obtained in the absence of any additive (Table 1, entry 10). Quantitative amounts of the additives were recovered at the end of the reaction demostrating that these functional groups are unaffected by the reaction conditions. The inertness of boronic acid, terminal alkyne, aniline and phenol is attributed to the neutral reaction conditions as the reactions of amines[42], phenols[31], boronic acids[43] and terminal alkynes[44] with diaryliodonium salts in the presence of a base are known. Although full consumption of **1a** was observed in the presence of thioanisole, **2a** was formed in only 55% yield. Diphenyl sulfide (27%) was observed as the major side product in the reaction (Table 4, entry 9). The formation of the diphenyl sulfide probably proceeds via the reaction of thioanisole with **1a** in the presence of copper to form diphenymethylsulfonium hexafluorophosphate and phenyl iodide.[45] Diphenymethylsulfonium hexafluorophosphate then decomposes to dephenylsulfide under the reaction conditions.

Effect of additives that may bind the catalytically active copper species and inhibit catalysis was also studied. While 2-isobutyrlcyclohexanone had no impact on the reaction (entry 10), a lower yield of **2a** was observed in the presence of 7-azaindole (entry 11). The presence of 1,10-phenanthroline was found to completely shut down the reaction (entry 12). The yield of the reaction was not affected by the presence of a radical scavenger, TEMPO (entry 13).

Table 4: Functional group tolerance of Cu-catalyzed reaction of sodium trifluorosulfinate with diaryliodonium salt



Entry	Additive	**2a** (%)[a]	Remaining additive (%)
1		91	100
2		93	90

Entry	Additive	**2a** (%)[a]	Remaining additive (%)
3		90	100
4		90	100
5		92	96
6		98	98
7		89	93
8		78	95
9		55[b]	77.6
10		93	83.5
11		45[c,d]	>95[e]
12		0[f]	>95[e]
13		92	87

All reactions were performed with **1a** (1 equivalent), CF_3SO_2Na (1.1 equivalents), and additive (1.0 equivalent) in DMF (0.2 M). (a) Assay yield based on HPLC analysis at 210 nm.(b) PhSPh (27%) was observed. (c) Unreacted **1a** (16%) was observed. (d) Formation of trace amounts of N-phenylated 7-azaindole was observed. (e) Trace amounts of DMF may overlap with the peak of additive on the HPLC spectrum, (f) Unreacted **1a** (90%) was observed.

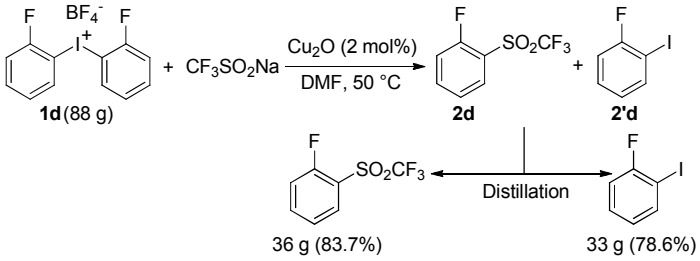
With regard to the mechanism of the reaction, the observation of complete consumption of **1a** along with almost quantitative yield of **2a** in the presence of a radical scavenger, TEMPO, suggests that the Cu-catalyzed reactions of diaryliodonium salts with CF_3SO_2Na may proceed via a non-radical pathway. Reaction pathways that involves Cu(I)-Cu(III) intermediates have been proposed for the Cu-catalyzed reactions of diaryliodonium sallts.[23,37,46] The lower yield obtained in the presence of Cu(II) catalyst (Table 1, entry 15) supports Cu(I) as catalytically active species. It is unclear how the reaction proceeds in the presence of metallic copper. Perhaps a layer of Cu_2O typically present on the surface of metallic copper catalyzes the reaction.[47]

