Regioselective C–H Trifluoromethylation of Aromatic Compounds by Inclusion in Cyclodextrins

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ABSTRACT: A regioselective radical C–H trifluoromethylation of aromatic compounds was developed using cyclodextrins (CDs) as additives. The C–H trifluoromethylation proceeded with high regioselectivity to afford the product in good yield, even on the gram scale. In the presence of CDs, some substrates underwent a single trifluoromethylation selectively, whereas mixtures of single- and double-trifluoromethylated products were formed in the absence of the CD. ^{1}H NMR experiments indicated that the regioselectivity was controlled by the inclusion of a substrate inside the CD cavity.

Fluorinated functional groups, including the trifluoromethyl (CF_3) group, are among the most important functional groups in drugs, agrochemicals, and organic functional materials. The introduction of the CF_3 group(s) results in a dramatic improvement in the molecular properties of the compound, such as lipophilicity, metabolic stability, and bioavailability.[1] The ideal method for introducing the CF_3 group is direct C–H trifluoromethylation. Radical C–H trifluoromethylation of five-membered heteroaromatic compounds proceeds regioselectively to afford only single products.[2] On the other hand, radical C–H trifluoromethylation of six-membered heteroaromatic compounds proceeds at almost all possible reaction sites, and mixtures of regioisomers are formed.[2c,2d] We succeeded in the regioselective C–H trifluoromethylation and related reactions of six-membered heteroaromatic compounds using CF_3 and related anion sources.[3,4] However, regioselective C–H trifluoromethylation of aromatic compounds is more difficult than that of heteroaromatic substrates.

The CF_3 radical has generally been used in the C–H trifluoromethylation of aromatic compounds. Trifluoromethylation proceeds at various reaction sites to give mixtures of regioisomers (Figure 1a).[2a,5] Although there have been several reports on *ortho*-selective C–H trifluoromethylation of aromatic substrates using a directing group to control the regioselectivity, there are some drawbacks: (1) the reaction site is limited to the *ortho*-position of the substrates; and (2) it is difficult to remove the directing groups from the products after the reaction (Figure 1b).[6]

We hypothesized that regioselective C–H trifluoromethylation of aromatic compounds could be realized by protecting several reaction sites using a cyclic molecule as an additive (Figure 1c). In this reaction system, aromatic molecules are included inside the cavity of the cyclic molecule, which protects some potential reaction sites.[7] Herein, we report the regioselective C–H trifluoromethylation of multisubstituted aromatic compounds using cyclodextrins (CDs) as the cyclic molecules, even on the gram scale. Single trifluoromethylation of the substrates proceeded selectively in the presence of the CD, whereas both single and double trifluoromethylation occurred in the absence of the CD. ^{1}H NMR experiments suggested the inclusion of aromatic substrates inside the CD cavity.

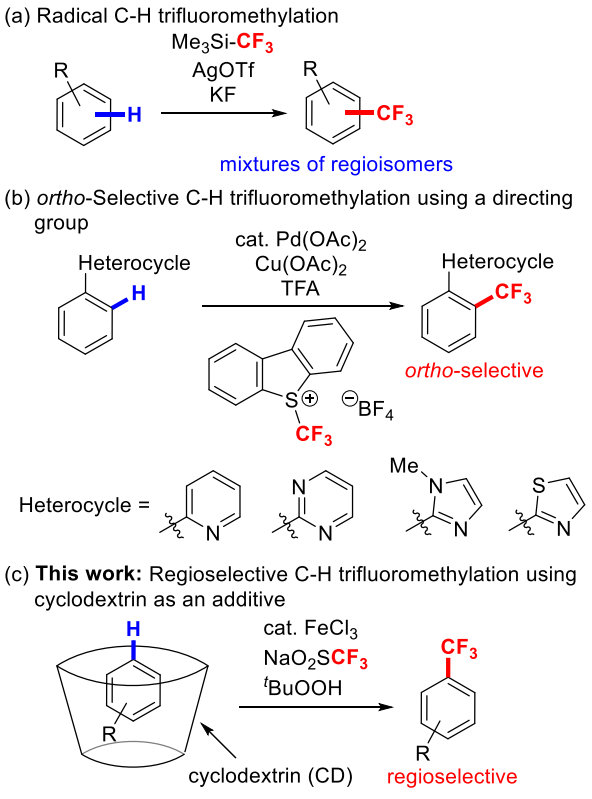
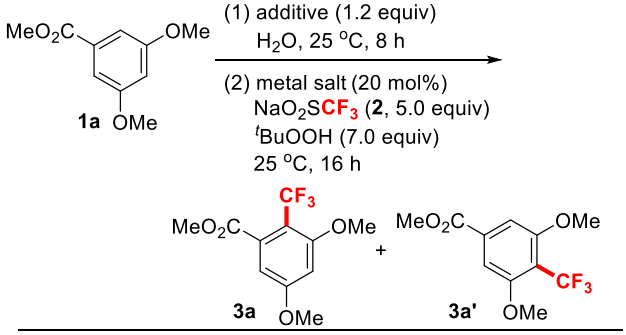


