

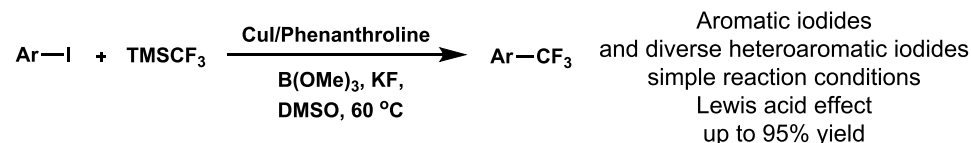
Efficient Copper-Catalyzed Trifluoromethylation of Aromatic and Heteroaromatic Iodides: The Beneficial Anchoring Effect of Boranes

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Supporting Information Placeholder



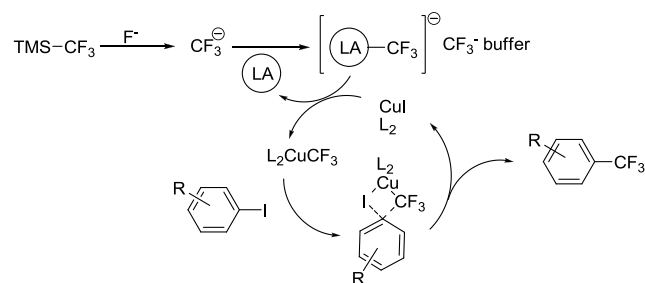
Efficient copper-catalyzed trifluoromethylation of aromatic iodides was achieved with TMSCF_3 in the presence of trimethoxyborane. The Lewis acid was used to anchor the in situ generated trifluoromethyl anion and suppress its rapid decomposition. Broad applicability of the new trifluoromethylating reaction was demonstrated in the functionalization of different aromatic and heteroaromatic iodides.

Due to their unique physical and biological properties compounds bearing the trifluoromethyl functional group have attracted significant attention in medicinal research, agrochemistry and materials science.¹ While the importance of this group is unquestionable, the introduction of the trifluoromethyl group into organic molecules in most cases is very challenging. The most important issues faced by trifluoromethylation reactions are the application of cheap, stable and readily available reagents, and the development of efficient, scalable, and selective processes. Trifluoromethylation has been achieved via transition metal-catalyzed oxidative couplings,² radical functionalizations,³ and in cross-coupling reactions. Besides the palladium catalyzed directed functionalization of aryl halides,⁴ several copper-based stoichiometric⁵ and catalytic methods were developed recently for the introduction of the trifluoromethyl group onto the aromatic core. The first copper catalyzed trifluoromethylation of iodides in the presence of a CuI/phenanthroline catalyst was reported by Amii and coworkers.^{6a} Though this catalytic reaction works efficiently, the use of expensive and relatively inaccessible TESCF_3 as the trifluoromethyl source makes this process less economic, especially for large scale syntheses. Later, Goossen utilized $\text{K}[\text{CF}_3\text{B(OMe)}_3]$ for copper catalyzed trifluoromethylation.^{6c} While this salt works efficiently, its sensitivity and instability limits its application.⁷

To circumvent the drawbacks of trifluoromethylborate salts and TESCF_3 , we aimed to develop a new procedure in which the relatively cheap and readily available TMSCF_3 is used as the trifluoromethyl source. The major problem with the application of TMSCF_3 in combination with a fluoride source is the

rapid generation of large amounts of the CF_3^- anion. Since the catalytic transformation is relatively slow, a significant amount of active CF_3^- is lost before entering the catalytic cycle. A potential solution to this problem would be the reversible quenching of the CF_3^- anion by the addition of a Lewis acid species, which would protect the rapidly produced trifluoromethyl anion and release it only slowly (Scheme 1). A good buffer system should be stable enough to stabilize the CF_3^- ion, while still labile enough to transfer CF_3^- to the copper cycle.