Although a stoichiometric amount of aryl iodide is generated as a co-product in the reaction, separation of the aryl iodide from aryl trifluoromethylsulfone by silica gel column chromatography was trivial in most

cases. While silica gel column chromatography is a convenient method of separating compounds on small scale, it can be difficult to scale up as well as be cost prohibitive to perform on a large scale. Distillation is the preferred method to separate a mixture of compounds with different boiling points on scale. To demonstrate the utility of a distillation protocol on preparetively relevant scale, the reaction of **1d** with CF_3SO_2Na was performed at 88 g scale (Scheme 1). The expected products **2d** and **2'd** were observed in the reaction mixture. A packed distillation column with a height equivalent to theoretical plates (HETP) of 19 with gradual variation of reflux ratio (ratio of liquid that is returned to the distillation column to the liquid drawn out as a collected fraction) from 4:1 to 6:1 under receiver pressure of around 15 mmHg was found to be sufficient to effect the desired separation**.** Analytically pure **2d** and **2'd** were isolated in 83.7% and 78.6% yield, respectively, after distillation of the reaction mixture (Scheme 1).

An aryl iodide and a sodium salt of the counteranion on the diaryliodonium salt are the co-products of the reported reaction. The recovered aryl iodide is a starting material for the synthesis of diaryliodonium salts used in the reaction and, therefore, does not represent a waste stream if it is recovered and recycled.

Scheme 1



In summary, a convenient method for the preparation of aryl trifluoromethylsulfones from the reactions of corresponding diaryliodonium salt and sodium trifluormethansulfinate has been developed. Both electron-rich and electron-poor aromatic diaryliodonium salts provided the coupled products in good yields. The reaction was tolerant of varying the counteranion of diaryliodonium salts. Tolerance of several common organic functional groups (nitro, cyano, acetyl, dialkylamino, formyl, boronic acid, terminal alkyne, unprotected amine, alcohol and pyridine) under the standard reaction conditions was rapidly demonstrated by performing reactions of diphenyliodonium hexafluorophosphate with sodium trifluormethansulfinate in the presence of additives containing these functional groups. Low yields of **IIa** observed in the presence of heterocyclic compounds such as 2-azaindole and 1,10-phenanthroline that may

bind the copper catalyst is a major limitation of the current methodology. The synthetic utility of the methodology was demonstrated by performing a reaction at 88 g. Fractional distillation of the reaction mixture allowed for the efficient recovery of the desired product as well as of the aryl iodide side product.

Experimental Section

General methods. All copper-catalyzed reactions were performed in a nitrogen filled glove box or using Schlenk techniques under a N_2 or Ar atmosphere. Anhydrous grade DMF, THF, toluene, 1,4-dioxane, acetonitrile, THF, aryl iodides, sodium trifluoromethanesulfinate and copper salts were purchased from commercial sources and were used without further purification. Diaryliodonium salts were either purchased from commercial sources or were synthesized by following literature procedures.[26,32,48] Column chromatography was performed using silica gel. ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra were recorded on a 400 or 600 or 700 MHz spectrometer, with chemical shifts reported in parts per million downfield from tetramethylsilane and referenced to residual proton (^{1}H) or deuterated solvent (^{13}C). HPLC analyses were performed by gradient elution with acetonitrile and either 0.1% aq H_3PO_4 or 0.1% aq $HClO_4$. Elemental analysis was performed using optimum combustion analysis on an elemental analyzer.

Procedure for Cu-catalyzed reaction of diphenyliodonium hexafluorophosphate (1a) with sodium trifluoromethanesulfinate (Table 1).

A 40-mL reaction vial equipped with a magnetic stir bar and fitted with a teflon-coated septum screw cap was charged with diphenyliodonium hexafluorophosphate (**1a**) (0.464 g, 1.09 mmol), sodium trifluoromethanesulfinate (0.176 g, 1.20 mmol) and copper salts/Cu (0.11 – 0.02 mmol) (except entries 1-5) inside an inert atmosphere glove box. Appropriate amount of solvent was added with a syringe to achieve the reaction concentration of 0.22-0.24 M. The reaction vial was heated to 50-80 °C, as appropriate, by placing the reaction vial inside a metal heating block and the reaction mixture was stirred for 14-18 h. Upon reaction completion, the reaction mixture was cooled to the room temperature and was brought outside of the glove box. In order to determine the amount of product formed, the reaction mixture was filtered through a filter funnel that was pre-packed with celite, the celite was rinsed with solvent (~8-10 mL) and was collected in a tared 25-mL Erlenmeyer flask. The weight of filtered solution (Wt_{prod}) was recorded.

