C–H Activation

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Palladium-Catalyzed Trifluoromethylation of (Hetero)Arenes with CF_3Br

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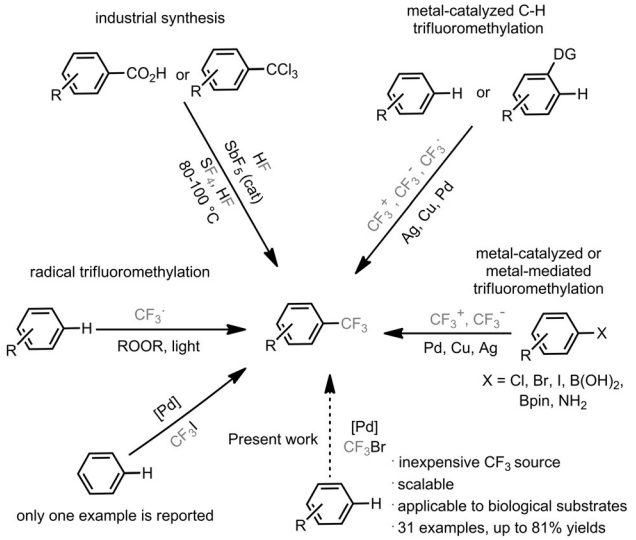
Abstract: *The CF_3 group is an omnipresent motif found in many pharmaceuticals, agrochemicals, catalysts, materials, and industrial chemicals. Despite well-established trifluoromethylation methodologies, the straightforward and selective introduction of such groups into (hetero)arenes using available and less expensive sources is still a major challenge. In this regard, the selective synthesis of various trifluoromethyl-substituted (hetero)arenes by palladium-catalyzed C–H functionalization is herein reported. This novel methodology proceeds under comparably mild reaction conditions with good regio- and chemoselectivity. As examples, trifluoromethylations of biologically important molecules, such as melatonin, theophylline, caffeine, and pentoxifylline, are showcased.*

Fluorinated compounds continue to be of major interest for the synthesis of pharmaceuticals, agrochemicals, liquid crystals, dyes, polymers, and functional materials. In general, the introduction of a CF_3 group leads to a significant change in the physical properties of the parent molecule. For example, trifluoromethylated drugs exhibit enhanced membrane permeability and increased bioavailability compared to their nonfluorinated analogues.[1] Already today, around 25% of all pharmaceuticals and 30% of the applied agrochemicals contain at least one or even more trifluoromethyl substituents, or a fluorine atom.[2] The vast majority of the known organofluorine compounds are made from relatively simple building blocks. Methodologies to incorporate CF_3 synthons at a later stage of a given synthesis make use of sophisticated trifluoromethylation reagents which are difficult to use on a larger scale. For all these reasons, there exists a strong interest in novel trifluoromethylation chemistry, which is also the subject of intense research in industry and academia.[3] Regarding synthesis, the most commonly applied industrial trifluoromethylation involves the substitution of either carboxy or trichloromethyl groups by hazardous fluorinating agents (Scheme 1).[4] Because of the harsh reaction conditions



Scheme 1. Trifluoromethylation of aryl and heteroaryl compounds. DG = donating group.

required in these transformations, several recent alternative trifluoromethylation protocols have been elegantly developed. Most of these alternative approaches are based on either transition-metal-mediated[5] or metal-catalyzed cross-coupling reactions[6] of arylboronic acids/esters, aryl halides, and either anilines or the corresponding diazonium salts.[7] Here, CF_3 groups can be regioselectively introduced to different aromatic scaffolds. However, multiple steps for the preparation of the starting materials are required and generation of the stoichiometric amounts of metal salts decrease the overall synthetic efficiency.

To overcome such drawbacks, direct C–H trifluoromethylation of (hetero)arenes has received considerable attention.[2,3a,b] However, this chemistry is significantly less developed despite the fact that it has great potential for medicinal and agrochemical syntheses.[8] For example, directing-group-assisted palladium- or silver-catalyzed oxidative trifluoromethylations were described by the groups of Yu[9] and Bräse.[10] Furthermore, related palladium-[11] and copper-catalyzed[12] oxidative trifluoromethylations were disclosed. In addition, the synthesis of advanced trifluoromethylated building blocks by radical processes were described by the groups of MacMillan[13] and Baran[14] using either visible light or *t*BuOOH (TBHP) to initiate CF_3 radical formation from eithr CF_3SO_2Cl or CF_3SO_2Na (Langlois reagent).

