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

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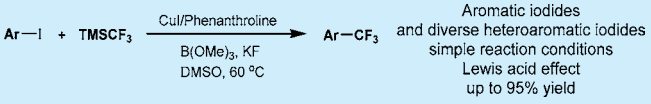
Supporting Information

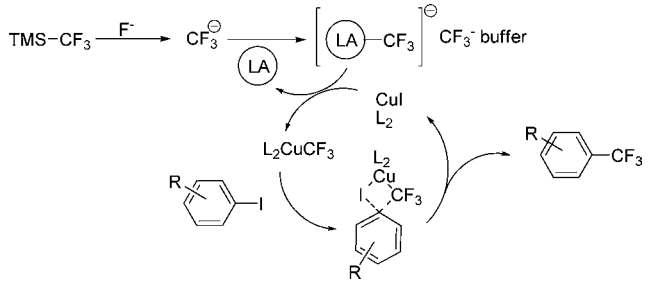
ABSTRACT: Efficient copper-catalyzed trifluoromethylation of aromatic iodides was achieved with $TMSCF_3$ in the presence of trimethylborate. The Lewis acid was used to anchor the in situ generated trifluoromethyl anion and suppress its rapid decomposition. Broad applicability of the new trifluoromethylating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



Because of 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 stoichiometric[5] and catalytic methods[6] 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 co-workers.[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 $K[CF_3B(OMe)_3]$ for copper-catalyzed trifluoromethylation.[6b] While this salt works efficiently, its sensitivity and instability limit 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).[8] 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 equiv $TMSCF_3$ and 3 equiv KF in the presence of 20% CuI and 20% phenanthroline ligand. The Lewis acid free reaction gave only 15% conversion in 2 h (Table 1, entry 1) that remained the same after 24 h. This finding is in agreement with the rapid KF triggered formation and decomposition of the CF_3 anion.[9] When we used 1 equiv of $TMSCF_3$, KF, and $B(OMe)_3$ the conversion increased to 36% after 2 h at 60 °C (entry 2), but the reaction stopped again. When we increased the amount of $TMSCF_3$ and KF to 3 equiv while maintaining $B(OMe)_3$ at 1 equiv (entry 3) the conversion rose to 70%, clearly demonstrating the buffering ability of the borate.

To our delight, when $TMSCF_3$:KF:$B(OMe)_3$ were applied in 3:3:3 equiv ratio the reaction reached 92% conversion in 2 h

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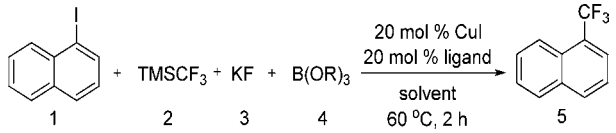
Table 1. Optimization Studies[a]



entry	solvent	ligand	borate	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	$B(OCH_2CF_3)_3$	3:3:3	2
10	DMSO	Phen	$B(OPr)_3$	3:3:3	64
11	DMSO	Phen	$B(O^iPr)_3$	3:3:3	10
12	DMSO	Phen	$B(OBu)_3$	3:3:3	48
13	DMSO	Phen	$B(O^tBu)_3$	3:3:3	37

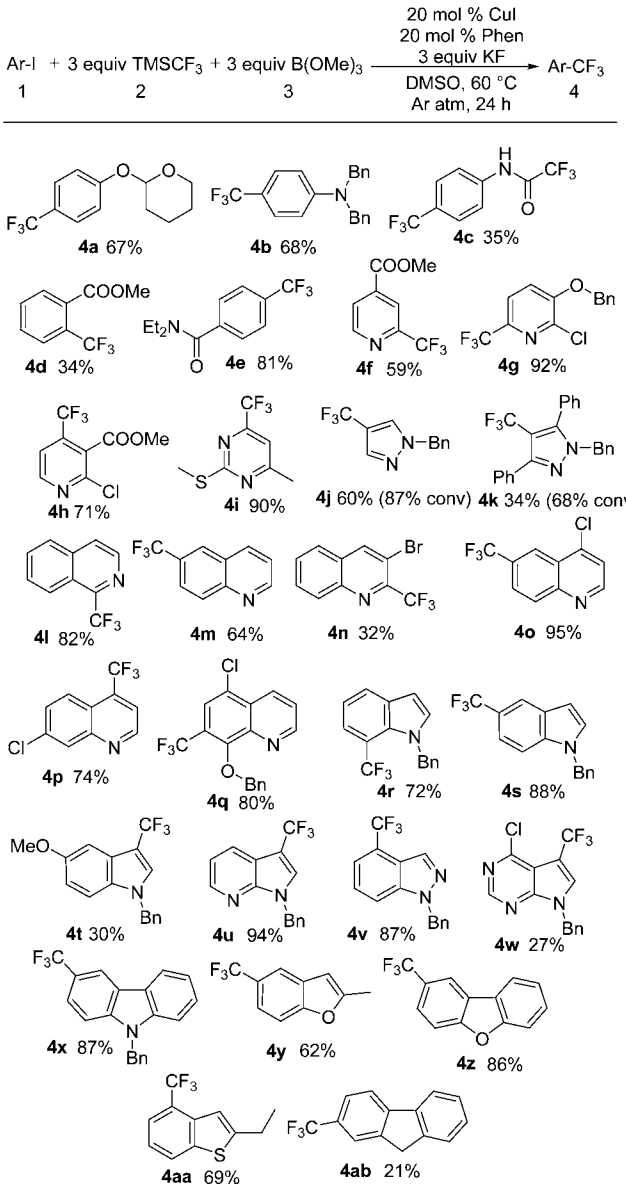
[a]CuI (0.07 mmol), 1,10-phenanthroline (0.07 mmol), aryl iodide (0.35 mmol) in 1 mL of anhydrous solvent at 60 °C. [b]% conversions of 1-iodonaphthalene were determined by GC–MS.