Next, the amount of the product present in the filtered solution was determined by HPLC analysis as follows. A small portion of the filtered solution (~0.6-1.1 g) was weighed into a tared 50-mL volumetric flask (Wt_{sample}). Acetonitrile was added to achieve a total volume of 50 mL; a small portion (1-1.5 mL) of this solution was then injected into an HPLC instrument. The area response corresponding to the product **IIa** was recorded (A_{prod}).

Assay yield calculation: The commercially available product **IIa** was weighed into a 50-mL volumetric flask (Wt_{std}), dissolved in 50 mL acetonitrile and was analysed by an HPLC instrument. The area corresponding to the product was recorded (A_{std}). The assay yield of **2a** in entries 1-17, Table 1 was determined by using the following formula:

$$\text{Assay yield (\%)} = \frac{A_{prod} \times Wt_{prod} \times Wt_{std} \times 100}{A_{std} \times Wt_{sample} \times \text{theroretical yield (g)}}$$

Procedure for Cu-catalyzed reaction of diphenyliodonium salts (1X) with sodium trifluoromethanesulfinate (Table 2).

A 40-mL reaction vial equipped with a magnetic stir bar and fitted with a teflon-coated screw cap septum was charged with diphenyliodonium salt (**1X,** X = PF_6^-, OTs^-, BF_4^-, $CF_3SO_3^-$) (1 equiv), sodium trifluoromethanesulfinate (1.2 equiv) and Cu_2O (0.02 equiv) inside an inert atmosphere glove box. Appropriate amount of DMF was added with a syringe to achieve the reaction concentration of 0.22-0.24 M. The reaction mixture was heated to 50 °C by placing the reaction vial inside a metal heating block and the reaction mixture was stirred for 14-18 h. Upon completion, the reaction mixture was cooled to the room temperature, brought outside the glove box. In order to determine the amount of the product formed, the reaction mixture was filtered through a filter funnel that was pre-packed with celite, the celite was rinsed with solvent (~8-10 mL), and was collected in a tared 25-mL Erlenmeyer flask. The assay yield of **2a** in entries 1-17, Table 1 was determined as described above.

General procedure for Cu-catalyzed reaction of diaryl iodonium salts with sodium trifluoromethanesulfinate (Table 3).

A 40-mL reaction vial equipped with a magnetic stir bar and fitted with a Teflon-coated screw cap was charged with the diaryl iodonium salt **1a-l** (1 equiv), sodium trifluoromethanesulfinate (1.1 equiv) and

copper(I) oxide (0.02 equiv). The vial was purged with N_2 for not less than 1 hour. DMF was purged with N_2 for not less than 60 minutes after which time the appropriate amount was added to the reaction vial to achieve a final concentration of 0.22-0.24 M. The vial was kept under N_2 and heated to an internal temperature of 50 ºC and stirred overnight (18 h). The reaction mixture was diluted with 12 mL of a 3:1 heptanes:ethyl acetate solution and was washed with 12 mL of 5% K_2CO_3 solution. The organic layer was filtered through a pad of celite and was then concentrated *in vacuo* to an oil. The product was isolated by silica gel column chromatography.

(Trifluoromethylsulfonyl)benzene (2a).[23,49] Following the general procedure, **1a** (0.368 g, 0.863 mmol) was reacted with sodium trifluoromethanesulfinate. The analytically pure product was isolated from the reaction mixture by silica gel column chromatography using 0-10% ethyl acetate in heptanes as the eluent. The title compound **2a** was obtained as a colorless oil. (0.155 g, 86%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.95 (d, *J* = 14 Hz, 2H), 7.76 (app t, *J* = 7.0 Hz, 1H), 7.59 (app t, *J* = 7.0 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 136.8 (s), 131.3 (s), 130.8 (s), 130.1 (s), 119.9 (q, *J* = 325.6 Hz). ^{19}F (564 MHz, $CDCl_3$) δ -78.45. Anal. Calcd for $C_7H_5F_3O_2S$: C, 40.00; H, 2.40. Found: C, 40.01; H, 2.31.