Figure 1. Several examples of C–H trifluoromethylation of aromatic compounds.

The difficulty in promoting regioselective radical C–H trifluoromethylation of aromatic compounds stems from the high reactivity of the CF_3 radical and the occurrence of the reaction at various sites. Treatment of aromatic substrate **1a** with NaO_2SCF_3 (**2**) and ^{t}BuOOH in the presence of $Cu(OTf)_2$ as a catalyst in H_2O afforded a mixture of trifluoromethylated product **3a** and its regioisomer **3a′** in 56% combined yield (**3a**/**3a′** = 2.2) (Table 1, entry 1).[8] We considered the use of cyclic compounds as additives to protect some potential reaction sites of **1a** sterically and thus promote regioselective C–H trifluoromethylation. Although several cyclic compounds such as calixarenes and pillararenes could be considered as candidates, C–H trifluoromethylation may also occur at the aromatic rings of these compounds. Therefore, we selected CDs because they are inexpensive and highly water-soluble, and do not contain any aromatic rings. We screened α-, β-, and γ-CDs (Table 1, entries 2–4), and achieved the best results with β-CD; that is, the ratio of trifluoromethylated product (**3a**/**3a′**) was improved to 5.1 (Table 1, entry 3). These results clearly showed that the size of the cyclic compound is important for controlling the regioselectivity. Next, several first-row transition metal salts were screened (Table 1, entries 5–11). In several entries, the yield of (**3a** + **3a′**) and the ratio (**3a**/**3a′**) were improved, and the best result was obtained when using a catalytic amount of $FeCl_3$ (Table 1, entry 6). Therefore, we performed the subsequent experiments using $FeCl_3$ as the catalyst.

Table 1. Investigation of Cyclodextrins and Several Transition Metal Salts[a]

