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# Fluorous synthesis of biaryl-substituted proline analogs by 1,3-dipolar cycloaddition and Suzuki coupling reactions

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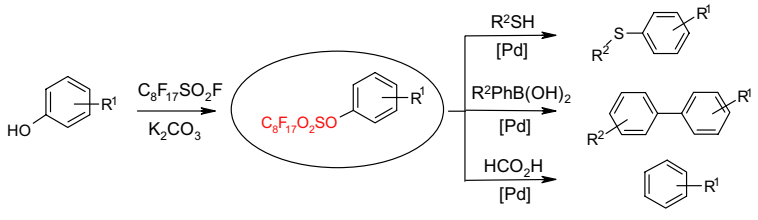
**Abstract**—A solution-phase synthesis of bicyclic prolines containing four points of diversity has been developed by a two-step synthesis involving 1,3-dipolar cycloaddition of perfluoroalkylsulfonyl-protected hydroxybenzaldehydes followed by Pd-catalyzed Suzuki coupling reaction of fluorous sulfonates with boronic acids. Both reactions are conducted under microwave irradiation and reaction mixtures are purified by solid-phase extractions without performing chromatography.


The combination of multicomponent reactions (MCRs) with post-condensation modifications has become a powerful tool for the synthesis of diversified library scaffolds.[1] Isolation of the desired product from a MCR mixture usually requires flash column chromatography or uses more than one polymer-supported scavengers to remove unreacted components.[2] Recently, fluorous tagging strategy[3] has been introduced to MCRs to simplify the reaction mixture purification.[4] The product bearing a fluorous tag can be easily isolated from non-fluorous components by fluorous liquid–liquid extraction or solid-phase extraction (SPE).[5] We have employed fluorous Boc-protected anilines in the synthesis of benzimidazole and quinoxalinone systems by an Ugi/de-Boc/cyclization reaction sequence.[6] We have also reported perfluorooctylsulfonyl ($C_8F_{17}SO_2$)-protected hydroxybenzaldehydes for Pd-catalyzed cross-coupling reactions to form aryl C–S, C–C, and C–H bonds (Scheme 1).[7] Reported in this letter is a new reaction sequence, which combines three-component 1,3-dipolar cycloadditions with Suzuki coupling reactions to synthesize biaryl-substituted proline analogs using fluorous benzaldehydes as the starting materials.

The 1,3-dipolar cycloaddition[8] has been widely used in conventional solution-phase synthesis and solid-phase synthesis[9] of proline-fused heterocyclic systems. This type of reaction is usually performed as a one-pot, three-component reaction of a dipolarophile with an in situ prepared azomethine ylide.[10] Fluorous alcohol protected amino acids have been used in the synthesis of novel tricyclic proline scaffolds.[3a] Perfluoroalkylsulfonyl-protected hydroxybenzaldehydes are now used for preparation of bicyclic proline analogs (Scheme 2). Amino




