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Modular Synthesis of Naphthothiophenes by Pd-Catalyzed Tandem Direct Arylation/Suzuki Coupling

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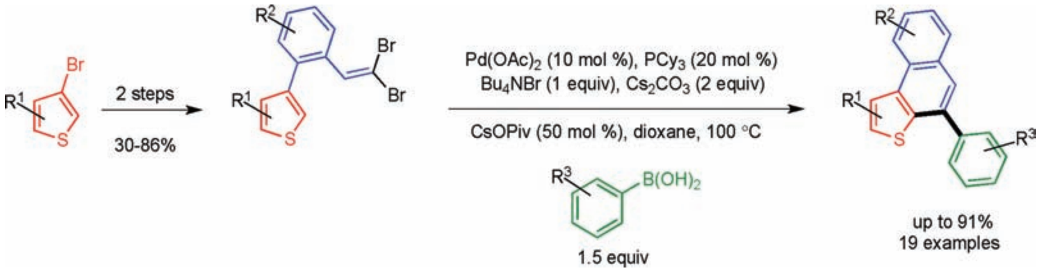
ABSTRACT



A short and highly modular three-step synthesis of a new class of substituted naphthothiophenes has been developed exploiting a Pd-catalyzed tandem direct arylation/Suzuki coupling transformation as the key step.

Polyaromatic thiophenes have recently attracted considerable attention in the field of material science as organic electronics.[1] Moreover, the thiophene core is an important substructure present in numerous pharmaceutically active compounds such as zileuton or raloxifene.[2] The development of efficient and reliable protocols for selective functionalization of thiophenes is an important task. Particularly, the use of Pd-catalyzed direct arylation strategies has become a powerful tool in this area,[3] as it provides an effective alternative that does not form reactive intermediates prior to the coupling step.[4,5] The development of new methodologies combining this direct arylation step with other transition-metal-catalyzed C–C-bond functionalization reactions in a tandem or domino fashion would be even more attractive. Such an approach would have several advantages since it significantly improves the efficiency, atom economy, and modularity of the synthesis.[6]

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Scheme 1. Retrosynthesis

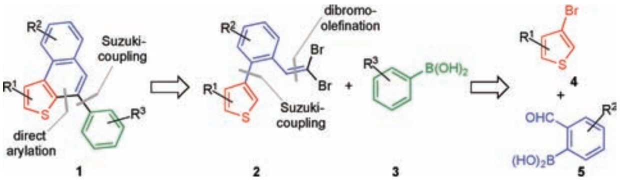
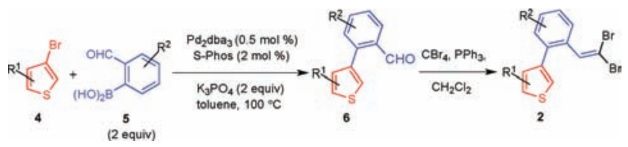
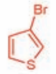
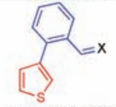
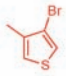
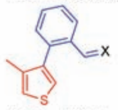
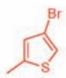
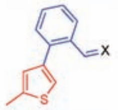
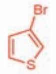
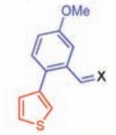
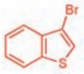
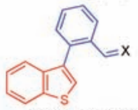
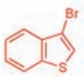
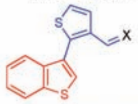


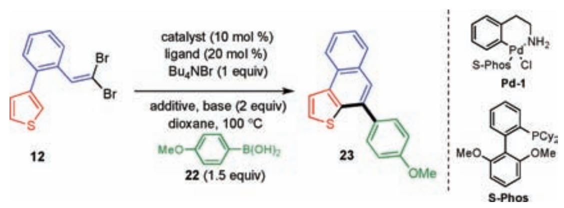
Table 1. Two-Step Synthesis of *gem*-Dibromoolefins of Type **2**[a]



entry	substrate	products
1	 7	 **11**; X = O (≥ 97%) **12**; X = CBr$_2$ (70%)
2	 8	 **13**; X = O (91%) **14**; X = CBr$_2$ (95%)
3	 9	 **15**; X = O (≥ 97%) **16**; X = CBr$_2$ (92%)
4	 7	 **17**; X = O (≥ 97%) **18**; X = CBr$_2$ (63%)
5	 10	 **19**; X = O (≥ 97%) **20**; X = CBr$_2$ (80%)
6[b]	 10	 **21**; X = CBr$_2$ (30%) over 2 steps

[a] For further details see Supporting Information. [b] The crude product of the Suzuki coupling was used for the olefination step due to inseparability of the product from homo coupling byproducts of the boronic acid.

