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Copper-Catalyzed Trifluoromethylation of Aryl Iodides with Potassium (Trifluoromethyl)trimethoxyborate

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Dedicated to Dr. Albrecht Marhold

Abstract: Potassium (trifluoromethyl)trimethoxyborate is introduced as a new source of CF_3 nucleophiles in copper-catalyzed trifluoromethylation reactions. The crystalline salt is stable on storage, easy to handle, and can be obtained in near-quantitative yields simply by mixing $B(OMe)_3$, CF_3SiMe_3, and KF. The trifluoromethylation reagent allows the conversion of various aryl iodides into the corresponding benzotrifluorides in high yields under mild, base-free conditions in the presence of catalytic quantities of a Cu^I/1,10-phenanthroline complex.

Keywords: aryl iodide · boron · copper · synthetic methods · trifluoromethylation

Introduction

The presence of trifluoromethyl groups in organic molecules has a profound effect on their physical and chemical properties. Trifluoromethyl-substituted compounds often display improved metabolic stability, better receptor binding selectivity, higher lipophilicity, increased bioavailability, or stronger dipole moments than non-fluorinated analogues.[1] New methods to introduce trifluoromethyl groups into organic substrates are thus of constant high interest for the synthesis of pharmaceuticals, agrochemicals, and functional materials.[2] Examples of commercially meaningful trifluoromethylarenes are depicted in Figure 1. Eli Lilly's fluoxetine (Prozac, Sarafene) is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. Approved in the late 1980s, it has long been one of the most widely prescribed antidepressants.[3] Trifloxystrobin, marketed by Bayer under the name of Flint, is a top-selling fungicide of the strobilurin class.[4] A *meta*-trifluoromethyl group on the phenyl ring is a key element of bleaching herbicides, such as norflurazon, diflufenican, and beflubutamid, that inhibit the synthesis of carotinoids.[2b] Compound ZLI-2857 is a typical example of highly fluorinated components of liquid-crystal mixtures used in LCD screens.[5]

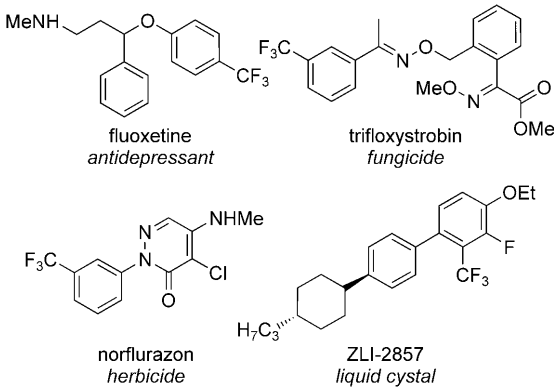

Figure 1. Trifluoromethylated pharmaceuticals, agrochemicals, and functional materials.

Historically, the Swarts reaction, which requires harsh reaction conditions, has been used to access simple benzotrifluoride building blocks from α,α,α-trichlorotoluenes and antimony pentafluoride or anhydrous hydrogen fluoride (Scheme 1).[6] The high demand for trifluoromethyl-substituted products has since driven substantial research aimed at establishing general methods for the trifluoromethylation of organic molecules. As illustrated in Figure 2, three classes of reagents have been described for this purpose, and these can be classified into 1) radical (e.g., Langlois' reagent and Umemoto's *N*-nitrososulfonamide), 2) electrophilic (e.g., Umemoto's thiophenium as well as Togni's hypervalent iodine derivatives), and 3) nucleophilic reagents (e.g., by Langlois and Ruppert).[7]

Based on these reagents, several protocols have been developed for the trifluoromethylation of sp^3 and sp^2 carbon centers (Scheme 1). Unfortunately, none of them are generally applicable. Electrophilic reagents are most suitable for the trifluoromethylation of electron-rich arenes: for exam-

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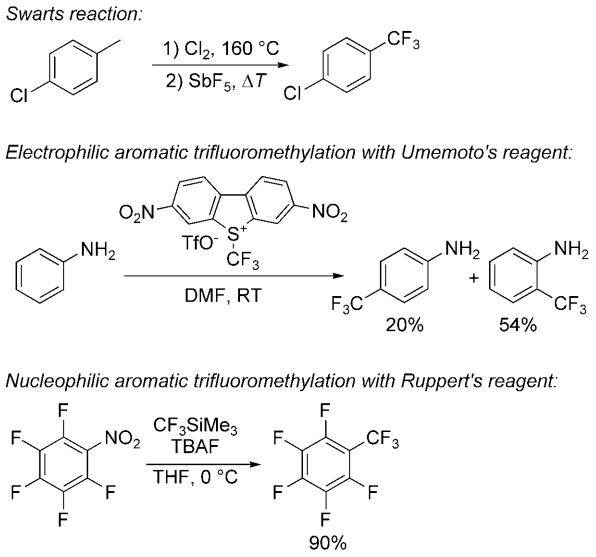


Scheme 1. Examples of non-catalytic synthetic procedures used to provide trifluoromethyl arenes.

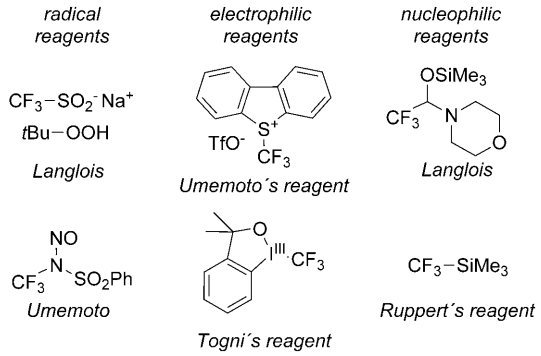


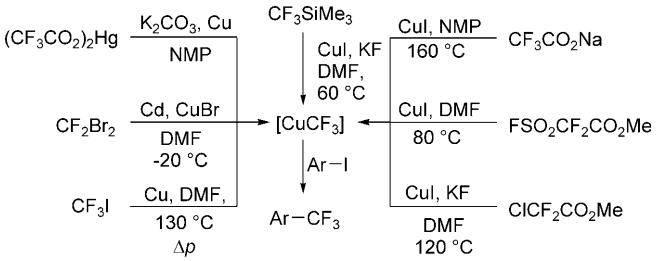
Figure 2. Examples of trifluoromethylation reagents.