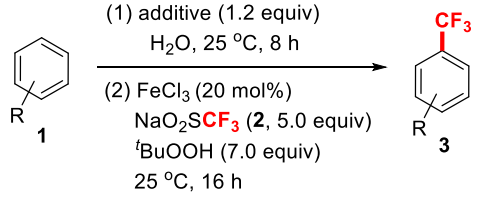


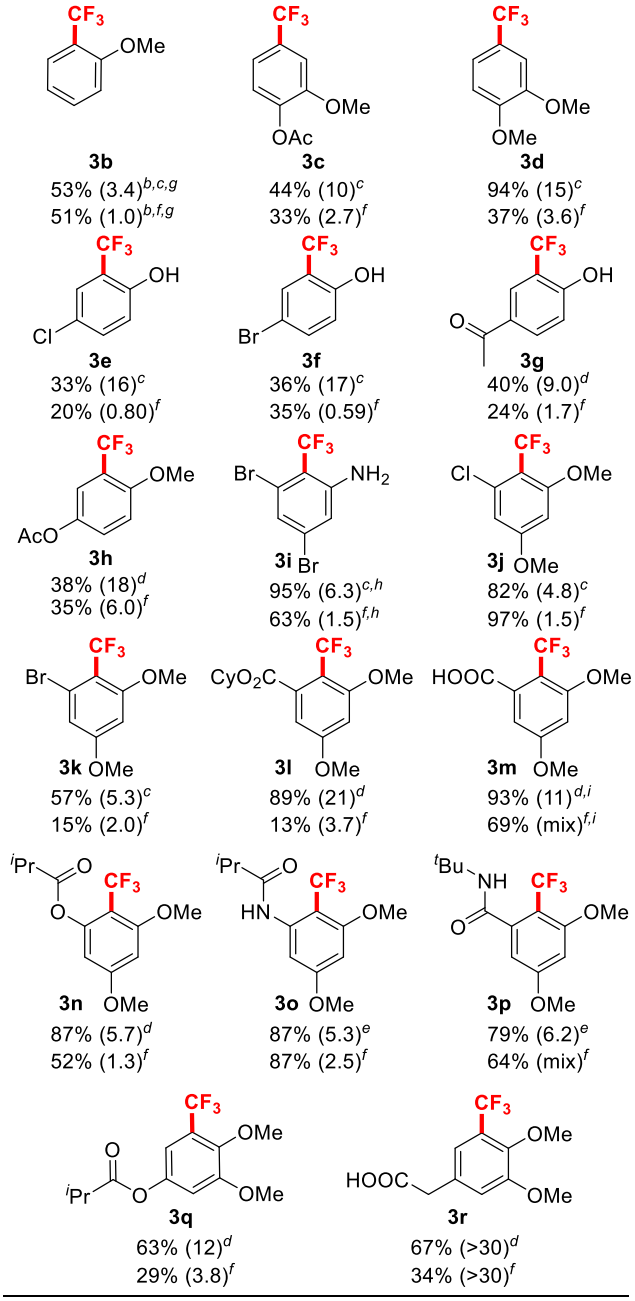
entry	additive	metal salt	yield / % (**3a**/**3a′**)
1	none	none	56 (2.2)
2	α-CD	none	55 (1.6)
3	β-CD	none	61 (5.1)
4	γ-CD	none	48 (4.4)
5	β-CD	$MnCl_2$	38 (6.0)
6	β-CD	$FeCl_3$	99 (19)
7	β-CD	$Fe(NO_3)_3$	91 (10)
8	β-CD	$CoCl_2$	46 (4.8)
9	β-CD	$NiCl_2{\cdot}6H_2O$	77 (4.2)
10	β-CD	$CuCl_2$	92 (8.1)
11	β-CD	$Cu(OTf)_2$	93 (6.7)

[a] Yield was determined by ^{19}F NMR using 2,2,2-trifluoroethanol as an internal standard. The ratio between trifluoromethylated product **3** and its regioisomer **3a′** (**3**/**3a′**) is described in parentheses.

We then investigated the substrate scope of the aromatic compounds (Table 2). The suitable size of

Table 2. Substrate Scope: Control of Regioselectivity[a]





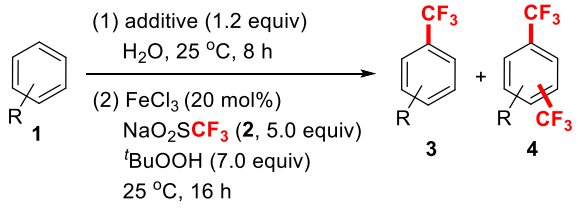
[a] Yield was determined by ^{19}F NMR using 2,2,2-trifluoroethanol as an internal standard. The ratio between trifluoromethylated product **3** and its regioisomer(s) **3a′** (**3**/**3a′**) is described in parentheses. [b] Solvent: H_2O:MeCN (5/1). [c] With α-cyclodextrin. [d] With β-cyclodextrin. [e] With γ-cyclodextrin. [f] Without cyclodextrin. [g] Catalyst: $Cu(OTf)_2$ instead of $FeCl_3$; Solvent: aqueous urea (0.10 M).[10] [h] Catalyst: $Cu(OTf)_2$ instead of $FeCl_3$. [i] Catalyst: $Cu(OTf)_2$ instead of $FeCl_3$; Solvent: H_2O:MeCN (5/1).

cyclodextrins existed depending on the size of substrates. The general trend was as follows: mono-substituted substrates, α-CD; di-substituted substrates, α- or β-CD; and tri-substituted substrates, β- or γ-CD. In all cases, the selectivity of the major products was improved dramatically when using CDs, and regioselective trifluoromethylation proceeded with good functional group tolerance. The yields of the trifluoromethylated products increased in several cases, probably owing to the improved solubility of the substrates.

