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CuCl-catalyzed *ortho* trifluoromethylation of arenes and heteroarenes with a pivalamido directing group†

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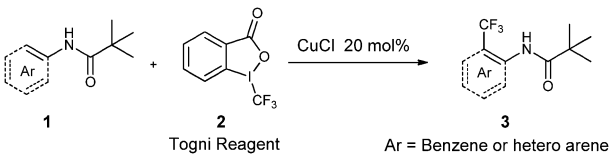
The CuCl catalyzed direct trifluoromethylation of sp^2 C–H bonds has been realized, using the Togni reagent as the CF_3 source. This reaction achieves the goal of regio-selectively converting C–H into C–CF_3 with ecological and readily available starting materials.

Trifluoromethylated arenes are important motifs in many pharmaceuticals, agrochemicals, and organic materials because of the strong electron-withdrawing nature and the large hydrophobic domain of a CF_3-group.[1] Consequently, extensive effort has been made on the trifluoromethylation of arenes. Although remarkable progress has been achieved *via* trifluoromethylation of aryl halides[2] or boronic acid,[3] undoubtedly, the most effective route to CF_3-substituted arenes would be direct trifluoromethylation of C–H bonds of arenes, thanks to its step economy. While direct trifluoromethylation of heteroarenes *via* electrophilic substitution (Minisci reaction) and deprotonation reactions have been successfully developed,[4,5] transition-metal catalyzed trifluoromethylation of aromatic C–H bonds (especially with high regio-selectivity) remains a challenge.[6] Recently, Yu's group reported directed *ortho* trifluoromethylation of 2-phenyl pyridine or *N*-aryl-benzamide catalyzed by Pd, using the Umemoto reagent as the CF_3 source.[7] The indirect trifluoromethylation method of aryl C–H bonds catalyzed by Ir and Cu subsequently was also reported.[8] However, to the best of our knowledge, direct trifluoromethylation of C–H bonds catalyzed by Cu, a non-toxic and less costly metal, still remains undeveloped. Herein we would like to report direct Cu-catalyzed trifluoromethylation of pivalamido arenes **1** with Togni reagent **2**.[9] Remarkably, this reaction affords trifluoromethylated pivalamido arenes **3** with high selectivity at the *ortho*-position, and even better results are obtained when it is applied to hetero-arenes (Scheme 1).



Scheme 1 Cu-catalyzed trifluoromethylation of pivalamido arenes.

Mechanistically, the reaction proceeds in a novel Cu-catalyzed radical pathway directed by a pivalamido group.

As part of our ongoing project on synthesizing functionalized aromatic nitrogenous compounds,[10] we attempted to prepare CF_3-substituted anilines, ideally by direct trifluoromethylation of aniline C–H bonds. The Togni reagent was chosen as the CF_3-source since it had been proven to be a readily available, easily handled and powerful trifluoromethylation reagent.[11] Unfortunately, the Togni reagent showed very high reactivity toward unmodified aniline without selectivity. Consequently, a common protecting strategy introducing an acyl group onto a nitrogen atom was applied. Thus, the uncontrollable trifluoromethylation was inhibited and we found that the reaction proceeded with copper catalyst loading. After various attempts, "optimal conditions" were found after screening (Table 1): 2 equiv. of Togni reagent, CuCl (20 mol%) as a catalyst, *t*-BuOH as a solvent and pivanilide as a substrate at 30 °C (Table 1, for details of condition optimization, see ESI†). Under the optimized conditions, 93% of *N*-phenyl pivalamide was converted and *o*-trifluoromethylated product **3a** (^{19}F: δ = −60.69 ppm) was isolated using column chromatography on silica gel in 65% yield. The reaction was monitored using ^{19}F NMR and the ratio of **3a** : **4a** : **5a** was 67 : 17 : 9 in the crude product (Table 1, entry 6). A range of ligands including glycol, 1,10-phenanthroline (1,10-phen) and *N*,*N*′-dimethylethylenediamine (DMEDA) were screened (entries 11–13), but none of them improved the yield of the *ortho*-product. During the reaction, CuCl was slowly transferred using the Togni reagent into Cu(II) species identified as cupric *o*-iodobenzoate **6** by XRD analysis (CCDC 923887, for crystal structure, see ESI†). Cu(II) *o*-iodobenzoate **6** is inert for the trifluoromethylation leading to a relatively high loading of CuCl. Other cupric salts such as $CuCl_2$ and $Cu(OTf)_2$ did not catalyze

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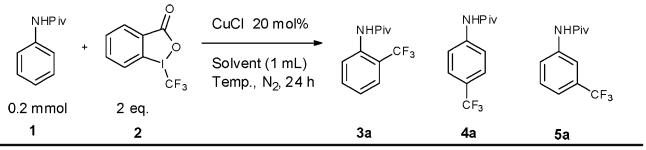
† Electronic supplementary information (ESI) available: Full experimental details, including ^{1}H and ^{13}C NMR data of new compounds. CCDC 923886, 923887 and 929074. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc41331d

