

A Highly Efficient Microwave-Assisted Suzuki Coupling Reaction of Aryl Perfluorooctylsulfonates with Boronic Acids

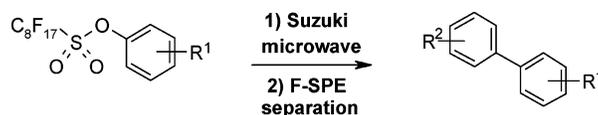
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ABSTRACT



A new strategy to improve the efficiency of Suzuki coupling reactions is introduced by combining fast microwave reaction with easy fluorous separation. Aryl perfluorooctylsulfonates derived from the corresponding phenols are coupled with aryl boronic acids to form biaryls under general microwave conditions. Both intermediates and products are purified by solid-phase extraction over FluoroFlash silica gel. Application of this tagging strategy to multistep synthesis of biaryl-substituted hydantoin is also described.

The palladium-catalyzed cross-coupling of aryl halides with aryl boronic acids (Suzuki coupling) is a powerful reaction for the construction of biaryls.¹ Its scope has been extended through the use of aryl triflates (ArOSO₂CF₃) or aryl nonaflates (ArOSO₂(CF₂)₃CF₃) as halide equivalents.² Aryl perfluoroalkylsulfonates prepared from a wide range of commercially available phenols have shown high reactivity, good stability for room-temperature storage and chromatography, and resistance towards hydrolysis.³

Applications of Suzuki coupling reactions for parallel and combinatorial syntheses have been explored by conducting the reaction under microwave irradiation⁴ or on solid support⁵ with a linker such as perfluoroalkylsulfonate.⁶ However, the

microwave reaction does not directly address the separation issue, which is usually the bottleneck of high-throughput synthesis. Microwave-assisted solid-phase reactions have limitations on solvent selection due to resin swelling and thermostability issues.⁷ We report here a new strategy that

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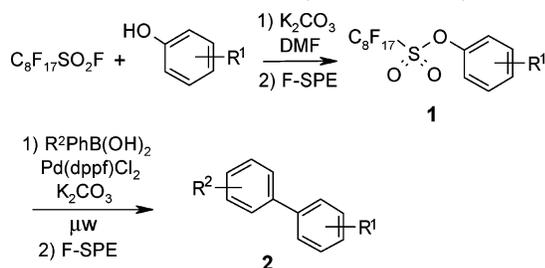
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Scheme 1. Fluorous Synthesis of Biaryls



significantly improves the efficiency of Suzuki coupling reactions by combining fast microwave reaction with easy fluororous separation.

Fluorous synthesis unites the attractive features of solution-phase chemistry with the convenient workup of solid-phase chemistry.⁸ Molecules attached with a perfluoroalkyl “phase tag” can be easily isolated from the reaction mixture by fluororous separation techniques such as fluororous solid-phase extraction (F-SPE).⁹ The fluororous Suzuki coupling reaction employs aryl perfluorooctylsulfonates (ArOSO₂(CF₂)₇CF₃) as precursors. The perfluorooctylsulfonyl group has enough fluorines (17) to serve as a fluororous tag for F-SPE. Recently, we reported the use of aryl perfluorooctylsulfonate tag in palladium-mediated cross-coupling reactions for the formation of a C–S bond.^{10,11} We now extend the application of this fluororous tag to the synthesis of the C–C bond of biaryls.

A variety of phenols were converted to the corresponding aryl perfluorooctylsulfonates by reacting them with commercially available perfluorooctylsulfonyl fluoride under mild conditions, using K₂CO₃ as a base in dimethylformamide (DMF) at 70 °C for 5 h (Scheme 1).¹² The crude aryl perfluorooctylsulfonate **1** has greater than 90% purity and is used directly for the next step reaction. If further purification is needed, this can be accomplished by crystallization from MeOH or by F-SPE purification on FluoroFlash