ple, phenols and anilines are trifluoromethylated in their *ortho* and *para* positions with Umemoto's reagent.[8]

Conversely, nucleophilic reagents can be used for the introduction of CF_3 groups into electron-deficient arenes. Ruppert's reagent, for example, can be used to substitute the nitro group of pentafluoronitrobenzene by CF_3.[9] Radical trifluoromethylations are possible starting with a range of trifluoromethyl derivatives, including CF_3I,[10] $(CF_3)_2Hg$,[11] $(CF_3)_2N_2$,[12] CF_3SO_2Na/tBuOOH,[13] or $CF_3N(NO)SO_2Ph$.[14] However, the substrate scope of each of the above reactions is limited.

One of the most effective methods for the regiospecific introduction of CF_3 groups into arenes is the trifluoromethylation of aryl halides by using $[CuCF_3]$ species. These reactive intermediates are usually generated in situ from copper or copper salts and trifluoromethylating reagents (Scheme 2).

Procedures reported by the groups of Yagupolskii[15] and Burton[16] to form $[CuCF_3]$ involve toxic mercury– or cadmium–CF_3 species, whereas the method reported by Kobayashi et al.[17] requires pressurized gaseous CF_3I. Chambers and

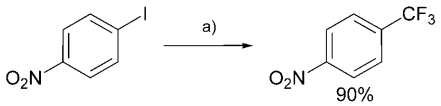


Scheme 2. Syntheses and coupling of $[CuCF_3]$.

co-workers utilized sodium trifluoroacetate as a cheap and widely available starting material to access $[CuCF_3]$ by CuI-promoted decarboxylation at 160 °C.[18] Unfortunately, this economically attractive transformation is usually plagued by side reactions that are caused by the formation of CF_2–carbene, and by competing Ullmann-type couplings of the aryl iodides. Degradation of the $[CuCF_3]$ species is often observed also in the CuI/KF-mediated decarboxylation of methyl chlorodifluoroacetate at 120 °C,[19] and in decarboxylative/desulfurization reactions of methyl trifluorosulfonyl difluoroacetate.[20]

Trifluoromethylcopper complexes can be generated under particularly mild conditions when using Ruppert's reagent (CF_3SiMe_3) in combination with a base (e.g., KF, tetrabutylammonium fluoride (TBAF) or KO*t*Bu).[21] In most trifluoromethylation protocols based on this reagent, copper was used in stoichiometric quantities because the copper-mediated substitution of iodide by CF_3 groups on the aryl iodide substrates proceeded much more slowly than the generation of the unstable $[CuCF_3]$ species.

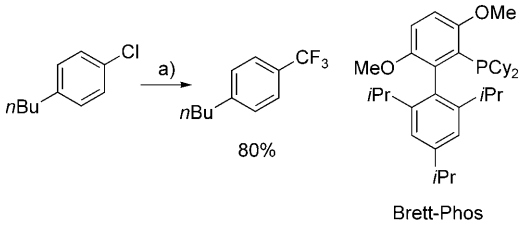
In 2009, Amii and co-workers demonstrated that the reaction rate for Cu-mediated processes can be enhanced by the addition of chelating nitrogen ligands. This led to the discovery of the first trifluoromethylation reaction based on Ruppert's reagent that was catalytic in copper (Scheme 3).[22] In the presence of a CuI/1,10-phenanthroline catalyst, several, mostly electron-deficient, aryl iodides were converted into the corresponding benzotrifluorides with a mixture of CF_3SiEt_3 and KF at 60 °C.



Scheme 3. Cu-catalyzed trifluoromethylation of aryl iodides. a) CF_3SiEt_3 (2 equiv), KF (2 equiv), CuI (10 mol %), 1,10-phenanthroline (10 mol %), DMF/*N*-methyl-2-pyrrolidinone (NMP), 60 °C, 24 h.

Based on the pioneering work by the groups of Grushin, Vicic, and Sandford, who demonstrated the feasibility of reductive eliminations of CF_3 groups from Ni, Pd^{II}, and Pd^{IV} complexes,[23] several Pd-catalyzed trifluoromethylation reactions have recently been developed. Yu and co-workers reported a Pd-catalyzed C–H activation of 2′-phenylpyri-

dines followed by trifluoromethylation of the resulting aryl–palladium species by stoichiometric amounts of the expensive electrophilic Umemoto reagent.[24] Very recently, Buchwald et al. achieved a major breakthrough in trifluoromethylation chemistry with their Pd-catalyzed trifluoromethylation of aryl chlorides (Scheme 4).[25]



Scheme 4. Pd-catalyzed trifluoromethylation of aryl chlorides. a) CF_3SiEt_3 (2 equiv), KF (2 equiv), [{Pd(allyl)Cl}$_2$] (3 mol%), Brett-Phos (9 mol%), dioxane, 120°C, 16 h.

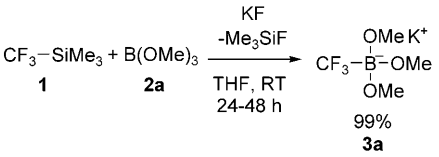
As the CF_3 source, a mixture of triethyl(trifluoromethyl)-silane, which is an expensive analogue of Ruppert's reagent, with KF was employed. In the presence of a catalyst generated from [{Pd(allyl)Cl}$_2$] and an electron-rich, sterically extremely hindered biphenylphosphane (Brett-Phos), various aryl chlorides were converted into the corresponding benzotrifluorides in 1,4-dioxane at 120°C.[25]

The progress achieved in the field of trifluoromethylation catalysis is impressive. However, these reactions suffer from the limited availability of inexpensive, stable, and easy-to-use trifluoromethylating reagents. Arguably, the most versatile nucleophilic CF_3 source known to date is CF_3SiMe_3 (Ruppert's reagent). However, its physical and chemical properties complicate its storage and handling. It is a highly volatile liquid, with a boiling point of only 55°C, and is sensitive to air and moisture. To act as a nucleophilic trifluoromethylation reagent, it must be activated by a precise amount of a suitable base.