The regioselectivity of trifluoromethylated anisole **3b** was improved by the addition of α-CD, and *ortho*-trifluoromethylated product **3b** was obtained as the major product.[9] In the case of 1,2- and 1,4-disubstituted aromatic compounds, C–H trifluoromethylation proceeded regioselectively when using α- or β-CD, and the corresponding trifluoromethylated aromatic compounds **3c–3h** were obtained in moderate to excellent yields with high regioselectivity. C–H trifluoromethylation of 1,3,5- and 1,2,4-trisubstituted aromatic compounds also proceeded regioselectively in the presence of β- or γ-CD, and trifluoromethylated compounds **3i–3r** were obtained in moderate to excellent yields.

Several substrates afforded a mixture of mono- and di-trifluoromethylated products **3** and **4** in the absence of CDs (Table 3). On the other hand, the ratio of mono-trifluoromethylated products **3s–3u** increased dramatically when β-CD was used, and good product yields (63%–94%) and high mono-selectivity were achieved. These results indicated that the CD protected the second reaction site by inclusion of the substrates.

Table 3. Substrate Scope: Single Trifluoromethylation[a]

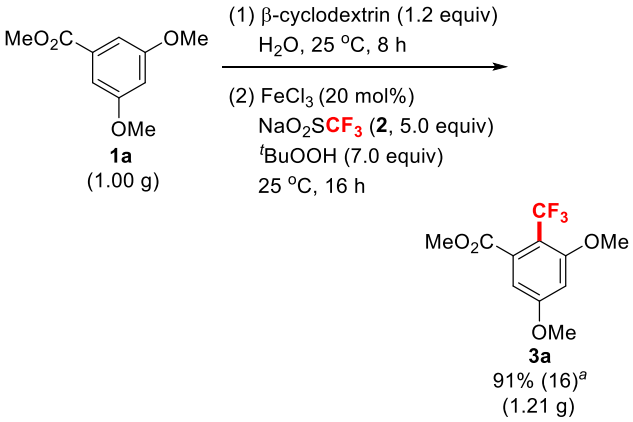


3s	3t	3u
63% (>30)[b]	92% (>30)[b,d]	94% (12)[b,d]
44% (3.4)[c]	95% (4.3)[c,d]	93% (2.6)[c,d]

[a]Yield was determined by ^{19}F NMR using 2,2,2-trifluoroethanol as an internal standard. The ratio between single trifluoromethylated product **3** and double trifluoromethylated product(s) **4** (**3**/**4**) is described in parentheses. [b]With β-cyclodextrin. [c]Without β-cyclodextrin. [d]Catalyst: $Cu(OTf)_2$ instead of $FeCl_3$; solvent: H_2O:MeCN (5/1).

Trifluoromethylation proceeded in excellent yield with high regioselectivity, even on the gram scale (Scheme 1). Treatment of a mixture of 1.00 g of **1a** and β-CD in H_2O with **2**, ^{t}BuOOH, and a catalytic amount of $FeCl_3$ at 25 °C gave 1.21 g of trifluoromethylated product **3a** in 91% yield (**3a**/**3a′** = 16).

Scheme 1. Gram-scale Synthesis of **3a**



[a]The ratio between trifluoromethylated product **3a** and its regioisomer **3a'** (**3a**/**3a'**) is described in parentheses.

To confirm the inclusion of aromatic substrates inside the cavity of the CD in water, ^1H NMR experiments were conducted in D_2O at the same concentration as the reaction mixture (Figures 2 and 3). Proton signals of the aromatic region of 4-chlorophenol (**1e**) were downfield-shifted by the addition of α-CD (Figure 2).[11] In addition, a change in the chemical shifts of the proton signals of α-CD was observed upon the addition of **1e** (Figure 3).[11] These results clearly suggested that **1e** was included inside the cavity of α-CD in water.

