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Lewis Acid-Catalyzed Electrophilic Trifluoromethylthiolation of (Hetero)Arenes

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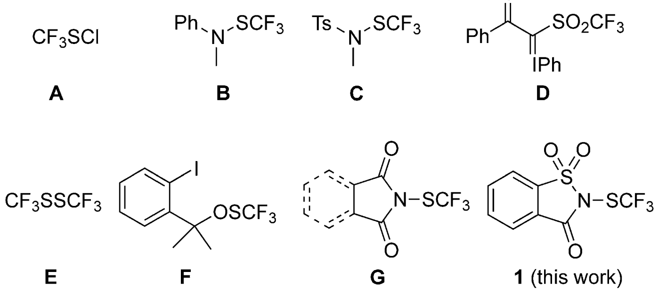
Abstract: (*N*-Trifluoromethylthio)saccharin has been applied as an electrophilic trifluoromethylthiolating reagent for a broad scope of heteroarenes, electron-donating group (EDG)-activated benzenes, and several electron-rich olefins. Iron(III) and gold(III) catalysts showed complementary activity for different substrates.

Keywords: electron-rich olefins; gold catalysts; heteroarenes; iron catalysts; trifluoromethylthiolation



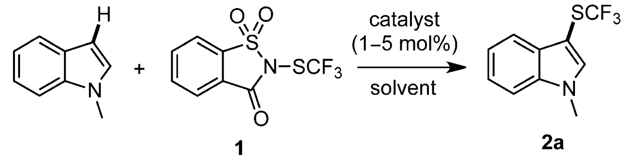
Scheme 1. Trifluoromethylthiolating reagents.

The trifluoromethylthio (SCF_3) group is a particularly important substituent because it has been well-established that introduction of this specific electron-withdrawing group into organic molecules can significantly increase their lipophilicity. Accordingly introduction of SCF_3 groups may significantly increase their transmembrane permeation, thus enhancing their bioactivity.[1] Thus installation of a SCF_3 group into small molecules, particularly arenes, is of considerable interest for the design and discovery of bioactive compounds. Consequently, the development of efficient methods for trifluoromethylthiolation of organics has attracted increasing attention.[2] Early work in the construction of C–SCF_3 bonds utilized nucleophilic SCF_3 sources.[3] Trifluoromethyl hypochlorothioite (CF_3SCl) was first used as an electrophilic trifluoromethylthiolating reagent.[4] Recently, several other classes of electrophilic trifluoromethylthiolating reagents (**B–G**) have been developed (Scheme 1), and they allowed the trifluoromethylthiolation of various substrates.[4]

Trifluoromethylthiolation of C–H bonds would be advantageous because direct transformation of C–H bonds represents a step- and atom-economic process. In this context, several classes of C–H substrates have been explored. Acidic C–H substrates such as terminal alkynes[4c,h,k] and activated methylenes[4g,h,l] are intrinsically reactive and have been successfully trifluoromethylthiolated using reagent **F** (which is less readily available). C–H trifluoromethylthiolation of (hetero)arenes is generally challenging. In 2012, Billard elegantly achieved the trifluoromethylthiolation of indoles using reagent **B** in the presence of a superstoichiometric amount of a strong acid,[4n] which may have issues of compatibility, and the C–H substrates are also limited to highly electron-rich heteroarenes. Billard recently introduced reagent **C** as a more electrophilic variant of **B** for α-trifluoromethylthiolation of carbonyl compounds.[4d] In 2013, Shibata designed novel hypervalent iodonium ylides for the mild trifluoromethylthiolation of indoles and activated enamines under copper-catalyzed conditions.[4f]

On the other hand, trifluoromethylthiolation *via* a C–H activation pathway has been recently reported. In 2013, Daugulis applied the strategy of a bidentate directing group to benzamides using CF_3SSCF_3 as an SCF_3 source.[4e] Shen recently reported the C–H trifluoromethylthiolation of "electron-neutral" arenes using reagent **G**,[4j] but an *ortho*-directing group (pyridyl) is necessary. Despite the progress, the arene substrates are still limited and it remains necessary to design new trifluoromethylthiolating reagents for diversified arenes. We reasoned that trifluoromethylthiolating reagents with enhanced electrophilicity should effect the C–SCF_3 coupling of a broader scope

Table 1. Optimization studies for an indole substrate.[a,b]



