

Palladium-Catalyzed 2,2,2-Trifluoroethylation of Organoboronic Acids and Esters**

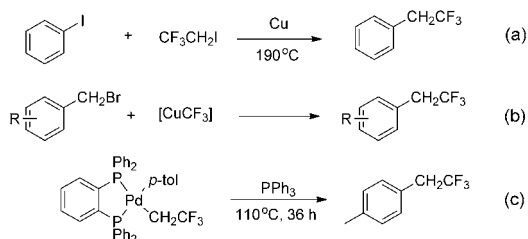
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The introduction of a fluorinated moiety into organic molecules can result in profound changes of the biological activities of these molecules, and therefore, this strategy has been widely used in drug design.^[1] Among various fluorinated moieties, the trifluoromethyl group (CF₃) has been the focus of increasing attention owing to its capacity to act as a lipophilic electron-withdrawing group.^[2] In stark contrast to the tremendous progress that has been made toward the direct introduction of a trifluoromethyl group into functionalized aromatic compounds,^[3] the analogous transformation to form (2,2,2-trifluoroethyl)arenes remains largely unexplored, despite many potential utilities of CF₃CH₂-containing products in medicinal chemistry and related fields.^[4] The copper(0)-mediated direct 2,2,2-trifluoroethylation of iodo-benzene with trifluoroethyl iodide (CF₃CH₂I) was reported by McLoughlin and Thrower in 1969.^[5] The product was obtained in only 15% yield despite the harsh reaction conditions and long reaction time employed by this method (Scheme 1 a). Furthermore, trifluoromethylations of benzyl bromides with [CuCF₃] species, which are generated from different precursors, are generally employed to afford

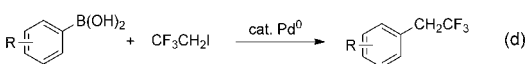
(trifluoroethyl)arenes^[6] (Scheme 1 b). Very recently, Shibata and co-workers reported the trifluoromethylation of benzyl bromides with [CuCF₃] species, which were generated in situ from an electrophilic trifluoromethylating reagent and a stoichiometric amount of copper, under mild reaction conditions with good substrate generality.^[7]

We surmised that a transition-metal-catalyzed 2,2,2-trifluoroethylation using readily available trifluoroethyl iodide (CF₃CH₂I) and organoboronic acids could provide an alternative method for the preparation of (2,2,2-trifluoroethyl)arenes; a process that has not been reported to date. Previously, it was believed that many (2,2,2-trifluoroethyl)metals (CF₃CH₂-M) are labile species (especially when the C–M bond possesses a highly ionic nature) because of their high tendency to β eliminate a fluoride ion, and that their stability is thus greatly affected by the degree of covalency of the C–M bond.^[8] The use of CF₃CH₂-M species in trifluoroethylation reactions is still largely unexplored. In 2004, Culkin and Hartwig reported a stoichiometric version of the formation of an Ar–CH₂CF₃ bond from a Pd^{II} species by heating the complex [(DPPBz)Pd(CH₂CF₃)(*p*-tol)] (prepared from [(DPPBz)Pd(CH₂CF₃)(I)] and *p*-tolyllithium; DPPBz = 1,2-bis(diphenylphosphanyl)benzene) at 110°C for 36 h (Scheme 1 c).^[9] However, slow oxidative addition of alkyl halides, high temperature and/or long reaction time for the reductive elimination, and an uncertain outcome of the transmetalation process with nucleophiles other than aryllithium reagents hampered the use of these methods^[9] as efficient catalytic processes. On the other hand, during the past decade, applications of bulky dialkylbiaryl^[10] and trialkyl phosphines^[11] along with N-heterocyclic carbenes (NHC)^[12] as supporting ligands have dramatically improved the efficiency and scope of Pd-catalyzed cross-coupling reactions, as exemplified by the remarkable success in the direct formation of aryl–CF₃^[3b] and aryl–F bonds.^[13] In light of these progresses, we felt that by using a suitable ligand, the efficient Pd-catalyzed cross-coupling reaction between readily available 2,2,2-trifluoroethyl iodide (CF₃CH₂I) and organoboronic acids (or esters) might be accomplished under mild conditions (Scheme 1 d).

