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Synthesis of PEG-Supported Organotrifluoroborates and Their Applications in Palladium-Catalyzed Homo-Coupling Reactions

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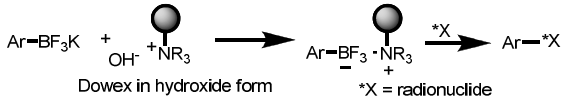
A general synthetic route to water-soluble PEG-supported organotrifluoroborates has been developed. In the presence of air and catalytic amounts of $Pd(OAc)_2$, the PEG-supported organotrifluoroborates undergo homo-coupling reactions smoothly at room temperature. No additional oxidizing agent, base, or phosphine ligands are required.

Introduction

Due to their ready availability, remarkable stability, and low toxicity, organotrifluoroborates are ideally suited for use in organic chemistry. This is especially true in the syntheses of pharmaceuticals. Recent studies have demonstrated that the organotrifluoroborate moiety can tolerate a wide variety of chemical transformations.[1] The importance of these reports is that they validate the fact that boronated intermediates can "carry" a variety of pharmaceutically important functional groups late into reaction sequences.

In the last few decades, our research group has been focusing on the development of novel radiolabeling chemistry using various organoboron reagents.[2] In radiolabeling chemistry, the removal of excess starting material is a significant issue. In earlier studies, we evaluated the feasibility of using polymeric organoborane reagents as a straightforward approach for removing the excess precursors.[3] The principle of this approach is that, upon reaction with a radionuclide, the desired radiolabeled product will be released into solution from the polymeric residue. By simple filtration, the polymeric byproduct and excess starting material can be easily removed resulting in a straightforward purification process. Though unique, this methodology found few practical applications because the polymeric organoborane precursors used were unstable under atmospheric conditions. Encouraged by the stability of organotrifluoroborates and the fact that their counterions are readily interchangeable,[4] we investigated the feasibility of combining the advantages of polymer-supports and trifluoroborate chemistry into radiolabeling chemistry protocols. We successfully established methods for the synthesis and characterization of Dowex-supported organotrifluoroborates. [5] The application of the Dowex-supported organotrifluoroborates in radioiodination [6] greatly simplified the purification procedure in the preparation of certain radiotracers (Scheme 1). However, most likely due to the insolubility of the Dowex-supported organotrifluoroborates in THF-H_2O system, the radiolabelling yields were slightly lower when compared to the yields in the corresponding reactions carried out in solution. In 2013, we discovered that Dowex-supported aryltrifluoroborates also readily undergo homo-coupling to generate biaryl compounds under ultrasound irradiation.[7] However, the reaction requires four equivalents of copper acetate and thus is not particularly environmentally benign. Interestingly, in 2012, Rombouts and Molander reported the synthesis of Amberlyt-supported organotrifluorborates [8] by adopting a similar ion exchange technology. They investigated the application of these solid-supported organotrifluoroborates in Suzuki cross-coupling reactions.



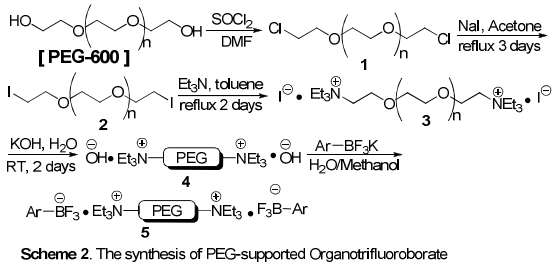
Scheme 1. Synthesis of Dowex-supported organotrifluoroborate for radiolabelling purpose

In a continuation of our studies relating to polymer-supported organotrifluoroborates, we investigated the synthesis of water-soluble PEG-supported organotrifluoroborates with the hope to increasing the halogenation yields. [9] During this study, we discovered that PEG-supported organotrifluoroborates undergo homo-coupling smoothly at room temperature in the presence of air and a catalytic amount of palladium acetate. Notably, no additional base, ligand, or oxidizing agent is required for the new coupling reaction. The reaction proceeds quite well for a variety of organotrifluoroborates, including aryltrifluoroborates bearing both electron-donating and electron-withdrawing groups, heteroaryltrifluoroborates, and alkenyltrifluorobates. Herein we wish to report the results of our studies.

