

Regioselective Oxidative Coupling Reactions of 3-Substituted Thiophenes with Arylboronic Acids

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ABSTRACT



Under optimized conditions, 3-substituted thiophenes (EWG = COOEt, PO(OEt)₂) undergo a facile and regioselective oxidative coupling reaction at carbon atom C4. The reactions were performed with various aryl boronic acids as nucleophiles in the presence of silver oxide (2.0 equiv), cesium trifluoroacetate (tfa) (1.0 equiv), benzoquinone (BQ) (0.5 equiv), and catalytic amounts of Pd(tfa)₂ (10 mol %) employing trifluoroacetic acid (TFA) as the solvent.

There have been significant efforts in recent years to realize Pd-catalyzed cross-coupling reactions with the conventionally used nucleophiles (e.g., organoboron reagents, organostannanes, organosilanes) by CH-activation, i.e. by employing arenes instead of haloarenes as reaction partners.¹ In order to achieve this goal, oxidative conditions are required and a plethora of methods have been described for this purpose, which need to be fine-tuned for the respective substrates. Mechanistically, oxidative coupling is different from conventional cross-coupling because the initial step is an electrophilic attack at the arene by Pd(II) but not a nucleophilic attack by Pd(0). In this respect, previously elaborated and established parameters

to predict the regioselectivity of cross-coupling reactions at heterocyclic substrates² are not valid in these reactions but have to be investigated.³ Based on our experience with five-membered heterocycles⁴ we have started a research program, which aims to elucidate and categorize important regioselectivity features of oxidative coupling reactions.⁵ One substrate class, which we have started to look at more closely, are thiophenes. In this respect, it was of particular interest to us to achieve a substitution in the 3- or 4-position as the 2- and 5-position of thiophenes can be readily addressed by electrophilic aromatic substitution chemistry⁶ or by conventional cross-coupling reactions.⁷ A recently published manuscript on the regioselectivity of oxidative coupling reactions with boronic acids at 2-substituted

(1) Reviews: (a) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, 46, 677–685. (b) Chen, X.; Engle, K.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, 48, 5094–5115. (c) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem., Int. Ed.* **2009**, 48, 9792–9826.

(2) Reviews: (a) Roger, J.; Gottumukkala, A. L.; Doucet, H. *Chem.-CatChem* **2010**, 2, 20–40. (b) Wang, J.-R.; Manabe, K. *Synthesis* **2009**, 1405–1427. (c) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, 36, 1036–1045. (d) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, 61, 2245–2267.

(3) For recent publications on Pd-catalyzed oxidative coupling reactions at heterocycles, see: (a) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, 47, 1473–1476. (b) Zhao, J.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2008**, 73, 7428–7431. (c) Kirchberg, S.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2009**, 48, 4235–4238. (d) Liu, B.; Qin, X.; Li, K.; Li, X.; Guo, Q.; Lan, J.; You, J. *Chem.—Eur. J.* **2010**, 16, 11836–11839. (e) Ranjit, S.; Liu, X. *Chem.—Eur. J.* **2011**, 17, 1105–1108.

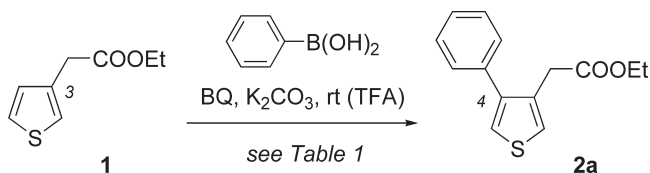
(4) Examples: (a) Bach, T.; Krüger, L. *Tetrahedron Lett.* **1998**, 39, 1729–1732. (b) Bach, T.; Heuser, S. *J. Org. Chem.* **2002**, 67, 5789–5795. (c) Schröter, S.; Bach, T. *Synlett* **2005**, 1957–1959. (d) Gross, S.; Heuser, S.; Ammer, C.; Heckmann, G.; Bach, T. *Synthesis* **2011**, 199–206.