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(12) **Representative Procedure for the Preparation of Aryl Perfluorooctylsulfonates.** To a mixture of 5-hydroxy-1-tetralone (3.24 g, 20.0 mmol) and K₂CO₃ (2.90 g, 21.0 mmol) in 15 mL of DMF was added perfluorooctylsulfonic fluoride (8.37 g, 16.7 mmol) dropwise through an addition funnel. After heating at 70 °C for 5 h, the mixture was poured onto 100 mL of water and extracted with EtOAc. The organic portion was dried over MgSO₄, and the solvent was evaporated under vacuum to give perfluorooctylsulfonate **1a** (9.79 g, 91% yield). The crude product was used for the next step. It can be further purified by recrystallization with MeOH or by F-SPE.

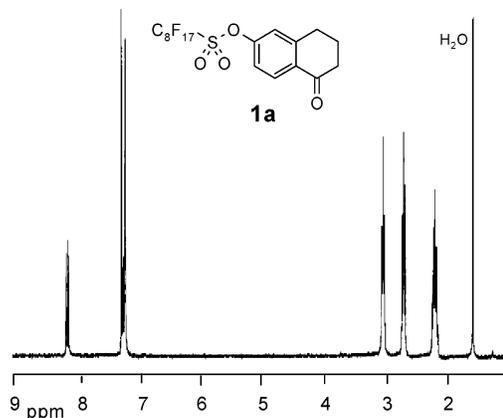


Figure 1. ¹H NMR (CDCl₃) of **1a** after F-SPE.

cartridges.¹³ Two F-SPE fractions need to be collected; the first elution with 80:20 MeOH/H₂O contains unreacted phenol and other nonfluorous compounds; the second elution with MeOH contains the desired aryl perfluorooctylsulfonate **1**. After F-SPE, the purity is greater than 95% (Figure 1).¹⁴

Suzuki coupling is a substrate-dependent reaction, which is reflected by numerous publications on the optimization of catalyst, base, solvent, and other reaction conditions.¹⁵ The lack of a general procedure suitable for a broad range of substrates limits the application of Suzuki reactions in high-throughput synthesis. As a powerful and easily controllable heating source, microwave irradiation can generate more consistent results than the conventional heating source.⁴ In our development of fluororous Suzuki coupling reactions, a literature procedure¹⁵ for the coupling of triflates was adapted for the reaction of aryl perfluorooctylsulfonates.¹⁶ Thus, we used [Pd(dppf)Cl₂] (dppf = 1,1'-bis(diphenylphosphino)ferrocene) as a catalyst, K₂CO₃ as a base, and 4:4:1 toluene/acetone/H₂O as a cosolvent. The reactions were conducted in a sealed-tube under single-mode microwave irradiation at 100–130 °C for 10 min. This general condition is compatible with a range of functionalized aryl perfluorooctylsulfonates with methoxy, aldehyde, ketone, and heterocyclic groups. It is also compatible with a broad range of boronic acids, including sterically hindered *ortho*-isopropoxy-substituted boronic acid and electron-deficient 3,4-dichlorophenylboronic acid (Table 1).¹⁷ The purification of the final product is straightforward; the organic layer of the