Results and discussion

The preparation of PEG-supported organotrifluoroborates was initiated using commercially available PEG-600. The synthetic

route, including reaction conditions and required reagents, is summarized in Scheme 2. The sequence involves the chlorination of the terminal hydroxyl groups in PEG-600 which is carried out in DMF at 60 °C by treatment with thionyl chloride.[10] Attempts to convert the chloro-modified PEG (**1**) directly into a quaternary ammonium chloride salt were unsuccessful. Therefore, the chloro-modified PEG was converted to the more reactive iodo-modified PEG (**2**).[11] The ^{13}C-NMR spectrum revealed that the desired Finkelstein reaction proceeded efficiently. Treatment of the resultant iodinated PEG with triethylamine, followed by iodide-hydroxide anion exchange, gave the key intermediate **4** (PEG bearing quaternary ammonium hydroxide groups) in excellent yield. To test the "loading" efficiency of the organotrifluoroborates on this modified PEG-600 (**4**), reaction with a stoichiometric amount of potassium 2-naphthylenyltrifluoroborate (1.0 mmol scale) in methanol-water (v/v 1:1, 20 mL) was chosen. The dramatic change of pH (from ~6.1 to ~7.9), due to the formation of by-product KOH, indicated clearly that the desired reaction had occurred. ^{1}H and ^{13}C NMR and IR spectroscopy, including appropriate resonances in the ^{11}B-NMR spectrum, confirmed the formation of the targeted PEG-supported 2-naphthylenyltrifluoroborate. Based on integrations of the broad but characteristic peaks in the ^{1}HNMR spectrum, the loading efficiency is essentially quantitative. Using the same reaction sequence, a series of water-soluble PEG- supported organotrifluoroborates (**5**) was synthesized.

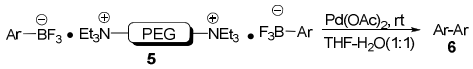


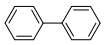
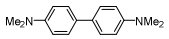
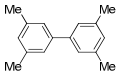
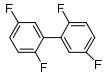
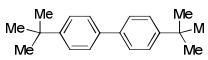
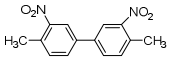
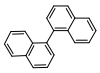
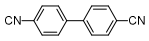
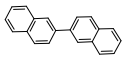
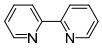
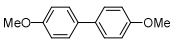
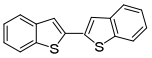
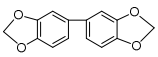
Scheme 2. The synthesis of PEG-supported Organotrifluoroborate

With the PEG-supported organotrifluoroborates (**5**) in hand, we investigated the homo-coupling reaction [9]. Although the transition metal-catalyzed, oxidative homo-coupling reactions of organoboron reagents are well known,[12-19] most procedures require elevated temperatures.[13-15] In addition, additives are generally necessary to achieve efficient catalyst activity. These additives include oxidizing agents (organic halides,[14] arylsulfonyl chloride,[15] *p*-benzoquinone[16]) to regenerate the Pd(II) species, bases to facilitate transmetallation,[14,15,17,18] and phosphine ligands[13,14] to stabilize the catalyst. In addition, most of the reported homo-coupling reactions are limited in scope and often do not proceed well for arylboronic acids bearing *orth*-substitutents,[16,19] electron-withdrawing groups,[19] or heteroaryl groups.[15,16,19] Therefore, development of an alternative general method would be desirable.

We discovered that, in the presence of a catalytic amount of $Pd(OAc)_2$, the homo-coupling reaction of PEG-supported organotrifluoroborates proceeds smoothly under atmospheric conditions in the absence of additives (oxidizing reagent, base, or ligand). Among the solvents screened, THF-H_2O (1:1) proved to be the most effective. To the best of our knowledge, this is the first room-temperature homo-coupling of organoboron compounds in aqueous media that proceeds in the absence of additives. As shown in Table 1, the reactions proceed smoothly for aryltrifluoroborates bearing both electron-donating (entries 1-8) and electron-withdrawing groups (entries 9-11). Heteroaryltrifluoroborates also undergo homo-coupling to give the desired products in good yields (entries 12-13).

