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## Protolytic defluorination of trifluoromethyl-substituted arenes

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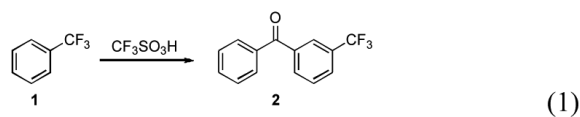
### Abstract

A series of trifluoromethyl-substituted arenes were studied in their reactions with Brønsted superacids. The products from these reactions suggest the formation of reactive electrophiles, such as carbocations, acylium cations, or equivalent electrophilic species. As such, Friedel-Crafts type reactions occur between these species and arene nucleophiles. NMR studies were done and the results suggest the formation of an acyl group from the trifluoromethyl groups in superacid.

### Introduction

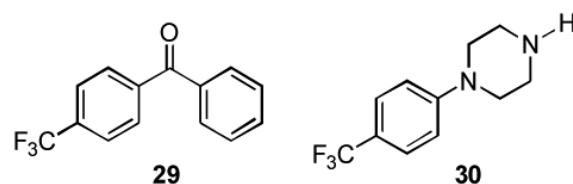
Perfluorinated alkyl groups can be incorporated into organic compounds to influence the charge distributions within the structure, lipophilicities of the compounds, and to impart other effects. In particular, many drugs and pharmaceutical agents utilize the trifluoromethyl group to give these desirable properties. While the trifluoromethyl group is generally considered to be a reasonably stable functional group, it can undergo decomposition reactions with some transition metal catalysts,<sup>1</sup> Lewis acids,<sup>2</sup> metal hydrides,<sup>3</sup> and base-catalyzed conditions.<sup>4</sup> Ionization of the C-F bond by strong Lewis acids is also a well-known route to carbocationic structures.<sup>5</sup> Although ionization of the C-F by Brønsted acids is known, this chemistry has not been studied in great detail.<sup>6</sup> Dissociative attachment of protons to 1-fluoroadamantane has been shown to give the stable 1-adamantyl cation (by loss of HF) in the gas phase and several theoretical studies have examined protonation of alkylfluorides.<sup>7</sup> Fornarini and coworkers studied the gas-phase protonation of  $\alpha,\alpha,\alpha$ -trifluorotoluene using FT-ICR methods and ab initio calculations.<sup>8</sup> Both experimental and theoretical results indicated that protonation occurs at the fluorine atoms with subsequent loss of HF. Recently, Bell and coworkers described a synthesis of benzoyl fluoride from  $\alpha,\alpha,\alpha$ -trifluorotoluene (**1**), Nb<sub>2</sub>O<sub>3</sub> (and other metal oxides), trifluoroacetic acid, trifluoroacetic anhydride, and molecular oxygen. They proposed a mechanism involving protonation of the fluorine atoms along with interactions at the catalyst surface.<sup>9</sup> A report by Hu and Wang also described Friedel-Crafts acylations involving  $\alpha,\alpha,\alpha$ -trifluorotoluene (and related substrates) in reactions with arenes in CF<sub>3</sub>SO<sub>3</sub>H.<sup>10</sup> A proposed mechanism involved protonations of the fluorine atoms and formation of benzylic cations.

During the course of our studies related to superacid chemistry, we observed that reactions of  $\alpha,\alpha,\alpha$ -trifluorotoluene (**1**) in the Brønsted superacid, CF<sub>3</sub>SO<sub>3</sub>H (triflic acid), often contained small amounts of benzoic acid or benzoyl fluoride in the product mixtures. We also observed a reaction in which compound **1** gave a small amount of 3-trifluoromethylbenzophenone (**2**, eq 1). These results prompted us to further examine the chemistry of trifluoromethyl-substituted arenes in superacids. The results of these studies are presented in this Article.