Entry	Solvent	Catalyst (mol%)	Temp. [°C]	Yield [%][b]
1	DCE	–	120	59
2	DCE	$AuCl_3$ (5)	120	96
3	DCM	$AuCl_3$ (5)	120	95
4	DCE	$AuCl_3$ (5)	80	95
5	DCE	$AuCl_3$ (5)	50	95
6	DCE	$AuCl_3$ (5)	30	79
7	DCE	$AuCl_3$ (1)	30	78
8	DCE	–	30	50
9	DCE	$FeCl_3$ (5)	30	72
10	DCE	$FeCl_3$ (5)	50	95
11[c]	DCE	$FeCl_3$ (5)	50	0
12	DCE	Zn $(OTf)_2$	50	63

[a] *Reaction conditions:* *N*-methylindole (0.1 mmol), (*N*-trifluoromethylthio)saccharin (**1**, 0.11 mmol), catalyst (1–5 mol%), solvent (2 mL), 30–120 °C, 16 h, sealed tube under Ar.

[b] Yield was determined by GC-MS.

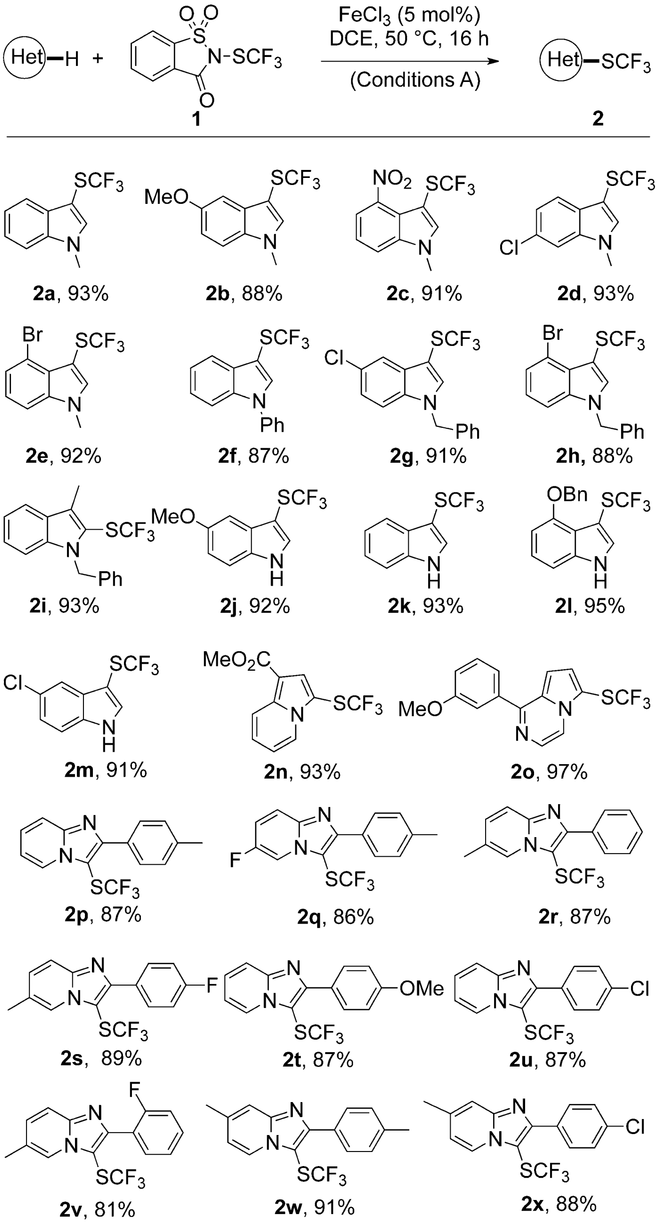
[c] *N*-Trifluoromethylthiophthalimide (**G**) was used as the SCF_3 source.

of arene substrates, which may serve to overcome some limitations of the current methodologies.

(*N*-Trifluoromethylthio)saccharin (**1**) was readily synthesized *via* the metathesis reaction between *N*-bromosaccharin and $AgSCF_3$. During the preparation of the manuscript, the same reagent was reported by Shen.[5] We initially employed a substituted indole as a substrate, and optimization of the reaction conditions has been performed for the coupling of *N*-methylindole with **1**. It was found that while an uncatalyzed reaction did yield the 3-trifluoromethylthiolation product **2a**, the reaction efficiency was only moderate even at a rather high temperature (Table 1, entry 1). Addition of $AuCl_3$ (5 mol%) led to a nearly quantitative reaction at above 50 °C (entries 2–5). Further lowering the temperature to 30 °C afforded a diminished yield (entry 6). Gratifyingly, the reaction efficiency is equally high when $FeCl_3$ (5 mol%) was used a cost-effective catalyst,[6] under which conditions (Conditions A) product **2a** was generated in 95% GC yield (entry 10). Other Lewis acids such as $Zn(OTf)_2$ only exhibited lower efficiency (entry 12). In contrast to the high activity of this trifluoromethylthiolating reagent, no conversion was detected when *N*-trifluoromethylthiophthalimide (**G**) was used (entry 11), suggesting that higher electrophilicity gave better yields.

