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Unusual ligand-dependent chemoselective Suzuki–Miyaura cross-coupling reactions of 3-bromo-4-trifloyl-thiophenes

Jizhou Wang *, Mark A. Seefeld, Juan Luengo

Department of Medicinal Chemistry, Oncology R&D, GlaxoSmithKline, 1250 S. Collegeville Rd., Collegeville, PA 19426, USA

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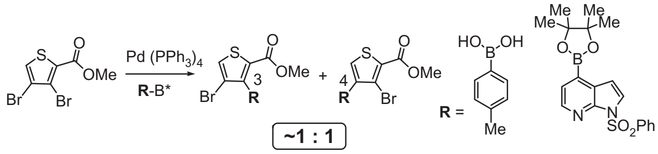
ABSTRACT

An unusual ligand-dependent chemoselective Suzuki–Miyaura cross-coupling reaction for 3-bromo-4-trifloyl-thiophenes was discovered. $Pd(PPh_3)_4$ showed selectivity for triflate over bromide, whereas the selectivity was reversed for $Pd(^tBu_3P)_2$.

The palladium-catalyzed Suzuki–Miyaura cross-coupling reactions of aryl halides and aryl triflates using arylboronic acids/esters to form biaryls are one of the most powerful reactions in organic synthesis.[1] It would be very valuable to realize selective mono-functionalization through Suzuki–Miyaura cross-coupling reactions for substrates bearing more than one halide/triflate. In palladium-catalyzed cross-coupling reactions, aromatic iodides are generally more reactive than the corresponding bromides or triflates; iodides undergoing the substitution preferentially.[1–3] On the other hand, the relative reactivity of aryl bromides and aryl triflates is dependent upon the reaction conditions used. For Stille[2a,c] and Kumada couplings,[2b,d] triflate/bromide selectivity is ligand-dependent, while for Negishi, Sonogashira, and Heck couplings, triflates are more active than bromides regardless of ligands.[2c,d] However, Suzuki–Miyaura cross-coupling reactions represent an exception. In such reactions, it is commonly observed that aryl triflates are less reactive than the corresponding bromides, and this selectivity is irrespective of catalysts.[2c,d] To date there is no well-accepted explanation why Suzuki–Miyaura cross-coupling reactions are different from other common cross-coupling reactions.[2d] However, we discovered that triflate/bromide selectivity is ligand-dependent for Suzuki–Miyaura cross-coupling reactions of 3-bromo-4-trifloyl-thiophenes. Herein we report the details of this unusual chemoselectivity.

As part of an ongoing medicinal chemistry program, there was a need to explore efficient routes to synthesize highly-substituted thiophenes.[4] We first examined the regioselective arylation of methyl 3,4-dibromo-2-thiophenecarboxylate under Suzuki–Miyaura cross-coupling conditions.[5] We expected that the adjacent 2-carboxylic acid ester group would activate the adjacent 3-bromide and that cross-coupling would occur here preferentially. However, a 1:1 mixture of 3- and 4-substituted products was obtained for both an electron rich and an electron poor boronic acid/ester and no appreciable selectivity was observed (Scheme 1).

Based on these results, we decided to explore the chemoselective Suzuki–Miyaura cross-coupling reactions of bromothiophene triflates. To the best of our knowledge, chemoselectivity of this reaction on the thiophene derivatives has never been studied. The first substrate we examined was methyl 4-bromo-3-trifloyl-thiophene-2-carboxylate **1**[6] in conjunction with the most commonly used catalyst, $Pd(PPh_3)_4$. Surprisingly, in the presence of K_2CO_3 (3.0 equiv) and $Pd(PPh_3)_4$ (5 mol %) at 70 °C, the Suzuki–Miyaura cross-coupling reaction between **1** and (4-methylphenyl)boronic acid **5** predominantly gave OTf-displacement product (71%), accompanied by 10% of disubstituted product, with no detectable Br-displacement product (Table 1, entry **1a**). Under the same conditions, cross-coupling of bromotriflate **1** with the more steric and electron-deficient boronic ester, 1-(phenylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo-[2,3-*b*]pyridine **6** predominantly resulted in triflate displacement (88%) without any disubstituted product (entry **2a**). In order to rule out the potential activation effects of the adjacent ester group on this chemo-selectivity, the Suzuki–Miyaura cross-coupling reactions of bis-ester **2**[7] were performed. To our delight, the same OTf versus Br selectivity was retained for bis-ester **2** although the amount of disubstituted products slightly increased. The bis-ester **2** reacted with **5** to produce OTf-displacement product in 55% yield and disubstituted product in 14% yield with no detectable Br-displacement product (entry **3a**), while **2** reacted



Scheme 1. Nonselective Suzuki–Miyaura cross-coupling reactions for 3,4-dibromothiophenes. Condition: 5 mol % $Pd(PPh_3)_4$, 3.0 equiv of K_2CO_3, 1.1 equiv of $RB(OR)_2$, dioxane/H_2O (5:1), 70 °C.