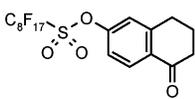
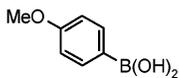
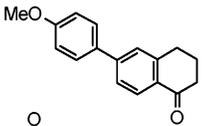
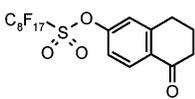
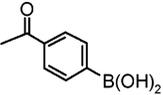
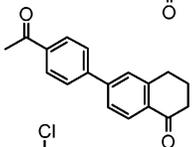
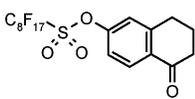
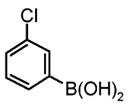
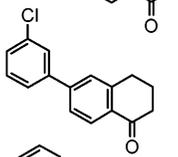
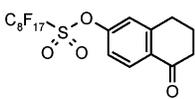
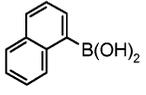
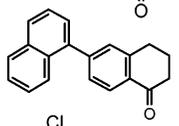
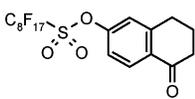
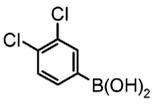
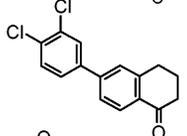
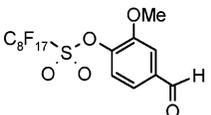
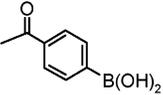
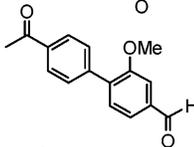
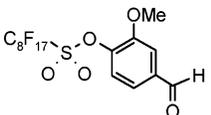
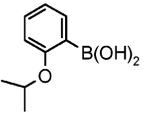
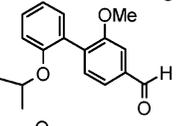
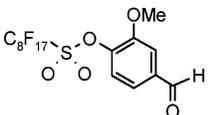
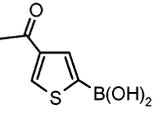
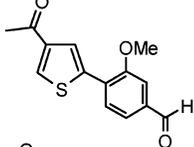
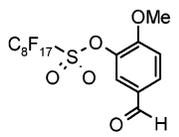
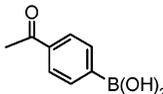
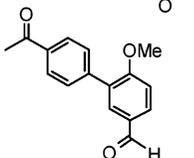
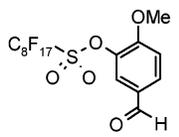
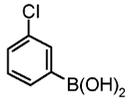
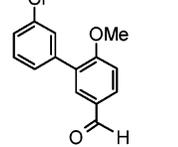
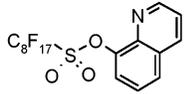
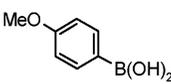
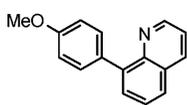
(13) FluoroFlash silica gel charged in the SPE cartridges contains a Si-(Me)₂C₈F₁₇ stationary phase. For more information about F-SPE, please log on to <http://www.fluorous.com/download/fspe.pdf>.

(14) Purities were assessed by ¹H NMR.

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(16) **Representative Procedure for the Suzuki Cross-Coupling Reaction.** A septum-sealed microwave tube charged with aryl perfluorooctylsulfonate **1a** (84.0 mg, 0.13 mmol), 4-methoxyboronic acid (18.9 mg, 0.12 mmol), Pd(dppf)Cl₂ (10.6 mg, 0.013 mmol), and K₂CO₃ (36.0 mg, 0.26 mmol) in 0.8 mL of a 4:4:1 acetone/toluene/H₂O cosolvent was irradiated in a monomode microwave cavity (150W, 130 °C, 10 min). The reaction mixture was washed with 1 mL of H₂O. The organic layer was loaded onto a 5 g FluoroFlash cartridge preconditioned with 80:20 MeOH/H₂O. The cartridge was eluted with 10 mL of 80:20 MeOH/H₂O. The fraction was concentrated to give biaryl **2a** (27.6 mg, 91% yield). The fluororous species were washed from the cartridge with 20 mL of MeOH.