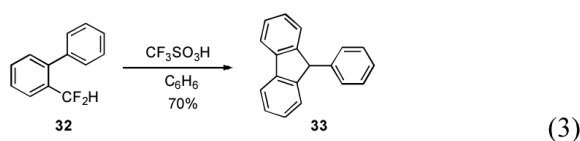
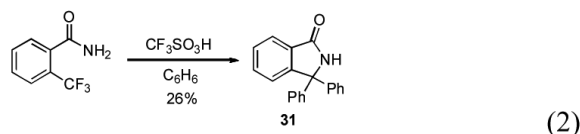


## Results and Discussion

Our initial studies examined the conversions of trifluoromethyl-substituted arenes in Friedel-Crafts type reactions with benzene using  $\text{CF}_3\text{SO}_3\text{H}$  as the acid (Table 1). We observed four basic types of reactivity patterns from these conversions. Several of the trifluoromethyl-substituted arenes formed both the benzophenone derivatives and triarylmethanol derivatives (entries 1-3). In most cases, the product ratio varied little with temperature. Compound **1** gives almost equal amounts of benzophenone (**11**, 41%) and triphenylmethanol (**20**, 54%) at 0°C, and at 25 °C the ratio shifts to **11**, 56% and **20**, 44%. Compound **1** does not react with benzene in the weaker acids of 98%  $\text{H}_2\text{SO}_4$  or  $\text{CF}_3\text{CO}_2\text{H}$ . Several compounds were capable of preferentially forming either the ketone (entries 5-8) or the alcohol (entries 4 and 9). Finally, some substrates were found to be completely unreactive to benzene in  $\text{CF}_3\text{SO}_3\text{H}$ , including the benzophenone derivative (**29**) and the heterocyclic derivative (**30**). We also examined the effects of added metal oxide catalyst ( $\text{Nb}_2\text{O}_3$ ), but the presence of this catalyst had only minor effects on reactivities and product distributions. While our results are similar to the recent work by Hu and Wang,<sup>10</sup> the formation of triarylmethanols has not been previously reported in reactions involving trifluoromethyl-substituted arenes.

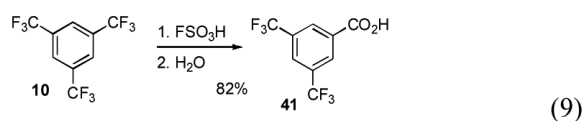
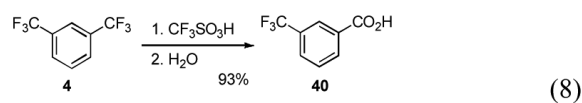
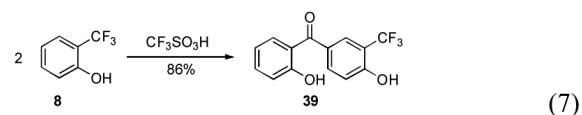
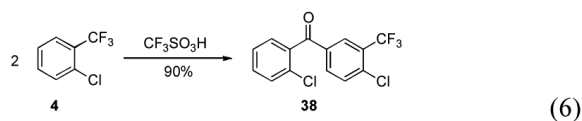
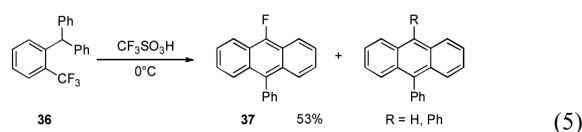
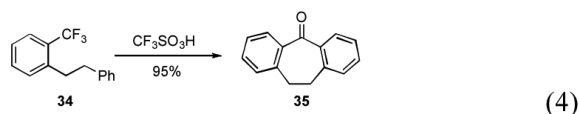


An interesting conversion was observed from the reaction of 2-(trifluoromethyl)benzamide with benzene in  $\text{CF}_3\text{SO}_3\text{H}$  (eq 2). Only unreacted starting material was recovered from the reaction at room temperature, however at 90°C, the 1-isoindolinone (**31**) is formed in fair yield with some unreacted starting material. A clean cyclization is observed in the reaction of the difluoromethyl derivative (**32**) with benzene in  $\text{CF}_3\text{SO}_3\text{H}$  (eq 3).



