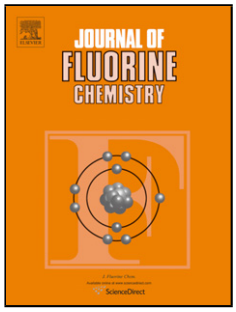

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Ligand-Free Trifluoromethylation of Iodoarenes by Use of 2-Aryl-2-trifluoromethylbenzimidazoline as New Trifluoromethylating Reagent

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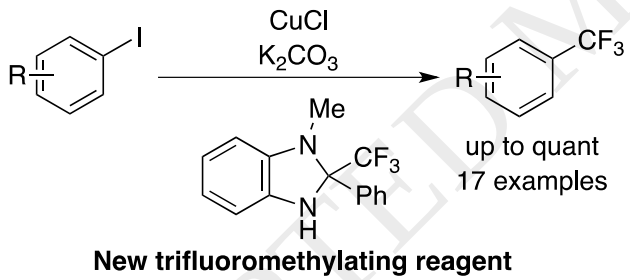
Graphical abstract



Highlights

- ・New trifluoromethylating reagent
- ・Relatively wide functional group tolerance
- ・Cu(I)-catalyzed trifluomethylation in the absence of ligand

Abstract

N-Methyl 2-aryl-2-trifluoromethylbenzimidazolines were synthesized and utilized in the

trifluoromethylation reaction of iodoarenes in the presence of copper(I) salt and base. Iodoarenes bearing electron-donating and electron-withdrawing groups were tolerant to this reaction in the absence of a ligand and gave trifluorotoluene derivatives in good to high yields.

The development of novel methods for the construction of fluorine-containing compounds is an important topic of research interest in organic chemistry because more than 20% of pharmaceuticals and agrochemicals contain fluorine atoms [1]. The trifluoromethyl group, in particular, possesses beneficial characteristics, such as high lipophilicity, permeability, and metabolic stability [2]. Much effort has been exerted in the development of novel trifluoromethylation reactions and trifluoromethylating reagents, [3] the latter of which are divided into nucleophilic [4], electrophilic [5], and radical trifluoromethylating reagents [6]. As interest in trifluoromethylated compounds has surged, the development of new types of trifluoromethylating reagents is desired for the syntheses of useful trifluoromethylated compounds.

Iodoarene is the representative substrate in trifluoromethylation reactions [7–10]. In metal-mediated trifluoromethylation reactions, copper salt is most commonly used because of the ease of generation of trifluoromethylcopper species. Chen's group firstly reported the trifluoromethylation of iodoarenes with copper(I) catalyst in which trifluoromethylcopper was the reactive species [11]. Thereafter, a variety of trifluoromethylating reagents, including the Ruppert-Prakash reagent [7], trifluoroacetate salt [8], fluoroform [9], and others [10], were synthesized and used in the trifluoromethylation reaction with copper(I) salt.

We reported an enantioselective transfer hydrogenation reaction of ketimines where benzothiazoline is used as the hydrogen donor in combination with a chiral phosphoric acid [12]. The aromatization of benzothiazoline to yield benzothiazole is the driving force of the reaction. We hypothesized that a trifluoromethyl group would be transferred from benzothiazoline derivatives to other molecules (Figure 1). Based on this hypothesis, we synthesized 2-aryl-2-trifluoromethylbenzimidazolines and evaluated them as a new type of trifluoromethylating reagent. The advantage of this new reagent includes easy synthesis and handling, low cost, no volatility, and moisture and air stability. In addition, trifluoromethyl source of the reagent is 2,2,2-trifluoroacetophenone which is stable and commercially available and one of the most economical and efficient trifluoromethyl source but rarely used as versatile trifluoromethylating reagent [10c]. We describe herein the ligand-free

trifluoromethylation of iodoarenes by use of 2-aryl-2-trifluoromethylbenzimidazoline in the presence of copper(I) salt.