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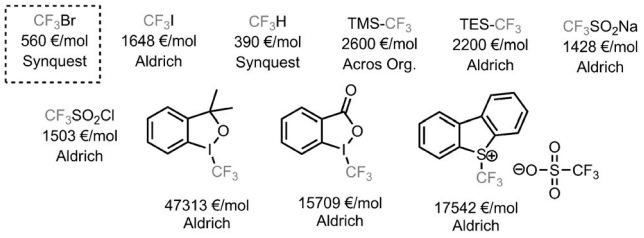


Figure 1. Price of selected trifluoromethylating agents. TES = triethylsilyl, TMS = trimethylsilyl.

Despite all these achievements, an ongoing challenge in the development of trifluoromethylation process is the use of available and less expensive CF_3 sources/reagents. The most commonly used CF_3 sources in organic synthesis and their actual prices per mole are shown in Figure 1. Among the commercially available trifluoromethylation sources, CF_3Br (commonly called as halon 1301) attracted our interest since this reagent is relatively inexpensive and still available in large quantities because of its use for fire suppression, etc.[15] Comparing CF_3Br with most other trifluoromethylation reagents, this compound can be produced with much less waste formation. However, it should be noted that CF_3Br, like most halofluorocarbons, has strong ozone depletion potential. Hence, proper measurements should be taken to avoid exposure of the reagent to the atmosphere. Despite the general advantages, the use of CF_3Br to generate trifluoromethylated products has been scarcely explored. Indeed, to the best of our knowledge only two publications from the group of Langlois, as well as Sugimori and co-workers, reported the synthesis of regioisomeric trifluoromethylated compounds in low yields.[16] In addition to CF_3Br, we also tested unactivated CF_3H under our optimized reaction conditions. Unfortunately we did not observe any trifluoromethylated product.

Based on our previous work on perfluoroalkylations,[8k] recently we became interested in exploring the use of CF_3Br for direct catalytic C–H trifluoromethylations. In this respect, we report herein the first palladium-catalyzed C–H trifluoromethylation of unfunctionalized (hetero)arenes without the necessity of directing groups.

In our initial studies, we investigated the trifluoromethylation of 1,4-dimethoxybenzene (**1a**) with CF_3Br in the presence of $Pd(OAc)_2$ and $BuPAd_2$ (*n*-butyl-di-1-adamantylphosphine) as a ligand. This catalyst system was chosen because it allows an efficient activation of various C–X bonds.[17] For effective catalytic testing, product yields were determined primarily by ^{19}F NMR spectroscopy. Indeed, 18% of the desired product (**1b**) is obtained in the presence of acetone and Cs_2CO_3 at 130 °C after 40 hours (see entry 1 of Table S1 in the Supporting Information). Testing various commercially available monodentate and bidendate phosphine ligands (see entries 1–13 of Table S2) under these reaction conditions led to lower yields or no product at all, thus demonstrating the challenging nature of this trifluoromethylation reaction.

To improve the C–H activation step and to enhance the yield of the desired product, different oxidants were added (Table S1, entries 2–10). In fact, in the presence of stoichiometric amounts of Ag_2O, $Cu(OAc)_2$, and BQ (benzoquinone) (slightly) improved yields are obtained (Table S1, entries 4, 6 and 9). To our surprise, addition of one equivalent of TEMPO (2,2,6,6-tetramethylpiperidinyloxyl) in the presence of the optimal palladium catalyst system led to 81% yield (69% of the isolated product) of the desired product (Table S1, entry 11)! Further optimization studies were conducted with different solvents and bases (see Table S2). Apart from the positive influence of TEMPO, the choice of the ligand ($BuPAd_2$) is also crucial for obtaining high product yields. As shown in Table S1 (entries 12–22), in the presence of other well-known mono- and bidentate phosphine ligands significantly lower yields of the desired product are achieved. Only traces of the desired product are obtained without any phosphine ligand present (Table S1, entry 26). As expected, no reaction occurred in the absence of Pd (Table S1, entry 27).

