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Palladium-catalyzed Suzuki–Miyaura couplings of potassium aryl trifluoroborates with 4-tosyloxycoumarins or 4-tosyloxyquinolin-2(1*H*)-one

Jie Wu,[a,b,*] Liang Zhang[a] and Hong-Guang Xia[a]

[a]*Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China*
[b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China*

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Abstract—$Pd(PPh_3)_4$ catalyzed Suzuki–Miyaura cross-coupling reactions of 4-tosyloxycoumarins or 4-tosyloxyquinolin-2(1*H*)-one with various potassium aryl trifluoroborates afforded the corresponding 4-substituted coumarins or 4-substituted quinolin-2(1*H*)-ones in good to excellent yield.

Among all the C–C bond forming crossing-coupling processes, palladium-catalyzed Suzuki–Miyaura coupling is one of the most important reactions.[1] Its great practical importance comes, in part, from the nontoxic, mild, and air-, water-stable nature of the boronic acid nucleophile. A drawback associated with the use of boronic acids is the structural ambiguity, namely, the formation of the trimeric anhydride (boroxine).[2] The purity of commercially available boronic acids is also of concern. Although purification via recrystallization, usually from water, affords a boronic acid of higher purity, removal of the water generally results in the formation of a mixture of boronic acid and the corresponding boroxine.

An encouraging improvement is the use of boronate esters and trifluoroborates. These boronic acid alternatives can circumvent the above-described issues. Boronate esters and trifluoroborates can be easily prepared by treatment of boronic acids with diols, or with potassium hydrogen fluorides,[3] respectively. Couplings of tetrabutylammonium aryl trifluoroborates or potassium aryl trifluoroborates with aryl iodides, bromides or chlorides have been reported.[4] What is missing is a system capable of handling tosylates. Tosylates are emerging as important alternatives to aryl/vinyl triflates and halides in Pd-catalyzed cross-coupling reactions. They are often more stable and easier to handle than the corresponding triflates both in the solid state and in solution. As a direct result of these described advantages, tosylates are becoming prominent substrates in cross-coupling reactions. This would be of great interest if tosylates are suitable partners in the coupling reactions of aryl trifluoroborates.

Recently, we have witnessed the important progress of using arenesulfonates as electrophiles for the cross-coupling reactions although tosylates are relatively unreactive compared to the corresponding halides and triflates.[5–11] In view of their easier preparation, increased stability, and less expense with relative to aryl triflates, it is of significant interest to develop a general protocol to employ arenesulfonates for transition metal-catalyzed Suzuki–Miyaura cross-coupling reactions of potassium aryl trifluoroborates. In connection with a chemical genetic approach of analyzing biological systems by using interfacing libraries of natural product-like molecules with biological assays,[12] we became interested in developing new approaches to the synthesis of coumarin and quinolin-2(1*H*)-one derivatives.[13] Herein, we disclose our preliminary results of palladium-catalyzed

Keywords: Suzuki–Miyaura couplings; Potassium aryl trifluoroborates; 4-Tosyloxycoumarins; 4-Tosyloxyquinolin-2(1*H*)-one; Palladium catalyst.
* Corresponding author. Tel.: +86 2155 664619; fax: +86 2165 102412; e-mail: jie_wu@fudan.edu.cn

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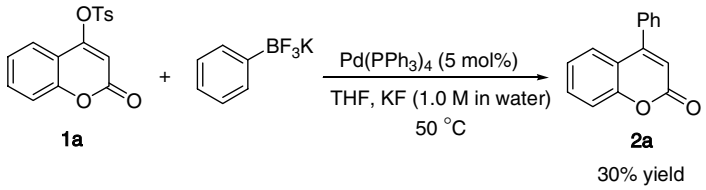
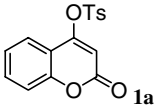
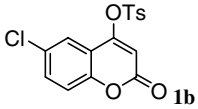
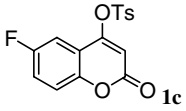
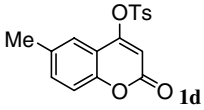
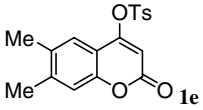
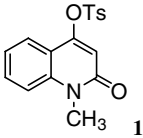
Suzuki–Miyaura couplings of 4-tosyloxycoumarins or 4-tosyloxyquinolin-2(1*H*)-one with potassium aryl trifluoroborates.