1-Methyl-2-(trfluoromethylsulfonyl)benzene (2b).[23] Following the general procedure, **1b** (1.15 g, 2.90 mmol) was reacted with sodium trifluoromethanesulfinate. The analytically pure product was isolated from the reaction mixture by silica gel column chromatography using 0-8% ethyl acetate in heptanes as the eluent. The title compound **2b** was obtained as a colorless oil (0.57 g, 88%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.68 (td, *J* = 7.6, 1.4, Hz, 1H), 7.48-7.43 (m, 2H), 2.73 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) 142.2 (s), 136.3 (s), 135.5 (s), 133.3 (s), 129.8 (s), 127.2 (s), 120.1 (q, *J* = 327.7 Hz), 20.6 (s). ^{19}F (564 MHz, $CDCl_3$) δ -78.34. Anal. Calcd for $C_8H_7F_3O_2S$: C, 42.86; H, 3.15%. Found C, 42.89; H, 2.91%.

1,3,5-Trimethyl-2-(trifluoromethylsulfonyl)benzene (2c). Following the general procedure, **1c** (2.0 g, 3.9 mmol) was reacted with sodium trifluoromethanesulfinate. The analytically pure product was isolated from the reaction mixture by silica gel column chromatography using 0-8% ethyl acetate in heptanes as the eluent. The title compound **2c** was obtained as a colorless oil (0.2 g, 20%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.91 (s, 2H), 2.29 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) 146.7 (s), 136.9 (s), 131.1 (s), 130.0 (s), 123.0 (q, *J*

= 336.7 Hz), 20.7 (s), 16.9 (s). ^{19}F (564 MHz, $CDCl_3$) δ -78.90. Anal. Calcd for $C_{10}H_{11}F_3O_2S$: C, 47.61%; H, 4.40. Found: C, 47.99; H, 3.99.

1-Fluoro-2-(trifluoromethylsulfonyl)benzene (2d). Following the general procedure, **1d** (1.0 g, 2.2 mmol) of bis(2-fluoromethylphenyl) tetrafluoroborate was reacted with sodium trifluoromethanesulfinate. The analytically pure product was isolated from the reaction mixture by silica gel column chromatography using 0-30% ethyl acetate in heptanes as the eluent. The title compound **2d** was obtained as a colorless oil (0.40 g, 79%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07-7.97 (m, 1H), 7.91-7.79 (m, 1H), 7.46 (td, *J* = 7.9, 1.0 Hz, 1H), 7.39-7.34 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.2 (d, *J* = 265.8 Hz), 139.3 (d, *J* = 9 Hz), 133.3 (s), 125.3 (d, *J* = 3.0 Hz), 119.7 (d, *J* = 12 Hz), 119.65 (q, *J* = 326.2 Hz), 118.1 (d, *J* = 19.6 Hz). ^{19}F (564 MHz,$CDCl_3$) δ -78.3 (d, *J* = 9.4 Hz), -103.8 (m).[22]

1-(Trifluoromethyl)-4-(trifluoromethylsulfonyl)benzene (2e). A 40-mL reaction vial equipped with a magnetic stir bar and fitted with a teflon-coated screw cap was charged with the diaryl iodonium salt **1e** (0.680 g, 1.35 mmol), sodium trifluoromethanesulfinate (0.232 g, 1.484 mmol) and copper(I) oxide (3.86 mg, 0.027 mmol). The vial was purged with N_2 for not less than1 hour. THF was purged with N_2 for not less than 30 minutes after which 6 mL was added to the reaction vial. The vial was kept under N_2 and heated to an internal temperature of 50 ºC and stirred overnight (6 h). The reaction mixture was filtered through a pad of celite and was washed with diethyl ether (10 mL). Celite (3 g) was added to the filtered solution and was concentrated *in vacuo*. The product adsorbed on celite was purified by silica gel column chromatography, eluting with 0-30% diethyl ether in pentane. The title compound **2e** was obtained as a white solid (0.238 g, 63%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.2 Hz, 2H), 7.96(d, *J* = 7.9 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.0 (q, *J* = 33 Hz), 135.1 (s), 131.4 (s) 127.0 (q, *J* = 3 Hz), 119.6 (q, *J* = 326.2 Hz) 112.7 (q, *J* = 282.4 Hz). ^{19}F (564 MHz, $CDCl_3$) δ -78.04, -63.74. Anal. Calcd for $C_8H_4F_6O_2S$: C, 34.54; H, 1.45. Found: C, 34.34; H, 1.25. mp 38-39 °C.