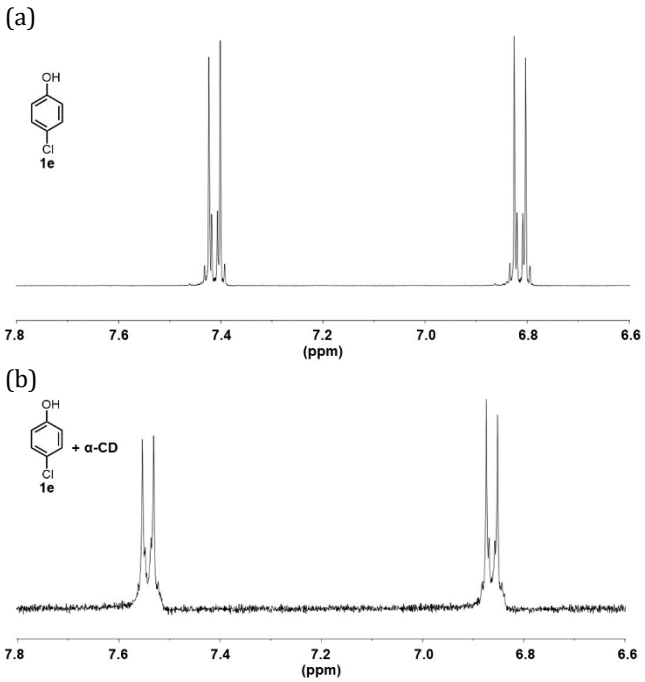


Figure 2. Partial ^1H NMR spectrum of (a) 4-chlorophenol (0.010 mmol/mL in D_2O) and (b) 4-chlorophenol and α-CD (0.010 mmol/mL in D_2O).

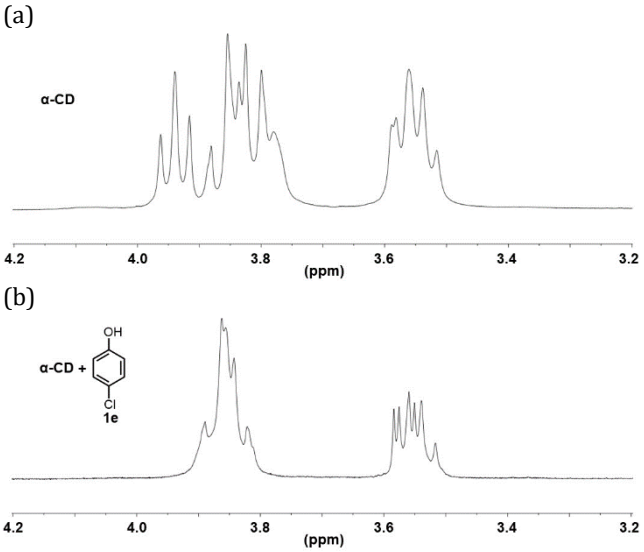


Figure 3. Partial ^{1}H NMR spectrum of (a) α-CD (0.010 mmol/mL in D_2O) and (b) α-CD and 4-chlorophenol (0.010 mmol/mL in D_2O).

In summary, we have successfully developed a regioselective C–H trifluoromethylation of aromatic compounds using CDs as additives. The selectivity of the major products was improved dramatically in the presence of the CDs, and regioselective trifluoromethylation proceeded with good functional group tolerance, even on the gram scale. The general trend for the suitability of the CDs was as follows: mono-substituted substrates, α-CD; di-substituted substrates, α- or β-CD; and tri-substituted substrates, β- or γ-CD. Mono-trifluoromethylated products were obtained selectively in the presence of the CD, whereas several aromatic substrates gave mixtures of mono- and di-trifluoromethylated products. The results of the ^{1}H NMR experiments indicated that the aromatic substrate was present inside the cavity of the CD in water. The use of cyclic compounds such as CDs is expected to be a useful and efficient strategy to control the regioselectivity in C–H transformations.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge at ##########################.

General experimental procedure and characterization data for products.

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Notes

The authors declare no competing financial interests.

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