Having a reliable C–H trifluoromethylation protocol in hand, we examined the substrate scope by employing structurally diverse arenes and heteroarenes. In the course of this different substituted electron-rich arenes were transformed into valuable trifluoromethylated compounds in moderate to good yields. Benzenes bearing methoxy groups at various positions are well-tolerated and the corresponding products are obtained in good yields (**1**–**4**; Figure 2). In the case of 1,2-dimethoxybenzene the sterically less hindered regioisomer is formed preferentially. Notably, trifluoromethylation of chloro-, bromo-, and fluoro-substituted anilines proceeded and gave the desired products, which constitute industrial important building blocks, in a straightforward manner (**5**–**9**). The compatibility with halide and free amino substituents illustrate an orthogonal reactivity to conventional C–X trifluoromethylation reactions. In addition, electron-withdrawing groups such as nitrile and ketone are tolerated (**10**, **11**, and **14**). Notably, new trifluoromethylated building blocks can be easily accessed by this methodology (**12** and **13**). The exclusive selectivity in these latter cases is a practical advantage. The reaction also worked well for non-activated arenes, thus giving moderate to good yields of the corresponding trifluoromethylated products (**15**–**17** and **19**). Even sterically hindered pentamethylbenzene underwent trifluoromethylation in moderate yield (**18**). Moreover, naphthalene was successfully trifluoromethylated in 78% yield and 3:1 regioselectivity (**20**).

To demonstrate the potential utility of this reaction for medicinal chemistry, the trifluoromethylation of different heterocycles was investigated. 1,2- and 1,3-dimethyl-substituted indoles underwent smooth trifluormethylation, thus giving high yields (**21** and **22**; Figure 2). Interestingly, the reaction worked well for 2-acetyl-1-methylpyrrole and 2-acetylpyrrole with good yields (**23** and **24**). Furthermore, *N*-methyl pyrrole afforded the 2-trifluormethlyated product **25** as a single isomer. In addition, 2-methylthiophene was also successfully trifluoromethylated (**26**). Importantly, selective C–H trifluoromethylation of biologically active molecules such as melatonin, theophylline, caffeine, and pentoxifylline led to the desired products in moderate to good yields upon isolation (**27** and **29**–**31**). Finally, our protocol was applied

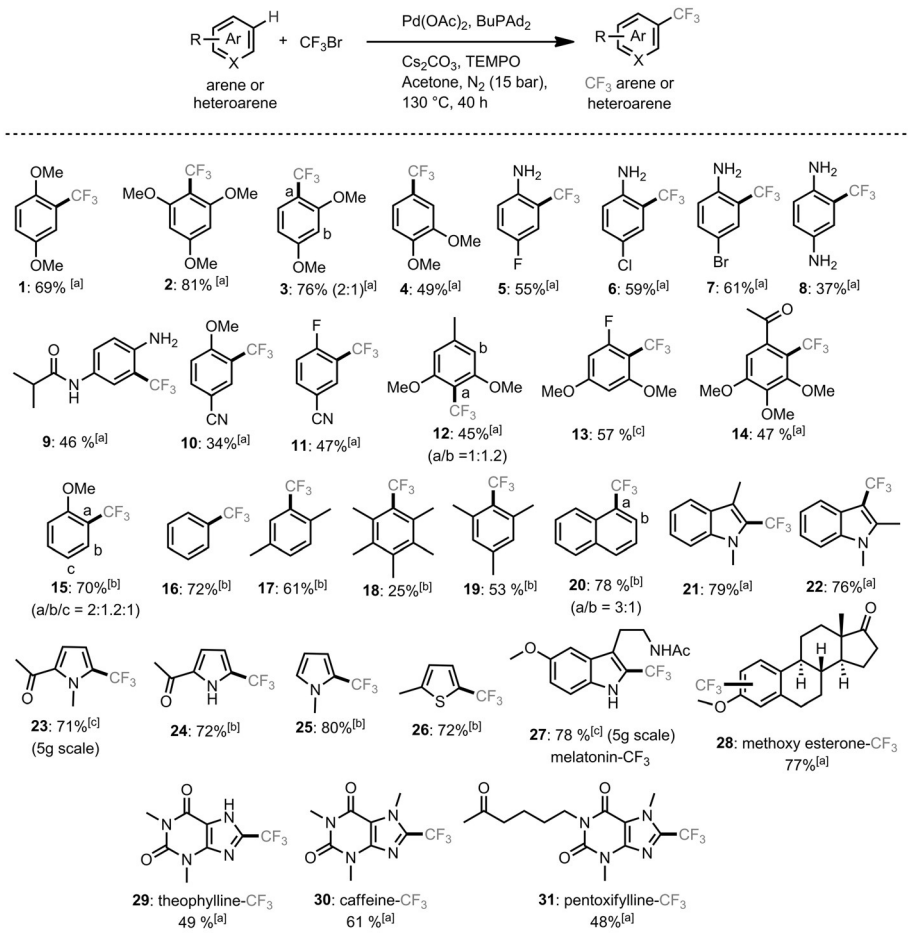
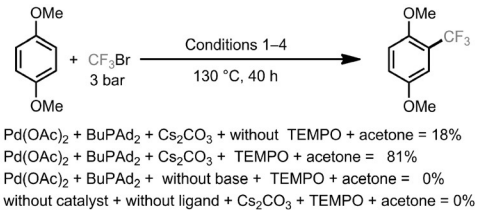