Table 1: Room Temperature Palladium-Catalyzed Homo-Coupling of PEG-Supported Organotrifluoroborates[a]



Entry	Reactant	Product		Yield (%)[b]	Entry	Reactant	Product		Yield (%)[b]
1	**5a**		**6a**	91	8	**5h**		**6h**	81
2	**5b**		**6b**	89	9	**5i**		**6i**	88
3	**5c**		**6c**	92	10	**5j**		**6j**	69
4	**5d**		**6d**	89	11	**5k**		**6k**	61
5	**5e**		**6e**	76	12	**5l**		**6l**	83
6	**5f**		**6f**	87	13	**5m**		**6m**	77
7	**5g**		**6g**	86					

a. Reaction carried out in THF-H_2O at room temperature in the presence of 5 mol% of $Pd(OAc)_2$.
b. Isolated yield.

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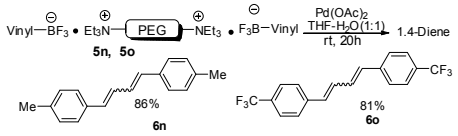
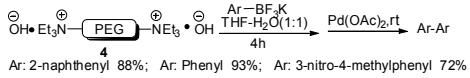
Under the same reaction conditions, the homo-coupling of PEG-supported alkenyltrifluoroborates also proceeds smoothly, generating a mixture of (*E,E*)-and (*Z,E*)-1,3-dienes (Scheme 3).



Scheme 3. Homo-coupling of PEG-supported alkenyltrifluoroborates

We then investigated the possibility of carrying out the reaction in a single reaction vessel. The *in-situ* generated PEG-supported organotrifluoroborates (without removing the KOH) were subjected to the $Pd(OAc)_2$ catalyzed reaction (Scheme 4). It was found that the reactions proceeded smoothly and gave the desired products in good yields.



Scheme 4. One-pot homo-coupling

Interestingly, reaction mixtures for the PEG supported homo-coupling reactions, using either isolated or *in-situ* generated organotrifluoroborates, turn black within 1 min after combining the components. Rapid formation of palladium black has been observed in several transition metal-catalyzed reactions using PEG as solvent.[20] In those reports, examination of the reaction mixtures using transmission electron microscopy (TEM) revealed the *in-situ* generation of palladium nanoparticles. The high catalytic activity of $Pd(OAc)_2$ shown in the homo-coupling of PEG-supported organotrifluoroborates encouraged us to examine the possibility of generating palladium nanoparticles in our system. TEM spectroscopy (Figure 1) clearly demonstrated the formation of palladium nanoparticles (about 150 nm in diameter) within 1 min at room temperature.

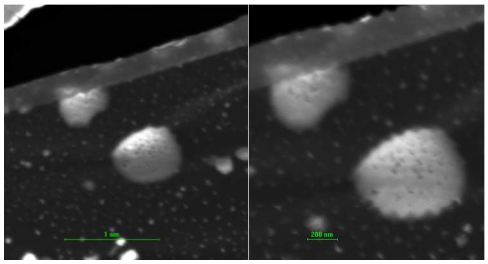
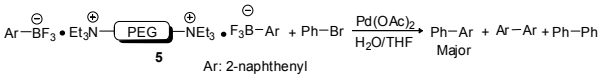


Figure 1. TEM study

Although it is known that, at elevated temperature, palladium nanoparticles can be generated in Suzuki cross-coupling reactions in the presence of longer chain PEG reagents and a base, the observation of nanoparticles in our system (relatively short PEGs with no added base) at room temperature is quite remarkable. Presumably, the existence of the quaternary ammonium group in the PEG-supported organotrifluoroborates promotes the formation the Pd-nanoparticles.[21]

We then examined the use of the PEG system in Suzuki cross-coupling reactions (Scheme 5). At room temperature, the cross-coupling reaction of phenyl bromide and PEG-supported 2-naphthylenyltrifluoroborate occurs readily but the reaction produces a mixture of the desired cross-coupling product along with the two homo-coupling products derived from 2-naphthylenyltrifluoroborate and phenyl bromide.