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* Corresponding author at present address: Influmedix Inc., 170 N Radnor Chester Rd., Radnor, PA 19087, USA. Tel.: +1 4845982376; fax: +1 4845982401.

E-mail addresses: jwang@influmedix.com, jizhou_wang@yahoo.com (J. Wang).

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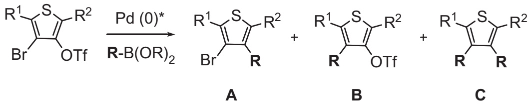
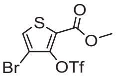
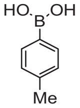
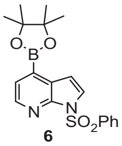
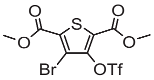
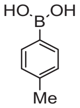
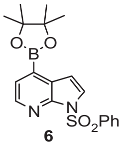
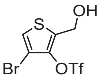
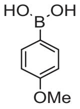
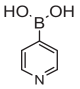
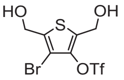
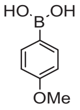
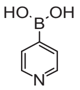
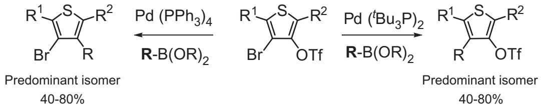
Table 1



Substrate	R-B(OR)$_2$	Entry	Pd(0)*	A%	B%	C%
 **1**	 **5**	**1a**	$Pd(PPh_3)_4$	**71**	nd	10
		1b	$Pd(^tBu_3P)_2$	nd	**81**	nd
	 **6**	**2a**	$Pd(PPh_3)_4$	**88**	nd	nd
		2b	$Pd(^tBu_3P)_2$	nd	**81**	nd
 **2**	 **5**	**3a**	$Pd(PPh_3)_4$	**55**	nd	14
		3b	$Pd(^tBu_3P)_2$	nd	**66**	Trace
	 **6**	**4a**	$Pd(PPh_3)_4$	**72**	nd	Trace
		4b	$Pd(^tBu_3P)_2$	**6**	**69**	Trace
 **3**	 **7**	**5a**	$Pd(PPh_3)_4$	**72**	nd	nd
		5b	$Pd(^tBu_3P)_2$	nd	**69**	Trace
	 **8**	**6a**	$Pd(PPh_3)_4$	**65**	nd	nd
		6b	$Pd(^tBu_3P)_2$	nd	**61**	nd
 **4**	 **7**	**7a**	$Pd(PPh_3)_4$	**85**	nd	nd
		7b	$Pd(^tBu_3P)_2$	nd	**43**	8
	 **8**	**8a**	$Pd(PPh_3)_4$	**45**	nd	nd
		8b	$Pd(^tBu_3P)_2$	nd	**42**	nd

[a] Condition: 2–5 mol % Pd(0)*, 3.0 equiv of K_2CO_3, 1.05 equiv of RB(OR)$_2$, dioxane or DME/H_2O (5:1), 70 °C.
[b] Yield: isolated by flash chromatography.
[c] nd: not detectable by LC–MS.



Scheme 2.

with **6** to give an exclusive OTf-displacement product in 72% yield along with a trace amount of disubstituted product (entry **4a**). Esters **1** and **2** were reduced to alcohols, **3**[6] and **4**[7] to enhance the electron density of the thiophene cores. Monoalcohol **3** reacted with both electron-rich boronic acid **7** and the more electron-poor boronic acid **8** to give exclusive OTf-displacement products in 72% (entry **5a**) and 65% (entry **6a**) yields, respectively. The same OTf versus Br selectivity was observed for bis-alcohol **4**, which coupled with both **7** and **8** to afford exclusively the OTf-replacement products in modest to good yields without any detectable disubstituted products (entries **7a** and **8a**).

On the other hand, when using the more hindered bisphosphine catalyst, $Pd(^tBu_3P)_2$ instead of the tetraphosphine catalyst [$Pd(PPh_3)_4$], a reversal of selectivity was observed. The reactions between monoester **1** and boronic acid **5** and boronic ester **6** gave exclusively Br-displacement products in high yield (entries **1b** and **2b**). The bis-ester **2** resulted in similar chemoselectivity, although a small amount (~6%) of the OTf-displacement product was produced when thiophene **2** was coupled with boronate **6** (entries **3b** and **4b**). The same bromide versus triflate selectivity was also observed for both monoalcohol **3** and bis-alcohol **4**, which reacted with both electron rich boronic acid **7** and electron poor boronic acid **8** to give exclusively the Br-replacement products in modest to good yield (entries **5b**, **6b**, 7b, and **8b**).