Previous work (stoichiometric processes)



This work (catalytic process)

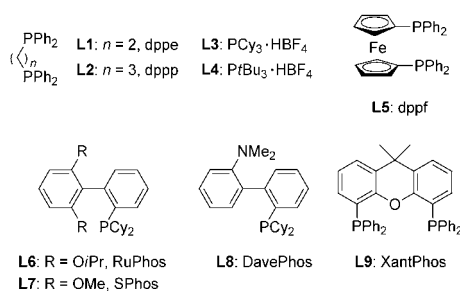


Scheme 1. Traditional methods versus our method for the preparation of (2,2,2-trifluoroethyl)arenes (*p*-tol = *para*-tolyl).

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Scheme 2. Various ligands used in Pd-catalyzed cross-coupling reactions. Cy = cyclohexyl.

Table 1: Survey of reaction conditions.^[a]

Entry	Ligand	Base	H ₂ O (equiv)	Molar ratio (1a:2)	Yield [%] ^[e]
1 ^[b]	L1	K ₃ PO ₄	–	1:2	trace
2 ^[b]	L2	K ₃ PO ₄	–	1:2	trace
3 ^[b]	L3	K ₃ PO ₄	–	1:2	trace
4 ^[b]	L4	K ₃ PO ₄	–	1:2	trace
5 ^[b]	L5	K ₃ PO ₄	–	1:2	4
6 ^[b]	L6	K ₃ PO ₄	–	1:2	34
7 ^[b]	L7	K ₃ PO ₄	–	1:2	20
8 ^[b]	L8	K ₃ PO ₄	–	1:2	20
9 ^[b]	L9	K ₃ PO ₄	–	1:2	50
10 ^[b]	L9	Cs ₂ CO ₃	–	1:2	59
11 ^[c]	L9	Cs ₂ CO ₃	18	1:2	78
12 ^[c]	L9	Cs ₂ CO ₃	18	1:3	80 (69)
13 ^[d]	L9	Cs ₂ CO ₃	18	1:2	92 (81)

[a] Unless stated otherwise, the reactions were run on a 0.2 mmol scale (1a) in dioxane (2 mL). [b] $x = 2.5$, base (2.5 equiv); $x:y = 1:6$ for monophosphine ligands, $x:y = 1:4$ for bisphosphine ligands. [c] $x = 2.5$, $y = 8.5$, Cs₂CO₃ (4.0 equiv). [d] The reaction was run on a 0.4 mmol scale (1a) in dioxane (3 mL), $x = 5$, $y = 17$, Cs₂CO₃ (4.0 equiv). [e] Yields determined by ¹⁹F NMR spectroscopy using PhCF₃ as an internal standard; data in parentheses refer to yields of isolated products. dba = *trans,trans*-dibenzylideneacetone.

ineffective in the current reaction (Table 1, entries 1–4). The rigid bidentate phosphine ligand dppf (L5), which is commonly used in Suzuki–Miyaura cross-coupling reactions, gave the desired product in a poor yield^[14] (Table 1, entry 5), thus suggesting a slow reductive elimination with this ligand at 80 °C. The dialkylbiaryl phosphine ligands developed by Buchwald and co-workers^[10] are known to substantially accelerate the reductive elimination, and RuPhos (L6) was more effective than SPhos (L7) and DavePhos (L8) in the current reaction (Table 1, entries 6–8). XantPhos (L9), which is a bidentate phosphine ligand with a wide bite angle, was found to be the best ligand among L1–L9 in the current reaction (Table 1, entry 9).^[15]

With the optimal combination of Pd and ligand established, we next investigated the influence of the base and additives. Cs₂CO₃ was found to be more effective than relatively weaker bases, such as K₃PO₄ and K₂CO₃, while

