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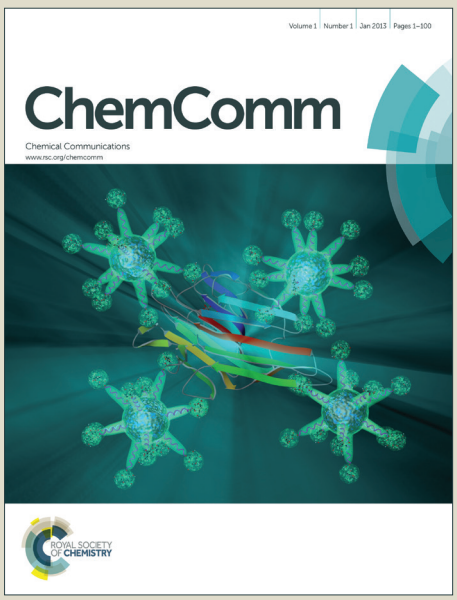

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Benzylic C–H trifluoromethylation of phenol derivatives

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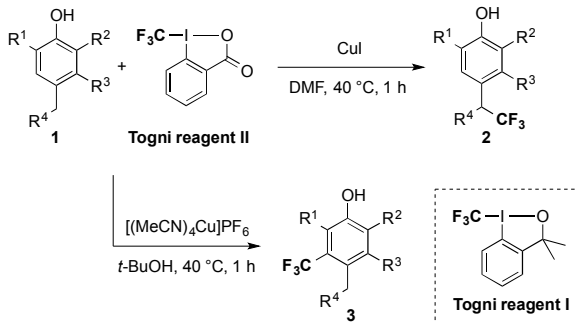
Phenol derivatives were trifluoromethylated using copper/Togni reagent. In dimethylformamide, the benzylic C–H bond at the *para* position of the hydroxyl group was selectively substituted with a CF_3 group. In contrast, aromatic C–H trifluoromethylation occurred in alcoholic solvents. Practical utility of the reactions was demonstrated by application to the synthesis of a potent enoyl-acyl carrier protein reductase (FabI) inhibitor.

Introduction of trifluoromethyl group(s) into organic molecules often results in significant improvements in metabolic stability, hydrophobicity, and lipophilicity.[1,2] Thus, trifluoromethyl substitution has attracted much attention in the pharmaceutical and agrochemical fields, and the development of efficient trifluoromethylation methodology is of continuing interest.[3]

Although phenols are widely found as structural components of bioactive compounds, only a few attempts to introduce a CF_3 group into phenols have been reported. In 2008, Togni and co-workers disclosed a trifluoromethylation of sodium phenolate derivatives.[4] However, the reaction was hard to control and various types of by-products were formed. They also fortuitously found that reaction of 2,4,6-trimethylphenol with Togni reagent I[3j,5] gave a C_{sp3}–H trifluoromethylated product.[4] However, only one substrate was examined, and neither the reaction time (4 days) nor the chemical yield was practically useful.

To date, various types of trifluoromethylation have been reported in the literature.[3] Among them, direct C–H trifluoromethylation is the most atom-economical strategy. Compared to aromatic C–H substitution reactions via either metal-catalyzed C–H activation[6] or addition of a trifluoromethyl radical[7], direct C_{sp3}–H trifluoromethylation has been less well studied.[8] During the course of our investigations on trifluoromethylation chemistry,[9] we found two types of solvent-dependent trifluoromethylation of phenols (Scheme 1). Herein, we describe Cu-catalyzed benzylic C_{sp3}–H and aromatic C_{sp2}–H trifluoromethylation of substituted phenol derivatives, using Togni reagent II.[3j,10]



Scheme 1 This work: C–H trifluoromethylations.

For screening of the reaction conditions, we selected phenol derivative **1a** bearing two methyl groups at the *ortho*- and *para*-positions and a *tert*-butyl group at the other *ortho*-position as a test substrate (Table 1). Preliminary experiments revealed that reactions of less substituted phenols tended to involve undesired side reactions, including oxidative dimerization and oligomerization, due to higher reactivity of *ortho* and *para* positions of phenols. The bulky *tert*-butyl group was introduced to suppress such undesired reactions, since the *tert*-butyl group can be removed under acidic conditions (*vide infra*). First, various metal salts were tested in CH_2Cl_2 at 40 °C (entries 1-7). The reaction proceeded cleanly in the presence of 20 mol % of CuI or CuOAc. It should be noted that a CF_3 group was selectively incorporated at the *para*-methyl group to give **2a** in 65 and 63% yield, respectively (entries 1 and 4); substitution at the *ortho*-methyl group and at the aromatic C–H group was negligible. Interestingly, a divalent copper species, $Cu(OAc)_2$, afforded **2a** in 78% yield (entry 5). On the other hand, the reaction did not proceed with iron salts (entry 7). MeCN, DMSO, and NMP were found to be good solvents (entries 8-10). Among the solvents screened, DMF was the solvent of choice, and **2a** was isolated in excellent yield (93%) under the described conditions (entry 11). In