1-Methoxy-4-(trifluoromethylsulfonyl)benzene (2f).[23] Following the general procedure, **1f** (0.750 g, 1.75 mmol) was reacted with sodium trifluoromethanesulfinate. The analytically pure product was isolated from the reaction mixture by silica gel column chromatography using 0-25% ethyl acetate in heptanes as the eluent. The title compound **2f** was obtained as a colourless oil (0.335 g, 80%). ^{1}H NMR (600 MHz, $CDCl_3$)

δ 8.11 (d, *J* = 9.0 Hz, 2H), 7.33-7.15 (m, 2H), 4.09 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.1 (s), 131.2 (s), 120.9 (s). 119.9 (q, *J* = 324.6 Hz) 115.2 (s), 55.9 (s). ^{19}F (564 MHz, $CDCl_3$) δ -83.65. Anal. Calcd for $C_8H_7F_3O_3S$: C, 40.00; H, 2.94. Found: C, 40.23; H, 2.49.

1-Bromo-4-(trifluoromethylsulfonyl)benzene (2g). Following the general procedure, **1g** (0.80 g, 1.5 mmol) was reacted with sodium trifluoromethanesulfinate. The analytically pure product was isolated from the reaction mixture by silica gel column chromatography using 0-8% ethyl acetate in heptanes as the eluent. The title compound **2g** was obtained as a white solid (0.311 mg, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.9 Hz, 2H), 7.85-7.83 (m, 2H), ^{13}C NMR (151 MHz, $CDCl_3$) δ. 133.4 (s), 132.8 (s), 132.0 (s), 130.3 (s), 119.6 (q, *J* = 326.0 Hz). ^{19}F (564 MHz, $CDCl_3$) δ -78.3. Anal. Calcd for $C_7H_4BrF_3O_2S$: C, 29.08; H, 1.39. Found: C, 29.21; H, 1.31. mp 63-64 °C**.**

1-Carboethoxy-4-(trifluoromethylsulfonyl)benzene (2h). Following the general procedure, **1h** (1.0 g, 1.9 mmol) was reacted with sodium trifluoromethanesulfinate. The analytically pure product was isolated from the reaction mixture by silica gel column chromatography using 0-8% ethyl acetate in heptanes as the eluent. The title compound **2h** was obtained as a white solid (0.551 g, 84%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37-8.27 (m, 2H), 8.13 (d, *J* = 8.4 Hz, 2H), 4.46 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, ^{3}H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.3 (s), 137.7 (s), 134.9 (s), 130.8 (s), 130.7 (s), 119.6 (q, *J* = 326.2 Hz), 62.3 (s), 14.3 (s). ^{19}F (564 MHz, $CDCl_3$) δ -82.8. Anal. Calcd for $C_{10}H_9F_3O_4S$: C, 42.56; H, 3.21. Found: C, 42.67; H, 3.09. mp 45-47 °C.

2-((Trifluoromethyl)sulfonyl)thiophene (2i).[50] Following the general procedure, **2i** (0.40 g, 0.86 mmol) was reacted with sodium trifluoromethanesulfinate. The analytically pure product was isolated from the reaction mixture by silica gel chromatography using 0-30% diethyl ether in hexanes as the eluent. The title compound **2i** was obtained as a white solid (0.122 g, 66%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.97 (d, *J* = 4.9 Hz, 1H), 7.90 (d, *J* = 3.8 Hz, 1H), 7.25 (appt, *J* = 4.4 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 139.7 (s), 139.6 (s), 130.6 (d, *J* = 1.7 Hz), 129.3 (s), 119.8 (q, *J* = 314.6 Hz). ^{19}F (376 MHz, $CDCl_3$) δ -78.7. Anal. Calcd for $C_5H_3F_3O_2S_2$: C, 27.78; H, 1.40. Found: C, 27.24; H, 1.24.