With the optimized conditions in hand, we next explored the scope and limitations of this coupling system (Table 2). *N*-Protected indoles bearing both electron-donating and electron-withdrawing groups in the benzene ring reacted in consistently high yields (**2a**–**2h**). The isolated yield of the product was equally high when a 3-methyl group was introduced into the indole ring (**2i**), indicative of the tolerance of steric hindrance. Furthermore, variation of the *N*-substituent to methyl, benzyl, and aryl groups has only a marginal influence on the reaction efficiency, and unprotected indoles are also well tolerated (**2j**–**2m**). In contrast, *N*-acetylindole failed to give any desired prod-

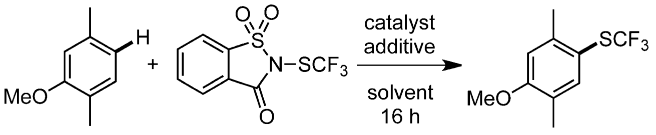
Table 2. Trifluoromethylthiolation of heteroarenes.[a,b]



[a] *Reaction conditions:* indole (0.1 mmol), (*N*-trifluoromethylthio)saccharin (0.21 mmol), $FeCl_3$ (5 mol%), DCE (2 mL), 50 °C, 12 h, sealed tube under Ar.

[b] Isolated yields.

Table 3. Optimization studies for an activated benzene.[a,b]



1 **3a**

Entry	Catalyst (mol%)	Additive (mol%)	Solvent	Temp [°C]	Yield [%][b]
1	$FeCl_3$ (10)	–	DCE	100	46
2	$Cu(OTf)_2$ (20)	–	DCE	120	ND
3	$AuCl_3$ (5)	–	DCE	120	ND
4	$FeCl_3$ (10)	$AgSbF_6$ (30)	DCE	100	95
5[c]	$FeCl_3$ (10)	$AgSbF_6$ (30)	DCE	100	<5
6	$FeCl_3$ (10)	$AgSbF_6$ (30)	DCE	80	72
7	$FeCl_3$ (5)	$AgSbF_6$ (15)	DCE	100	81
8	$FeCl_3$ (10)	$AgSbF_6$ (30)	DCM	100	90
9	$FeCl_3$ (10)	$AgSbF_6$ (30)	dioxane	100	N.D.
10	$FeCl_3$ (10)	AgOTf (30)	DCE	100	73
11	$FeCl_3$ (10)	AgOAc (30)	DCE	100	<5
12	$Fe(OTf)_3$ (10)	–	DCE	100	76
13	HOTf (50)	–	DCE	100	48
14	$Zn(OTf)_2$	–	DCE	100	<5

[a] *Reaction conditions:* 2,5-dimethylanisole (0.1 mmol), (*N*-trifluoromethylthio)saccharin (0.11 mmol), catalyst, additive, solvent (2 mL), 80–120 °C, 16 h, sealed tube under Ar.

[b] Yield was determined by GC-MS.

[c] *N*-Trifluoromethylthiophthalimide (**G**) was used as the SCF_3 source.

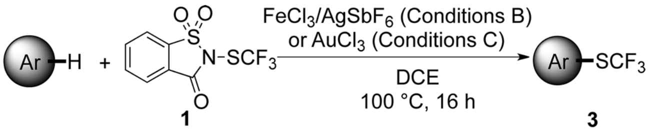
uct, likely due to the lower nucleophilicity caused by the electron-withdrawing group.