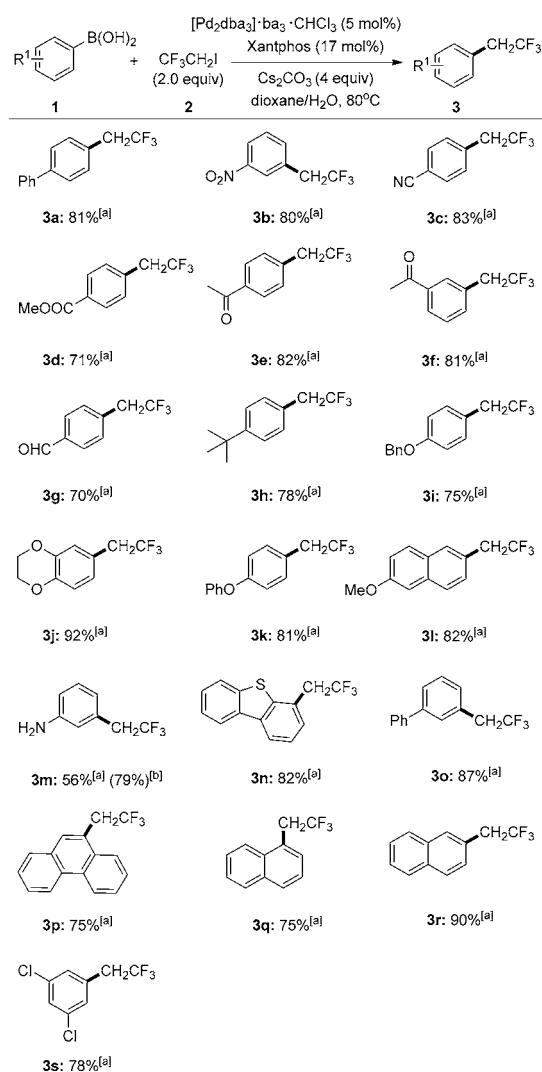
KOAc proved to be completely ineffective with essentially no formation of the desired product. The addition of water, which is known to facilitate the transmetalation step, was found to be beneficial for the reaction, although the amount of added water had to be carefully optimized (Table 1, entry 11). Increasing the amount of CF₃CH₂I did not significantly improve both the conversion of 1a and the product yield (Table 1, entries 11 and 12). We hypothesized that CF₃CH₂I may cause a partial inhibition of the catalyst through side (redox) reactions with Pd⁰ and/or phosphine ligands, because a considerable amount of CF₃CH₃ was observed in the reaction. The yield of the product was further improved by increasing the amount of the catalyst, and 4-(2,2,2-trifluoroethyl)-1,1'-biphenyl (3a) was isolated in 81 % yield (Table 1, entry 13; optimized reaction conditions).

We next examined the substrate scope of the cross-coupling reaction between CF₃CH₂I (2) and boronic acids 1 (Scheme 3) using the optimized reaction conditions. Various boronic acids 1 were treated with 2, and the corresponding (trifluoroethyl)arenes 3 were smoothly obtained in good to excellent yields. This method tolerates various functional groups attached to the aryl boronic acid; the reactions with aryl boronic acids that contain either electron-withdrawing groups, such as nitro (1b), cyano (1c), ester (1d), acetyl (1e and 1f), and formyl (1g), or electron-donating groups, such as *tert*-butyl (1h) and benzyloxy (1i), afforded the desired products in 70–92 % yields. It is worth noting that the reaction also tolerates free amino groups (NH₂), and that no *N*-trifluoroethylated product was observed. Such trifluoroethylated anilines were previously obtained through multistep syntheses by reduction of the corresponding nitrobenzenes.^[4g]

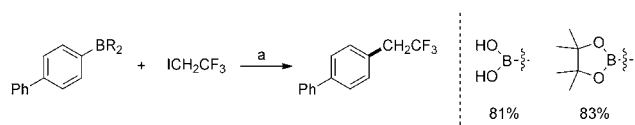
Many boronic acids are prepared from organoboronic esters by hydrolysis, however, this transformation step can be low-yielding.^[16] Therefore, organoboronic esters might be more favorable substrates in some cases. To our delight, pinacol boronic esters could also participate in the current trifluoroethylation under the optimized reaction conditions to give the trifluoroethylated product in 83 % yield (Scheme 4).