Figure 2. Palladium-catalyzed trifluoromethylation of (hetero)arenes: Substrate scope. Reaction conditions: **1a** (0.2 mmol), CF_3Br (3–10 bar), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), Cs_2CO_3 (2.0 equiv), TEMPO (1.0 equiv), acetone (0.5–2 mL), 130°C, 40-50 h, N_2 (15 bar). See the Supporting Information for the reaction procedure for every substrate. [a] Yields of product isolated after column chromatography. [b] Yields determined by ^{19}F NMR spectroscopy using 1,4-difluorobenzene as an internal standard. [c] Reaction scale on 5 grams (see the SI for reaction procedure).



Scheme 2. Mechanistic studies: Selected control experiments.

successfully to an estrone derivative, but a mixture of two regioisomeric products was obtained in 77% yield (**28**). Notably, most of the trifluoromethylation experiments were run on a 0.2–1 mmol scale. However, reactions on a 5 gram scale are also possible (**23** and **27**).

To investigate the mechanism of this novel trifluoromethylation protocol, control experiments of the benchmark reaction (1,4-dimethoxybenzene) and in situ spectroscopic measurements were performed. As shown in Scheme 2, no trifluoromethylation occurred in the absence of palladium, ligand, and base.

Among the various additives, TEMPO is the most efficient promotor of this reaction (see Tables S1 and S2 and Scheme S1 in the Supporting Information). Notably, a similar effect using Rupperts reagent has been observed by Liu and co-workers.[11a] As shown in Figure 3, a radical mechanism is proposed for this novel transformation based on EPR investigations. More specifically, a mixture of $Pd(OAc)_2$ and $BuPAd_2$ suspended in toluene saturated with CF_3Br gave a clear EPR signal, which corresponds to a CF_3 radical (see the Supporting Information). This electrophilic radical is supposed to react directly with the arene. Subsequent reaction with $PdBrL_2$ leads to $HPdL_2Br$, which is detected by NMR spectroscopy. Final quenching with Cs_2CO_3 converts **B** into the active species **A** and closes the catalytic cycle. Interestingly, in this mechanistic proposal the role of the specific Pd^0L_2 complex is to cleave the CF_3–Br bond homolytically to release the CF_3 radical. The positive role of TEMPO is explained by its function both as single-electron reducing agent, as well as an oxidizing agent, which facilitates the subtle interplay between the different palladium species (for more details see the Supporting Information).

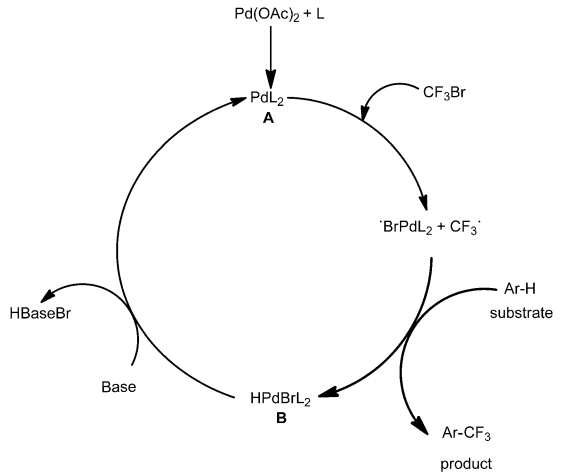


Figure 3. Proposed reaction mechanism.

In summary, we have developed the first general palladium-catalyzed trifluoromethylation reaction of arenes using CF_3Br. Compared to most trifluoromethylation protocols there is no need to apply very costly CF_3 reagents as well as strong oxidants, or peroxides. Crucial for the success of this transformation is the use of a specific palladium catalyst and addition of TEMPO as a mild redox mediator. This methodology worked well for electron-rich and electron-neutral arenes and heteroarenes, even on gram scale. Further improvements of the catalyst performance are currently under way in our laboratory.

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