1-nitro-4-(trifluoromethylsulfonyl)benzene (2k).[20] Following the general procedure, **1i** (0.50 g, 1.0 mmol) was reacted with sodium trifluoromethanesulfinate. The analytically pure product was isolated from the reaction mixture by silica gel column chromatography using 0-8% ethyl acetate in heptanes as the

eluent. The title compound **2i** was obtained as a white solid (109 mg, 41%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57-8.50 (m, 2H), 8.34-8.26 (m, 2H).^{13}C NMR (151 MHz, $CDCl_3$) δ 152.4 (s), 137.1 (s), 132.3 (s), 124.9 (s), 119.6 (q, J = 339.7 Hz). ^{19}F (564 MHz, $CDCl_3$) δ -75.5. Anal. Calcd for $C_7H_4F_3NO_4S$: C, 32.95; H, 1.58; N, 5.49 Found: C, 32.78; H, 1.37; N, 5.30. mp 80-82 °C**.**

Table 3, entry 12: Following the general procedure, **1l** (0.50 g, 1.0 mmol) was reacted with sodium trifluoromethanesulfinate. A mixture of **2l** and **2a** was isolated from the reaction mixture by silica gel column chromatography using 0-15% ethyl acetate in heptanes as the eluent. The mixture of **2l** and **2a** was obtained as a white solid (199 mg, 81%) in a ratio of 1.2:1.0 as determined by ^{1}H NMR spectroscopy.

Table 3, entry 13: Following the general procedure, **1m** (0.60 g, 1.1 mmol) was reacted with sodium trifluoromethanesulfinate. **2k (**0.17 g**)** was isolated from the reaction mixture by silica gel column chromatography using 8% ethyl acetate in heptane and **2f** (0.10 g) was isolated using 15% ethyl acetate in heptanes as the eluent.

Fractional distillation procedure for the separation of 2d and 2'd.

A distillation apparatus consisting of the three stacked vacuum insulated cylindrical columns of 2.54 cm internal diameter and 45 cm length each was set-up (Figure 1). One of the columns was packed with stainless steel wire-mesh while the other two were packed with stainless steel random packing. The columns were not characterized for the number of theoretical stages but were approximated to have around 19 stages based on assumed HETP (height equivalent to theoretical plate) of 5 cm. A vacuum insulated cylindrical section equipped with a solenoid valve was used to connect a condenser and a column with random packing to control the liquid returned to the packed column and fraction withdrawal.

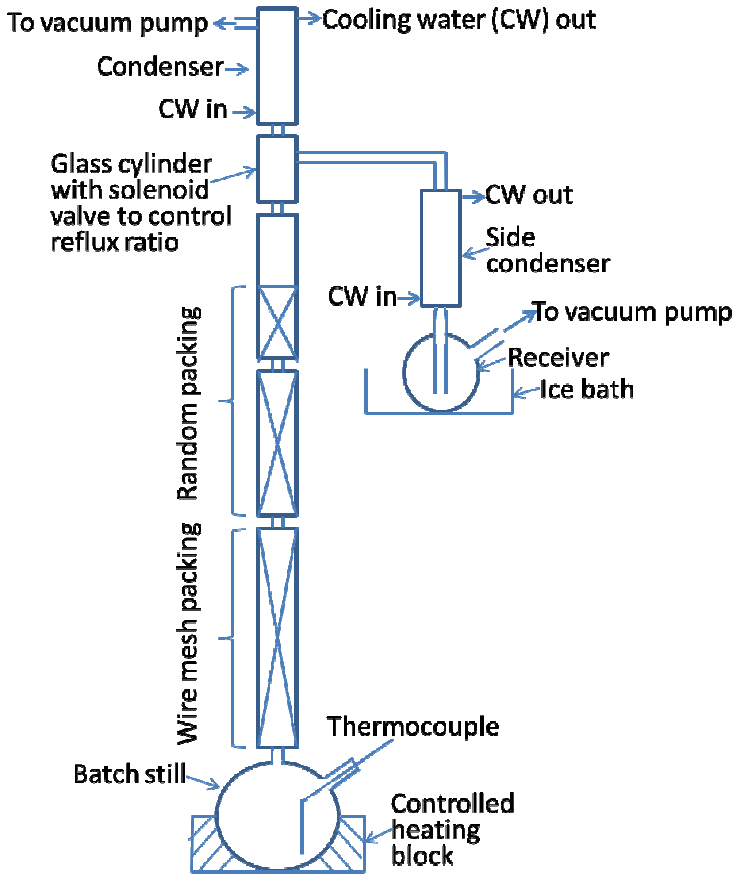
A reaction solution (111.73 g) containing a mixture of **2d**, **2'd** (70.94 g, rest of the weight was DMF) was charged to a 500-mL four-neck round-bottom flask and was heated with a heating mantle equipped with the temperature and heating rate control. The solution was diluted with additional 84 g of DMF to establish vapor-liquid contact through better wetting of the packing and to pre-heat the column packing during initial total reflux. Furthermore, a magnetic stirrer was placed in the batch still to avoid 'liquid bumping' so as to avoid any solution carryover into the packed column. The vacuum was applied at the top condenser and controlled at around 15 mmHg throughout the operation. Both the vapor and the internal batch still temperatures were monitored using thermocouples. The top condenser jacket temperature was maintained