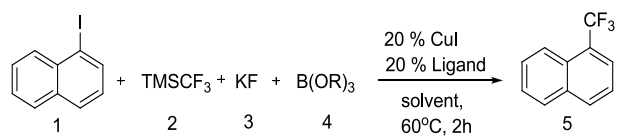
Scheme 1. Lewis Acid-buffered copper-catalyzed trifluoromethylation



As a starting point we examined the trifluoromethylation of 1-iodonaphthalene with 3 eq. TMSCF_3 and 3 eq. KF in the presence of 20% CuI and 20% phenanthroline ligand. The Lewis acid free reaction gave only 15% conversion in 2 hours (Table 1. Entry 1.) that remained the same after 24 hours. This finding is in agreement with the rapid KF triggered formation and decomposition of the CF_3^- anion.⁸ When we used 1 eq. of

TMSCF₃, KF, and B(OMe)₃ the conversion increased to 36% after 2 hours at 60 °C (Entry 2.), but the reaction stopped again. When we increased the amount of TMSCF₃ and KF to 3 equivalents while maintaining B(OMe)₃ at 1 equivalent (Entry 3.) the conversion rose to 70%, clearly demonstrating the buffering ability of the borate.

Table 1. Optimization studies ^[a]



En-try	Solvent	Ligand	Borane	2:3:4 ratio	conv. [%] [b]
1	DMSO	Phen	-	3:3:0	15
2	DMSO	Phen	B(OMe) ₃	1:1:1	36
3	DMSO	Phen	B(OMe) ₃	3:3:1	70
4	DMSO	Phen	B(OMe)₃	3:3:3	92
5	DMSO	Me ₄ -Phen	B(OMe) ₃	3:3:3	81
6	DMSO	8-OH-Quinoline	B(OMe) ₃	3:3:3	0
7	DMSO	sparteine	B(OMe) ₃	3:3:3	13
8	DMSO	Phen	B(OEt) ₃	3:3:3	85
9	DMSO	Phen	B(OCH ₂ CF ₃) ₃	3:3:3	2
10	DMSO	Phen	B(OPr) ₃	3:3:3	64
11	DMSO	Phen	B(O ⁱ Pr) ₃	3:3:3	10
12	DMSO	Phen	B(Obu) ₃	3:3:3	48
13	DMSO	Phen	B(O ^t Bu) ₃	3:3:3	37

[a] CuI (0.07 mmol), 1,10-phenanthroline (0.07 mmol), aryl iodide (0.35 mmol) in 1 mL anhydrous Solvent at 60 °C, % GC yield [b] conversions were determined by GC-MS

To our delight, when TMSCF₃:KF:B(OMe)₃ were applied in 3:3:3 equivalents ratio the reaction reached 92% conversion in 2 hours (Entry 4.).⁹ Next, we examined the effect of the ligand and the Lewis acid on the reaction. Only the phenanthroline based ligand proved to be applicable for the transformation (Entries 4-7.). Variation of the Lewis acid showed that the bulkier the alkyl group on the borane the less able it is to stabilize the CF₃ anion, resulting in a lower conversion. Changing the methyl group to ethyl resulted in 81% conversion (Entry 8.), while the use of propyl, iso-propyl, butyl and tert-butyl borates led to 64%, 10%, 48% and 37% conversion respectively (Entries 10-13.). Replacement of ethyl group with 1,1,1-trifluoroethyl group, the borane become completely ineffective in the coupling due probably to its increased electron deficiency (Entry 9.).¹⁰ To identify the optimal conditions for the trifluoromethylation of 1-iodonaphthalene the temperature, copper loading, fluoride source and the solvent were also varied. As a result of this multi dimension parameter screening we found that the use of 20 mol% CuI as copper source, 20 mol% 1,10-phenanthroline as ligand, KF as fluoride source, and anhydrous DMSO as solvent are optimal for the coupling that is best run under argon at 60 °C. With these conditions in hand we explored the scope and limitations of the Lewis-acid enabled copper-catalyzed trifluoromethylation.