Table 2. Optimization of the Tandem Suzuki Coupling/Direct Arylation Reaction Conditions



entry	catalyst	ligand	base	yield[a] (%)
1[b,c]	Pd(OAc)$_2$	$P^tBu_3\cdot HBF_4$	Cs$_2$CO$_3$	8
2[b]	Pd(OAc)$_2$	$P^tBu_3\cdot HBF_4$	Cs$_2$CO$_3$	30
3	Pd(OAc)$_2$	$P^tBu_3\cdot HBF_4$	Cs$_2$CO$_3$	50
4	Pd(PPh$_3$)$_4$	–	Cs$_2$CO$_3$	13
5	**Pd-1**	–	Cs$_2$CO$_3$	62 (45)[f]
6	Pd(OAc)$_2$	S-Phos	Cs$_2$CO$_3$	17
7	**Pd-1**	–	K$_2$CO$_3$	36
8	**Pd-1**	–	$K_3PO_4\cdot H_2O$	26
9[d]	**Pd-1**	–	Cs$_2$CO$_3$	54
10	Pd(OAc)$_2$	PPh$_3$	Cs$_2$CO$_3$	30
11	Pd(OAc)$_2$	TFP	Cs$_2$CO$_3$	54
12	Pd(OAc)$_2$	PCy$_3$	Cs$_2$CO$_3$	72
13	PdCl$_2$	PCy$_3$	Cs$_2$CO$_3$	27
14[e]	Pd$_2$dba$_3$	PCy$_3$	Cs$_2$CO$_3$	50
15[h]	**Pd(OAc)$_2$**	**PCy$_3$**	**Cs$_2$CO$_3$**	**76 (66)**[f,g]
16[i]	Pd(OAc)$_2$	PCy$_3$	Cs$_2$CO$_3$	65

[a] Yields were determined by NMR spectroscopy using mesitylene as the internal standard. [b] Reaction was run in toluene. [c] Reaction was performed without Bu$_4$NBr. [d] Water (5 equiv) was added to the reaction mixture. [e] 5 mol % Pd$_2$dba$_3$ were used. [f] Isolated yield. [g] On a 0.2 mmol scale 66% of **23** could be isolated. [h] CsOPiv (50 mol %) was added. [i] 5 mol % of Pd(OAc)$_2$ were used.

In the course of our ongoing research in the field of Pd-catalyzed tandem reactions utilizing *gem*-dibromoolefins[7] as key intermediates, we have recently reported efficient approaches toward *N*-fused heterocycles.[8] Encouraged by these findings, we have realized a short and highly modular three-step synthesis of a new class of naphthothiophenes of general structure **1** (Scheme 1).

According to our retrosynthetic analysis we suggested that the target structures should be accessible in a tandem transformation from *gem*-dibromoolefins of type **2** and boronic acids **3** utilizing a direct arylation/Suzuki coupling approach. We proposed that the required *gem*-dibromoolefin precursors **2** could be synthesized in a straightforward manner starting from readily available 3-bromothiophenes **4** by Suzuki coupling with 2-formyl substituted phenylboronic acids **5** followed by subsequent Ramirez olefination (Scheme 1). In particular the use of two distinct Suzuki couplings in this approach enables a high degree of modularity for the synthesis of **1**.

We selected four 3-bromothiophene derivatives (**7**–**10**) as building blocks for the synthesis of six functionalized *gem*-diolefin intermediates (**12**, **14**, **16**, **18**, **20**, and **21**) as depicted in Table 1. For the initial Suzuki coupling step toward aldehydes of type **6** we found that conditions reported by Buchwald and co-workers employing Pd$_2$dba$_3$/S-Phos and K$_3$PO$_4$ were well suited for our

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(8) (a) Bryan, C. S.; Lautens, M. *Org. Lett.* **2008**, *10*, 4633–4636. (b) Chai, D. I.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 3054–3061.