Scheme 5. Suzuki coupling with PEG-supported organotrifluoroborates

Experimental section

All reagents were used as received. Chemical shifts for ^1H NMR and ^{13}C NMR spectra were referenced to TMS and measured with respect to the residual protons in the deuterated solvents. For polymeric compounds, the major peaks are summarized. Potassium organotrifluoroborates were synthesized according to literature procedures.[22]

Synthesis of chloro-modified PEG-600 (1). The reported procedure[9] was adopted with little modification. Commercially available PEG-600 (6.0 g, 10 mmol) was dissolved in a mixture of $SOCl_2$ (24 mL) and dimethyl formamide (6 mL). The reaction mixture was stirred at 60 ^oC for 24 hours. After cooling to room temperature, the solvent was removed under reduced pressure. The reaction flask was placed in an ice-water bath and then a saturated aqueous solution of K_2CO_3 was added slowly to destroy the residual thionyl chloride. The reaction mixture was then concentrated under reduced pressure and extracted with dichloromethane (3 x 50 mL). The combined organic layer was dried using anhydrous Na_2SO_4. After filtration and removal of solvent under vacuum, the chloro-modified PEG was obtained in nearly quantitative yield. ^1H NMR (300 MHz, $CDCl_3$): δ 3.64-3.71 (m, PEG-CH_2). ^{13}C NMR (300 MHz, $CDCl_3$): 69.6-70.4 (PEG-CH_2), 41.8 (PEG-CH_2-Cl).

Synthesis of iodo-modified PEG-600 (2). To a solution of chloro-modified PEG-600 (7.0 g, 11 mmol) in dry acetone (60 mL), sodium iodide (5.0 g, 33 mmol) was added. The reaction mixture was refluxed for 3 days, cooled to room temperature, and the solvent partially evaporated under reduced pressure. The reaction mixture was extracted using dichloromethane (3 x 50 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum to yield 8.5 g of iodo-modified PEG-600 (94%). ^1H NMR (300 MHz, $CDCl_3$): δ 3.64-3.71 (m, PEG-CH_2). ^{13}C NMR (250 Hz, $CDCl_3$): 69.6-70.4 (PEG-CH_2), 62.9 (PEG-CH_2I).

Synthesis of PEG-600 bearing quaternary ammonium iodide groups (3). Iodo-modified PEG-600 (8.2 g, 10 mmol) was dissolved in freshly distilled triethylamine (30 mL) and then dry toluene (60 mL) was added. The reaction mixture was refluxed for 2 days, cooled to room temperature, and the solvents removed under reduced pressure. The oily product was washed with hexanes (3 x 50 mL) and dried overnight under vacuum to yield 10.1 g of the desired compound. ^1H NMR (300 MHz, $CDCl_3$): δ 3.64-3.71 (m, PEG-CH_2), 3.51-3.58 (m, NEt_3-CH_2), 1.37-1.43 (m, NEt_3-CH_3). ^{13}C NMR (300

MHz, $CDCl_3$): 68.2 (PEG-CH_2), 62.4 (PEG-CH_2-N), 55.3 (PEG-CH_2-N), 52.1 (NEt_3-CH_2), 6.2 (NEt_3-CH_3).