**Scheme 1.** Pd-Catalyzed cross-coupling of aryl perfluorooctylsulfonates.

*Keywords*: Fluorous synthesis; 1,3-Dipolar cycloadditions; Multicomponent reactions; Proline; Microwave reactions; Suzuki coupling; Perfluorooctylsulfonyl; Solid-phase extraction.
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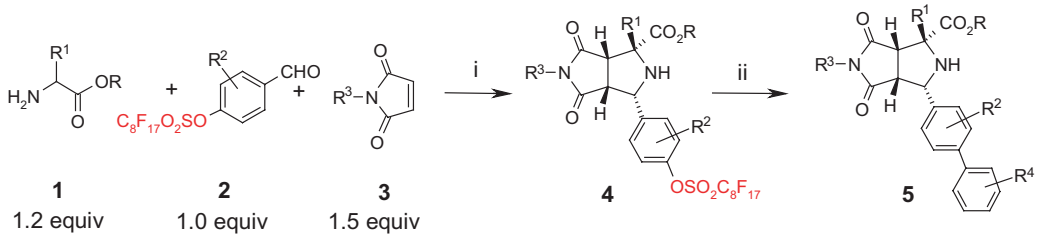
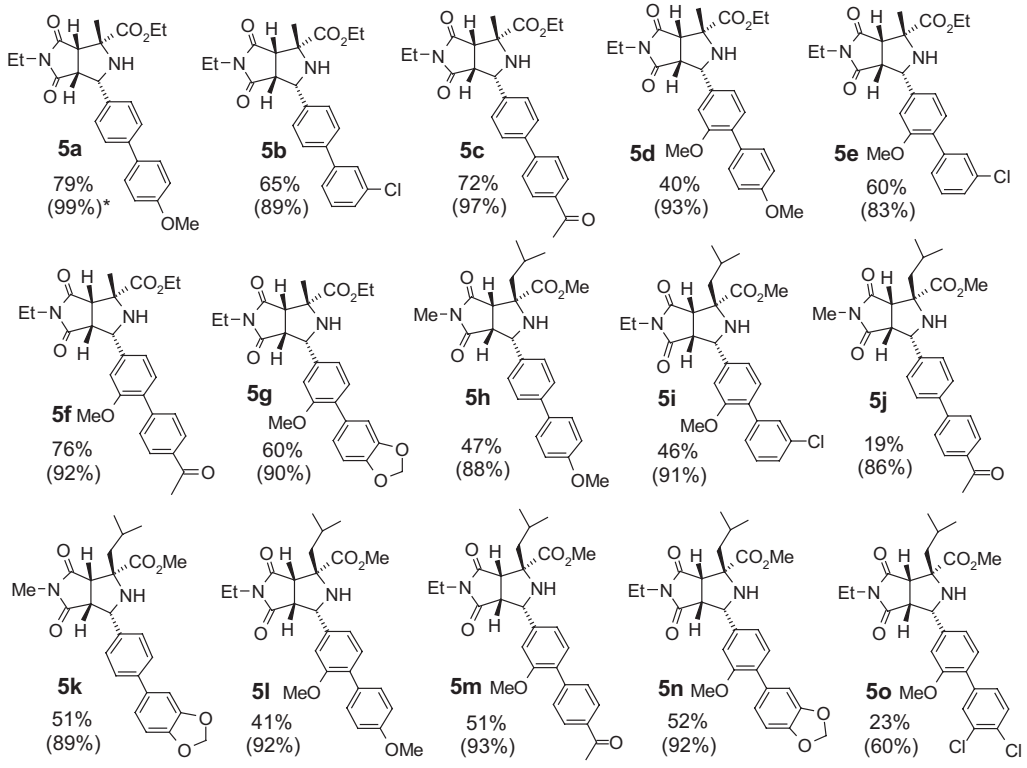



$R^1$ = Me, *i*-Pr; $R^2$ = H, 3-MeO; $R^3$ = Me, Et; $R^4$ = 4-MeO, 3-Cl, 4-Ac, 3,4-diCl, 3,4-methylenedioxy

i) $Et_3N$, DMF, microwave (250 w, 150°C, 15 min), SPE, 40-75%. ii) $R^4PhB(OH)_2$ (1.0 equiv), $Pd(dppf)Cl_2$ (0.1 equiv), $K_3PO_4$, MePhH-acetone-$H_2O$ (4:4:1), microwave (150 w, 120°C, 12 min), SPE, 19-79%.




**Scheme 2.** Fluorous synthesis of biaryl substituted prolines. *Numbers in parentheses are LC–MS purities at UV254.

ester **1**, benzaldehyde **2**, and maleimide **3** each with a diversity point were condensed under microwave irradiation (250 W, 150 °C, 15 min) to produce bicyclic proline **4** as a single diastereomer; two ring-fused hydrogen atoms are *cis* to the $R^1$ and *trans* to the phenyl group.[11] The perfluoroalkylsulfonyl-protected hydroxybenzaldehyde was used as the limiting agent. The cycloaddition product as the fluorous component was isolated from the reaction mixture by SPE with Fluoro*Flash*® cartridges.[12] Excess reagents and other non-fluorous components were collected in the first fraction eluted with 80:20 MeOH–$H_2O$, while the fluorous proline **4** was collected in the second fraction eluted with MeOH. Separations of reaction mixtures have also been accomplished by flash chromatography using the Isco Combi*Flash* OptiX 10 system equipped with fluorous RediSep cartridges (Fig. 1).[13] Because fluorous separation is based on fluorine affinity, only two major peaks were shown in the chromatography trace. All the non-fluorous compounds eluted out with the solvent front, whereas fluorous proline analog **4a** had a good retention (9.5 min) on the cartridge.