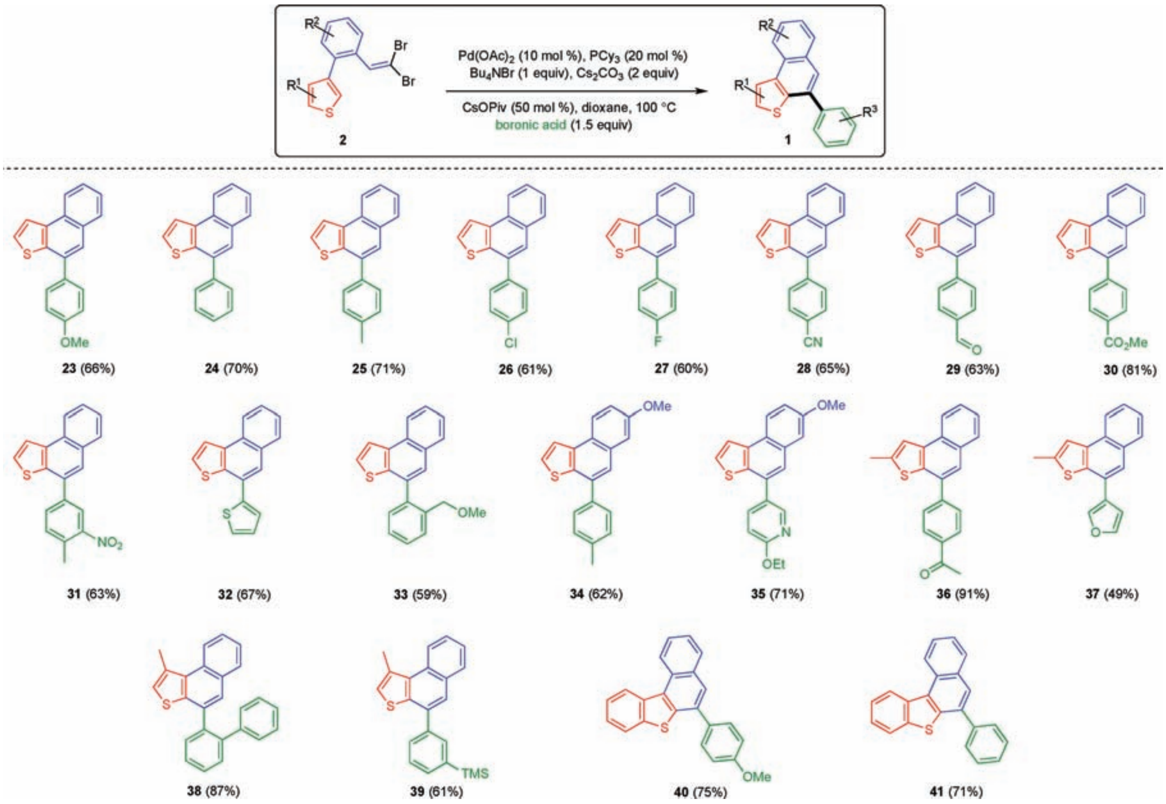

Figure 1. Substrate scope of the direct arylation/Suzuki coupling approach.

system providing products **11**, **13**, **15**, **17**, and **19** in excellent yields (Table 1).[9] The subsequent conversion into the desired *gem*-dibromoolefins could be achieved in good to excellent yields by applying the standard Ramirez olefination conditions using a combination of PPh_3 and CBr_4.[10] With these building blocks in hand, we next focused on the optimization of the proposed tandem transformation.

We selected the reaction of the prototype *gem*-dibromoolefin **12** and boronic acid **22** as our test system (see Table 2). Reactions in toluene using a $Pd(OAc)_2$/$P^tBu_3 \cdot HBF_4$ catalyst system and Cs_2CO_3 as the base led to the formation of trace amounts of **23** (entry 1).[5c] Fortunately, we observed that the addition of Bu_4NBr has a significant effect on the reaction resulting in the exclusive formation of regioisomer **23** (entry 2).[5a,b] Motivated by this observation, we screened different solvent systems and identified 1,4-dioxane as our solvent of choice (entry 3). Altering the Pd/L system to $Pd(PPh_3)_4$ dramatically decreased the yield (entry 4), while the S-Phos-complex **Pd-1** was found to be beneficial (entry 5).[11] Interestingly, the yield dropped to 17% when the reaction was carried out with $Pd(OAc)_2$/S-Phos instead of complex **Pd-1** (entry 6), indicating that the Pd-source has a significant impact on the outcome of the reaction.