The present trifluoroethylation reaction could also be combined with well-established transition-metal-catalyzed carbon–boron bond formation reactions.^[17] For example, trifluoroethylation of the pinacol boronic ester 4a, which was obtained by borylation of 2-bromo-1*H*-indene,^[18] smoothly gave 2-(2,2,2-trifluoroethyl)-1*H*-indene (5a) in 58 % yield (Scheme 5). Hydroboration of substituted phenylacetylenes^[19] followed by trifluoroethylation of the resulting alkenyl pinacol boronic esters 4b and 4c furnished substituted trifluoroethyl styrenes 5b and 5c in 72 % and 56 % yield, respectively (Scheme 5). It is worth noting that the reaction proceeds with complete control of stereochemistry, and that these products are generally difficult to obtain by the use of previously reported methods.^[5–9]

To further demonstrate the synthetic application of our trifluoroethylation protocol, we applied the method to the late-stage trifluoroethylation of biologically active compounds. Installation of the pinacol boronic ester group was accomplished in two steps from the estrone (6) by a palladium-catalyzed borylation of the corresponding triflate. The borylation reaction smoothly gave the desired boronic



Scheme 3. Cross-coupling of $\text{CF}_3\text{CH}_2\text{I}$ (2) with various aryl boronic acids (1). Reaction conditions: $\text{ArB}(\text{OH})_2$ (0.4 mmol), dioxane (3 mL), H_2O (133 μL). [a] Yield of isolated product. [b] Yield was determined by ^{19}F NMR spectroscopy by using PhCF_3 as an internal standard.

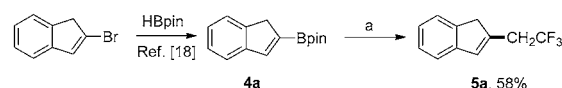


Scheme 4. Trifluoroethylation of aryl boronic esters. a) Optimized reaction conditions as described in Table 1, entry 13.

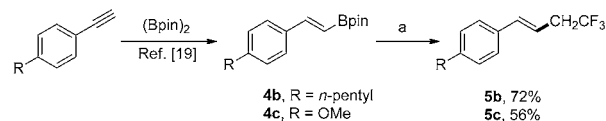
ester product in 75% yield in the presence of 5 mol% $[\text{Pd}(\text{dppf})\text{Cl}_2]$ (Scheme 6). When we tried the trifluoroethylation under the optimized reaction conditions (Table 1, entry 13), 3-trifluoroethyl-3-deoxyestrone (7) was obtained in 37% yield; however, increasing the amount of catalyst $[\text{Pd}_2\text{dba}_3] \cdot \text{CHCl}_3$ (10 mol%) significantly improved the yield to 83% (Scheme 6).

In conclusion, the first transition-metal-catalyzed 2,2,2-trifluoroethylation reaction has been successfully developed

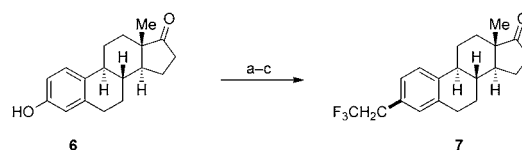
Trifluoromethylation of alkenylbromide



Hydrotrifluoroethylation of alkyne



Scheme 5. Trifluoroethylation of alkenyl boronic esters. a) Optimized reaction conditions as described in Table 1, entry 13. Yields are those for trifluoroethylation step. In the reaction of 4b, H_2O was not added because of the high lipophilicity of the compound. pin = pinacolato.



Scheme 6. Trifluoroethylation of biologically active estrone 6. a) Tf_2O (1.1 equiv), NEt_3 (2.0 equiv), 90%; b) $[\text{Pd}(\text{dppf})\text{Cl}_2]$ (5 mol%), $(\text{Bpin})_2$ (1.5 equiv), KOAc (2.5 equiv), 75%; c) $[\text{Pd}_2\text{dba}_3] \cdot \text{CHCl}_3$ (10 mol%), XantPhos (34 mol%), $\text{CF}_3\text{CH}_2\text{I}$ (4 equiv), Cs_2CO_3 (8 equiv), 83%.

by using the readily available reagent $\text{CF}_3\text{CH}_2\text{I}$. With this method, a wide range of aryl boronic acids were efficiently converted into the desired (trifluoroethyl)arenes, and the method could also be extended to the trifluoroethylation of aryl and alkenyl boronic esters. It can be easily envisaged that aryl and alkenyl iodides, bromides, chlorides, and phenols are suitable substrates for borylation and subsequent trifluoroethylation reactions. The method is amenable to the late-stage trifluoroethylation of biologically active molecules. Given the high potential of trifluoroethyl-containing compounds as biologically active agents, the mild reaction conditions that were employed, and the easy access to the reagents and catalyst/ligand systems, this synthetic methodology promises to find many applications in the life-science-related fields.

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