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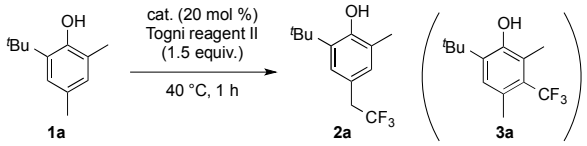
contrast, the use of MeOH resulted in formation of the aromatic trifluoromethylation product **3a** as the major product (entry 14). While both monovalent and divalent copper species were equally effective catalysts in CH_2Cl_2, CuI gave a better yield than $Cu(OAc)_2$ in DMF (entries 11 and 12). It is noteworthy that 10 mol % of CuI was enough for this transformation; no reaction occurred in the absence of copper catalyst (entries 13,15).

Table 1 Screening of the reaction conditions[a]

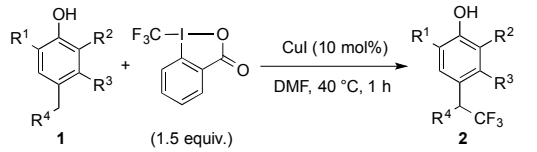


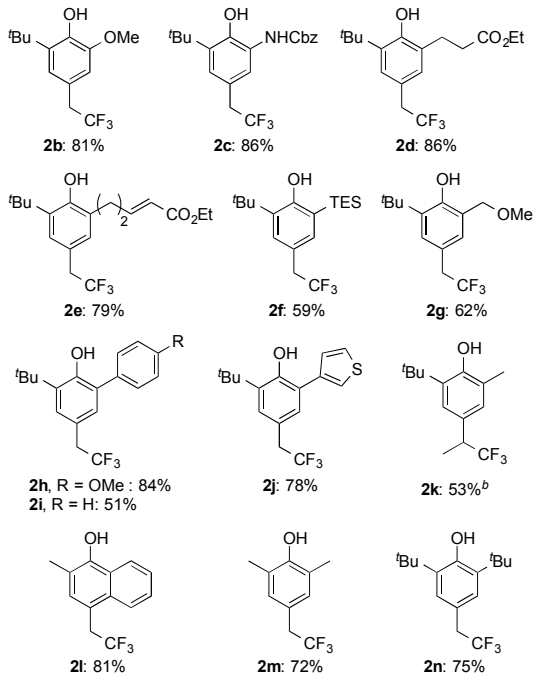
Entry	Catalyst	Solvent	Yield of **2a** (%)[b]
1	CuI	CH_2Cl_2	65
2	$[(MeCN)_4Cu]PF_6$	CH_2Cl_2	38
3	CuTc	CH_2Cl_2	51
4	CuOAc	CH_2Cl_2	63
5	$Cu(OAc)_2$	CH_2Cl_2	78
6	$Cu(OTf)_2$	CH_2Cl_2	28
7	$Fe(OAc)_2$	CH_2Cl_2	trace
8	CuI	MeCN	72
9	CuI	DMSO	50
10	CuI	NMP	61
11	CuI	DMF	93[c]
12	$Cu(OAc)_2$	DMF	83
13[d]	CuI	DMF	93[c]
14	CuI	MeOH	5[e]
15	-	DMF	N.R.[f]

[a] The reactions were carried out with catalyst (20 mol %) and Togni reagent II (1.5 equiv.) at 40 °C for 1 h on a 0.2 mmol scale, unless otherwise mentioned. [b] Determined by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield. [d] Run with 10 mol % CuI. [e] Compound **3a** was obtained in 25% yield. [f] No reaction.