These tosylates were prepared simply from the corresponding 4-hydroxycoumarins or 4-hydroxy-1-methylquinolin-2(1*H*)-one with *p*-toluenesulfonyl chloride in the presence of triethylamine. Initial studies were performed in THF, with the presence of KF (1.0 M in water) as base, by using different palladium catalysts ($Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, and $Pd_2(dba)_3$) in the reaction of 4-tosyloxycoumarin **1a** with potassium phenyltrifluoroborate at 50 °C. To our delight, we observed the formation of the corresponding product **2a** when $Pd(PPh_3)_4$ was employed, albeit in low yield (30%) (Scheme 1). Only trace amount of product **2a** was detected when other palladium catalysts were used.



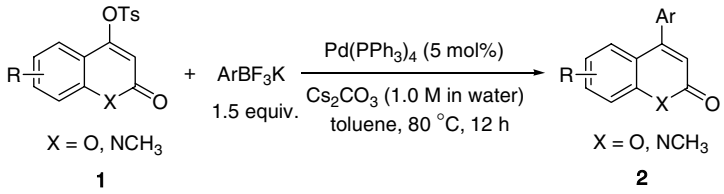
Scheme 1. Reaction of 4-tosyloxycoumarin **1a** with potassium phenyltrifluoroborate catalyzed by $Pd(PPh_3)_4$.

Table 1. Palladium-catalyzed Suzuki–Miyaura cross-coupling reactions of tosylates with potassium aryl trifluoroborates[a]

Entry	Substrate **1**	$ArBF_3K$	Product	Yield (%)[b]
1	 **1a**	$C_6H_5BF_3K$	**2a**	86
2	**1a**	4-F–$C_6H_4BF_3K$	**2b**	80
3	**1a**	4-Me–$C_6H_4BF_3K$	**2c**	89
4	 **1b**	$C_6H_5BF_3K$	**2d**	46
5	**1b**	4-F–$C_6H_4BF_3K$	**2e**	92
6	**1b**	4-Me–$C_6H_4BF_3K$	**2f**	87
7	 **1c**	$C_6H_5BF_3K$	**2g**	61
8	**1c**	4-F–$C_6H_4BF_3K$	**2h**	86
9	**1c**	4-Me–$C_6H_4BF_3K$	**2i**	77
10	 **1d**	$C_6H_5BF_3K$	**2j**	58
11	**1d**	4-F–$C_6H_4BF_3K$	**2k**	89
12	**1d**	4-Me–$C_6H_4BF_3K$	**2l**	85
13	 **1e**	4-Me–$C_6H_4BF_3K$	**2m**	86
14	 **1f**	4-F–$C_6H_4BF_3K$	**2n**	48
15	**1f**	4-Me–$C_6H_4BF_3K$	**2o**	68

[a] Reaction conditions: 4-tosylate (0.125 mmol), $ArBF_3K$ (1.5 equiv), Cs_2CO_3 (1.0 mL, 1.0 M in water), $Pd(PPh_3)_4$ (5 mol %), toluene (1.0 mL), 80 °C, 12 h.

[b] Isolated yields.



Scheme 2. Palladium-catalyzed Suzuki–Miyaura cross-coupling reactions of tosylates with potassium aryl trifluoroborates.

Among the solvents (THF, MeCN, MeOH, toluene) and bases (Cs_2CO_3, Na_2CO_3, KF, CsF, K_3PO_4, LiOH; 1.0 M in water) screened, toluene was the best solvent and Cs_2CO_3 (1.0 M in water) was the best base in the reactions. Further study showed that the reaction worked most efficiently at 80 °C and it went to completion in 12 h (with 86% isolated yield).