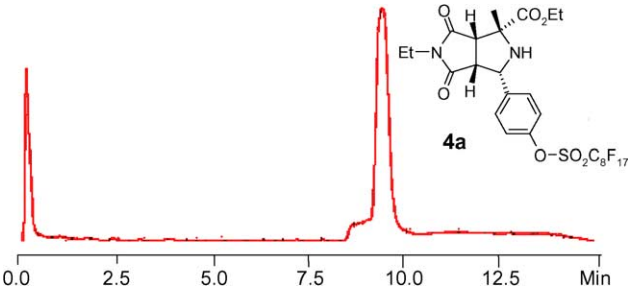



**Figure 1.** Flash chromatography of a cycloaddition mixture using Isoc Combi*Flash* OptiX 10 with a fluorous cartridge. Flow rate 15 mL/min, 20–30 psi, 80:20 MeOH–$H_2O$ for 8 min and then 100% MeOH for 7 min, UV245.

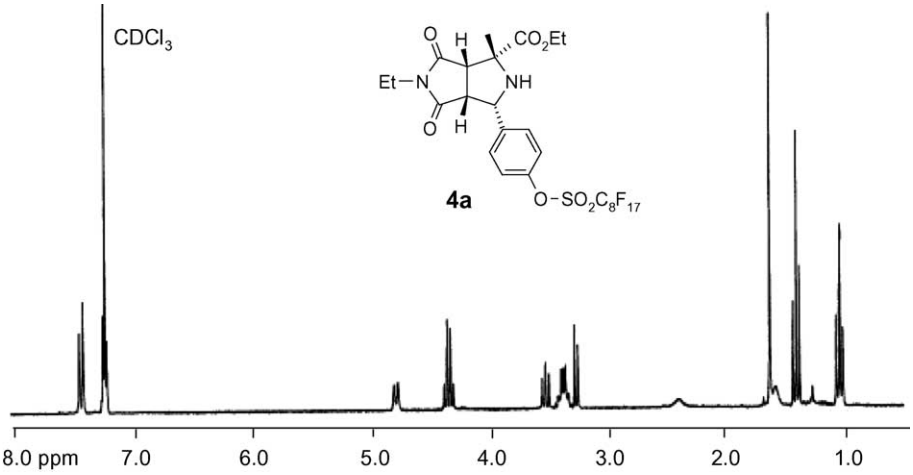



**Figure 2.** $^{1}$H NMR (270 MHz) of fluorous bicyclic proline **4a**.

In addition to easy SPE separation, another feature of fluorous synthesis is that intermediates could be analyzed by conventional analytical methods such as TLC, LCMS, and NMR. Figure 2 shows the $^{1}$H NMR of a SPE purified fluorous proline analog **4a**. If reactions were performed by solid-phase synthesis with immobilized polymer supports instead of fluorous tags, analysis of the attached intermediates would be a difficult task.

The Suzuki reactions of an equimolar amount of fluorous sulfonates and boronic acids were also conducted under microwave irradiation (150 W, 120 °C, 12 min) using Pd(dppf)$Cl_2$ as a catalyst, $K_2PO_4$ as a base, and toluene–acetone–$H_2O$ as a co-solvent.[14] Final products were purified by SPE with normal silica gel eluted with 15:85 EtOAc–hexanes. Structures of 15 substituted proline analogs are listed in Scheme 2. Yields of Suzuki coupling reactions were in the range of 19–70% and most products had greater than 85% purities as analyzed by LC–MS.

In summary, a straightforward two-step protocol for parallel synthesis of biaryl substituted proline analogs has been developed using perfluoroalkylsulfonyl-protected hydroxybenzaldehydes as the starting material. The fluorous sulfonyl group played three different roles in the multistep synthesis; as a 'phase tag' to facilitate reaction mixture purification, as a protecting group to protect the phenol functionality, and as a triflate equivalent to promote cross-coupling reactions. The combination of microwave and fluorous technologies has demonstrated the advantage of speeding up reaction and separation processes. This highly efficient methodology could have good application potential for small library synthesis.