Table 1 Optimization for trifluoromethylation of pivanilide



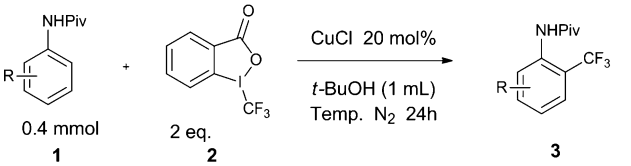
No.	Solvent	Temp. (°C)	Conversion (%)	Ratio of **3a** : **4a** : **5a**
1	CH_3OH	30	54	32% : 15% : 7%
2	EtOAc	30	87	58% : 23% : 6%
3	CH_3CH	30	83	50% : 22% : 11%
4	1,4-Dioxane	30	43	28% : 10% : 5%
5	$CHCl_3$	30	82	47% : 23% : 12%
6	*t*-BuOH	30	93	67% : 17% : 9%
7	CH_2OHCH_2OH	30	Trace	
8	Toluene	30	Trace	
9	THF	30	Trace	
10	*t*-BuOH	60	94	62% : 24% : 8%
11[a]	*t*-BuOH	30	88	55% : 23% : 10%
12[b]	*t*-BuOH	30	56	40% : 11% : 5%
13[c]	*t*-BuOH	30	69	48% : 13% : 8%

[a] 20 mol% of glycol was added as a ligand. [b] 20 mol% of 1,10-phen was added as a ligand. [c] 20 mol% of DMEDA was added as a ligand.

this reaction either, although they were active to catalyze many reactions with diaryliodonium salts.[10b,12]

Under the optimized conditions, the substrate scope was investigated, and the results are summarized in Table 2. In all cases, the isolated yield of the *ortho*-CF_3 product was presented to observe the selectivity. Firstly, electron-donating groups such as 4-methyl and 4-methoxyl pivanilide were tested in the reaction and the major products were isolated in 69% and 63% yield, respectively. To confirm the structure of the product, the single crystal of **3c** was analyzed using XRD (Fig. 1, CCDC 929074). After careful isolation using column chromatography on silica gel, side product **5b** (^{19}F: δ = −61.77 ppm) was also obtained and confirmed using NMR and XRD analysis (CCDC 923886, for crystal structure, see ESI†). When 4-isopropyl pivanilide was used, the product was obtained in 55% yield at 90 °C. The trifluoromethylation of substrates with electron-withdrawing groups,

Table 2 Trifluoromethylation of various pivanilides



No.	Product	Temp. (°C)	Conversion (%)	NMR-yield (%)	Isolated yield (%)
1	**3a**, R = H	30	93	67	65
2	**3b**, R = 4-Me	60	85	70	69
3	**3c**, R = 4-OMe	60	77	67	63
4	**3d**, R = 4-i-Pr	90	65	60	55
5	**3e**, R = 4-F	90	46	46	42
6	**3f**, R = 4-Cl	90	45	40	32
7	**3g**, R = 4-Br	90	55	53	49
8[a]	**3h**, R = 4-CO_2Et	120	40	35	30
9	**3i**, R = 3-OMe	45	70	48	40
10	**3j**, R = 3,4-diMe	80	71	57	48
11	**3k**, R = 3-OMe-4-Cl	100	67	55	40
12	**3l**, R = benzo	60	60	58	54

[a] Reaction time: 36 h.

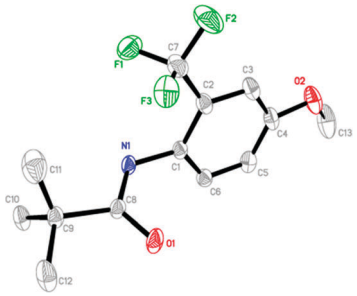
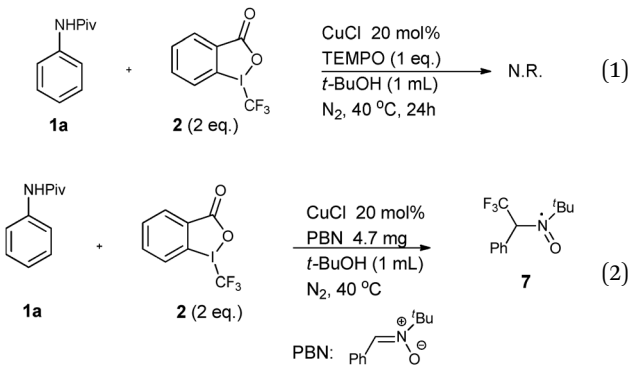


Fig. 1 Crystal structure of **3c**.