(entry 4).[10] 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 borate the less able it is to stabilize the CF_3 anion, resulting in a lower conversion. Changing the methyl group to ethyl resulted in 81% conversion (entry 8), while the use of propyl, isopropyl, 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 borate become completely ineffective in the coupling due probably to its increased electron deficiency (entry 9).[11] 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 multidimension parameter screening we found that the use of 20 mol % CuI as copper source, 20 mol % 1,10-phenanthroline as ligand,[12] 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 GC–MS.[13] 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 the 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 enabled trifluoromethylation by preparing a diverse set of trifluoromethylated compounds, including heterocyclic derivatives (Scheme 2). To demonstrate the applicability of the method

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), $TMSCF_3$ (6 mmol), Ar, 60 °C, % isolated yield.

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** in 67, 68 and 35% yield, respectively. Ester and amide derivatives of aromatic carboxylic acids also proved 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 halogen functions beyond the iodo group afforded the desired products **4f**, **4g** and **4h** in good to excellent yield (59, 92 and 71%). The reaction was also

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successful with 6-iodo-4-methyl-2-(methylthio)-pyrimidine and the trifluoromethylated compound was isolated in 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 in 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 a bromo substituent next to the trifluoromethyl group (32%). The analogous chloro-iodoquinoline derivatives gave the appropriate trifluoromethylated products **4o**, **4p** and **4q** in 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**) in 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 provided the appropriate heterocycles **4u**, **4v**, **4w** and **4x** in 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**) in 62% isolated yield, while in an analogous reaction 2-(trifluoromethyl)-dibenzofuran (**4z**) was isolated in 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.

Regarding the beneficial effect of trimethyl borate in the coupling reaction we monitored the reaction by in situ NMR measurements. We supposed that the liberation of trifluoromethyl anion from $TMSCF_3$ takes place quickly by interaction with fluoride anion, but in the presence of borate a significant part of the formed CF_3^- anion is stabilized *in situ* by the borate. The formation of CF_3-borate and Cu-CF_3 complexes was identified by ^{19}F-NMR measurements. The presence of a peak at −29.2 ppm refers to the presence of Cu-CF_3 species, while the peak at −65.5 ppm proved the presence of $CF_3B(OMe)_3$. These findings support our hypothesis regarding the formation of Lewis acid−base adduct of the CF_3 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 $TMSCF_3$ as a readily available CF_3 source and trialkyl borates as Lewis acid for the temporary trapping of the CF_3^- anion generated by KF from the trifluoromethylating agent. The transformation has 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 $TESCF_3$ and unstable trifluoromethylborate salts, previously utilized as CF_3 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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Notes

The authors declare no competing financial interest.

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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 became ineffective in trifluormethylation. For results of stability studies of trifluoromethyl borate salts, see the Supporting Information.

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(9) The in situ NMR studies showed the formation of CHF_3 and CDF_3.

(10) For time-conversion curves, see the Supporting Information.

(11) For further details, see the Supporting Information.

(12) Although the reaction of 1-iodonaphthalene reached high conversion after 24 h with 5% copper catalyst and phenanthroline ligand, for most of the substrates a higher catalyst loading (20 mol %) was necessary to obtain full conversion.

(13) Results of functional group tolerance study with GC−MS in case of 21 substrates can be found in the Supporting Information. The goal of these experiments was to establish the functional group tolerance of the transformation. We intended to identify functional groups that allow for high (or low) conversion in the coupling. To achieve this we used GC−MS analysis to predict the steric and electronic influence of functional groups on the reaction and the necessity of protecting groups. Being aware of the limitations of the applied analytical methodology, we believe that the data provided is still solid enough to make the appropriate conclusions as is exemplified in the preparation of the compounds summarized in Scheme 2, where yields of isolated products were provided.