We herein report on the use of potassium (trifluoromethyl)trialkoxyborates as easily accessible, storage-stable, one-component nucleophilic trifluoromethylation reagents. These nonvolatile crystalline salts are accessible in one step from Ruppert's reagent, trialkoxyborates, and potassium fluorides. In combination with copper phenanthroline catalysts, they allow the trifluoromethylation of various aryl iodides in good yields without an additional base.

Results and Discussion

Synthesis of the trifluoromethylating reagents: The foundation for this work was laid in 2003, when one of us discovered that Ruppert's reagent reacts with trialkyl borates to generate quaternary borate salts.[26] Since then, we have developed a reliable synthetic process that gives convenient access to multigram quantities of the trimethoxy derivative (Scheme 5).



Scheme 5. Synthesis of potassium trimethoxy(trifluoromethyl)borate.

Hence, potassium (trifluoromethyl)trimethoxyborate (**3a**) can be generated simply by stirring a mixture of CF_3SiMe_3, $B(OMe)_3$, and KF in anhydrous THF over several hours. The progress of the reaction is monitored by the disappearance of the suspended KF. Following the addition of pentane, the product precipitates and can be isolated in near-quantitative yield by filtration.

Compound **3a** is a colorless, crystalline, air-stable solid. Even after being left in an open vessel for several days, no signs of decomposition were observed by NMR spectroscopic analysis. The salt melts at 116–118°C with decomposition. When dissolved in polar organic solvents such as DMF, decomposition starts at slightly lower temperatures (approx. 80°C). Its identity was confirmed by X-ray crystal structure analysis, which showed that each asymmetric unit cell contained three molecules of **3a** with one coordinated THF. All hydrogen atoms were placed in calculated positions and refined by using a riding model. In Figure 3, only one anion is depicted to clarify the important structural features. Selected bond lengths and angles are given in the legend. A complete representation of the unit cell content is given in the Supporting Information.

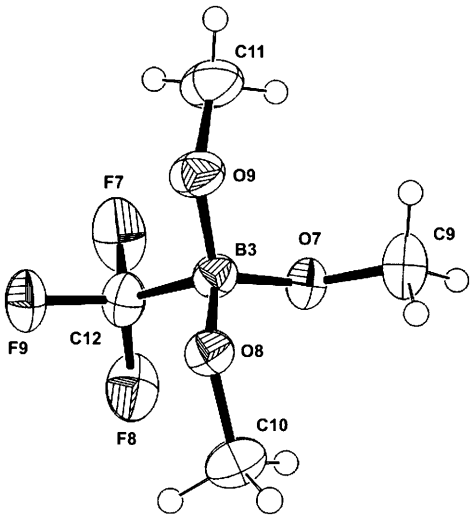
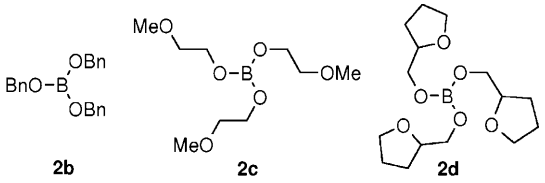


Figure 3. Molecular structure of the anion **3a**; thermal ellipsoids shown at the 50% probability level. Selected bond lengths [Å] and angles [°]: B3–O7 1.488(6), B3–O8 1.1.473(6), B3–O9 1.455(6), B3–C12 1.646(7); O7-B3-O8 115.1(4), O7-B3-O9 116.4(4), O9-B3-O8 101.2(4), O7-B3-C12 103.7(4), O8-B3-C12 110.0(4), O9-B3-C12 110.6(4).

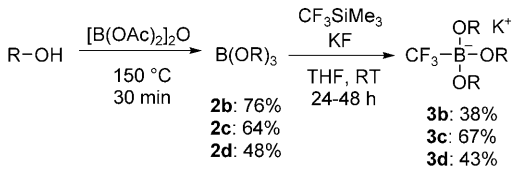
The effect that variation of the boron substituents has on the reactivity and thermal stability of such borate salts was

investigated. Various trisubstituted borates were assessed as precursors to the (trifluoromethyl)trialkoxyborate salts **2b–d** (see below). Tribenzyl borate (**2b**) was included with the goal of increasing the lipophilicity and thermal stability of the corresponding borate salt by introducing larger substituents. The purpose of the ether-functionalized alkyl chains in the borates **2c** and **2d** was to facilitate B–CF_3 bond cleavage in the trifluoromethyl borate salts by providing a high concentration of alternative electron-pair donors in direct proximity to the boron center.



The most convenient precursor for the synthesis of these trialkyl borates was found to be tetraacetyl diborate, which is accessible by heating boric acid in acetic anhydride.[27] Tetraacetyl diborate reacts rapidly with alcohols under formation of the corresponding trialkyl borates **2b–d** (see above) along with acetic acid.

After distillation, the borates were converted into the potassium (trifluoromethyl)trialkoxyborate salts **3b–d** by the procedure outlined in Scheme 6. The overall yields after purification by crystallization were satisfactory, but may certainly be improved by individual optimization of the crystallization step.



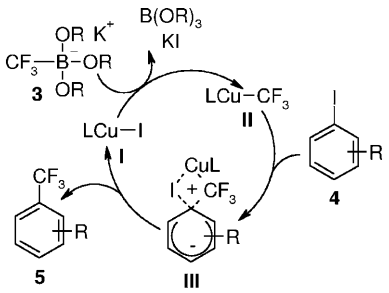
Scheme 6. Synthesis of potassium (trifluoromethyl)trialkoxyborates **3b–d**.

The thermal stability of **3b** was indeed improved over that of **3a**, with decomposition of the solid starting only above 170 °C.