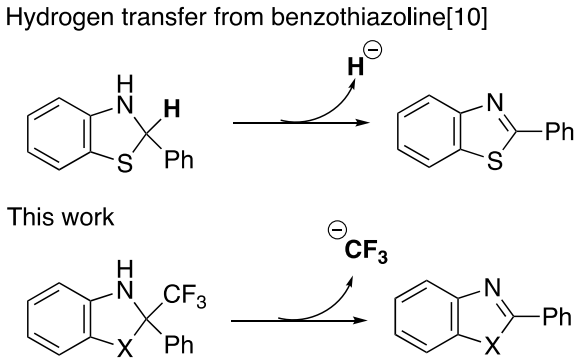
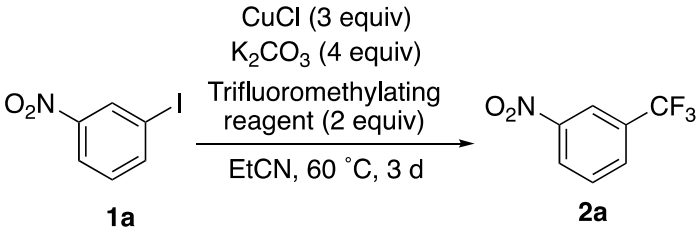
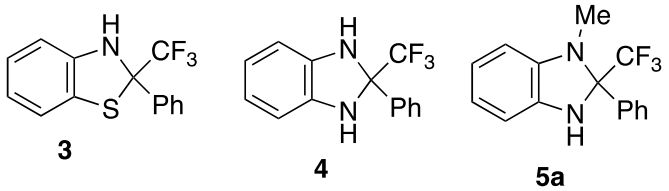


Figure 1. Transfer of trifluoromethyl group by aromatization.

We commenced with the development of a new trifluoromethylating reagent (Table 1). We synthesized benzothiazoline **3** and benzimidazoline **4** by mixing 2,2,2-trifluoroacetophenone and 2-aminobenzenethiol or 1,2-phenylenediamine in autoclave conditions, respectively, and attempted to carry out the trifluoromethylation reaction of 3-nitro-1-iodobenzene (**1a**) in the presence of copper(I) chloride and potassium carbonate. However, the yields of 3-trifluoromethyl-1-nitrobenzene (**2a**) were very low. The attempted reaction with **4** furnished 2*H*-benzimidazole **6** in 35% yield, and **1a** and **4** were recovered in 100% and 28% yield, respectively (Scheme 1). This indicates that the conversion of **4** hardly proceeded and the hydrogen transfer reaction competed with the trifluoromethyl group transfer reaction. Thus, a methyl group was introduced to the nitrogen atom in **4** to suppress the hydrogen transfer from the benzimidazoline skeleton [13]. When *N*-methyl 2-phenyl-2-trifluoromethylbenzimidazoline (**5a**) was applied to the trifluoromethylation reaction, desired product **2a** was generated in 49% yield. Gratifyingly, a new trifluoromethylating reagent was developed by employing a benzimidazoline skeleton.

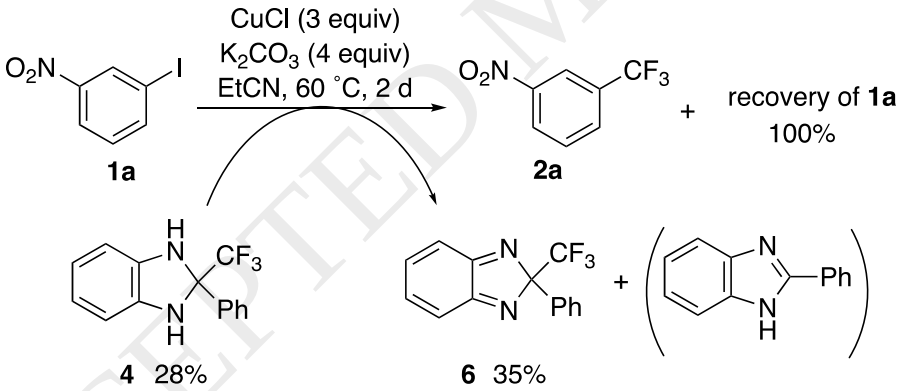
Table 1. Examination of trifluoromethylating reagents.





Entry	Trifluoromethylating reagent	Yield of **2a** (%)[b)]
1	**3**	0
2	**4**	5
3	**5a**	49

a) Reaction conditions: **1a** (0.10 mmol), trifluoromethylating reagent (0.20 mmol), copper chloride (0.30 mmol), potassium carbonate (0.40 mmol), and propionitrile (1.0 mL). b) NMR yields based on ^{19}F NMR measurement.

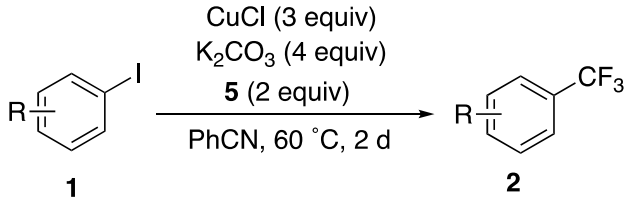


Scheme 1. Formation of 2*H*-benzimidazole from benzimidazoline.