Next, we investigated the effect of different bases including K_2CO_3 and K_3PO_4, but no improvement could be observed (entries 7 and 8) suggesting that Cs_2CO_3 is the ideal base for this transformation. The addition of water (entry 9) which is known to exhibit positive effects also resulted in lower yields (compare entries 5 and 9).[8b,12] We turned our attention to ligand screening and identified PCy_3 as an appropriate candidate for this reaction (entries 10 to 12). It is important to note that Pd-sources other than $Pd(OAc)_2$ were detrimental to yields under these conditions (entries 13 and 14). Finally, we observed that the addition of 50 mol % CsOPiv,[13] which might act as a proton shuttle for a concerted metalation–deprotonation mechanism, could further increase the yield of the tandem reaction up to 76%.[14] Attempts to lower the catalyst

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[9] Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.

[10] Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745–1747. For a modification, see:Bryan, C.; Aurregi, V.; Lautens, M. *Org. Synth.* **2009**, *86*, 36–46.

[11] (a) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686–6687. (b) Chai, D. I.; Hoffmeister, L.; Lautens, M. *Org. Lett.* **2011**, *13*, 106–109.

[12] Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505–3508.

[13] No beneficial effect was observed, when only CsOPiv was used as the base.

[14] Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.

[15] While further studies are necessary to rationalize a possible mechanism for the tandem process, we assume that the Suzuki coupling occurs prior to direct arylation according to our recent observations on a similar system (see ref 8b).

loading to 5 mol % resulted in slightly lower yields and formation of impurities (entry 16).[15]

With our optimized conditions in hand (Figure 1), we next investigated the scope of the reaction regarding the electronic nature of the boronic acid coupling partner. It was found that electron-rich (**23**), electron-neutral (**24**), and electron-poor (**29** and **30**) boronic acids can be tolerated to form the desired products in good to excellent yields (Figure 1). Furthermore, sterically more demanding (**33** and **38**), heteroaromatic (**32**, **35**, and **37**), and halogen substituted boronic acids (**26** and **27**) can be used without any problems (Figure 1). Under our conditions, various substitution patterns on the thiophene moiety at the 3- and 4-position (for instance **37** or **39**) or the use of a more electron-rich benzothiophene substrate (**40** and **41**) were also tolerated. Additional substituents at the aromatic ring next to the *gem*-dibromoolefin moiety were also accepted (**34** and **35**). The only limitation of our protocol was observed for precursor **21**, as only trace amounts of the expected products could be identified. This suggests that the presence of an additional thiophene made the reaction more sluggish.

We were able to obtain an X-ray crystal structure for **40** to confirm the expected polyaromatic structure of this new compound class also indicating these molecules are twisted along their biaryl axis (Figure 2).

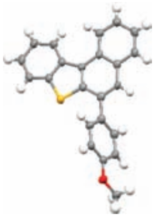
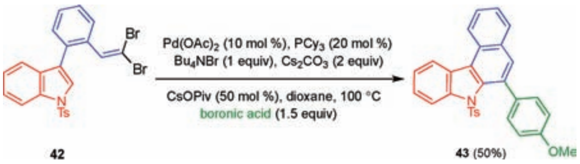


Figure 2. Structure of **40** in the crystalline state (gray, carbon; white, hydrogen; red, oxygen; yellow, sulfur).

Due to the broad generality of our direct arylation/Suzuki coupling strategy for the synthesis of naphthothiophenes, we questioned if these conditions could also be applied for the functionalization of *gem*-dibromoolefins connected to an indole moiety to form substituted carbazoles. Since carbazoles are well-known to exhibit important biological activities, this modification would open a practical entry to a broad variety of related derivatives.[16]

We were pleased to find that *gem*-dibromoolefin **42** reacts smoothly with 3-methoxyphenyl boronic acid **22** to form carbazole **43** under our previously optimized tandem conditions (Scheme 2). An extension of this methodology toward other heterocycles is currently under investigation in our group and will be reported separately.

Scheme 2. Synthesis of Carbazol **43**[a]



[a] For the synthesis of **42**, see Supporting Information.

In conclusion, we have developed a short, highly modular and reliable synthesis of a new class of naphthothiophenes employing a tandem direct arylation/Suzuki coupling transformation as the key step. A remarkable number of boronic acids bearing different electronic and steric properties could be successfully used to access the target structures in good to excellent yields. Due to the simplicity and high overall yield of our approach, it is suited for the generation of novel polyaromatic thiophenes relevant to applications in biology and material science. In addition its potential to synthesize carbazoles opens an attractive entrance toward this important compound class.

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Supporting Information Available. Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] (a) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303–4427. (b) Choi, T. A.; Czerwonka, R.; Fröhner, W.; Krahl, M. P.; Reddy, K. R.; Franzblu, S. G.; Knölker, H.-J. *ChemMedChem* **2006**, *1*, 812–815.