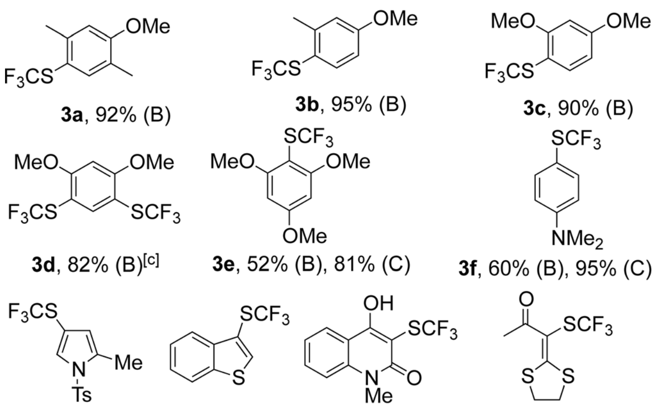
The catalytic reaction can be smoothly extended to imidazol[1,2-*a*]pyridines, another class of electron-rich heterocycles. 2-Arylimidazol[1,2-*a*]pyridines bearing various substituents in the aryl ring and in the backbone all underwent efficient trifluoromethylthiolation at the 3-position (**2p**–**2x**), and the products were isolated in high yield (81–91%). Structurally related heterocycles such as an ester-substituted indolizine (**2n**) and a related pyrrolo[1,2-*a*]pyrazine (**2o**) are also viable substrates, and the trifluoromethylthiolation occurred selectively at the 2-position, respectively, on the basis of NMR analysis. The regioselectivity for these two substrates is consistent with that in the Pd-catalyzed C–H olefination reactions,[7] indicating that the Friedel–Crafts (electrophilic C–H functionalization) mechanism is likely operational.

Extension of arene substrates to activated benzenes such as 2,5-dimethylanisole under Conditions A only gave inferior results even at a higher temperature (Table 3, entry 1). Thus further screenings have been performed. It was found that some commonly used Lewis acid catalysts such as $AuCl_3$ and $Cu(OTf)_2$ are inactive (entries 2, 3, 14). Although low reactivity was observed for $FeCl_3$, introduction of $AgSbF_6$ significantly improved the catalytic activity as a result of an enhancement of the Lewis acidity of the catalyst likely *via in situ* generation of $Fe(SbF_6)_3$ (entry 4).[8] Using other silver salt additives such as AgOTf and AgOAc or using $Fe(OTf)_3$ as the catalyst all afforded moderate or lower yields (entries 10–12), suggesting that the electrophilicity of the Fe(III) catalyst is of significance. Control experiments revealed that $AgSbF_6$ alone gave essentially no reaction. Thus the optimal conditions have been established with $FeCl_3$/$AgSbF_6$ (10 mol%/30 mol%) as the catalyst in DCE at 100 °C (Conditions B). Lewis acid catalysis has been shown superior in this reaction because replacing it with a Brønsted acid such as HOTf (50 mol%) resulted in a rather low yield (entry 13).

By applying the Conditions B, the scope of the arene substrate has been explored (Table 4). Benzenes activated by methyl and methoxy groups at different positions are viable substrates and trifluoromethylthiolation occurred at the position *para* to a methoxy group (**3a**–**3e**, 81–95%). Furthermore, bistrifluoromethylthiolation was achievable for 1,3-dimethoxybenzene (**3d**) when an excess of (*N*-trifluoromethylthio)saccharin was employed. In contrast, essentially no reaction occurred for simple anisole or 1,4-dimethoxybenzene, indicative of the limitation to the electronic effects and to the proper position of the EDG. *N,N*-Dimethylaniline is also an viable substrate, although the reaction occurred at the 4-position in moderate yield (**3f**). Significantly, switching to $AuCl_3$ (1 mol%) as the sole catalyst (Conditions C) increased the isolated yield to 95%, suggesting that a judicious choice of Fe(III) and Au(III) catalysts can lead to superior efficiency.[9] In addition,

Table 4. Trifluoromethylthiolation of activated benzenes and olefins.[a,b]





3a, 92% (B) | **3b**, 95% (B) | **3c**, 90% (B)

3d, 82% (B)[c] | **3e**, 52% (B), 81% (C) | **3f**, 60% (B), 95% (C)

3g, 76% (B) | **3h**, 91% (B) | **3i**, 75% (B) | **3j**, 70% (B), 95% (C)

[a] *Conditions B:* (hetero)arene or olefin (0.2 mmol), (*N*-trifluoromethylthio)saccharin (0.21 mmol), FeCl$_3$ (0.02 mmol), AgSbF$_6$ (0.06 mmol), DCE (3 mL), 100 °C, 16 h, sealed tube under Ar. *Conditions C:* (hetero)arene or olefin (0.2 mmol), (*N*-trifluoromethylthio)saccharin (0.21 mmol), AuCl$_3$ (0.002 mmol), DCE (3 mL), 100 °C, 16 h, sealed tube under Ar.

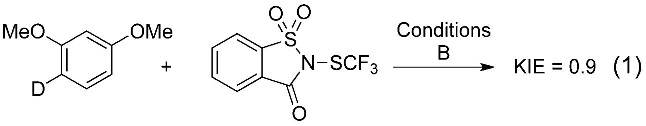
[b] Isolated yield after column chromatography.