Synthesis of PEG-600 bearing quaternary ammonium hydroxide groups (4). To the solution of PEG-600 bearing quaternary ammonium iodide groups (2.0 g, 2.2 mmol) in water (10 mL), potassium hydroxide (224 mg, 4.0 mmol) was added. The reaction mixture was stirred for 2 hours at room temperature and then the solvent was partially removed under reduced pressure. The product was extracted into EtOAc (3 x 50 mL). The organic layer was dried using anhydrous $MgSO_4$ and then the solvent removed under vacuum to give 1.4 g of product (91% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64-3.71 (m, PEG-CH_2), 3.51-3.58 (m, NEt_3-CH_2), 1.38-1.43 (m, NEt_3-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 68.4 (PEG-CH_2), 62.9 (PEG-CH_2-N), 55.5 (PEG-CH_2-N), 52.3 (NEt_3-CH_2), 6.2 (NEt_3-CH_3).

Typical procedure for the synthesis of PEG-supported aryl trifluoroborates (5). To a solution of PEG-600 bearing quaternary ammonium hydroxyl groups (396 mg, 0.50 mmol) in H_2O (10 mL), a solution of 2-naphthylenyltrifluoroborate (246 mg, 1.05 mmol) in MeOH (10 mL) was added in one portion. The reaction mixture was stirred for 4 hours and then the solvent removed under reduced pressure. Dry $CHCl_3$ (3 x 20 mL) was used to extract the PEG-supported aryl trifluoroborates (this removes unreacted Naph-BF_3K and potassium iodide which are insoluble). After filtration, the solvent was removed under reduced pressure; 471 mg of product was obtained (82%). Characteristic NMR peaks of compounds **5a-5m** were listed below:

5a ^{1}H NMR (300 MHz, $CDCl_3$): δ.7.26-7.93 (m), 3.28-3.69 (m), 2.37-2.74 (m), 0.79-0.92 (m). ^{13}C NMR (300 MHz, $CDCl_3$): 132.9, 130.3, 128.2, 126.0, 124.2, 70.0, 69.8, 69.5, 62.9, 55.7, 52.8, 6.8.

5b ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58-7.62 (m), 6.78-6.92 (m), 3.58-3.75 (m, PEG-CH_2), 3.10-3.24 (m, NEt_3-CH_2) 2.35-2.41 (m), 1.05-1.18 (m, NEt_3-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 140.5, 125.8, 124.2, 69.0, 68.8, 68.6, 68.3, 62.7, 55.3, 52.6, 22.1, 6.6.

5c ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.46 (m), 7.16-7.21 (m), 3.50-3.65 (m, PEG-CH_2), 3.00-3.14 (m, NEt_3-CH_2), 1.13-1.27 (m), 1.01-1.16 (m, NEt_3-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 147.8, 130.1, 123.0, 69.6, 69.3, 63.4, 55.8, 52.6, 33.5, 31.0, 6.5.

5d ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87-8.01 (m), 7.17-7.68 (m), 3.54-3.77 (m, PEG-CH_2), 3.20-3.39 (m, NEt_3-CH_2), 1.15-1.26 (m, NEt_3-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 140.5, 136.8, 130.9, 127.6, 125.5, 125.3, 124.1, 69.0, 68.9, 68.7, 68.6, 62.9, 55.6, 52.8, 6.7.

5e ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67-8.01 (m, Naph-H), 7.33-7.36 (m, Naph-H), 3.52-3.67 (m, PEG-CH_2), 3.10-3.21 (m, NEt_3-CH_2), 1.05-1.17 (m, NEt_3-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 132.0, 131.3, 129.5, 128.8, 126.3, 126.2, 124.4, 123.7, 123.3, 69.1 (PEG-CH_2), 69.0, 68.8, 62.8 (PEG-CH_2-N), 55.4 (PEG-CH_2-N), 52.6 (NEt_3-CH_2), 6.4 (NEt_3-CH_3).

5f ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.52 (m), 6.74-6.79 (m), 3.57-3.81 (m, PEG-CH_2), 3.30-3.41 (m, NEt_3-CH_2), 1.20-1.26 (m, NEt_3-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 157.8, 135.7, 132.8, 113.1, 69.5, 69.3, 68.7, 64.2, 57.0, 54.9, 54.0, 7.5.