The functional group tolerance of the transformation was established on a set of 21 aromatic and heteroaromatic iodides

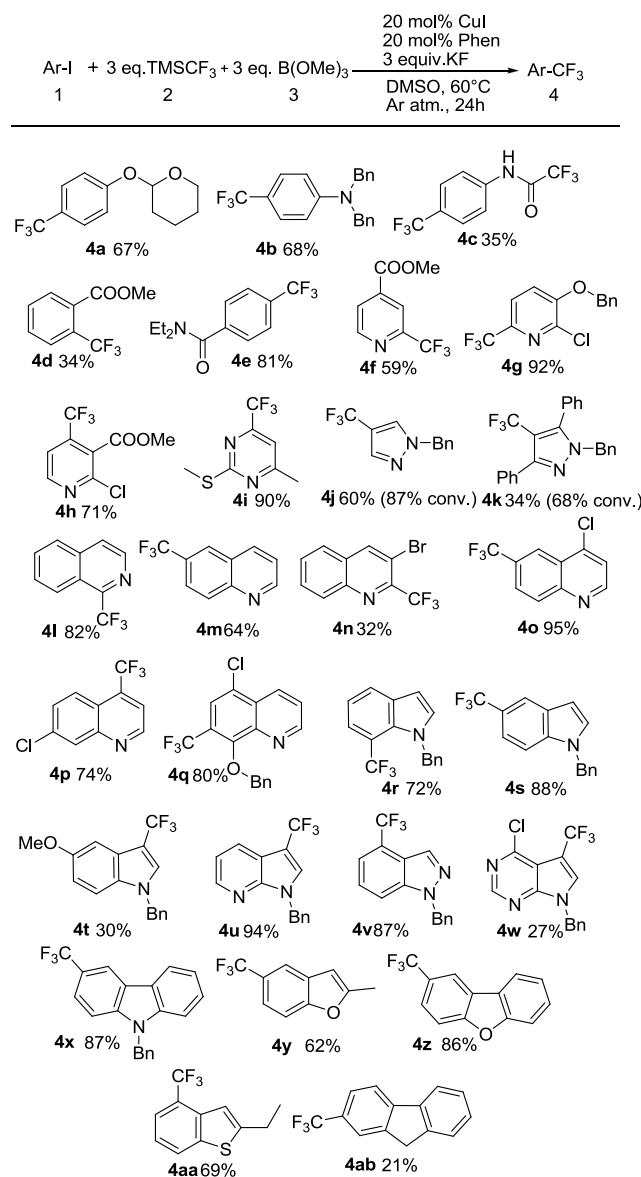
having different electronic and steric properties, as well as protecting groups. In the first round the reactions were analyzed by GCMS.¹¹ On the basis of these studies we established that the trifluoromethylation can be achieved with aryl iodides containing both electron donating and electron withdrawing groups, however in the latter case the reactions were faster. The presence of bulky substituents in ortho position was also tolerated, however longer reaction times were necessary to reach complete conversion. We have also established that for the successful coupling free hydroxyl and amino groups (including indoles) should be protected.

Having established the functional group tolerance we aimed to prove the synthetic utility of the Lewis-acid enable trifluoromethylation by preparing a diverse set of trifluoromethylated compounds, including heterocyclic derivatives (Scheme 2.). To demonstrate the applicability of the method for the trifluoromethylation of functionalized aromatic iodides we performed successfully the trifluoromethylation of a protected phenol and two protected anilines, and isolated the appropriate products **4a**, **4b**, and **4c** with 67%, 68% and 35% yield respectively. Ester and amide derivatives of aromatic carboxylic acids did also prove to be excellent substrates, and their trifluoromethyl substituted derivatives (**4d**, **4e**) were obtained in moderate to good yield (34%, 81%).

The application of pyridine derivatives bearing ester-, protected alcohol- and halogene functions beyond the iodo group resulted the desired products **4f**, **4g** and **4h** with good to excellent yield (59%, 92% and 71%). The reaction was also successful with 6-iodo-4-methyl-2-(methylthio)-pyrimidine and the trifluoromethylated compound was isolated with 90% yield (**4i**). In the case of 1-benzyl-4-iodopyrazole and sterically hindered 1-benzyl-3,5-diphenyl-4-iodopyrazole the reactions were not complete (87% and 68% conversion) but the desired trifluoromethylated products **4j**, **4k** were isolated with 60% and 34% yield. Functionalization of 1-iodoisoquinoline and 6-iodoquinoline gave the desired trifluoromethylated isoquinoline (**4l**) and quinoline (**4m**) in 82% and 64% yields. We also prepared the quinoline **4n** bearing bromo substituent next the trifluoromethyl group (32%). The analogous chloro-iodo-quinoline derivatives gave the appropriate trifluoromethylated products **4o**, **4p** and **4q** with good yields (95%, 74% and 80%). The coupling of benzyl protected indole derivatives, 5-iodoindole, 7-iodoindole and 5-methoxy-3-iodoindole afforded the appropriate products (**4r**, **4s**, **4t**) with 72%, 88% and 30% isolated yields respectively.