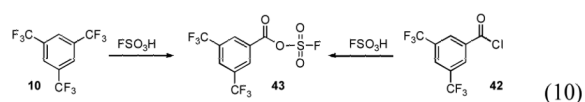
In the absence of benzene, products of cyclizations and dimerizations are obtained. When 1-phenethyl-2-(trifluoromethyl)benzene (**34**) is reacted with  $\text{CF}_3\text{SO}_3\text{H}$ , 5-suberone (**35**) is

formed as the exclusive product (eq 4).<sup>11</sup> The triarylmethane (**36**) undergoes cyclization in  $\text{CF}_3\text{SO}_3\text{H}$ , however a mixture of substituted anthracenes is formed (eq 5). 9-Fluoro-10-phenylanthracene (**36**) is the major product, isolated in 53% yield. Reactions of 1-chloro-2-(trifluoromethyl)benzene (**4**) and 2-(trifluoromethyl)-phenol (**8**) in neat  $\text{CF}_3\text{SO}_3\text{H}$  provide the dimerization products in high yields (eq 6-7). There is no evidence for further reaction (i.e., trimerization), so formation of the benzophenone derivatives (**38-39**) must deactivate the remaining trifluoromethyl group to ionization. We have also found that some trifluoromethyl-substituted arenes provide clean conversions to the carboxylic acids (**40-41**) from superacidic reactions and hydrolytic workup (eqs 8-9). These results are in accord with an earlier study from  $\text{H}_2\text{SO}_4$ , which showed formation of benzoic acids from electron deficient trifluoromethyl-substituted arenes.<sup>12</sup>



The reactions of trifluoromethyl-substituted arenes in  $\text{CF}_3\text{SO}_3\text{H}$  give products that suggest the formation of carbocationic or acylium ion intermediates. This is consistent with the mechanisms proposed by both Bell and Hu.<sup>9,10</sup> In order to gain further mechanistic insights

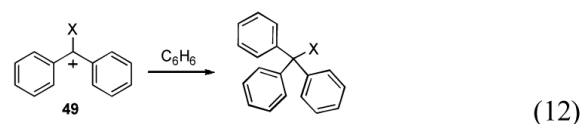
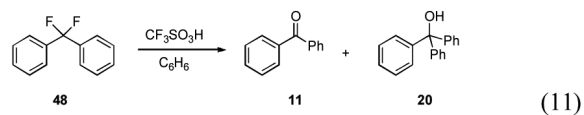
into this chemistry,  $^{13}\text{C}$  NMR experiments were done. Our initial experiments were done by reacting  $\alpha,\alpha,\alpha$ -trifluorotoluene (**1**) in  $\text{CF}_3\text{SO}_3\text{H}$  ( $H_o -14$ ), however the spectra were dominated by the  $^{13}\text{C}$  signals arising from the solvent  $\text{CF}_3\text{SO}_3\text{H}$ , and the intermediate(s) appeared to rapidly convert to the dimeric product (**2**). In order to simplify the  $^{13}\text{C}$  spectra,  $\text{FSO}_3\text{H}$  ( $H_o -15$ ) was used as the acid and 1,3,5-tris(trifluoromethyl)benzene (**10**) was used as the arene substrate. We reasoned that the deactivating effects of the trifluoromethyl groups should prevent dimerization and any unreacted trifluoromethyl groups could serve as an internal NMR standard. When compound **10** is mixed with  $\text{FSO}_3\text{H}$ , an up-field  $^{13}\text{C}$  signal slowly appeared as a singlet at about  $\delta$  180 (Figure 1, spectrum B). This suggests the formation of a carbonyl group, and since the peak is a well-defined singlet, there can be no fluorine atoms remaining on the carbon. The observed  $^{13}\text{C}$  spectrum is consistent with the formation of a mixed carboxylic acid anhydride. To test this hypothesis, 3,5-bis(trifluoromethyl)benzoyl chloride (**42**) was dissolved in  $\text{FSO}_3\text{H}$  and the  $^{13}\text{C}$  spectrum was recorded (Figure 1, spectrum A). Very similar spectra are observed from both compounds **10** and **42**, although signals arising from unreacted **10** are present in its mixture (spectrum B). We propose that these substances form the same species in superacid - the mixed anhydride (**43**) with fluorosulfonic acid (eq 10).