The ether-substituted salts **3c** and **3d** melted with decomposition at 106–108 °C and 142–144 °C, respectively.

Copper-mediated trifluoromethylation reactions: We next evaluated whether the (trifluoromethyl)trialkoxyborate salts were suitable CF_3 sources in copper-mediated trifluoromethylation reactions. A plausible mechanism for such a process is outlined in Scheme 7.[18,22]

Initially, the trifluoromethyl borate salt **3** would react with a ligand-stabilized copper halide complex **I** under formation of a trifluoromethylcopper complex **II**. In a concerted σ-bond metathesis step, the CF_3 group would then be transferred from the copper to the aryl iodide **4** with formation of the benzotrifluoride product **5** and regeneration of the initial copper(I) halide complex (**I**). An analogous concerted nucleophilic aromatic substitution mechanism was proposed by Chambers and co-workers for the copper iodide-mediated decarboxylative coupling of sodium trifluoroacetate and aryl iodides, on the basis of kinetic studies and Hammett plots.[18]



Scheme 7. Proposed mechanism of the Cu-catalyzed trifluoromethylation.

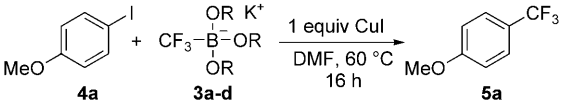
Our search for a suitable protocol for the trifluoromethylation of aryl halides led us to investigate conditions under which the trifluoromethyl borate salts **3a–d** would transfer their CF_3 groups onto copper complexes. Thus, we mixed equimolar quantities of the borate salt **3a** and CuI in DMF at room temperature, and analyzed the resulting suspension by ^{19}F NMR spectroscopic analysis. The appearance of a new signal at $\delta = -28.14$ ppm indicated the presence of an anionic $[CF_3CuI]^-$ species.[15b,28] This finding confirms that, even in the absence of an external base, the borate reagent is able to transfer its CF_3 group.

Encouraged by this finding, we next treated the electron-rich, moderately reactive aryl iodide 4-iodoanisole (**4a**) with two equivalents of each potassium (trifluoromethyl)trialkoxyborate salt **3a–d** in the presence of stoichiometric quantities of CuI in DMF at 60 °C. After 16 h, GC analysis revealed that appreciable quantities of 4-trifluoromethylanisole (**5a**) had formed in all cases (Table 1).

These results demonstrate that all borate salts **3a–d** can indeed serve as nucleophilic CF_3 sources. Salt **3b** gave marginally better results than **3a**, **3c**, and **3d**, suggesting that the influence of reagent stability dominates over that of reactivity for achieving good yields. A control experiment revealed that without the copper source, no consumption of the starting materials takes place.

Encouraged by the results of the copper-mediated trifluoromethylation, we set out to develop a catalytic version of this reaction (Scheme in Table 2). As the model, we again chose the reaction of **4a** with **3a**. Although it had not performed best, we selected **3a** for the screening reactions on the basis that it has the lowest molecular weight and is accessible in high yield from commercially available trimethyl borate. Catalytic loadings of copper(I) iodide (20 mol %) initially led to substoichiometric turnover of the copper and to unsatisfactory yields of the desired 4-trifluoromethylanisole (**5a**) at 60 °C in DMF (Table 2, entry 1). Amii and co-work-

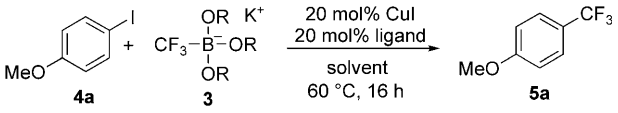
Table 1. CuI-mediated trifluoromethylation of 4-iodoanisole (**4a**) with the trifluoromethyl borates **3a–d**.[a]



Entry	Borate salt	**5a** [%][b]
1	**3a**	35
2	**3b**	46
3	**3c**	39
4	**3d**	35

[a] Reaction conditions: **4a** (0.50 mmol, 117 mg), **3a–d** (1.00 mmol), CuI (0.50 mmol, 95.2 mg), anhydrous DMF (2 mL), 60 °C, 16 h. [b] Yields were determined by GC analysis using *n*-tetradecane as the internal standard.

Table 2. Optimization of the Cu-catalyzed trifluoromethylation reaction of **4a** with **3a**.[a]



Entry	Borate salt	Ligand	Solvent	**5a** [%][b]
1	**3a**	–	DMF	6
2	**3a**	2,2′-bipyridine	DMF	6
3	**3a**	bathophenanthroline	DMF	46
4	**3a**	1,10-phenanthroline	DMF	55
5	**3a**	1,10-phenanthroline	DMF	46[c] 40[d]
6	**3a**	1,10-phenanthroline	toluene	0
7	**3a**	1,10-phenanthroline	THF	5
8	**3a**	1,10-phenanthroline	DMSO	71
9[e]	**3a**	1,10-phenanthroline	DMSO	80
10[e]	**3b**	1,10-phenanthroline	DMSO	66
11[e]	**3c**	1,10-phenanthroline	DMSO	95
12[e]	**3d**	1,10-phenanthroline	DMSO	83

[a] Reaction conditions: **4a** (0.50 mmol, 117 mg), **3a** (1.00 mmol), CuI (0.10 mmol, 19.1 mg), ligand (20 mol%), anhydrous and deoxygenated solvent (2 mL), 60 °C, 16 h. [b] Yields were determined by GC analysis using *n*-tetradecane as internal standard. [c] Reaction temperature 40 °C. [d] Reaction temperature 80 °C; 1,4-dimethoxybenzene (6%) was formed as a byproduct. [e] 1.5 mmol of the borate salt. A detailed screening table is presented in the Supporting Information.

ers had reported that the rate of the copper-mediated iodide–CF_3 exchange is usually much lower than that of the CF_3 group transfer from trifluoromethylation reagents to the copper.[22] As a result, copper iodide is produced in insufficient amounts to take up all CF_3 groups before the reagent decomposes. The key to achieving a catalytic turnover thus lay in facilitating the concerted σ-bond metathesis step by increasing the nucleophilicity of the [$CuCF_3$] species, for example, by use of electron-donating nitrogen ligands. Consequently, we investigated whether the yields could be improved by adding chelating amine ligands (Table 2, entries 2–4). Among the ligands tested, only phenanthroline derivatives promoted more than one turnover of the copper catalyst. In the presence of 1,10-phenanthroline, the product was obtained in 55% yield (Table 2, entry 4).

