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Palladium-Catalyzed Buchwald–Hartwig Type Amination of Fluorous Arylsulfonates

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Abstract

Palladium-catalyzed cross-coupling reactions of aryl perfluorooctanesulfonates with amines are introduced. Application of the fluorous tag in multistep synthesis of triaryl-substituted pyrimidine is also described.

Keywords

fluorous synthesis; palladium-catalyzed amination; Buchwald–Hartwig amination; perfluorooctanesulfonyl fluoride; aryl perfluorooctanesulfonates

1. Introduction

Palladium-mediated organic transformations, such as Suzuki–Miyaura, Heck, and Buchwald–Hartwig reactions, are powerful synthetic methods for formation of carbon–carbon and carbon–heteroatom bonds.¹ Solid-phase synthesis employs substrates attached to sulfonamide, Wang, PMB, Rink, and other linkers for palladium-catalyzed cross-coupling reactions to simplify reaction mixture purifications.² We have recently engaged in the development of fluorous tags for solution-phase synthesis.³ Perfluorooctanesulfonyl-attached phenols have been used for palladium-catalyzed reactions to form aryl carbon–carbon, carbon–sulfur, and carbon–hydrogen bonds (Scheme 1, a–c).⁴ Reported in this paper is an extension of this chemistry for Buchwald–Hartwig type amination to form aryl carbon–nitrogen bond (Scheme 1, d).

Aryl triflates ($\text{ArOSO}_2\text{CF}_3$) and aryl nonaflates ($\text{ArOSO}_2(\text{CF}_2)_3\text{CF}_3$) are well-known aryl halide equivalents for palladium-catalyzed coupling reactions.⁵ Solid-supported aryl sulfonate linkers have also been developed.⁶ Solution-phase and solid-supported aryl perfluoroalkanesulfonates can be easily prepared from a wide range of commercially available phenols. They have high reactivity, good stability for room temperature storage, chromatography purification, and resistance towards hydrolysis.⁷ In the development of fluorous Suzuki reactions, we found that aryl perfluorooctanesulfonates ($\text{ArOSO}_2(\text{CF}_2)_7\text{CF}_3$) had similar characters and literature procedures developed for reactions of aryl triflates⁸ can be easily transferred to reactions of aryl perfluorooctanesulfonates.^{4a} It is also noteworthy that perfluorooctanesulfonates contain a light fluorous C_8F_{17} tag, they usually have good solubility in common reaction solvents such as DMF, toluene, and THF.

2. Results and discussion

Aryl perfluorooctanesulfonates **1a–c** for palladium-catalyzed coupling reactions were readily prepared by reaction of commercially available phenols with perfluorooctanesulfonyl fluoride

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under general conditions using K_2CO_3 as a base and dimethylformamide (DMF) as a solvent at 70 °C for 5 h (Scheme 2).⁹ The crude aryl perfluorooctanesulfonates **1a–c** usually have greater than 90% purity after workup. They were used directly for the cross-coupling reactions. If needed, sulfonates can be further purified by recrystallization from MeOH or by fluorous solid-phase extraction (F-SPE) using a FluoroFlash cartridges.¹⁰ After loaded the sample on the cartridge, it was first eluted with 80:20 MeOH/H₂O to remove non-fluorous impurities, then with MeOH to obtain aryl perfluorooctanesulfonate **1** with purity typically greater than 95%. Sulfonates **1a–c** shown in Scheme 2 represent three kinds of substrates; compound **1a** has a carbonyl functionality, compound **1b** is heterocyclic, and compound **1c** has an electron rich methoxy substitution.

With the aryl perfluorooctanesulfonates in hand, we examined Buchwald–Hartwig type amination reactions following reported procedures using $Pd(OAc)_2$ and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) as a catalyst, Cs_2CO_3 as a base, and toluene as a solvent.¹¹ Reactions under both microwave and oil-bath heating conditions were evaluated. Under microwave irradiation at 120–150 °C up to 30 min, reactions did not reach completion. Formation of dark-brown precipitate suggested that the incomplete reactions could be caused by rapid decomposition of the catalyst under the microwave heating.

Under optimized thermo amination conditions of heating the reaction mixture at 80–90 °C for 48 h,¹² aryl perfluorooctanesulfonates **1a–c** were reacted with different amines including primary amines (butylamine and benzylamine), secondary and cyclic amines (morpholine and 1-(2-pyridyl)pyrazine) (Table 1). Since excess amount of amine (2–3 equiv) was used to push the reaction to completion, unreacted amine also existed in the reaction mixture as the non-fluorous component. The desired products have to be purified by flash chromatography with normal silica gel instead of by F-SPE. Reactions with **1a** and **1b** gave good yields of amination products **2**, while the electron-rich sulfonate **1c** gave no amination product. We have not tried other reaction conditions reported in literature for triflates that resulted good yields of amination products.¹³

After the study of palladium-catalyzed reactions of aryl perfluorooctanesulfonates, we applied the fluorous tagging strategy in the synthesis of triaryl-substituted pyrimidine compound **6** (Scheme 3). In the multistep synthesis, the perfluorooctanesulfonyl group has three potential functions: as a phenol protecting group, as a fluorous tag for reaction mixture separation, and as an activating group for palladium-catalyzed coupling. The fluorous tag is removed during the cross-coupling reaction in a traceless fashion; no additional step is needed for the tag cleavage.