A variety of 4-(*p*-toluenesulfonyloxy)coumarins and potassium aryl trifluoroborates have thus been examined for palladium-catalyzed cross-coupling reactions under the optimized conditions, and the results are summarized in Table 1. As shown there, the conditions have proved to be efficient for coupling a range of tosylates with potassium aryl trifluoroborates (Table 1 and Scheme 2). Complete conversion and good to excellent isolated yields were observed for all arenesulfonates employed. Potassium aryl trifluoroborates either with electron-rich or electron-withdrawing substitutions all gave similar yields. For example, 80% or 89% yield of product **2b** or **2c** was obtained when 4-tosyloxycoumarin **1a** reacted with potassium 4-fluorophenyl trifluoroborate or potassium 4-methylphenyl trifluoroborate (entries 2 and 3). Furthermore, 4-(*p*-toluenesulfonyloxy)-1-methyl-quinolin-2(1*H*)-one **1f** was tested suitable in the cross-coupling reactions although the yields were lower comparing coumarin substrates (entries 14 and 15).

Although the mechanism is not clear since there is no supporting evidence at present, a possible mechanistic rationalization for the reaction is proposed. The initial event was an oxidative addition of palladium(0) to the tosylate. The intermediate generated then underwent transmetalation in the presence of aryl trifluoroborates, followed by a reductive elimination to afford the corresponding product and palladium(0), which completed the catalytic cycle.

In conclusion, we have described efficient Suzuki–Miyaura cross couplings of tosylates with potassium aryl trifluoroborates catalyzed by $Pd(PPh_3)_4$. The advantage of this method includes good substrate generality, the use of air-stable, inexpensive tosylate under mild conditions, and experimentally operational ease. The reaction employing aryl arenesulfonates as substrates is currently under investigation in our research group, which will be reported in due course.

General procedure: A mixture of 4-tosylate **1** (0.125 mmol), potassium aryltrifluoroborate (0.187 mmol), and $Pd(PPh_3)_4$ (7.2 mg, 5 mol %) was added into a reaction tube under nitrogen atmosphere. Then toluene (1.0 mL) and aqueous cesium carbonate (1.0 mL, 1.0 M solution) were added subsequently. The reaction mixture was stirred for 12 h at 80 °C. After the reaction was completely monitored by TLC, the organic phase was separated, and purified directly by flash chromatography column (silica gel) to afford the corresponding product. Selected examples: *4-p-tolyl-2H-chromen-2-one* **2c**:[14] 89% yield, ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.46 (s, 3H), 6.36 (s, 1H), 7.24 (t, $J = 7.5$ Hz, 1H), 7.35 (m, 4H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.53 (m, 2H). ^{13}C NMR (125.7 MHz) δ 161.1, 156.0, 154.5, 140.2, 132.6, 132.1, 129.8, 128.7, 127.3, 124.3, 119.4, 117.6, 115.2, 21.6. MS [$C_{16}H_{12}O_2$], *m*/*z* (M^++1): calcd 237, found 237. *6,7-Dimethyl-4-p-tolyl-2H-chromen-2-one* **2m**: 86% yield, ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.23 (s, 3H), 2.35 (s, 3H), 2.46 (s, 3H), 6.27 (s, 1H), 7.17 (s, 1H), 7.23 (s, 1H), 7.35 (t, $J = 9$ Hz, 4H). ^{13}C NMR (125.7 MHz): δ 161.4, 155.7, 152.7, 141.9, 139.7, 132.9, 132.8, 129.5, 128.4, 127.0, 117.9, 116.8, 113.9, 21.4, 20.2, 19.3. MS [$C_{18}H_{16}O_2$], *m*/*z* (M^+): calcd 264, found 264. HRMS: Anal. Calcd for $C_{18}H_{16}O_2$, 264.1150. Found, 264.1156. *1-Methyl-4-p-tolylquinolin-2(1H)-one* **2o**: 68% yield, ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.78 (s, 3H), 6.69 (s, 1H), 7.18 (t, $J = 7$ Hz, 1H), 7.31 (m, 4H), 7.43 (d, $J = 8.5$ Hz, 1H), 7.59 (m, 2H). ^{13}C NMR (125.7 MHz): δ 162.1, 151.0, 140.4, 138.7, 134.2, 130.6, 129.3, 128.9, 127.8, 122.6, 121.9, 120.7, 114.5, 29.5, 21.3. MS [$C_{17}H_{15}NO$], *m*/*z* (M^+): calcd 249, found 249. HRMS: Anal. Calcd for $C_{17}H_{15}NO$, 249.1154. Found, 249.1168.

Acknowledgments

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