A systematic variation of the copper salts revealed that the counterion can considerably affect the reaction outcome. Good yields of **5a** were obtained with catalysts generated from copper(I) and copper(II) chloride (57 and 56%, respectively), copper(I) bromide (51%), or copper(I) acetate (58%). More strongly coordinating anions, such as fluoride or cyanide, were found to have an adverse effect on the activity of the catalyst (0 and 18%, respectively). The initial oxidation state of the copper salts was of less importance. Regardless of the copper salt employed, the reaction mixtures turned orange within a few minutes, indicating the presence of copper(I) complexes. Overall, copper iodide remained the copper source of choice. It is commercially available in anhydrous form, nonhygroscopic, and easy to store and handle.

The optimal reaction temperature was found to be 60 °C. Below this temperature, the reaction was rather slow, and at temperatures above 80 °C, salt **3a** decomposed with formation of volatile hydrofluorocarbons (Table 2, entry 5). The trimethyl borate formed in the process then reacts with **4a** under formation of 1,4-dimethoxybenzene.

The reaction could further be improved by optimizing the reaction solvent (Table 2, entries 6–8). The Cu salt was only poorly soluble in nonpolar reagents, such as toluene and THF, and only low yields were detected in these solvents. The use of basic amines as (co)solvents, such as quinoline, also had an adverse effect on the reaction outcome. Reasonable yields were obtained by using polar aprotic solvents, such as DMF, NMP, and *N*,*N*′-dimethylpropylene urea (DMPU) (55, 54, and 54%, respectively). The most effective solvent was found to be DMSO (Table 2, entry 8). By using a catalyst system consisting of 20 mol% of CuI and 1,10-phenanthroline in DMSO at 60 °C, the product was obtained in 71% yield, which could be increased to 80% when 3 rather than 2 equivalents of **3a** were employed (Table 2, entry 9). Under these reaction conditions, salts **3b–d** were investigated (Table 2, entries 10–12). A nearly quantitative conversion of **4a** into **5a** was observed when the more reactive CF_3 source, **3c**, was employed (Table 2, entry 11). This result demonstrates that, under the mild reaction conditions of the catalytic protocol, the beneficial effect of the reagent reactivity dominates over that of thermal stability.

Although **3a** was not the best trifluoromethylating reagent tested, we continued employing it as the CF_3 source due to its low molecular weight and good availability from simple trimethyl borate. Having found an optimized catalytic protocol for the model system, we next set out to explore the generality of the trifluoromethylation reaction with regard to the aryl iodide coupling partner. This required the development of an efficient workup procedure because the isolation of benzotrifluorides is sometimes as difficult as their synthesis. Simple benzotrifluorides are very volatile and hard to separate from excess solvent by distillation. Moreover, their R_f values are similar to those of the corresponding aryl iodides, complicating their separation from residual starting material by using column chromatography. Thus, it is advantageous to ensure that the aryl iodide start-

ing materials are fully consumed before working up the reaction.

The compounds are best isolated in a three-step process that was originally developed for the isolation of volatile arenes formed from Cu-catalyzed protodecarboxylation reactions.[29] First, the copper catalyst and residual borate salts are removed by diluting the reaction mixture with diethyl ether, washing it with aqueous ammonia solution, and drying the organic phase. Second, the diethyl ether is distilled off through a Vigreux column. Third, the resulting crude product is purified by Kugelrohr distillation at ambient pressure.

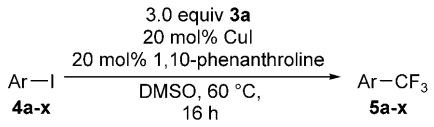
Under the optimized reaction conditions and using the described workup procedure, various trifluoromethylated arenes and heteroarenes were prepared and isolated in good yields (Table 3). Both electron-rich and -poor aryl iodides were smoothly converted, and most functional groups were tolerated. Heterocyclic substrates, such as iodopyridine and iodothiophene, also gave good results.

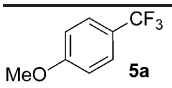
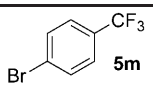
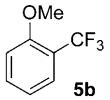
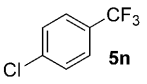
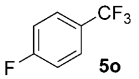
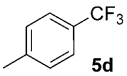
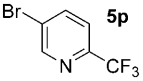
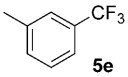
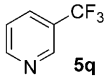
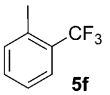
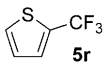
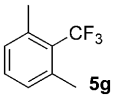
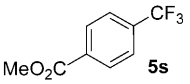
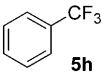
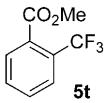
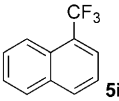
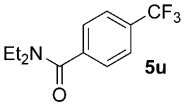
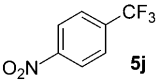
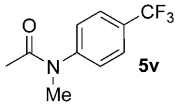
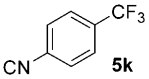
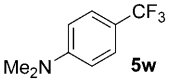
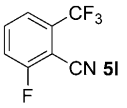
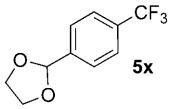
Sterically crowded substrates, such as **4g**, underwent the trifluoromethylation in moderate yields. Somewhat lower yields were obtained with compound **5w**, which contains an alkylamino group. We attribute this to a reduced activity of the copper catalyst resulting from its coordination by the amine group.

