C–C Coupling

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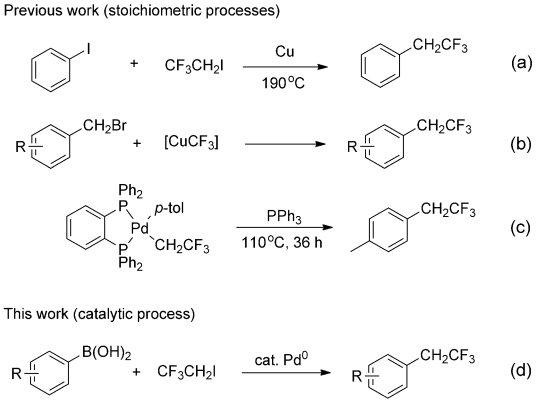
Palladium-Catalyzed 2,2,2-Trifluoroethylation of Organoboronic Acids and Esters**

*Yanchuan Zhao and Jinbo Hu**

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 (CF_3) 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 CF_3CH_2-containing products in medicinal chemistry and related fields.[4] The copper(0)-mediated direct 2,2,2-trifluoroethylation of iodobenzene with trifluoroethyl iodide (CF_3CH_2I) 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 1a). Furthermore, trifluoromethylations of benzyl bromides with [$CuCF_3$] species, which are generated from different precursors, are generally employed to afford (trifluoroethyl)arenes[6] (Scheme 1b). Very recently, Shibata and co-workers reported the trifluoromethylation of benzyl bromides with [$CuCF_3$] 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]



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

We surmised that a transition-metal-catalyzed 2,2,2-trifluoroethylation using readily available trifluoroethyl iodide (CF_3CH_2I) 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 (CF_3CH_2–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 CF_3CH_2–M species in trifluoroethylation reactions is still largely unexplored. In 2004, Culkin and Hartwig reported a stoichiometric version of the formation of an Ar–CH_2CF_3 bond from a Pd^{II} species by heating the complex [(DPPBz)Pd(CH_2CF_3)(*p*-tol)] (prepared from [(DPPBz)Pd(CH_2CF_3)(I)] and *p*-tolyllithium; DPPBz = 1,2-bis(diphenylphosphanyl)benzene) at 110°C for 36 h (Scheme 1c).[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–CF_3[3h] 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 (CF_3CH_2I) and organoboronic acids (or esters) might be accomplished under mild conditions (Scheme 1d).

Considering that the reductive elimination may be rate-limiting in the cross-coupling reaction (as reported by Culkin and Hartwig),[9] we first examined various supporting ligands for the palladium catalyst, especially those known to be able to efficiently facilitate reductive elimination (Scheme 2 and Table 1). 4-Biphenylboronic acid (**1a**) was used as a model substrate, and the reaction was carried out in dioxane at 80°C using K_3PO_4 as a base (Table 1, entries 1–9). Flexible bidentate phosphine ligands (**L1** and **L2**) and sterically hindered trialkyl phosphine ligands (**L3** and **L4**) were

[*] Y. Zhao, Prof. Dr. J. Hu
Key Laboratory of Organofluorine Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Ling-Ling Road, Shanghai, 200032 (China)
E-mail: jinbohu@sioc.ac.cn

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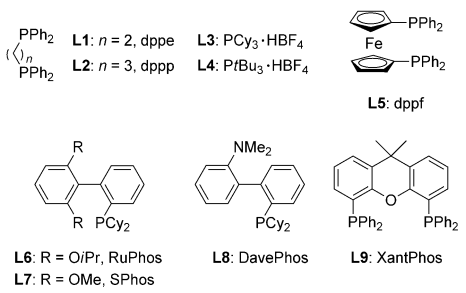
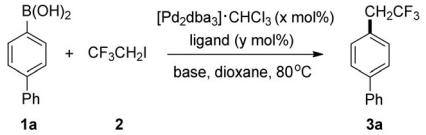


Scheme 2. Various ligands used in Pd-catalyzed cross-coupling reactions. Cy = cyclohexyl.

Table 1: Survey of reaction conditions.[a]



Entry	Ligand	Base	H_2O (equiv)	Molar ratio (**1a**:**2**)	Yield [%][e]
1[b]	**L1**	K_3PO_4	–	1:2	trace
2[b]	**L2**	K_3PO_4	–	1:2	trace
3[b]	**L3**	K_3PO_4	–	1:2	trace
4[b]	**L4**	K_3PO_4	–	1:2	trace
5[b]	**L5**	K_3PO_4	–	1:2	4
6[b]	**L6**	K_3PO_4	–	1:2	34
7[b]	**L7**	K_3PO_4	–	1:2	20
8[b]	**L8**	K_3PO_4	–	1:2	20
9[b]	**L9**	K_3PO_4	–	1:2	50
10[b]	**L9**	Cs_2CO_3	–	1:2	59
11[c]	**L9**	Cs_2CO_3	18	1:2	78
12[c]	**L9**	Cs_2CO_3	18	1:3	80 (69)
13[d]	**L9**	Cs_2CO_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, Cs_2CO_3 (4.0 equiv). [d] The reaction was run on a 0.4 mmol scale (**1a**) in dioxane (3 mL), x = 5, y = 17, Cs_2CO_3 (4.0 equiv). [e] Yields determined by ^{19}F NMR spectroscopy using $PhCF_3$ 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]