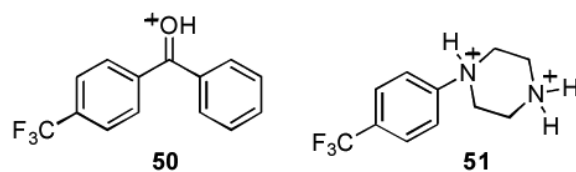
While the conversion of **42** to the mixed anhydride **43** would involve the loss of  $\text{HCl}$ , it is less obvious how **10** leads to **42** in the Brønsted acid. Based on the observed chemistry of the trifluoromethyl-substituted arenes, we propose that anhydride **43** is formed by protonation(s) of the trifluoromethyl group with some involvement of the fluorosulfonate group (Scheme 1). Initial protonation of a fluorine atom forms the benzylic carbocation **44** by loss of a molecule of  $\text{HF}$ . Despite the being an exceptionally weak nucleophile, the fluorosulfonate anion likely reacts with **44** to form the sulfonate ester **45**. Formation of the carbonyl group may occur by one of two routes. Based on Bell's proposed mechanism for conversion of  $\alpha,\alpha,\alpha$ -trifluorotoluene to the benzoyl fluoride,<sup>8</sup> sulfur fluoride may eliminate to directly provide the acid fluoride (**45**, route A). Presumably, such a step requires a four-center transition state. If a second protonation were to occur and another sulfonate ester group formed, compound **47** would be generated. This unusual intermediate (**47**) could then provide **46** by an elimination of the acid anhydride. Alternative mechanisms can be formulated involving intermolecular attack of a sulfonate anion at a sulfonic ester group. In accord with this mechanism, triflic anhydride has been observed as a by-product in the dimerization of **1** in  $\text{CF}_3\text{SO}_3\text{H}$ . Presumably, the initial ionization of **10** is the slow step, because the  $^{13}\text{C}$  NMR shows only the carbonyl product (**43**) and unreacted starting material (**10**). None of the intermediates are formed as persistent, observable species.

The suggested mechanism provides a reasonable explanation for the observed chemical conversions of the trifluoromethyl-substituted arenes. For example, a mixed anhydride (i.e., **43**) is expected to be a good source of the acyl group, leading to dimers (**38** and **39**) and the benzoic acid (**40** and **41**) derivatives. We found that benzophenone itself does not react with benzene in  $\text{CF}_3\text{SO}_3\text{H}$  solution, so the ketone products are not the direct source of the triarylmethanols (**20-28**). As a mechanistic test, we also reacted difluorodiphenylmethane with benzene in  $\text{CF}_3\text{SO}_3\text{H}$  (eq 11). Benzophenone and triphenylmethanol were formed in roughly equal amounts. Thus, the triarylmethanol products may arise from the reaction of a benzylic cation (i.e., **44**) with benzene. The intermediate product would be a difluorodiphenylmethane, which is further ionized in superacid and leads to the triarylmethanol (eq 12). Benzophenone is completely protonated in superacidic triflic acid (**49**,  $\text{X}=\text{OH}$ ), but

the reaction requires a more electrophilic species. This suggests either the fluorine-substituted (**49**, X=F) or the triflate-substituted carbocation (**49**, X=OTf) reacts with benzene leading to the triphenylmethanol (**20**).



As described by Wang and Hu,<sup>10</sup> protonation of the fluorine atoms leads to carbocations and related intermediates. Since the initial ionization of the trifluoromethyl group produces a benzylic carbocation, arenes with electron-deficient ring systems are expected to be less reactive. Compounds such as **29** and **30** did not undergo reaction, because they are protonated in superacid, giving ions **50** and **51**. Evidently, further ionization of the C-F bond is inhibited by the existing cationic centers.



## Conclusions

In summary, trifluoromethyl-substituted arenes react in superacid to give Friedel-Crafts-type products with benzene. Both intra and intermolecular reactions can give products in good yields. The products are consistent with the formation of carbocations or their equivalent reactive intermediates. These reactions are evidently facilitated by the benzylic-type stabilization of the carbocationic species. Low temperature <sup>13</sup>C NMR experiments suggest the formation of mixed acid anhydrides in some reactions of trifluoromethyl-substituted arenes. The results further confirm that carbon-fluorine bonds may be efficiently cleaved in the condensed phase by Brønsted acids.

## Experimental

### General details

All the reactions were performed with oven-dried glassware and conducted under an Ar atmosphere. Trifluoromethanesulphonic acid (CF<sub>3</sub>SO<sub>3</sub>H) was distilled from an Ar atmosphere prior to its use. All commercially available compounds and anhydrous solvents were used as received. <sup>1</sup>H and <sup>13</sup>C NMR were obtained from a 500 MHz spectrometer and low resolution mass spectra were obtained from a capillary GC (DB-5 column) equipped with a mass selective detector. High-resolution mass spectra were obtained from the analytical services department at the University of Illinois, Champaign-Urbana.