Fluorous benzaldehyde **1d** was condensed with phosphonate **3** to form α , β -unsaturated ketone **4**. A small amount (not quantified) of detagged byproduct was observed under basic reaction conditions. Compound **4** was then used for cycloaddition with benzamidine to form pyrimidine **5**. Because of low solubility of **4** and **5** in organic solvents, these two fluorous intermediates were purified by crystallization instead of F-SPE. Compound **4** was purified by crystallization with hexanes/Et₂O, whereas compound **5** was precipitated out by adding water to the reaction mixture. Easy isolations of **4** and **5** demonstrated the technical compatibility of fluorous molecules with conventional purification methods. Compound **5** was coupled with benzylamine under optimized amination conditions described above to give the targeted triaryl-substituted pyrimidine **6** in 76% yield.¹⁴

In summary, the scope of previously developed aryl perfluorooctanesulfonate-based fluorous coupling reactions for formation of aryl carbon-carbon, carbon-sulfur, and carbon-hydrogen bonds has been extended to Buchwald–Hartwig type amination to form aryl carbon-nitrogen

bond. We have also demonstrated the utility of fluorous tag in multistep synthesis of a triaryl-substituted pyrimidine scaffold, which has potential application in parallel analog synthesis.

Acknowledgements

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9. General procedures for the preparation of aryl perfluorooctanesulfonates **1**: To a mixture of phenol (20.0 mmol) and K₂CO₃ (21.0 mmol) in DMF (15 mL) was added perfluorooctanesulfonyl fluoride (16.7 mmol) dropwise through an addition funnel. After heating at 70 °C for 5 h, the mixture was poured into water (100 mL), and was extracted with ethyl acetate. The organic layer was dried over MgSO₄, and the solvent was evaporated under vacuum to give aryl perfluorooctanesulfonate **1** in 85–90% yields. The crude product was used for the next step reaction. If needed, the crude product could be further purified by recrystallization from MeOH or by F-SPE.
10. FluoroFlash SPE cartridges are packed with silica gel with a stationary phase of Si (Me)₂CH₂CH₂C₈F₁₇. They are commercially available from Fluorous Technologies, Inc. (www.fluorous.com).
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12. General procedures for cross-coupling reactions of aryl perfluorooctanesulfonates with amines: Fluorous sulfonate **1b** (0.129 g, 0.205 mmol), Pd(OAc)₂ (6 mg, 0.03 mmol), BINAP (22 mg, 0.04 mmol), and Cs₂CO₃ (95 mg, 0.29 mmol) were added to a flask under a nitrogen atmosphere. Benzylamine (46 mg, 0.43 mmol) in toluene (3 mL) was added. The mixture was stirred at 90 °C for 48 h. After cooling, the reaction mixture was directly loaded to a silica gel column, eluted with 3:1 hexanes/EtOAc to give product (29.3 mg, 0.13 mmol) in 61% yield.
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14. Analytical data for compound **6**: ^1H NMR (270 MHz, CDCl_3): δ 8.73 (2H, dd, $J = 2.3, 8.0$ Hz), 8.26 (2H, d, $J = 8.9$ Hz), 8.19 (2H, d, $J = 8.7$ Hz), 7.83 (1H, s), 7.60–7.45 (3H, m), 7.44–7.28 (5H, m), 7.07 (2H, d, $J = 8.8$ Hz), 6.76 (2H, d, $J = 8.7$ Hz), 4.43 (3H, broad s), 3.91 (3H, s). ^{13}C NMR (67.5 MHz, CDCl_3): δ 164.2, 164.0, 163.5, 161.6, 150.3, 138.8, 138.7, 130.4, 128.8, 128.7, 128.4, 127.5, 126.4, 114.1, 112.6, 107.8, 55.5, 47.9. LRMS (APCI) m/z 444.2 $[\text{M} + \text{H}]^+$.

Scheme 1.

Scheme 2.

Scheme 3.

Table 1

Amination of aryl perfluorooctanesulfonates

$\text{Rf}_8\text{O}_2\text{S}-\text{O}-\text{C}_6\text{H}_4-\text{R}^1 + \text{R}^2-\text{N}(\text{R}^{2'})-\text{H}$ <p>1 equiv 2-3 equiv</p>		$\xrightarrow[\text{80-90 } ^\circ\text{C, 48 h}]{\text{Pd(OAc)}_2 \text{ (10 mol\%)} \\ \text{BINAP (15 mol\%)} \\ \text{Cs}_2\text{CO}_3 \text{ (1.5 equiv)} \\ \text{toluene}}$	$\text{R}^2-\text{N}(\text{R}^{2'})-\text{C}_6\text{H}_4-\text{R}^1$ <p>2</p>	
F-sulfonate	amine	product	yield	purity*
<p>1a</p>	BuNH ₂		66%	91%
	67%	>99%
	61%	95%
	71%	92%
<p>1b</p>	BuNH ₂		73%	90%
	61%	96%
	81%	71%
<p>1c</p>			not detected	

* assessed by LC-MS (UV 254 nm)