at 5 °C while the side condenser temperature was maintained at -10 °C using two different recirculating chillers. The cold trap and the receiver were kept in a dry ice/acetone bath to minimize vapor loss to vacuum lines. The column was run at total reflux at the batch still temperature of 60 °C. Slowly the batch still temperature was increased to 90 °C and the fraction containing predominantly **2'd** was collected at the reflux ratio of 4:1 until no liquid fraction was observed in the receiver. The first receiver was replaced with a new receiver, the batch still temperature was increased to 135 °C and the fraction containing **2d** was collected. The recovery of **2'd** was 93.4% while the recovery of **2d** was 100%. Please note that the recovery percentages are for the distillation only and are different than the yields reported in the text (Scheme 1), which represent the overall process yield.

Procedure for Cu-catalyzed reaction of diphenyliodonium hexafluorophosphate (2a) with sodium trifluoromethanesulfinate in the presence of additives (Table 4).

A 40-mL reaction vial equipped with a magnetic stir bar and fitted with a teflon-coated screw cap septum was charged with **1a** (0.20 g, 0.47 mmol), sodium trifluoromethanesulfinate (0.081 g, 0.52 mmol), additive (0.47 mmol) and Cu_2O (1.34 mg, 9.39 μmol) inside an inert atmosphere glove box. DMF (2 mL) was added with a syringe. The reaction mixture was heated to 50 °C by placing the reaction vial inside a metal heating block and the reaction mixture was stirred for 14-18 h. Upon completion, the reaction mixture was removed from the heating block and was brought outside of the glove box. In order to determine the amount of product formed and the amount of unreacted additive remaining, the reaction mixture was filtered through a filter funnel that was pre-packed with celite, the celite was rinsed with THF (~4-6 mL), and was collected in a tared 25-mL Erlenmeyer flask. The assay yield of **2a** in entries 1-13, Table 4 was determined as described above for the general procedure for the reactions reported in Table 1. To determine the amounts of the additive remaining after the reaction, the commercially available additive was weighed into a 50-mL volumetric flask (Wt_{std}), acetonitrile was added to achieve a total volume of 50 mL and a small portion (1-1.5 ml) of this solution was injected into an HPLC instrument. The area corresponding to the additive was recorded (A_{std}). The amount of the additive remaining after the reaction was determined by using the formula described for the reactions reported in Table 1.

Figure 1: Distillation apparatus set up



Acknowledgments: The design, study conduct, analysis and financial support of the study were provided by AbbVie. Steven C. Cullen, Shashank Shekhar and Nandkishor Nere are AbbVie employee.

Supporting Information Available: ^{1}H, ^{19}F and ^{13}C NMR spectra of aryl trifluoromethyl sulfones.This material is available free of charge via the Internet at http://pubs.acs.org.

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