(5) For recent publications addressing the issue of regioselectivity in Pd(II)-mediated reactions at heteroarenes, see: (a) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, 63, 1970–1980. (b) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, 129, 12072–12073. (c) Zhao, J.; Huang, L.; Cheng, K.; Zhang, Y. *Tetrahedron Lett.* **2009**, 50, 2758–2761. (d) Liang, Z.; Yao, B.; Zhang, Y. *Org. Lett.* **2010**, 12, 3185–3187. (e) Lapointe, D.; Markiewicz, T.; Whipp, C. J.; Toderian, A.; Fagnou, K. *J. Org. Chem.* **2011**, 76, 749–759.

(6) Review: Schatz, J. In *Science of Synthesis*, Vol. 9; Maas, G., Ed.; Thieme: Stuttgart, 2001; pp 287–392.

thiophenes (vide infra)⁸ prompts us to disclose our results on the oxidative coupling of 3-substituted thiophenes.

Table 1. Screening Different Conditions for Oxidative Cross-Coupling^a



entry	Pd catalyst	Ag(I) source	time (h)	conv ^b (%)	yield ^b (%)	rr ^c
1	PdCl ₂	Ag ₂ O	48	22	8	n.d.
2	PdCl ₂ (PPh ₃) ₂	Ag ₂ O	48	65	40	97/3
3	Pd(OAc) ₂	Ag ₂ O	48	69	40	99/1
4	Pd(tfa) ₂	Ag ₂ O	48	99	81	95/5
5	Pd ₂ (dba) ₃	Ag ₂ O	48	96	72	93/7
6 ^d	Pd(tfa) ₂	AgOTf	26	71	38	84/16
7 ^d	Pd(tfa) ₂	AgBF ₄	26	74	45	88/12
8 ^d	Pd(tfa) ₂	AgF	26	91	66	92/8
9 ^d	Pd(tfa) ₂	Ag ₂ O	26	90	76	93/7
10 ^d	Pd(tfa) ₂	—	26	27	16	59/41
11 ^d	—	Ag ₂ O	26	<5	<5	n.d.

^a Reaction conditions: Pd catalyst (0.1 equiv), Ag(I) source (3.0 equiv), phenylboronic acid (2.0 equiv), BQ (0.5 equiv), K₂CO₃ (1.0 equiv), TFA (c = 0.2 M). ^b Conversion and yields were determined by GC using *n*-undecane as an internal standard. ^c The ratio of regioisomers was determined by GC. ^d Cs₂CO₃ (1.0 equiv) was used instead of K₂CO₃.

Previous studies regarding a C–C bond formation at thiophenes with aryl boronic acids were conducted by Demir et al., Shi et al., and Studer et al. The first group employed Mn(OAc)₃ as a promoter to achieve a selective C2-arylation by a radical type pathway.⁹ The Shi group employed oxidative coupling conditions (O₂, Pd(OAc)₂, Cu(OAc)₂ in TFA) and observed a regioselective reaction at C2 of benzothiophene.^{3a} The Studer group made use of a strong 2-pyridine directing group at C2 to facilitate an arylation at C3 under Rh¹⁰ or Pd catalysis¹¹ employing 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) as the oxidant. In the most recent contribution by Studer, Itami et al.⁸ 2-substituted thiophenes were shown to react at C4 when using TEMPO as the oxidant and a catalyst combination of Pd(OAc)₂ and 2,2'-bipyridine (bipy). Benzothiophene reacted at C3 under these conditions and 3-methoxythiophene at C4.