Having established the optimal reaction conditions, the scope of the reaction was investigated by using various phenol derivatives (Table 2). Phenols having an electron-donating heteroatom group were good substrates, and **2b** and **2c** were obtained in high yields. Various functional groups, such as ester, α,β-unsaturated ester and silyl, were tolerated in the reaction (**2d-f**). C–H trifluoromethylation at the *para*-benzylic position of the phenols occurred in preference to aromatic trifluoromethylation under our reaction conditions, even for substrates with another aromatic ring (**2h-j**). Encouraged by these results, we investigated the reaction of **1k** having a secondary alkyl C–H bond. Although the reaction became slower, probably due to steric repulsion, an acceptable yield was obtained when the reaction was carried out at 90 °C. The presence of a *tert*-butyl group is not essential, and reactions of naphthyl substrate **1l** and 2,4,6-trimethylphenol **1m** proceeded smoothly to afford the corresponding products **2l** and **2m** in 81 and 72% yield, respectively. In addition, 2,6-di-*tert*-butyl-4-methylphenol (BHT), which is a well-known radical scavenger that has been used for mechanistic studies of several trifluoromethylation reactions, was also a good substrate of our reaction (**2n**).

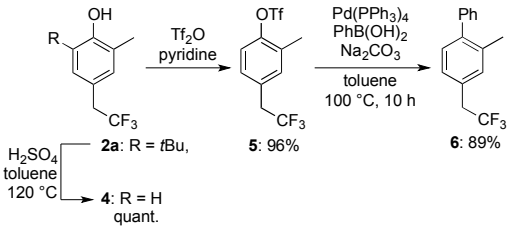
Table 2 Substrate scope[a]





[a] The reactions were carried out with CuI (10 mol %) and Togni reagent II (1.5 equiv.) in DMF at 40 °C for 1 h on a 0.2 mmol scale, unless otherwise mentioned. [b] Run at 90 °C.

To confirm the usefulness of the present reaction, we examined transformation of the product **2a** (Scheme 2). The *tert*-butyl group was readily removed under acidic conditions to give **4** in quantitative yield. After triflation, Suzuki-Miyaura cross-coupling reaction was conducted under the described conditions, giving **6** in 89% yield.



Scheme 2 Further transformations of the product.

We also applied this reaction to achieve an efficient synthesis of a potent enoyl-acyl carrier protein reductase (FabI) inhibitor **9**, which is effective against resistant bacteria[11] (Scheme 3). Thus, starting from **2b**, removal of the *tert*-butyl

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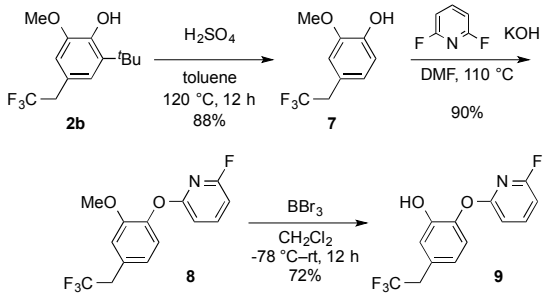
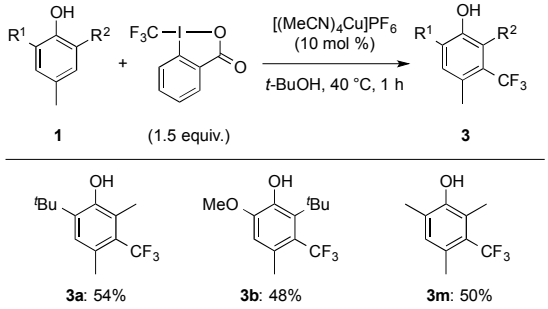
group gave compound **7** in 88% yield. Simple addition reaction of the obtained phenol **7** to 2,6-difluoropyridine provided diaryl ether **8** in good yield under basic conditions. Finally, the methyl group was removed by treatment with BBr_3, affording the target compound **9** in 72% yield.



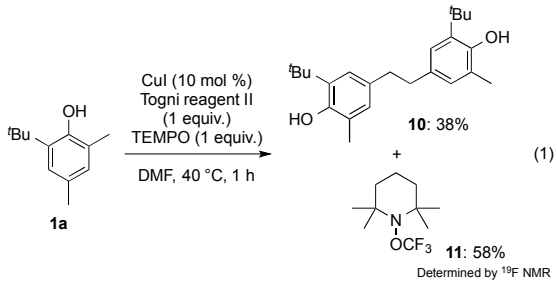
Scheme 3 Synthesis of a potent FabI inhibitor **9**.

As described above (Table 1, entry 14), the reaction pathway changed when MeOH was used as the solvent.[12] This solvent-dependent product switching seems general, and may be due to competitive decomplexation of the putative Cu phenoxide with a large excess of the alcoholic solvent (*vide infra*). Although the chemical yield should be improved, *meta*-substituted compounds **3a**, **3b**, and **3m** were obtained as major products in moderate yield (Scheme 4).