**General synthetic method A (products 11-28, 31, 33):**

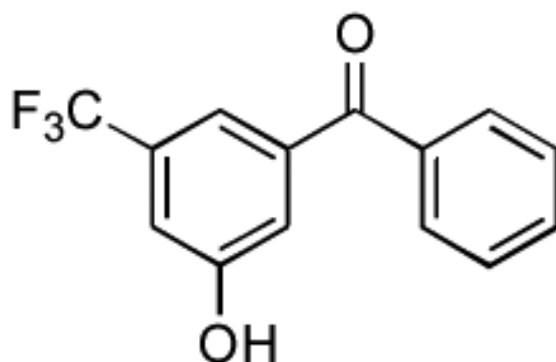
The trifluoromethyl-substituted arene (1 mmol) is dissolved in C<sub>6</sub>H<sub>6</sub> (2 mL). If the reaction is done at 0°C, then CHCl<sub>3</sub> (1 mL) is added as a cosolvent. Trifluoromethanesulfonic acid (2 mL) is then added. The mixture is then stirred for at least 4 hr. after which it is poured over several grams of ice. The solution is extracted twice with chloroform and the organic extracts are washed with water followed by brine (2x). The solution is dried over sodium sulfate and the products are isolated by removal of solvent. In some cases, the major product(s) could be isolated by column chromatography (hexane:ether). However, some of the benzophenone/triarylmethanol product mixtures (**11/20**, **12/21**, **13/22**) were inseparable by column chromatography.

**General synthetic method B (products 35, 37, 40, 41):**

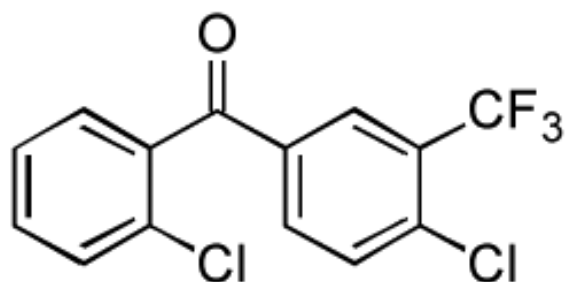
The trifluoromethyl-substituted arene (1 mmol) is dissolved in CHCl<sub>3</sub> (2 mL). Trifluoromethanesulfonic acid (2 mL) is then added. The mixture is then stirred for at least 4 hr. after which it is poured over several grams of ice. The solution is extracted twice with chloroform and the organic extracts are washed with water followed by brine (2x). The solution is dried over sodium sulfate and the products are isolated by removal of solvent.

**3-Hydroxy-5-(trifluoromethyl)benzophenone (18).**

MP 77-79°C (C<sub>6</sub>H<sub>6</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.82 (m, 2H), 7.65 (m, 1H), 7.55 (m, 4H), 7.27 (s, 1H), 6.89 (bs, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 196.1, 156.6, 139.5, 136.5, 133.4, 132.3 (q, *J*<sub>C-F</sub>=33 Hz), 130.2, 128.7, 123.3 (q, *J*<sub>C-F</sub>=271 Hz), 119.9, 119.0 (q, *J*<sub>C-F</sub>=4 Hz), 116.7 (q, *J*<sub>C-F</sub>=3 Hz). Low resolution mass spectroscopy (EI), *m/z*: 266 (M<sup>+</sup>), 189, 161, 105, 77. High resolution mass spectroscopy (EI), calcd, C<sub>14</sub>H<sub>9</sub>O<sub>2</sub>F<sub>3</sub> 266.05547, found 266.05635.