For our own study, the 3-substituted thiophene **1** was chosen as a test substrate. In preliminary oxidative coupling experiments it showed superior behavior as compared to 3-methylthiophene. In addition, the activated methylene group allows for further reactions (vide infra). A screening for optimal reaction conditions was performed. Some of the results are listed in Table 1. The choice of benzoquinone (BQ) as a ligand and trifluoroacetic acid (TFA) as a solvent was inspired by previous experiments.^{3a,12} Among possible palladium sources, palladium trifluoroacetate (Pd(tfa)₂) was the most efficient when silver(I) oxide was used as the oxidant (entries 1–5). It was subsequently found that cesium is slightly better than potassium in promoting the reaction. With the same oxidant (Ag₂O), the reaction was almost complete after 26 h in the presence of Cs₂CO₃ (entry 9) while it required 48 h to go to completion with K₂CO₃ (entry 4). Regarding the oxidant, silver(I) fluoride (entry 8) was approximately as effective as silver(I) oxide whereas other silver sources were inferior (entries 6, 7). In the absence of a silver oxidant, the reaction proceeded very slowly and nonselectively (entry 10). Without a palladium catalyst only traces of product could be obtained (entry 11). Although the benefit of Cs₂CO₃ was marginal when using silver(I) oxide, for nonbasic silver sources (e.g., AgOTf or AgBF₄) yield and regioselectivity dropped dramatically without its addition.

It was found that the slightly more expensive cesium trifluoroacetate Cs(tfa) was for preparative purposes better suited as a cesium source than Cs₂CO₃, because there is no CO₂ evolution when dissolving it in TFA. With this minor modification the optimized conditions of entry 9 were applied to a number of arylboronic acids, which could be successfully coupled at the C4 position of thiophene **1** (Scheme 1). In general, the reaction proceeded well for a number of phenylboronic acids, which exhibit weak or no donor or acceptor substituents in the *para*-position (products **2a**, **2d**, **2e**, **2h**). It appears as if the acceptor-substituted boronic acids fail to deliver the aryl residue to the palladium while the donor-substituted boronic acids are sensitive toward hydrolysis. Typically, anisylboronic acid underwent hydro-deborylation while nitro-substituted and trifluoromethyl-substituted phenylboronic acids reacted sluggishly (<30% conversion after 24 h). Hetarylboronic acids have not yet been tested. Steric hindrance was not an issue with *ortho*-substituted boronic acids (product **2b**) and 1-naphthylboronic acid (product **2f**) both reacting well. Mesitylboronic acid, however, failed to produce any coupling products.

The regioisomeric ratio (rr) (C4-substituted product vs regioisomers at C2/C5) was determined by ¹H NMR integration of the respective methylene protons of the acetate. Given the high reactivity of thiophenes toward electrophilic substitution at carbon atoms C2/C5, the regioselectivity outcome is surprising. In line with the earlier findings of Studer, Itami et al.⁸ it might be

(7) For regioselective Suzuki cross-coupling reactions on thiophenes, see: (a) Pereira, R.; Iglesias, B.; de Lera, A. R. *Tetrahedron* **2001**, *57*, 7871–7881. (b) D  ng, T. T.; D  ng, T. T.; Rasool, N.; Villinger, A.; Reinke, H.; Fischer, C.; Langer, P. *Adv. Synth. Catal.* **2009**, *351*, 1595–1609.

(8) Kirchberg, S.; Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2387–2391.

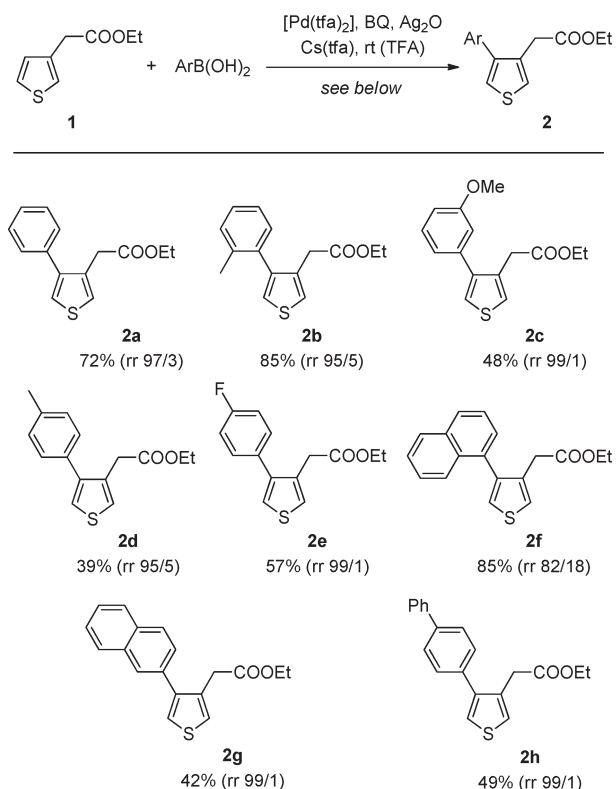
(9) (a) Demir, A. S.; Reis,   .; Emrullahoglu, M. *J. Org. Chem.* **2003**, *68*, 578–580. (b) Demir, A. S.; Findik, H.; Saygili, N.; Subasi, N. T. *Tetrahedron* **2010**, *66*, 1308–1312.