5g ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.03-7.10 (m), 6.71-6.75 (m), 5.81-5.83 (m, OCH_2O), 3.54-3.67 (m, PEG-CH_2), 3.18-3.30 (m, NEt_3-CH_2), 1.14-1.25 (m, NEt_3-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 146.3, 145.5, 141.3, 139.9, 126.3, 124.1, 111.6, 107.5, 69.8 (PEG-CH_2), 65.4 (PEG-CH_2-N), 53.2 (NEt_3-CH_2), 7.6 (NEt_3-CH_3).

5h ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72-7.78 (m), 6.62-7.09 (m), 3.57-3.79 (m, PEG-CH_2), 3.42-3.55 (m, NEt_3-CH_2), 3.00-3.15 (m, NMe_2), 1.25-1.44 (m, NEt_3-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 151.7, 148.5, 133.4, 133.3, 133.2, 132.3, 129.2, 110.9, 70.5 (PEG-CH_2), 64.4 58.0, 57.3 (PEG-CH_2-N), 54.2 (NEt_3-CH_2), 8.2 (NEt_3-CH_3).

5i ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.54 (m, Ph-H), 6.50-6.88 (m, Ph-H), 3.57-3.79 (m, PEG-CH_2), 3.30-3.49 (m, NEt_3-CH_2), 1.25-1.39 (m, NEt_3-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 152.3, 151.6, 146.1, 146.0, 144.2, 133.6, 133.0, 127.7, 127.1, 69.7 (PEG-CH_2), 64.7 (PEG-CH_2-N), 54.0 (PEG-CH_2-N), 52.6 (NEt_3-CH_2), 8.6 (NEt_3-CH_3).

5j ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61-8.16 (m), 7.01-7.21 (m), 3.49-3.70 (m), 3.25-3.45 (m), 2.25-2.65 (m, Me), 1.09-1.30 (m, NEt_3-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 148.6, 144.5, 144.1, 136.7, 131.2, 126.3, 126.2, 69.2 (PEG-CH_2), 65.6 (PEG-CH_2-N), 57.6 (PEG-CH_2-N), 54.3 (NEt_3-CH_2), 20.1(Ph-Me), 6.4 (NEt_3-CH_3).

5k ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64-7.81 (m, Ph-H), 7.70-7.54 (m, Ph-H), 3.51-3.75 (m, PEG-CH_2), 3.40-3.49 (m, NEt_3-CH_2), 1.29-1.33 (m, NEt_3-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 164.9, 141.6, 135.6, 132.2, 115.5, 111.4, 69.7 (PEG-CH_2), 64.6 (PEG-CH_2-N), 57.3 (PEG-CH_2-N), 54.2 (NEt_3-CH_2), 8.2 (NEt_3-CH_3).

5l ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31-8.50 (m), 7.26-7.56 (m), 3.57-3.73 (m, PEG-CH_2), 3.41-3.49 (m, NEt_3-CH_2), 1.32-1.37 (m, NEt_3-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 161.2, 148.0, 141.5, 127.2, 116.5, 70.1, 64.4, 57.2, 54.2, 8.2

5m ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53-7.89 (m), 7.19-7.26 (m), 3.52-3.67 (m, PEG-CH_2), 3.08-3.17 (m, NEt_3-CH_2), 1.05-1.09 (m, NEt_3-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 138.8, 124.6, 122.5, 122.3, 69.0, 68.8, 68.7, 62.8, 55.4, 52.8, 22.1, 6.9.

5n ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01-7.55 (m), 6.29-6.77 (m, CH=CH), 3.59-3.80 (m, PEG-CH_2), 3.36-3.47 (m, NEt_3-CH_2), 2.25-2.37 (Ph-Me), 1.18-1.26 (m, NEt_3-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 137.3, 135.6, 134.9, 133.9, 129.6, 129.1, 128.6, 125.5, 70.2, 70.1, 69.9 (PEG-CH_2), 64.1 (PEG-CH_2-N), 56.8, 54.0 (NEt_3-CH_2), 20.9 (PH-Me), 7.9 (NEt_3-CH_3).