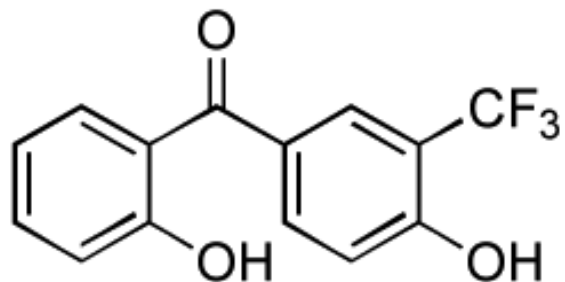
**2',4-Dichloro-3-(trifluoromethyl)benzophenone (38).<sup>13</sup>**

MP 138-139°C (hexanes). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.17 (s, 1H), 7.86 (dd, *J*=1.5, 8.0 Hz, 1H), 7.62 (d, *J*=8.0 Hz, 1H), 7.51-7.48 (m, 2H), 7.43-7.40 (m, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 192.9, 137.9, 137.2, 135.1, 134.0, 132.0, 132.0, 131.4, 130.4, 129.3, 129.2 (q, *J*<sub>C-F</sub>=32 Hz), 129.1 (q, *J*<sub>C-F</sub>=5 Hz), 127.1, 122.3 (q, *J*<sub>C-F</sub>=271 Hz). Low resolution mass spectroscopy (EI), *m/z*: 320/318 (M<sup>+</sup>), 209/207, 181/179, 141/139, 113/111. High resolution mass spectroscopy (EI), calcd, C<sub>14</sub>H<sub>9</sub>OF<sub>3</sub>Cl<sub>2</sub> 317.98262, found 317.98381.



### 2',4-Dihydroxy-3-(trifluoromethyl)benzophenone (39).

MP 77-79°C (CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.2 (s, 1H), 8.10 (dd, *J* = 0.4, 2.0 Hz, 1H), 7.76 (d, *J* = 1.9 Hz, 1H), 7.69-7.66 (m, 1H), 7.59-7.56 (m, 1H), 7.45-7.40 (m, 2H), 7.07 (d, *J* = 8.5 Hz, 1H), 7.02 (m, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 168.1, 162.3, 147.5, 136.9, 133.1, 130.6, 127.1 (q, *J*<sub>C-F</sub> = 4 Hz), 126.4, 124.3, 123.4 (q, *J*<sub>C-F</sub> = 31 Hz), 122.8 (q, *J*<sub>C-F</sub> = 271 Hz), 119.8, 117.9, 111.3. Low resolution mass spectroscopy (EI), *m/z*: 282 (M<sup>+</sup>), 162, 142, 121, 93. High resolution mass spectroscopy (EI), calcd, C<sub>14</sub>H<sub>9</sub>O<sub>3</sub>F<sub>3</sub> 282.05039, found 282.05132.



### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

### Acknowledgments

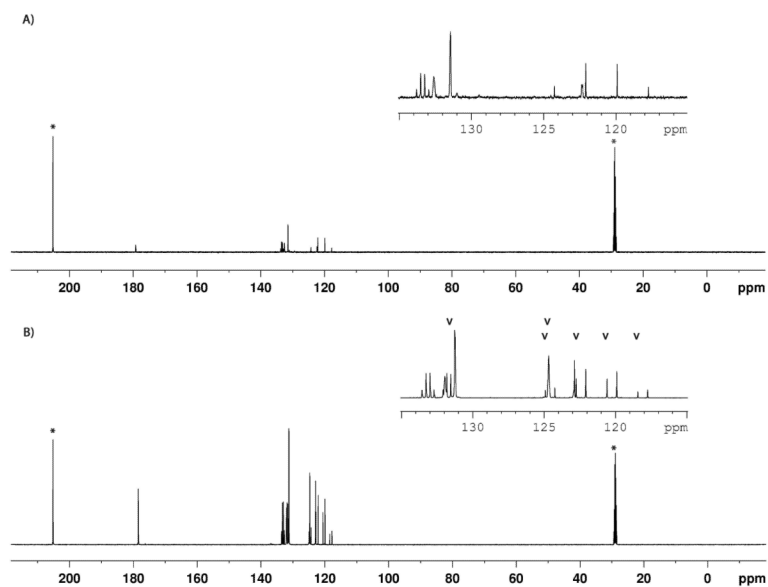
We gratefully acknowledge the support of the National Science Foundation (CHE-0749907) and the NIH-National Institute of General Medical Sciences (GM085736-01A1).