(10) Vogler, T.; Studer, A. *Org. Lett.* **2008**, *10*, 129–131.

(11) Kirchberg, S.; Vogler, T.; Studer, A. *Synlett* **2008**, 2841–2845.

(12) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634–12635.

Scheme 1. 4-Substituted Thiophenes **2** Obtained by Reaction of Different Boronic Acids with Ethyl 2-(Thiophen-3-yl)acetate (**1**)^a

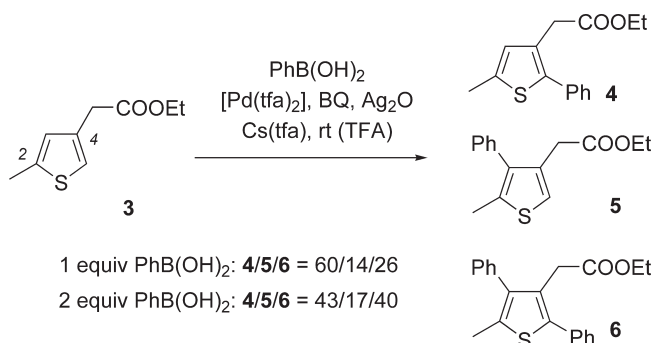


^a The regioisomeric ratio (rr) is given in brackets.

conceivable that the primary reaction of Pd(II) occurs at C5 but the aryl group is delivered intra- or intermolecularly to the C4 carbon atom. This hypothesis is supported by the reaction of 2,4-disubstituted thiophene **3**, which upon reaction with phenylboronic acid gave three products **4–6** the relative ratio of which varied depending on the equivalents of boronic acid being used (Scheme 2). The reactions were run for 24 h (ca. 70% conversion), and product analysis was performed by ¹H NMR integration. The results were further validated by GC/MS analysis. When 1 equiv of phenylboronic acid was used, the major product was C5-substituted product **4**. The C3-substituted product **5** was formed in minor amounts presumably due to the fact that electrophilic palladium attack at the thiophene occurs at C5 but not at C2. With 2 equiv of phenylboronic acid, double substitution (product **6**) prevailed but the major monosubstituted product was still product **4**.

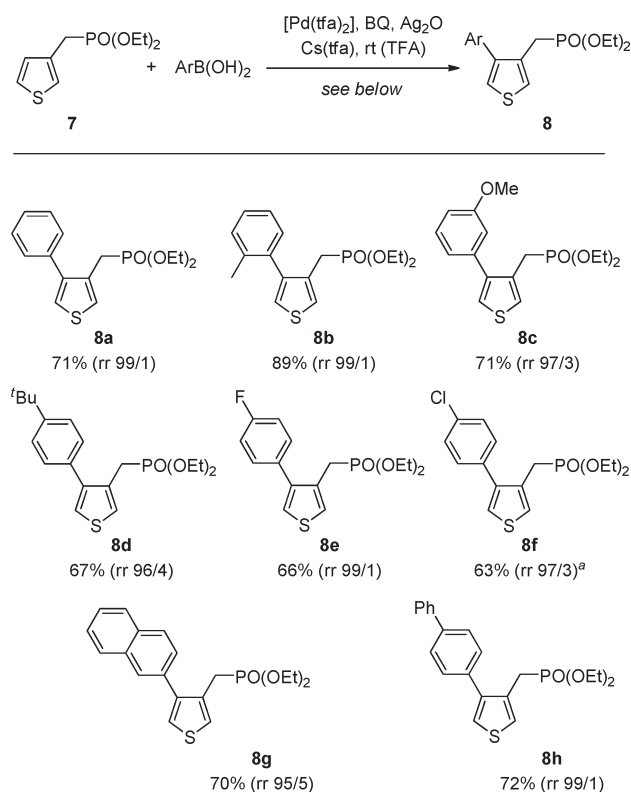
In search for other 3-substituted thiophenes, which carry an electron-withdrawing group at the methylene bridge, we turned to the readily available¹³ phosphonate **7**. Gratifyingly, this compound showed to be even better suited to oxidative coupling reactions than acetate **1**. Reactions