In the reaction of 4-bromo- and 4-chloro-1-iodobenzene the trifluoromethylation occurred selectively at the carbon–iodine bond, and the corresponding benzotrifluorides **5m** and **5n** were obtained in good yields. A ^{19}F NMR spectroscopic analysis of the crude reaction mixture confirmed that no conversion at the bromide or the chloride moiety took place. This finding is in agreement with the observations made for transformations of preformed $CuCF_3$ species, which are usually limited to aryl iodides. Under the reaction conditions, no side products, such as deiodinated arenes or pentafluoroethylated compounds, were detected by GC and ^{19}F NMR spectroscopic analyses of the reaction mixtures. Only unconverted aryl iodide was found along with decomposition products of the trifluoromethylating reagent.

The examples in Table 3 reveal that the new reagent can be used for the trifluoromethylation of both electron-rich and -poor aryl iodides. It is sufficiently mild to be tolerated by substrates containing moderately reactive carbon electrophiles, for example, esters, amides, and nitriles. However, aryl iodides containing particularly reactive carbonyl groups, for example, ketones and aldehydes, could be converted only in protected form. This is in agreement with findings for related nucleophilic trifluoromethylation procedures. As a consequence of the strongly basic nature of the CF_3 anionic species involved in such transformations, compounds with acidic protons are also unsuitable substrates.

Table 3. Scope of the Cu-catalyzed trifluoromethylation.[a]



Product	Yield [%][b]	Product	Yield [%][b]
 **5a**	77	 **5m**	93
 **5b**	83	 **5n**	75
 **5c**	91	 **5o**	81
 **5d**	74	 **5p**	81
 **5e**	92	 **5q**	82
 **5f**	70	 **5r**	85
 **5g**	59	 **5s**	84
 **5h**	91	 **5t**	96
 **5i**	97	 **5u**	95
 **5j**	81	 **5v**	96
 **5k**	95	 **5w**	52
 **5l**	76	 **5x**	84

[a] Reaction conditions: **3a** (2.54 g, 12.0 mmol), CuI (152 mg, 0.80 mmol), 1,10-phenanthroline (144 mg, 0.80 mmol), **4** (4.00 mmol), anhydrous and deoxygenated DMSO (8.0 mL), 60 °C, 16 h. [b] Isolated yields.

Conclusion

Potassium (trifluoromethyl)trialkoxyborates were introduced as nucleophilic CF_3 reagents for catalytic cross-couplings. They are stable, easy to store and handle crystalline salts that are readily accessible from the corresponding trialkoxyborates, Ruppert's reagent, and potassium fluoride.

Potassium (trifluoromethyl)trimethoxyborate (**3a**) was successfully employed in copper-catalyzed trifluoromethylations of aryl iodides. The optimized catalyst system, consisting of 20 mol% of copper(I) iodide and 1,10-phenanthroline, allows the smooth conversion of various aryl iodides

into their benzotrifluoride derivates in DMSO at 60 °C. The reaction is applicable to both electron-deficient and -rich arenes, as well as heteroarenes, and tolerates a broad range of functional groups. In all cases, the yields are comparable or in excess of those achieved with Ruppert's reagent. The latter is a low-boiling liquid, whereas the new trifluoromethylation reagents have advantageous properties that simplify their use, being nonvolatile, air-stable salts. Moreover, they are able to transfer the CF_3 groups under mild and neutral conditions with liberation of trimethyl borate without the need for basic additives.

The properties of the CF_3 borate salts depend on the alkoxy substituents, and it is thus likely that by varying these side chains, even more effective trifluoromethylating reagents can be developed in the near future. The new reagents may also open up new opportunities for other trifluoromethylation reactions including Buchwald's recently discovered Pd-catalyzed trifluoromethylation of aryl chlorides.

Experimental Section

General: All reactions were performed under a nitrogen atmosphere in oven-dried glassware using Teflon-coated stirrer bars. Solvents were purified by standard procedures and deoxygenated by passing argon through the liquid for 30 min prior to use. Unless otherwise noted, all other materials were obtained from commercial suppliers and used without further purification. Potassium fluoride was dried in vacuo ($<3\times10^{-3}$ mbar) at 200 °C overnight and stored under nitrogen. All reactions were monitored by GC analysis using *n*-tetradecane as an internal standard. Response factors of the products with regard to *n*-tetradecane were obtained experimentally by analyzing known quantities of the substances. Column chromatography was performed by using a Combi Flash Companion-Chromatography-System (Isco-Systems) and RediSep packed columns (12 g). Gas chromatographic analyses were performed with a HP-5 capillary column (Phenyl Methyl Siloxane; 30 m × 320×0.25 and a time program: 2 min at 60 °C followed by 30 °C min^{-1} ramp to 300 °C and then 3 min at this temperature. NMR spectra were recorded at 25 °C by using $CDCl_3$, [D_6]DMSO, or D_2O as solvent, with ^{1}H, ^{13}C, ^{19}F, and ^{11}B resonances at 600/400, 151/101, 128, and 376 MHz, respectively. Mass spectrometry was performed with a GC-MS Varian Saturn 2100 T instrument; the ionization was achieved by EI AGC. CHN elemental analysis was performed with a Hanau Elemental Analyzer vario Micro cube. Infrared spectra were recorded with a Perkin–Elmer Fourier transform spectrometer; liquids were analyzed as a thin film between NaCl plates and solids as KBr pellets. Frequencies are reported in wavenumbers (cm^{-1}). Synthetic procedures and characterization data for known compounds are given in the Supporting Information.