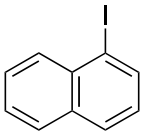
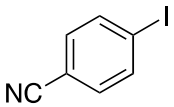
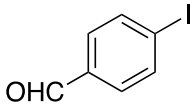
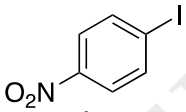
Then, we optimized the reaction conditions and continued our investigation of the 2-substituents of **5**. 4-Fluorophenyl and 4-methoxyphenyl groups were introduced to *N*-methylbenzimidazoline because we speculated that the electron-withdrawing and electron-donating properties would have an influence on the transfer reaction of the trifluoromethyl group. In particular, we expected that the introduction of a 4-methoxyphenyl group at 2-position would accelerate the transfer of the trifluoromethyl group. We examined

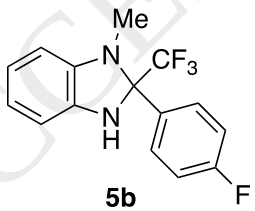
5a–**c** in the reactions with 1-iodonaphthalene (**1b**) and 4-cyano- (**1c**), 4-formyl- (**1d**), and 4-nitro-1-iodobenzenes (**1e**). Remarkable changes in yields were not observed, indicating that the substituents on benzimidazoline did not have an impact on the trifluoromethyl group transfer.

Table 2. Screening for 2-substituents of *N*-methylbenzimidazoline.

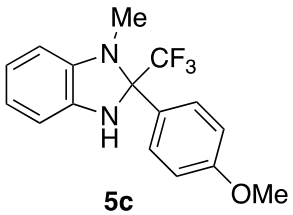


1 **2**

1	Trifluoromethylating reagent	Yield (%)[b]
 **1b**	**5a**	70
	5b	80
	5c	72
 **1c**	**5a**	89
	5b	83
	5c	88
 **1d**	**5a**	58
	5b	70
	5c	71
 **1e**	**5a**	quant
	5b	93
	5c	89



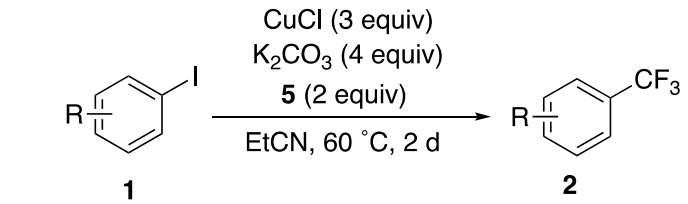
5b

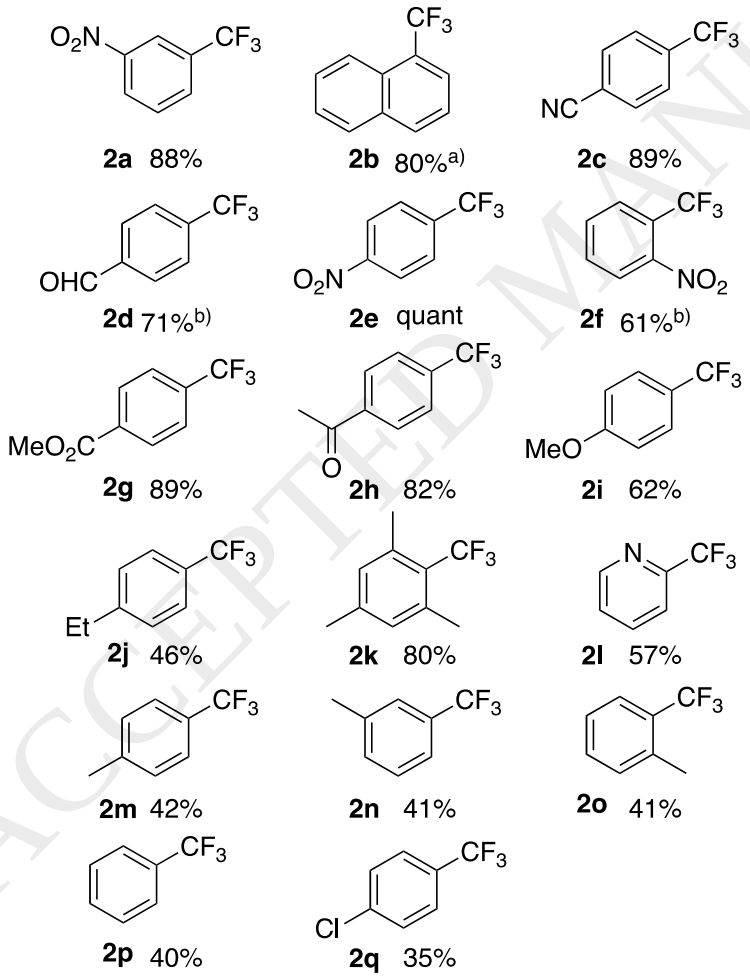


5c

With the optimized reaction conditions in hand, we studied the substrate scope of iodoarenes (Scheme 2). The trifluoromethylation reaction using benzimidazoline had wide functional group tolerance. Iodoarenes having electron-withdrawing groups, such as nitro, cyano, ester, formyl, and carbonyl groups, gave trifluoromethylated products **2c**–**h** in good