Scheme 2. Regioselectivity in the Oxidative Coupling Reaction of Substrate **3** with Phenylboronic Acid



went to completion under standard conditions in 24 h delivering the respective products **8** in good yields and with high regioselectivity (Scheme 3).

Scheme 3. Reaction of Boronic Acids with Diethyl (Thiophen-3-ylmethyl)phosphonate (**7**) Providing 4-Substituted Thiophenes **8**



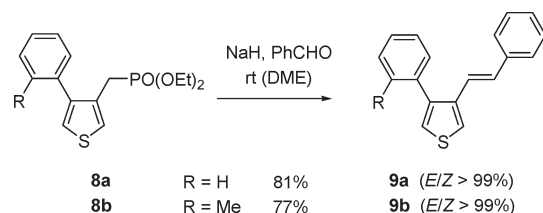
^a Reaction was carried out for 36 h instead of 24 h.

The phosphonates are more stable under the oxidative conditions than acetates **1** and **2**. In cases, in which the reaction was not complete after 24 h (e.g., product **8f**), further stirring led to complete conversion resulting in higher yields. The reaction with *para*-chloroboronic acid worked sluggishly with substrate **1** but gave a good yield in the reaction with phosphonate **2**.

(13) Lukovskaya, E. V.; Bobyleva, A. A.; Fedorova, O. A.; Fedorov, Yu. V.; Anisimov, A. V.; Didane, Y.; Brisset, H.; Fages, F. *Russ. Chem. Bull.* **2009**, 58, 1509–1515.

It appears too early to draw further mechanistic conclusions, and further studies are warranted. Given the low reactivity of other 3-substituted thiophenes, it appears as if there is an activating/directing effect by the electron-withdrawing groups COOEt and PO(OEt)₂. As mentioned previously, 3-methylthiophene reacted sluggishly under the conditions applied to substrates **1** and **7** whereas 3-ethynylthiophene did not undergo oxidative coupling reactions at all.

Scheme 4. Olefination Reaction Performed with Benzaldehyde and Phosphonates **8**



In order to demonstrate that the intermediate phosphonates **8** can be employed for further reactions at the activated methylene group a short study was undertaken regarding a possible olefination reaction.¹⁴ Reactions were

(14) Tedjamulia, M. L.; Stuart, J. G.; Tominaga, Y.; Castle, R. N.; Lee, M. L. *J. Heterocycl. Chem.* **1984**, *21*, 1215–1219.

performed with benzaldehyde (Scheme 4) as the electrophile employing sodium hydride as the base and 1,2-dimethoxyethane (DME) as the solvent. The reaction proceeded smoothly delivering the respective olefins **9** in good yields and with perfect diastereoselectivity. Related products synthesized from aromatic aldehydes are known to undergo photocyclization to obtain naphtho[1,2-*b*]thiophenes.¹⁴

In summary, we could show that acetate **1** and phosphonate **7** are suitable substrates for regioselective oxidative cross-coupling reactions with several boronic acids. Yields are moderate to high, and the regioselectivity in favor of an attack at C-4 is close to perfect in most cases. The effect of the two groups COOEt and PO(OEt)₂ on the regioselectivity of oxidative coupling reactions needs to be further studied. In addition, the question, at what stage does the aryl transfer from the boronic acid to palladium occur, will be addressed in further experiments.

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Supporting Information Available. Representative experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.