Potassium (trifluoromethyl)tris(2-methoxyethyl)borate (3c): An oven-dried 100 mL crimp-top vial was charged with potassium fluoride (2.63 g, 45.2 mmol), then evacuated and refilled with nitrogen three times. Anhydrous THF (60 mL), tris(2-methoxyethyl) borate (11.8 g, 49.5 mmol), and (trifluoromethyl)trimethylsilane (Ruppert's reagent; 7.68 g, 54.0 mmol, 8.6 mL) were added and the suspension was stirred until a colorless solution was obtained (approx. 24–48 h). The mixture was concentrated to dryness, anhydrous pentane (100 mL) was added and the resulting colorless solid was filtered, washed with anhydrous pentane (2×50 mL) and dried in vacuo to yield **3c** as a colorless solid (10.5 g, 67 %). M.p. 106–108 °C; ^{1}H NMR (400 MHz, D_2O): $\delta=3.62$–3.71 (m, 6H; CH_2), 3.48–3.56 (m, 6H; CH_2), 3.33 ppm (s, 9H; CH_3); ^{13}C NMR (101 MHz, D_2O): $\delta=$ 73.1 (CH_2), 60.1 (CH_2), 58.0 ppm (CH_3); ^{19}F NMR (376 MHz, D_2O): $\delta=$ −74.73 ppm (m); ^{11}B NMR (128 MHz, D_2O): $\delta=-1.12$ ppm (m); IR (KBr): $\tilde{\nu}=2895$ (m), 1559 (w), 1090 (s), 872 (m), 682 cm^{-1} (s); elemental analysis calcd (%) for $C_{10}H_{21}BF_3KO_3$ (296): C 34.90, H 6.15; found: C 34.81, H 6.28.

Potassium (trifluoromethyl)tris(tetrahydrofurfuryl alcohol)borate (3d): An oven-dried 100 mL crimp-top vial was charged with potassium fluoride (2.37 g, 40.9 mmol), then evacuated and refilled with nitrogen three times. Anhydrous THF (60 mL), tris(tetrahydrofurfuryl alcohol) borate (13.9 g, 43.9 mmol), and (trifluoromethyl)trimethylsilane (Ruppert's reagent; 6.83 g, 48.0 mmol, 7.6 mL) were added and the suspension was stirred until a colorless solution was obtained (approx. 24–48 h). The mixture was concentrated to dryness, anhydrous pentane (100 mL) was added and the resulting colorless solid was filtered, washed with anhydrous pentane (2×50 mL) and dried in vacuo to yield **3d** as a colorless solid (7.47 g, 43 %). M.p. 142–144 °C; ^{1}H NMR (400 MHz, D_2O): $\delta=3.96$ (m, 3H; CH_2), 3.69–3.81 (m, 6H; CH_2), 3.56 (m, 3H; CH_2), 3.46 (m, 3H; CH_2), 1.80–1.98 (m, 9H; CH_2), 1.50–1.61 ppm (m, 3H; CH_2); ^{13}C NMR (101 MHz, D_2O): $\delta=79.5$, 68.0, 63.6, 26.8, 25.2 ppm; ^{19}F NMR (376 MHz, D_2O): $\delta=-74.87$ ppm (q); ^{11}B NMR (128 MHz, D_2O): $\delta=-1.16$ ppm (m); IR (KBr): $\tilde{\nu}=2881$ (m), 1653 (w), 1559 (w), 1080 (s), 898 cm^{-1} (m); elemental analysis calcd (%) for $C_{16}H_{27}BF_3KO_6$ (422): C 45.51, H 6.44; found: C 45.86, H 6.58.

***N*-Methyl-4-iodoacetanilide (4v)**: A modified literature procedure was followed.[30] A 100 mL round-bottomed Schlenk flask with a rubber septum was charged with sodium hydride suspension in mineral oil (60 %, 480 mg, 12 mmol), which was washed with anhydrous pentane (20 mL), and evacuated and refilled with nitrogen three times. A solution of 4-iodoacetanilide (2.61 g, 10.0 mmol) in anhydrous THF (50 mL) was added and the mixture was stirred for 15 min. Methyl iodide (1.70 g, 12.0 mmol, 747 μL) was added at 5 °C and stirring was continued for 1 h at RT. The reaction mixture was diluted with $CHCl_3$ (50 mL) and washed with 1 N HCl (100 mL). The washing was re-extracted with $CHCl_3$ (2× 20 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to yield **4v** as a colorless solid (2.81 g, 83 %). M.p. 144–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.70$ (m, 2H; CH), 6.92 (m, 2H; CH), 3.20 (s, 3H; CH_3), 1.83 ppm (s, 3H; CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=170.0$ (CO), 144.1, 138.7, 128.9, 92.6, 36.9 (CH_3), 22.3 ppm (CH_3); MS (Ion trap, EI): *m*/*z* (%): 275 (36) $[M]^+$, 233 (100), 105 (18), 77 (21), 63 (17), 56 (68); IR (KBr): $\tilde{\nu}=2927$ (w), 1644 (s, C=O), 1482 (s) 1379 (m), 1006 (m), 823 (m), 552 cm^{-1} (m); elemental analysis calcd (%) for $C_9H_{10}INO$ (275): C 39.30, H 3.66, N 5.09; found: C 39.53, H 3.66, N 5.07.

***p*-(1,3-Dioxolan-2-yl)iodobenzene (4x)**: A modified procedure was followed.[31] A 100 mL round-bottomed flask was fitted with a dropping funnel filled with 3 Å molecular sieves and a condenser. The reaction vessel was charged with 4-iodobenzaldehyde (1.56 g, 6.45 mmol), *p*-toluenesulfonic acid (207 mg, 1.20 mmol), ethylene glycol (16.7 g, 269 mol, 15 mL), and $CHCl_3$ (50 mL). The mixture was heated to reflux for 16 h, then cooled to RT, and washed with water (50 mL) and saturated aqueous sodium bicarbonate (50 mL). The combined washings were re-extracted with $CHCl_3$ (2×20 mL), and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated to yield **4x** as a colorless solid (1.74 g, 98 %). M.p. 48–50 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.73$ (d, ^3J(H,H)=8.3 Hz, 2H; CH), 7.23 (d, ^3J-(H,H)=8.3 Hz, 2H; CH), 5.76 (s, 1H; CH), 3.99–4.14 ppm (m, 4H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=137.6$, 137.3, 128.2, 103.0, 95.0 (CH), 65.2 ppm (CH_2); MS (Ion trap, EI): *m*/*z* (%): 275 (100) $[M]^+$, 231 (29), 204 (22), 105 (43), 91 (15), 73 (41), 51 (16); IR (KBr): $\tilde{\nu}=2874$ (w), 1589 (w), 1420 (m), 1076 (s), 1005 (s), 817 cm^{-1} (s); elemental analysis calcd (%) for $C_9H_9IO_2$ (276): C 39.16, H 3.29; found: C 39.23, H 3.40.