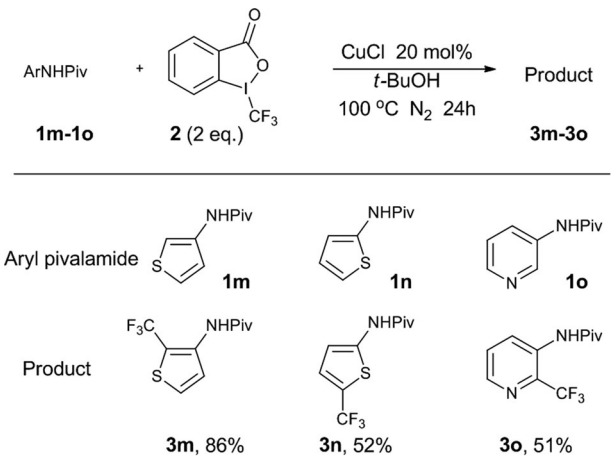
such as 4-F (at 90 °C), 4-Cl (at 90 °C), 4-Br (at 90 °C), and 4-CO_2Et (at 120 °C), afforded the major product in 42%, 32%, 49% and 30% yield, respectively, and the remaining starting materials were recovered. 3-MeO, 3,4-diMe, 3-MeO-4-Cl pivanilides were trifluoromethylated to give major products in synthetically useful yields. 2-Naphthyl pivalamide was also successfully converted to **3l** in 54% yield.

Inspired by the successful trifluoromethylation of phenyl pivalamide with high selectivity, we turned to test hetero-aryls, such as thienyl and pyridyl pivalamide. Considering that amino thiophene is not readily available and the direct pivalation is unpractical, the thienyl pivalamides were prepared alternatively from halo-thiophene and pivalamide *via* C–N coupling reaction.[13] The trifluoromethylation of 3-thienyl and 3-pyridyl pivalamide was performed at 100 °C to give the 2-CF_3 product in 86% and 51% yield, respectively (Scheme 2). However, the trifluoromethylation of 2-thienyl pivalamide exclusively provided the 5-CF_3 product in 52% yield, presumably because of the highest reactivity at the 5-position.

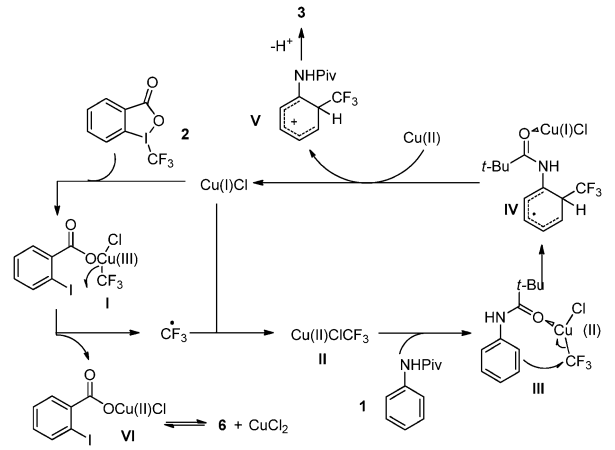
To get insight into the mechanism, two controlled experiments of **1a** and **2** were performed: (1) no product was observed under the standard conditions when 0.2 mmol of TEMPO, a radical scavenger, was added; (2) under the standard conditions when PBN was added, the adduct of CF_3-radical and PBN was found using EPR (Electron Paramagnetic Resonance, see ESI† for details).[14] *These results clearly showed a radical pathway for the reaction.*



Based on the above findings, we propose a mechanism for the reaction (Scheme 3). Firstly, oxidative addition to CuCl by Togni reagent **2** gives Cu(III) species **I**, which facilely generates the CF_3 radical (the existence was proved by trapping it with PBN, eqn (2)).[15] Secondly, the combination of the CF_3 radical and CuCl produces Cu(II) species **II**, which is also suggested in a previous report.[14] Then the weak coordination of **II** with a pivalamido group provides



Scheme 2 Trifluoromethylation of heterocyclic compounds.



Scheme 3 Proposed mechanism.

complex **III**. Subsequently, **III** undergoes intramolecular trifluoromethylation to give radical intermediate **IV**. Then the oxidation of **IV** by Cu(II) species (generated *in situ*) affords the precursor **V** of product **3**, returning Cu(I) species to the catalytic cycle. Apparently, the undirected attack of CF_3 to **1** would produce a mixture of *o*-, *m*-, *p*-isomer of **3**, but this process seems to be relatively slow in our reaction. When a radical scavenger was added, the CF_3 radical was trapped and the reaction ceased (eqn (1)).

In summary, CuCl-catalyzed direct trifluoromethylation of sp^2 C–H bonds was realized, using the Togni reagent as the CF_3 source. It is worth mentioning that this reaction achieves the goal of converting C–H into C–CF_3 with environmentally friendly and readily available starting materials, which would be of great benefit to the synthesis of trifluoromethyl compounds. The utility of the pivalamido group holds the opportunities to introduce different functional groups onto the aryl group or transform it into different functional groups through known methods. Hence, the successful regio-selective trifluoromethylation of pivalamido arenes and hetero-arenes provides new access to many synthetic therapeutic agents.

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