[c] An excess (2.1 equiv.) of (*N*-trifluoromethylthio)saccharin was used.

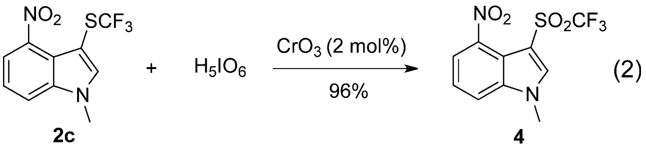
Conditions C also proved optimal for 1,3,5-trimethoxybenzene as substrate (**3e**, 81%), which stands in contrast to the outcome using the Conditions B, where only 52% was obtained.

These conditions are also complementary to Conditions A in terms of less reactive heterocycles. Benzothiophene, which failed to undergo any conversion under the Conditions A, coupled smoothly under the Conditions B to afford **3h** in 91% yield. Although no reaction occurred for *N*-acetylindole under Conditions A, *N*-tosyl-2-methylpyrrole underwent efficient coupling at the 4-position under Conditions B (**3g**, 76%). Furthermore, several EDG-activated olefin substrates have also been identified. Thus the selective trifluoromethylthiolation of an α-oxoketene dithioacetal (**3j**) and 4-hydroxy-1-methylquinolin-2(1*H*)-one (**3i**) has been achieved in good to high yield.

To gain some insights into the mechanism of this reaction, intramolecular KIE has been estimated using 1-deutero-2,4-dimethoxybenzene under the monosubstitution conditions [Eq. (1)]. ^{1}H NMR analysis of the isolated product gave $k_H/k_D = 0.9$,[10] This observed inverse KIE value may suggest an inverse equilibrium isotope effect entangled with an insignificant KIE.[11] Therefore the C–H cleavage is probably not involved in the rate-limiting step and this result is consistent with the Friedel–Crafts trifluoromethylthiolation mechanism.



Further derivatization of a coupled product has been demonstrated. CrO$_3$-catalyzed per-oxidation of **2c** by periodic acid afforded the corresponding sulfone **4** in nearly quantitative yield [Eq. (2)], which belongs to another class of useful fluorine-containing products.[12]



2c | **4**

In summary, we have demonstrated (*N*-trifluoromethylthio)saccharin as a highly electrophilic trifluoromethylthiolating reagent that proved active for the selective trifluoromethylthiolation of a variety of electron-rich arenes and olefins in the presence of a Lewis acid catalyst such as Fe(III) and Au(III). The trifluoromethylthiolation likely occurs *via* the Friedel–Crafts mechanism and a broad scope of (hetero)-arenes including indoles, imidazol[1,2-*a*]pyridines, indolizines, and electron-deficient group-activated benzenes have been established. Iron(III) and gold(III) catalysts can offer complementary activity for different substrates. With its high electrophilicity, the (*N*-trifluoromethylthio)saccharin reagent is expected to effect the trifluoromethylthiolation of other less reactive substrates, and work in this direction is currently underway in our laboratory and will be reported in due course.

Experimental Section

General Procedure for Conditions A

(*N*-Trifluoromethylthio)saccharin (0.21 mmol, 59.5 mg) and indole (0.2 mmol) were added to a pressure tube equipped with a magnetic stir bar. FeCl$_3$ (0.01 mmol, 1.7 mg, 5 mol%) and DCE (2 mL) were added. The tube was sealed and then placed into a preheated oil bath at 50 °C and heated for 12 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to provide the final product.

General Procedure for Conditions B

(*N*-Trifluoromethylthio)saccharin (0.21 mmol, 59.5 mg) and a C−H substrate (0.2 mmol) were added into a pressure tube equipped with a magnetic stir bar. $FeCl_3$ (0.02 mmol, 3.4 mg, 10 mol%), $AgSbF_6$ (0.06 mmol, 20.6 mg, 30 mol%) and DCE (2 mL) were added. The reaction tube was placed into a preheated oil bath at 100 °C and heated for 16 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give the final product.

General Procedure for Conditions C

(*N*-Trifluoromethylthio)saccharin (0.21 mmol, 59.5 mg) and a C−H substrate (0.2 mmol) were added into a pressure tube equipped with a magnetic stir bar. $AuCl_3$ (0.002 mmol, 0.6 mg, 1 mol%) and DCE (2 mL) were then added. The reaction tube was placed into a preheated (100 °C) oil bath and headed for 16 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to afford a pure product.

Acknowledgements

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