### Notes and references

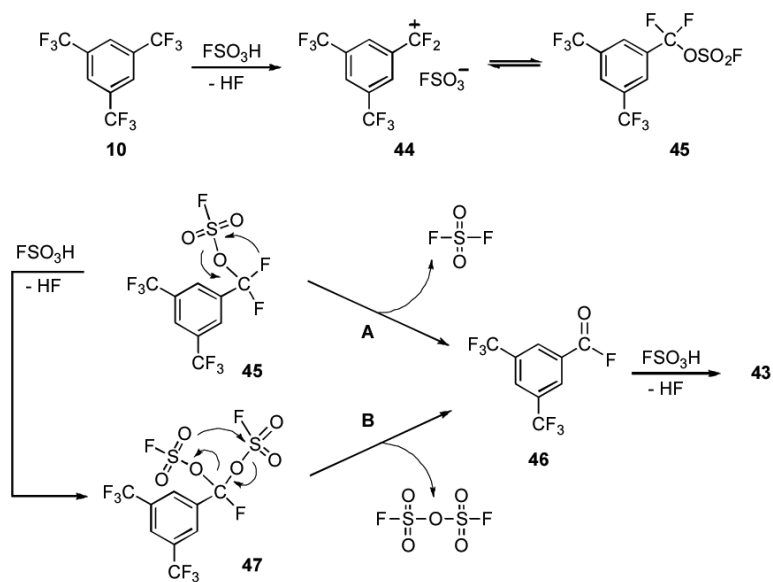
- (a) Kraft BM, Lachicotte RJ, Jones WD. *J. Am. Chem. Soc.* 2001; 123:10973. [PubMed: 11686701]  
(b) Meier G, Braun T. *Angew. Chem. Int. Ed.* 2009; 48:1546.(c) Kiplinger JL, Richmond TG, Osterberg CE. *Chem. Rev.* 1994; 94:373.
- Klahn M, Fischer C, Spannenberg A, Rosenthal U, Krossing I. *Tetrahedron Lett.* 2007; 48:8900.
- Schirok H, Paulsen H, Kroh W, Chen G, Gao P. *Org. Proc. Res. Dev.* 2010; 14:168.
- Hayakawa Y, Kimoto H, Cohen LA, Kirk KL. *J. Org. Chem.* 1998; 63:9448.
- Olah, GA.; Prakash, GKS. *Carbocation Chemistry*. Wiley; NY, NY: 2004.
- Amii H, Uneyama K. *Chem. Rev.* 2009; 109:2119. [PubMed: 19331346]
- (a) Abboud J-LM, Notario R, Ballesteros E, Herreros M, Mo O, Yanez M, Elguero J, Boyer G, Claramunt R. *J. Am. Chem. Soc.* 1994; 116:2486.(b) Hess BA Jr, Zahradnik R. *J. Am. Chem. Soc.* 1990; 112:5731.(c) Laerdahl JK, Covicir PU, Bache-Andreassen L, Uggerud E. *Org. Biomol. Chem.* 2006; 4:135. [PubMed: 16358008]

8. Aschi M, Chiavarino B, Crestoni ME, Fornarini S. *J. Phys. Chem.* 1996; 100:19859.
9. Zakzeski J, Fan IS, Bell AT. *Appl. Catal. A.* 2009; 360:33.
10. Wang F, Hu J. *Chin. J. Chem.* 2009; 27:27.
11. The same conversion was reported in ref. 10.
12. Le Fave GM. *J. Am. Chem. Soc.* 1949; 71:4148.
13. Product **38** is formed with a minor amount of a regioisomer (~95:5 ratio). Purification may be done by recrystallization from benzene.