Table 1. Structures and Yields of Biaryls

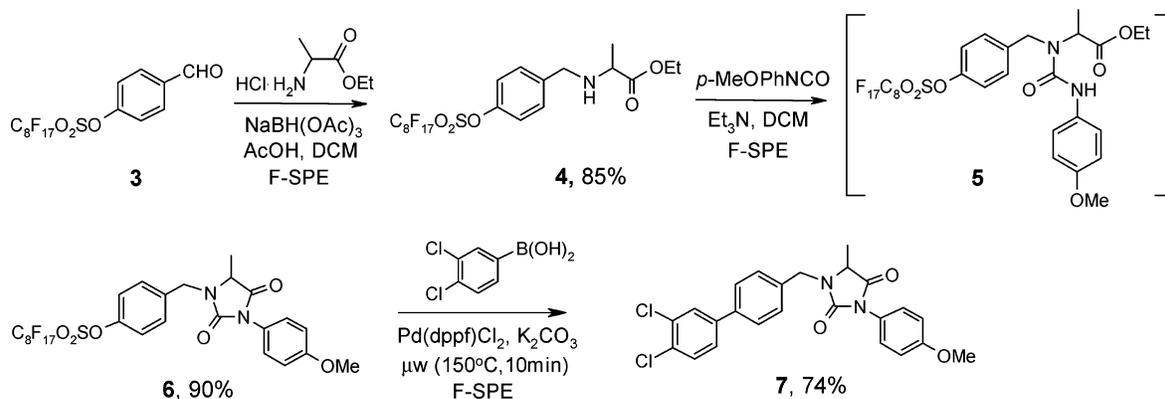
entry	aryl perfluorooctylsulfonate 1	boronic acid	biaryl 2	yield
1				2a 90%
2				2b 89%
3				2c 93%
4				2d 87%
5				2e 87%
6				2f 95%
7				2g 75%
8				2h 78%
9				2i 95%
10				2j 88%
11				2k 81%

reaction mixture was directly loaded onto a FluoroFlash SPE cartridge. The biaryl product was collected in the fraction of 80:20 MeOH/H₂O, while the cleaved fluorosulfonate tag remained on the cartridge until the wash with MeOH was

(17) Pd-catalyzed microwave reactions were conducted under a license from Personal Chemistry.

done. To avoid the coelution of the other organic component in the MeOH/H₂O fraction, boronic acid was used as the limiting agent (~0.95 equiv). After F-SPE, biaryl compounds were isolated in 75–95% yields with purity greater than 90%.¹⁴ No detectable amount of dppe ligand was observed by ¹H NMR analysis.¹⁸

Scheme 2. Fluorous Synthesis of Biaryl-Substituted Hydantoin **7**



We also demonstrated the use of the fluorous sulfonyl tag in a multistep synthesis of a biaryl-substituted hydantoin **7** (Scheme 2). The hydroxyl group of 4-hydroxybenzaldehyde was protected by converting it to a fluorous sulfonate. The tagged benzaldehyde **3** underwent a reductive amination reaction. The resulting amine **4** was treated with an isocyanate to form urea **5**, which spontaneously cyclized to form hydantoin **6**. In the last step, the fluorous sulfonyl group was detagged by the Suzuki coupling reaction to form the C–C bond of biaryl **7**. The efficiency of this multistep synthesis is facilitated by easy F-SPE purification of the reaction intermediates **4** and **6**. The perfluorosulfonyl tag has been demonstrated to be tolerant to reductive amination and isocyanate reactions. The tagged intermediates were also found to be stable during F-SPE separations.

In this fluorous multistep synthesis, the tagging is accomplished at the phenol derivatization and the detagging is conducted at the Suzuki cross-coupling step. No synthetic steps are added just for the sake of putting in and taking off the fluorous tag. In addition to simplifying the intermediate purification, the perfluorosulfonyl group has the functions

of protecting the hydroxyl group in the early steps and activating the phenol for cross-coupling at the last step. The high solubility of aryl perfluorooctylsulfonates in common organic solvents and the high thermostability of the perfluorosulfonyl tag render the fluorous molecules good substrates for solution-phase microwave reactions. Other than formation of C–C and C–S bonds, the perfluorooctylsulfonate moiety is amenable to other kinds of cross-coupling reactions to form C–H, C–N, C–O, C–P, and C–CN bonds. We believe this readily available, highly efficient, and synthetically versatile fluorous tag will have broad applications in solution-phase parallel and combinatorial syntheses.

Acknowledgment. We thank the National Institutes of General Medical Sciences for the SBIR funding (1R43GM-66415-01 and 2R44GM062717-02).

Supporting Information Available: ^1H NMR spectra for aryl perfluorooctylsulfonates **1a–d**, biaryls **2a–k**, compounds **4** and **6**, and biaryl-substituted hydantoin **7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(18) No further quantitative analysis has been attempted to detect the residue of catalyst and ligand in final products.

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