General procedure for Cu-catalyzed trifluoromethylations: An oven-dried crimp-top vial equipped with a septum cap and a stirrer bar was charged with copper(I) iodide (152 mg, 0.80 mmol), 1,10-phenanthroline (144 mg, 0.80 mmol), and **3a** (2.54 g, 12.0 mmol). The reaction vessel was closed, then evacuated and refilled with nitrogen three times. Anhydrous deoxygenated DMSO (8.0 mL) and aryl iodide (4.00 mmol) were added by using a syringe. Solid aryl iodides were weighed directly in the reaction vessel. The resulting orange–brown suspension was stirred for 16 h at 60 °C. After cooling to ambient temperature, the orange solution was diluted with Et_2O (20 mL) and washed with 1 N HCl (50 mL). Acidic

washing was omitted for basic products. The washing was re-extracted with Et_2O (2×10 mL) and the combined organic layer was washed with conc. ammonia (25%, 50 mL) to remove traces of copper salts. The washing was re-extracted with Et_2O (2×10 mL) and the combined organic layer was washed with brine (30 mL), dried over $MgSO_4$ and concentrated by distillation over a 50 cm Vigreux column. The crude product was purified by Kugelrohr distillation at ambient pressure, if not noted otherwise.

4-Bromo-2-trifluoromethylpyridine (5p): Synthesized from **4p** (1.14 g, 4.00 mmol), copper(I) iodide (152 mg, 0.80 mmol), 1,10-phenanthroline (144 mg, 0.80 mmol), and **3a** (2.54 g, 12.0 mmol) according to the general procedure to yield **5p** as a colorless solid after recrystallization from methanol (732 mg, 81%). M.p 36–38 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (d, ^4J(H,F) = 1.7 Hz, 1H; CH), 8.03 (dd, ^3J(H,H) = 8.3, J(H,F) 2.2 Hz, 1H; CH), 7.60 ppm (d, ^3J(H,H) = 8.3 Hz, 1H; CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.3, 144.7 (q, ^2J(C,F) = 35.2 Hz), 140.0, 124.0, 121.7 (q, ^3J(C,F) = 2.9 Hz), 121.3 ppm (q, ^1J(C,F) = 273.6 Hz; CF_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −68.00 ppm (d, J = 13.75 Hz); MS (Ion trap, EI): m/z (%): 226 (100) $[M]^+$, 225 (45), 208 (17), 206 (17), 158 (18), 156 (19), 146 (48), 126 (25), 96 (11), 69 (39); IR (NaCl): $\tilde{\nu}$ = 2937 (w), 1581 (w), 1334 (s), 1181 (s), 1097 (s), 1010 (m), 843 cm^{-1} (w); elemental analysis calcd (%) for $C_6H_3BrF_3N$ (226): C 31.89, H 1.34, N 6.20; found: C 31.65, H 1.65, N 6.07.

***N*-Methyl-4-trifluoromethylacetanilide (5v)**: Synthesized from **4v** (1.10 g, 4.00 mmol), copper(I) iodide (152 mg, 0.80 mmol), 1,10-phenanthroline (144 mg, 0.80 mmol), and **3a** (2.54 g, 12.0 mmol) according to the general procedure to yield **5v** as a colorless solid after recrystallization from *n*-hexane (832 mg, 96%). M.p 84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, ^3J(H,H) = 8.1 Hz, 2H; CH), 7.31 (d, ^3J(H,H) = 8.1 Hz, 2H; CH), 3.26 (s, 3H; CH_3), 1.89 ppm (s, 3H; CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.9 (CO), 147.5, 138.8, 127.0 (d, ^2J(C,F) = 58.3 Hz), 123.6 (q, ^1J(C,F) = 272.8 Hz; CF_3), 37.0 (CH_3), 22.4 ppm (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −62.60 ppm; MS (Ion trap, EI): m/z (%): 217 (32) $[M]^+$, 175 (91), 174 (100), 145 (19), 127 (14), 95 (8), 75 (10); IR (NaCl): $\tilde{\nu}$ = 3061 (w), 1661 (s, C=O), 1610 (s), 1325 (s), 1159 (s), 1120 (s), 1066 (m), 858 cm^{-1} (m); elemental analysis calcd (%) for $C_{10}H_{10}F_3NO$ (217): C 55.30, H 4.64, N 6.45; found: C 55.15, H 4.79, N 6.51.

***p*-(1,3-Dioxolan-2-yl)trifluoromethylbenzene (5x)**: Synthesized from **4x** (1.10 g, 4.00 mmol), copper(I) iodide (152 mg, 0.80 mmol), 1,10-phenanthroline (144 mg, 0.80 mmol), and **3a** (2.54 g, 12.0 mmol) according to the general procedure to yield **5x** as a colorless oil (741 mg, 84%). B.p. (Kugelrohr) 220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.75 (m, 4H; CH), 5.87 (s, 1H; CH), 3.94–4.19 ppm (m, 4H; CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.4, 131.1 (q, ^2J(C,F) = 32.4 Hz), 126.8, 125.3 (q, ^3J(C,F) = 3.7 Hz), 124.0 (q, ^1J(C,F) = 272.8 Hz; CF_3), 102.7 (CH), 65.3 ppm (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −62.68 ppm; MS (Ion trap, EI): m/z (%): 218 (15) $[M]^+$, 217 (100), 173 (18), 149 (17), 145 (16), 127 (12), 119 (14), 73 (35); IR (NaCl): $\tilde{\nu}$ = 2890 (brs), 1930 (brs), 1621 (w), 1585 (m), 1427 (s), 1325 (s), 1125 (s), 1017 (s), 833 cm^{-1} (m); elemental analysis calcd (%) for $C_{10}H_9F_3O_2$ (218): C 55.05, H 4.16; found: C 55.13, H 4.02.

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