5o ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.61 (m), 6.41-6.83 (m, CH=CH), 3.52-3.63 (m, PEG-CH_2), 3.30-3.48 (m, NEt_3-CH_2), 1.23-1.43 (m, NEt_3-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 143.8, 133.4, 131.4, 127.9, 127.4, 125.7, 125.3, 121.8, 109.6, 107.8, 70.4, 69.7 (PEG-CH_2), 64.0 (PEG-CH_2-N), 56.7, 54.3 (NEt_3-CH_2), 8.0 (NEt_3-CH_3).

General procedure for palladium-catalyzed homocoupling of PEG-supported organotrifluoroborates. To a 50 ml flask, the PEG-supported organotrifluoroborate (0.20 mmol), $Pd(OAc)_2$ (2.0 mg, 5 mol%), THF (5 mL), and water (5 mL) were added. The reaction mixture was stirred at the room temperature and monitored using TLC. The reaction was allowed to proceed until completion and then the mixture was extracted using EtOAc (3 x 15 mL). After removal of the solvent, the product was purified using silica gel column chromatography. The ^{1}H NMR and ^{13}C NMR spectra of known compounds **6a**,[15] **6b**,[16] **6c**,[16] **6d**,[15] **6e**,[18] **6f**,[13] **6g**[23], **6h**,[16] **6i**[24], **6j**, **6k**,[7] **6l**[25], **6m**[18], **6n**[26], **6o**[27] are consistent with the literature values. **6j**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (s, 2H), 7.75 (d, J = 9 Hz, 2H), 7.47 (d, J = 9 Hz, 2H), 2.66 (s, 6H). ^{13}C NMR (300 Hz, $CDCl_3$): 149.7, 137.6, 133.6, 133.4, 131.0, 122.8, 19.9.

Conclusions

In summary, a general synthetic route to water-soluble, PEG-supported organotrifluoroborate reagents has been developed. In the presence of a catalytic amount of $Pd(OAc)_2$, the PEG-supported organotrifluoroborates undergo homo-coupling under very mild reaction conditions. The additive-free reaction conditions, as well as the wide reaction scope, provide a useful synthetic tool for symmetric biaryls. A TEM study revealed the formation of palladium nanoparticles in these homo-coupling reactions.