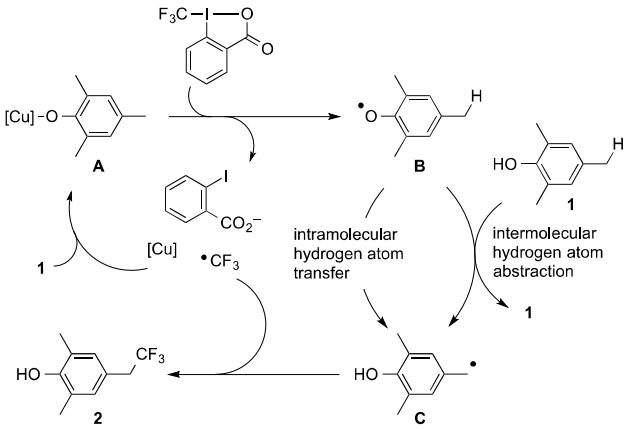


Scheme 4 Aromatic C–H trifluoromethylation.

To obtain information regarding the reaction mechanism, we examined the reaction in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), a well-known radical-trapping reagent (eq 1). In this case, 38% of dimer product **10** was isolated together with 58% of TEMPO-CF_3 adduct **11**, while trifluoromethylation product **2a** was obtained in only 8% yield. Although the **1a**-TEMPO adduct was not detected, formation of dimer product **10** suggests that the benzyl radical intermediate might be involved in the reaction cycle. In accordance with this idea, a small amount of **10** was detected in the crude mixture when solvents other than DMF were used (Table 1). On the other hand, the reaction of the corresponding methyl ether derivative having no phenolic hydroxyl group did not proceed, indicating that the phenolic hydroxyl group plays a critical role in this trifluoromethylation.



Based on the above results, we consider that the mechanism of the benzylic C_{sp3}–H trifluoromethylation is as illustrated in Scheme 5. The active copper ion seems to be the divalent species,[13] since $Cu(OAc)_2$ was also a good catalyst (Table 1, entry 12). Treatment of CuI with phenol **1** in the presence of Togni reagent may provide copper(II)-phenoxide complex **A**. This complex **A** would be oxidized by Togni reagent to afford a phenoxy radical species **B** with simultaneous formation of a trifluoromethyl radical equivalent. Then, this phenoxy radical abstracts a hydrogen atom at the *para*-benzylic position of another phenol in an intermolecular fashion, affording intermediate **C**. An alternative possibility would be intramolecular hydrogen atom transfer from the *para*-benzylic position to the oxygen radical.[14] Since the *O*-trifluoromethylated product was not detected in the present reaction, we speculate that the hydrogen atom transfer step is much faster than *O*-trifluoromethylation between the phenoxyl radical and the trifluoromethyl radical, probably due to steric hindrance of *ortho*-substituents.[15] The rate of hydrogen atom abstraction is presumed to be sensitive to steric hindrance, which might be one of the reasons for the site-selectivity of the reaction. The resulting benzylic radical would react with a trifluoromethyl radical equivalent, affording the corresponding product.



Scheme 5 Proposed catalytic cycle for benzylic C-H trifluoromethylation of phenols.

In summary, we have developed a catalytic C–H trifluoromethylation at the *para*-benzylic position of phenol derivatives using a Cu catalyst and Togni reagent II. The solvent is critical in terms of product switching; the reaction in *t*-BuOH provides aromatic C-H trifluoromethylation products, while

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benzylic C–H trifluoromethylation occurs preferentially in other solvents. Further transformation of the products and application of the reaction to the synthesis of a potent FabI inhibitor were demonstrated. Previously, a trifluoroethyl unit on an aryl ring has been constructed by either 1) cross-coupling reaction of a 1,1,1-trifluoroethyl unit with aryl halide[16] or 2) substitution reaction of benzyl halide and alcohol derivative with a trifluoromethyl anion equivalent.[17,18] The present work provides an alternative method to synthesize such compounds. Further details, including an examination of the scope of this reaction, will be reported in due course.

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13 It cannot be ruled out that a Cu (I) species generated through reduction of the Cu(II) species by phenol participates in the reaction cycle.

14 We cannot rule out the possibility that a carboxyl radical derived from reduction of Togni reagent II by Cu(I) species may abstract the hydrogen atom.

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