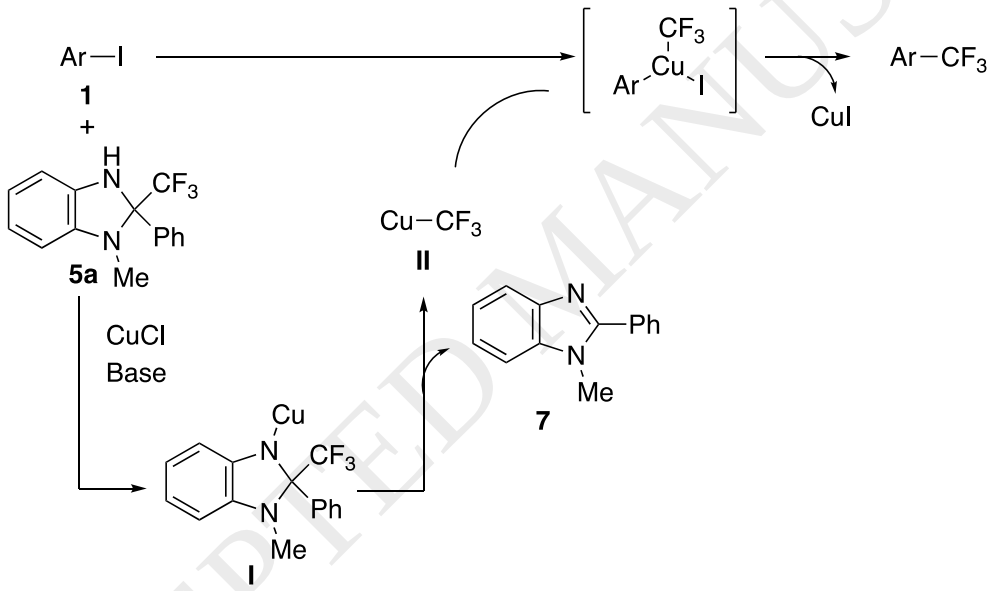
to excellent yields. On the other hand, the reaction of iodoarenes bearing electron-donating groups provided corresponding trifluorotoluenes **2i**–**k** in moderate to good yields. 2-Iodopyridine also furnished 2-trifluoromethylpyridine **2l** in 57% yield. When 2-, 3-, and 4-iodotoluenes, iodobenzene, and 1-chloro-4-iodobenzene were subjected to the trifluoromethylation reaction, corresponding trifluorotoluenes **2m**–**q** were obtained in approximately 40% yields. This might be due to the high volatility of the trifluoromethylated products in the reaction conditions.





Scheme 2. Substrate scope of iodoarenes. NMR yields based on ^{19}F NMR measurement. a) **5b** was used in place of **5a**. b) **5c** was used in place of **5a**.

The proposed reaction mechanism is shown in Scheme 3. The reaction of benzimidazoline, copper (I) chloride, and base afforded **I**, and the subsequent elimination of benzimidazole **7** generated trifluoromethyl copper species **II**. NMR analysis of the mixture of **5a**, potassium carbonate, and copper (I) chloride showed the signal of trifluoromethyl copper species **II** at -27.6 ppm, which is consistent with the NMR data of the previous report.[7g] This result supports the proposed mechanism. Following oxidative addition to the iodoarene and reductive elimination provided the trifluoromethylated arene. The reason for the high yields of iodoarenes bearing electron-withdrawing groups compared to the yields of iodoarenes bearing electron-donating groups is ascribed to the promotion of the former oxidative addition step.



Scheme 3. Proposed reaction mechanism.

In conclusion, we have achieved the trifluoromethylation of iodoarenes by developing a new type of trifluoromethylating reagent. Inspired by the hydrogen transfer reaction of benzothiazoline, we synthesized 2-trifluoromethylbenzimidazoline, which functioned as a trifluoromethylating reagent in the presence of copper(I) salt. The aromatization of benzimidazoline to furnish benzimidazole is the driving force of the reaction. The salient features of the present reaction are as follows: (1) the addition of ligand is not required and (2) the reaction has wide functional group tolerance to give trifluorotoluenes in good to high

yields.

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[13] Synthesis of **5a** was described in Supporting Information.