Our results show that Br/OTf selectivity in Suzuki–Miyaura cross-coupling reactions is ligand-dependent for 3-bromo-4-trifloyl-thiophenes. The triflate was displaced selectively over the bromide when $Pd(PPh_3)_4$ was used as the catalyst. When $Pd(^tBu_3)_2$ was used instead, the bromide reacted preferentially (Scheme 2). These observations represent a reversal in chemo-selectivity in contrast to a common observation that aryl bromides are more active than aryl triflates in Suzuki–Miyaura cross-coupling reactions regardless of the catalyst employed.[2c,d] Our catalyst preference trend is also opposite to that observed for Stille coupling reactions, where selectivity reportedly depends on the coordination number of the phosphine ligands, with bisphosphine palladium ligands favoring OTf-substitution, and tetraphosphine palladium favoring Br-displacement.[2a]

It is difficult to give a definite answer for such ligand-dependent chemoselectivity in Suzuki–Miyaura cross-coupling reactions since relatively little is known about the mechanistic details of Suzuki–Miyaura cross-coupling reactions.[1,8] One plausible explanation of the ligand-dependent Br/OTf chemoselectivity is that the rate determining step (oxidative addition vs transmetalation) of Suzuki–Miyaura reaction of 3-bromo-4-trifloyl-thiophenes is ligand-dependent. When PPh_3 is employed as the ligand, the potential chelation of the sulfur atom of thiophene to the less steric-hindered $Pd(PPh_3)_4$ might decelerate the oxidation addition rate and cause oxidative addition to be the rate determining step. The resulting OTf over Br selectivity is consistent with the corresponding oxidative addition rate, I > OTf > Br.[2b,9] But when the ligand is switched from PPh_3 to $^tBu_3P$, the more electron-rich $^tBu_3P$ greatly promotes the oxidative addition of the C—Br bond.[3a] In addition, the much greater steric hindrance of $^tBu_3P$ may also accelerate the oxidative addition by preventing the chelation of-sulfur atom of thiophene to the Pd center.[10] As a result, the rate determining step shifts from the previous oxidative addition to the relatively slower transmetalation and gives reversal Br/OTf selectivity. Detailed kinetic studies will be needed to test these hypotheses.

In conclusion, unprecedented chemo-selectivity in ligand-dependent Suzuki–Miyaura cross-coupling reactions of 3-bromo-4-trifloyl-thiophenes has been discovered. This discovery provides important synthetic applications, since the remaining bromide/triflate is a valuable functional group, and can be used as a precursor for a variety of cross-coupling reactions. Similar studies on other five-membered aromatic systems, such as furan and pyrrole, are under investigation, and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated (experimental procedures and characterization data for **1**, **2**, **3**, **4**, **1a**, **1b**, **2a**, **2b**, **3a**, **3b**, **5a**, **4b**, **7a**, **7b**, **8a**, and **8b** are available upon requests) with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.026.

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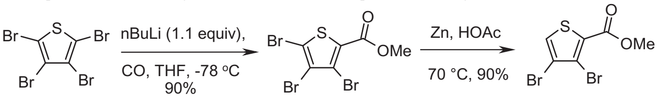
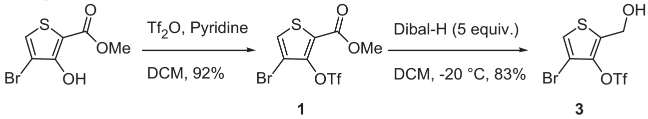
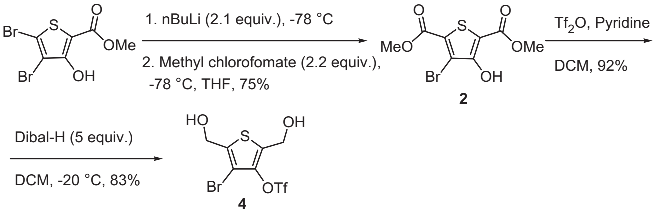
5. Preparation of methyl 3,4-dibromo-2-thiophenecarboxylate:



6. Preparation of alcohol **1** and **3**:



7. Preparation of bis-esters **2** and **4**:



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10. Guram, A. S.; Wang, X.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J. *J. Org. Chem.* **2007**, *72*, 5104; Notes. General procedure for Suzuki cross-coupling reactions: To a solution of 3,4/4,3-bromotriflate thiophene (0.5 mmol, 1.0 equiv) in dioxane or DME/H2 O (5 mL/1 mL) were added K2 CO3 (1.5 mmol, 3.0 equiv), Pd(0) (5 mol %), and boronic acid/ester (0.525 mmol,1.05 equiv). The reaction mixture was heated to 70 C in a sealed tube. The reaction process was monitored by LC–MS. After the reaction was done, the reaction mixture was concentrated under vacuum and purified by silica gel chromatography.