The reaction of *N*-benzyl protected derivatives of *N*-heterocycles such as 3-iodo-7-azaindole, 4-iodoindazole, 6-chloro-7-iodo-7-deazapurine and 4-iodocarbazole resulted the appropriate heterocycles **4u**, **4v**, **4w** and **4x** with good yields (94%, 87%, 27% and 87%). Iodo derivatives of benzofuran and dibenzofuran reacted smoothly under the optimized conditions. Trifluoromethylation of 2-methyl-5-iodobenzofuran gave the appropriate product (**4y**) with 62% isolated yield, while in an analogous reaction 2-(trifluoromethyl)-dibenzofuran (**4z**) was isolated with 86% yield. Replacement of the oxygen in the heterocyclic compound by sulfur did not cause significant changes in reactivity and 2-ethyl-5-trifluoromethyl benzothiophene (**4aa**) was obtained in 69% yield. For comparison we have also performed the trifluoromethylation on the carbacyclic compound 2-iodofluorene, and we isolated the trifluoromethylated product (**4ab**) only in 21% yield.

Scheme 2. Synthesis of trifluoromethylated compounds in copper catalyzed trifluoromethylation^a



^a CuI (0.4 mmol), 1,10-phenanthroline (0.4 mmol), KF (6 mmol.), aryl iodide (2.00 mmol.), DMSO (anh., 4.0 mL) B(OMe)₃ (6 mmol.), TMSCF₃ (6 mmol.), Ar, 60 °C, % isolated yield

Regarding the beneficial effect of trimethoxy borane in the coupling reaction we monitored the reaction by in situ NMR measurements. We supposed that the liberation of trifluoromethyl anion from TMSCF₃ takes place quickly by interaction with fluoride anion, but in the presence of borane a significant part of the formed CF₃⁻ anion is stabilized *in situ* by the borane. The formation of CF₃-borane and Cu-CF₃ complexes was identified by ¹⁹F-NMR measurements. The presence of a peak at -29.2 ppm refers to the presence of Cu-CF₃ species, while the peak at -65.5 ppm proved the presence of CF₃B(OMe)₃. These findings support our hypothesis regarding the formation of Lewis acid-base adduct of the CF₃ anion with trimethylborane.

In conclusion, we have developed a Lewis-base enabled approach for the copper-catalyzed trifluoromethylation of aromatic and heteroaromatic iodides. The transformation utilizes

TMSCF₃ as a readily available CF₃ source and trialkoxy boranes as Lewis acid for the temporary trapping of the CF₃⁻ anion generated by KF from the trifluoromethylating agent. The transformation has a good functional group tolerance and its synthetic utility was demonstrated through the synthesis of several trifluoromethylated aromatic and heteroaromatic molecules. The advantage of the procedure is that it eliminates the use of expensive TMSCF₃ and unstable trifluoromethylborate salts, previously utilized as CF₃ source in the copper-catalyzed trifluoromethylation. Moreover, the developed conditions offer an efficient synthetic tool for the introduction of trifluoromethyl group into aromatic and heteroaromatic rings, providing easy access to compounds of high added value for pharmaceutical research.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data and NMR spectra for all compounds. "This material is available free of charge via the Internet at <http://pubs.acs.org>."

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript

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- ⁷ On the basis of our experience the salt works only when it is freshly prepared. Upon storage, it quickly lost its activity in several days and become ineffective in trifluoromethylation. For results of stability studies of trifluoromethyl borate salts, see Supporting Information)
- ⁸ The in situ NMR studies showed the formation of CHF₃ and CDF₃.
- ⁹ For time-conversion curves see Supporting Information
- ¹⁰ For further details see Supporting Information
- ¹¹ Results of functional group tolerance study with GCMS in case of 21 substrates can be found in the supporting information.