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11. General procedure for 3-component 1,3-dipolar cycloaddition reactions. Preparation of **4a** ($R^1 = CH_3$, $R^2 = H$, $R^3 = Et$): A solution of perfluorooctyl-protected 4-hydroxybenzaldehyde (0.33 g, 0.54 mmol), L-alanine ethyl ester hydrochloride (0.10 g, 0.65 mmol), *N*-ethylmaleimide (0.067 g, 0.54 mmol), and $Et_3N$ (152 μL, 1.08 mmol) in 1.2 mL of DMF was irradiated in a monomode microwave reactor (CEM Explorer®) at 150 °C for 15 min. The crude mixture was diluted with EtOAc and washed with $H_2O$. The concentrated organic layer was loaded onto a 5-g Fluoro*Flash*® cartridge, eluted with 80:20 MeOH–$H_2O$ (2 × 8 mL) and then MeOH (2 × 8 mL). Concentration of the MeOH fraction gave desired product **4a** in 71% yield: $^1$H NMR ($CDCl_3$) $\delta$ 1.03 (t, $J$ = 7.1 Hz, 3H), 1.40 (t, $J$ = 7.3 Hz, 3H), 1.62 (s, 3H), 2.41 (br s, 1H), 3.27 (d, $J$ = 7.4 Hz, 1H), 3.30–3.44 (m, 2H), 3.52 (dd, $J$ = 7.8, 8.8 Hz, 1H), 4.34 (q, $J$ = 6.7 Hz, 2H), 4.80 (d, $J$ = 8.9 Hz, 1H), 7.27 (d, $J$ = 8.8 Hz, 2H), 7.47 (d, $J$ = 8.8 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.1, 14.2, 24.0, 34.0, 49.6, 54.9, 60.8, 61.9, 67.1, 107–115 (m, 8 fluorinated carbons), 121.3, 129.1, 137.9, 149.4, 172.2, 174.2, 175.3; LRMS (APCI) 829.0 ($M^+$+H).
12. Fluoro*Flash*® SPE cartridges are available from Fluorous Technologies, Inc. (www.fluorous.com).
13. Web address for Isco: www.isco.com.
14. General procedures for Suzuki coupling reactions. Preparation of **5k**: To a mixture of proline **4b** ($R^1$ = *i*-Pr, $R^2 = H$, $R^3 = Me$) (29 mg, 0.03 mmol), $K_3PO_4$ (15 mg, 0.07 mmol), 3,4-(methylenedioxy)phenylboronic acid (4.9 mg, 0.14 mmol), $PdCl_2$(dppf)·$CH_2Cl_2$ complex (3 mg, 0.03 mmol) in 0.6 mL of 4:4:1 toluene–acetone–$H_2O$ was purged with argon for 2 min. The mixture was irradiated in a monomode microwave reactor at (CEM Explorer®) 120 °C for 12 min. The crude mixture was loaded onto a Supelco cartridge packed with 2 g of normal silica gel and topped with a pad of Celite (1 g, added manually), eluted with 15:85 EtOAc/hexanes (10 mL). Evaporation of the solvent gave desired product **5k** (12.4 mg, 89% yield). $^1$H NMR ($CDCl_3$) $\delta$ 0.88 (d, $J$ = 6.6 Hz, 3H), 1.00 (d, $J$ = 6.6 Hz, 3H), 1.67–1.82 (m, 2H), 2.04–2.12 (m, 1H), 2.71 (d, $J$ = 7.6 Hz, 1H), 2.84 (s, 3H), 3.24 (d, $J$ = 7.4 Hz, 1H), 3.54 (dd, $J$ = 7.8, 9.0, Hz, 1H), 3.89 (s, 3H), 4.63 (t, $J$ = 8.1 Hz, 1H), 6.00 (s, 2H), 6.88 (d, $J$ = 8.5 Hz, 1H), 7.06–7.09 (m, 2H), 7.35 (d, $J$ = 8.3 Hz, 2H), 7.50 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 22.2, 24.3, 24.6, 25.0, 43.1, 50.5, 52.5, 56.5, 61.8, 70.3, 101.2, 107.7, 108.6, 120.7, 126.9, 127.5, 135.1, 135.8, 140.9, 147.2, 148.2, 172.9, 174.9, 175.7; LRMS (APCI) 465.2 ($M^+$+H).