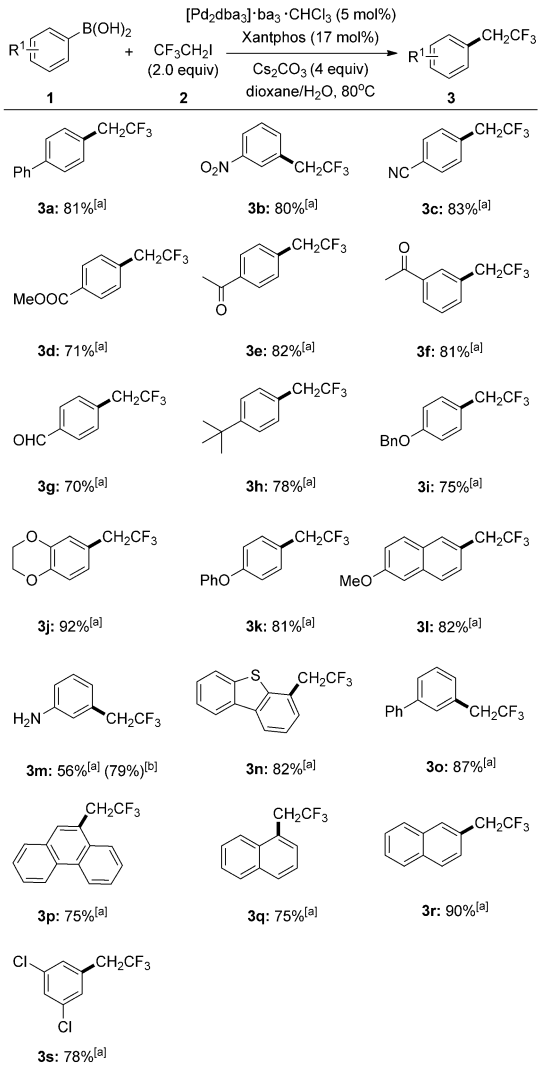
With the optimal combination of Pd and ligand established, we next investigated the influence of the base and additives. Cs_2CO_3 was found to be more effective than relatively weaker bases, such as K_3PO_4 and K_2CO_3, while KOAc proved to be completely ineffective with essentially no formation of the desired product. The addition of water, which is known to facilitate the transmetalation step, was found to be benefical for the reaction, although the amount of added water had to be carefully optimized (Table 1, entry 11). Increasing the amount of CF_3CH_2I did not significantly improve both the conversion of **1a** and the product yield (Table 1, entries 11 and 12). We hypothesized that CF_3CH_2I may cause a partial inhibition of the catalyst through side (redox) reactions with Pd^0 and/or phosphine ligands, because a considerable amount of CF_3CH_3 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 CF_3CH_2I (**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 (NH_2), and that no *N*-trifluoroethylated product was observed. Such trifluoroethylated anilines were previously obtained through multistep syntheses by reduction of the corresponding nitrobenzenes.[4g]

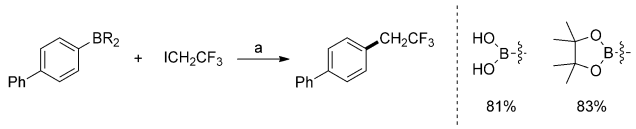
Many boronic acids are prepared from organoboronic esters by hydrolysis, however, this transformation step can be low-yielding.[16] Therefore, organoboronic esters might be more favorable substrates in some cases. To our delight, pinacol boronic esters could also participate in the current trifluoroethylation 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



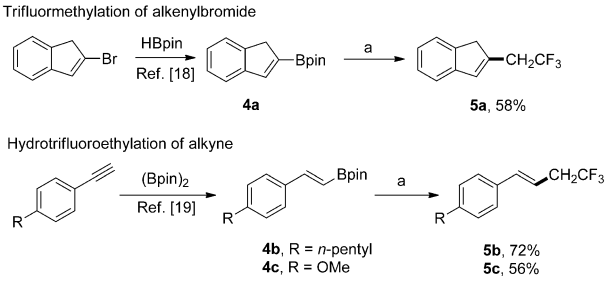
Scheme 3. Cross-coupling of CF_3CH_2I (**2**) with various aryl boronic acids (**1**). Reaction conditions: $ArB(OH)_2$ (0.4 mmol), dioxane (3 mL), H_2O (133 μL). [a] Yield of isolated product. [b] Yield was determined by ^{19}F NMR spectroscopy by using $PhCF_3$ as an internal standard.



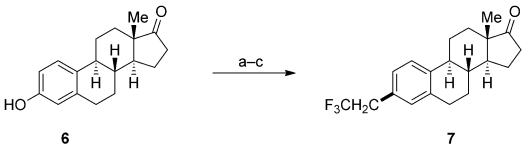
Scheme 4. Trifluoroethylation of aryl boronic esters. a) Optimized reaction conditions as described in Table 1, entry 13.

ester product in 75% yield in the presence of 5 mol% $[Pd(dppf)Cl_2]$ (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 $[Pd_2dba_3]\cdot CHCl_3$ (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



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) $[Pd(dppf)Cl_2]$ (5 mol%), $(Bpin)_2$ (1.5 equiv), KOAc (2.5 equiv), 75%; c) $[Pd_2dba_3]\cdot CHCl_3$ (10 mol%), XantPhos (34 mol%), CF_3CH_2I (4 equiv), Cs_2CO_3 (8 equiv), 83%.

by using the readily available reagent CF_3CH_2I. 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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