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Notes and references

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[1] Reviews: G. A. Molander and N. Ellis, *Acc. Chem. Res.,* 2007, **40**, 275; S. Darses and J.-P. Genet, *Chem. Rev.,* 2008, **108**, 288.
[2] Reviews: G. W. Kabalka, M.-L. Yao, M. R. Akula, L. Yong, *Pure Applied Chem.* 2012, **84**, 2309; G. W. Kabalka, *J. Label. Compd. Radiopharm.,* 2007, **50**, 888; G. W. Kabalka, *Acc. Chem. Res.,* 1984, **17**, 215.
[3] G. W. Kabalka, Z. Wang, J. F. Green, M. M. Goodman, *Appl. Rad. Isotopes,* 1992, **43**, 389; G. W. Kabalka, V. Namboodiri, M. Akula, *Radiolabelled Compds. Radiopharm.,* 2001, **42**, P5793.
[4] S. De and M. E. Welker, *Org. Lett.,* 2005, **7**, 2481; A. S. Vieira, P. F. Fiorante, J. Zukerman-Schpector, D. Alves, G. V. Botteselle and H. A. Stefani, *Tetrahedron,* 2008, **64**, 7234.
[5] L. Yong, M.-L. Yao, J. F. Green, H. Kelly, G. W. Kabalka, *Chem. Comm.,* 2010, **46**, 2623.
[6] L. Yong, M.-L. Yao, H. Kelly, J. F. Green, G. W. Kabalka, *J. Label. Compd. Radiopharm.,* 2011, **54**, 173.
[7] B. Musolino, M. Quinn, K. Hall, V. Coltuclu, G. W. Kabalka, *Tetrahedron Lett.,* 2013, **54**, 4080.
[8] V. Colombel, M. Presset, D. Oehlrich, F. Rombouts, G. A. Molander, *Org. Lett.* 2012, **14**, 1680.
[9] The iododeboronation of those PEG-supported organotrifluoroborates was investigated (unpublished result). It was found that using chloramine-T/NaI system in aqueous THF the reactions produced the desired aryl iodides in good to excellent yields.
[10] M. Alvaro, C. Aprile, H. García, E. Peris, *Eur. J. Org. Chem.,* 2005, 3045.
[11] M. B. Smith, J. March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (6th ed.), 2007, New York: Wiley-Interscience.
[12] Z. Z. Song, H. N. C. Wong, *J. Org. Chem.,* 1994, **59,** 33; M. Moreno-Mañas, M. Pérez, R. Pleixats, *J. Org. Chem.,* 1996, *61,* 2346; S. Punna, D. D. Díaz, M. G. Finn, *Synlett,* 2004, 2351; C. Adamo, C. Amatore, I. Ciofini, A. Jutand, H. Lakmin, *J. Am. Chem. Soc.,* 2006, **128**, 6829; H. Lakmini, I. Ciofini, A. Jutand, C. Amatore, C. Adamo, *J. Phys. Chem. A.,* 2008, 112, 12896.
[13] M. S. Wong, X. L. Zhang, *Tetrahedron Lett.* 2001, **42**, 4087; A. Prastaro, P. Ceci, E. Chiancone, A. Boffi, G. Fabrizi, S. Cacchi, *Tetrahedron Lett.* 2010, **51**, 2550.
[14] A. Lei, X. Zhang, *Tetrahedron Lett.* 2002, **43**, 2525.
[15] G. W. Kabalka, L. Wang, *Tetrahedron Lett.* 2002, **43**, 3067.
[16] Y. Yamamoto, *Synlett,* 2007, 1913.
[17] K. A. Smith, E. M. Campi, W. R. Jackson, S. Marcuccio, C. G. M. Naeslund, G. B. Deacon, *Synlett,* 1997, 131.
[18] J. P. Parrish, Y. C. Jung, R. J. Floyd, K. W. Jung, *Tetrahedron Lett.,* 2002, **43**, 7899.
[19] Y. Yamamoto, R. Suzuki, K. Hattori, H. Nishiyama, *Synlett,* 2006, 1027.
[20] T. M. Razler, Y. Hsiao, F. Qian, R. Fu, R. K. Khan, W. Doubleday, *J. Org. Chem.,* 2009, **74**, 1381.
[21] For tetraalkylammonium salt promoted Pd-nanoparticle formation see lit.: M. T. Reetz, E. Westermann, *Angew. Chem., Int. Ed.,* 2000, **39**, 165.
[22] E. Vedejs, R. W. Chapman, S. C. Fields, S. Lin, M. R. Schrimpf, *J. Org. Chem.,* 1995, **60**, 3020.
[23] C. Zhou, R. C. Larock, *J. Org. Chem.,* 2006, **71**, 3184.
[24] R. Leroux, R. Simon, N. Nicod, *Lett. Org. Chem.*, 2006, **3**, 948.
[25] L.-Y. Liao, X. Kong, X. Duan, *J. Org. Chem.,* 2014, **79**, 777.
[26] L. Hintermann,; M. Schmitz,; Y. Chen, *Advanced Synthesis & Catalysis*, 2010, **352**, 2411.
[27] F. Babudri, G. M. Farinola, F. Naso, R. Ragni, G. Spina, *Synthesis*, 2007, **19**, 3088.

Synthesis of PEG-Supported Organotrifluoroborates and Their Applications in Palladium-Catalyzed Homo-Coupling Reactions

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A general synthetic route to water-soluble PEG-supported organotrifluoroborates has been developed. In the presence of air and catalytic amounts of $Pd(OAc)_2$, the PEG-supported organotrifluoroborates undergo homo-coupling reactions smoothly at room temperature. No oxidizing agent, base, or phosphine ligands are required.