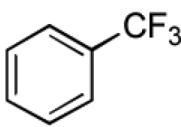
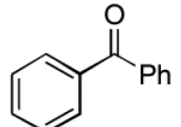
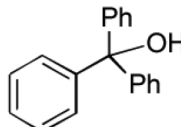
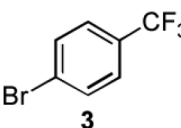
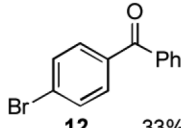
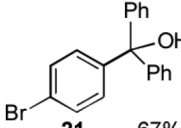
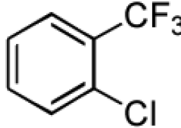
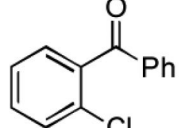
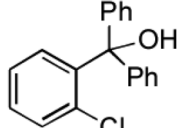
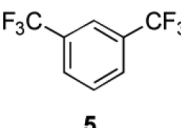
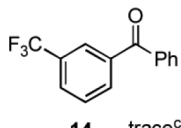
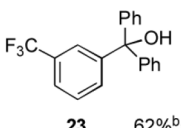
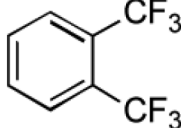
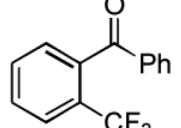
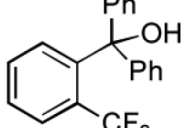
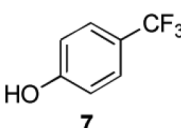
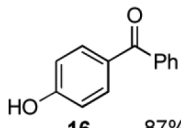
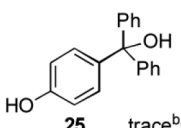
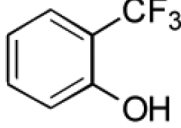
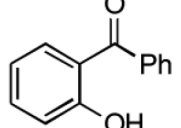
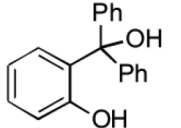
**Figure 1.**  $^{13}\text{C}$  NMR spectrum A: 3,5-bis(trifluoromethyl)benzoyl chloride (**42**) in  $\text{FSO}_3\text{H}$  with  $\text{d}_6$ -acetone external standard (labeled as \*);  $^{13}\text{C}$  NMR spectrum B: 1,3,5-tris(trifluoromethyl)benzene (**10**) in  $\text{FSO}_3\text{H}$  with  $\text{d}_6$ -acetone external standard (labeled as \*); peaks arising from unreacted **10** indicated by v designation).

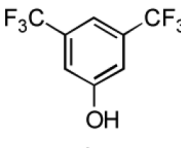
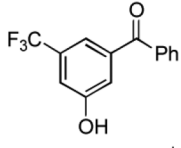
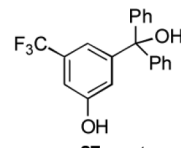
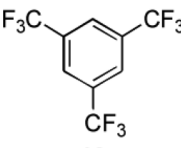
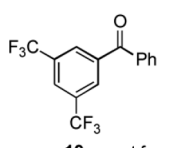
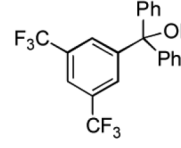
**Scheme 1.**

Proposed mechanism for the conversion of **10** to **43** in  $\text{FSO}_3\text{H}$ .

Table 1

Products and yields from the reactions of trifluoromethyl-substituted arenes with benzene in  $\text{CF}_3\text{SO}_3\text{H}$ .

Entry	Substrate	Products and Yields	
1	 <b>1</b>	 <b>11</b> 56% <sup>a</sup>	 <b>20</b> 44% <sup>a</sup>
2	 <b>3</b>	 <b>12</b> 33% <sup>a</sup>	 <b>21</b> 67% <sup>a</sup>
3	 <b>4</b>	 <b>13</b> 65% <sup>a</sup>	 <b>22</b> 35% <sup>a</sup>
4	 <b>5</b>	 <b>14</b> trace <sup>c,d</sup>	 <b>23</b> 62% <sup>b,d</sup>
5	 <b>6</b>	 <b>15</b> 84% <sup>b</sup>	 <b>24</b> trace <sup>c</sup>
6	 <b>7</b>	 <b>16</b> 87% <sup>b</sup>	 <b>25</b> trace <sup>b,c</sup>
7	 <b>8</b>	 <b>17</b> 75% <sup>b</sup>	 <b>26</b> trace <sup>b,c</sup>

Entry	Substrate	Products and Yields	
8		 <b>18</b> 79% <sup>b,e</sup>	 <b>27</b> trace <sup>c,e</sup>
9		 <b>19</b> not formed	 <b>28</b> 32% <sup>b</sup>

<sup>a</sup>Relative yield determined by GC-FID

<sup>b</sup>Isolated yield

<sup>c</sup>Detected by GCMS

<sup>d</sup>reaction done at 0°C

<sup>e</sup>reaction done at 80°C