Oxidative C–H Arylation

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Oxidative Biaryl Coupling of Thiophenes and Thiazoles with Arylboronic Acids through Palladium Catalysis: Otherwise Difficult C4-Selective C–H Arylation Enabled by Boronic Acids**

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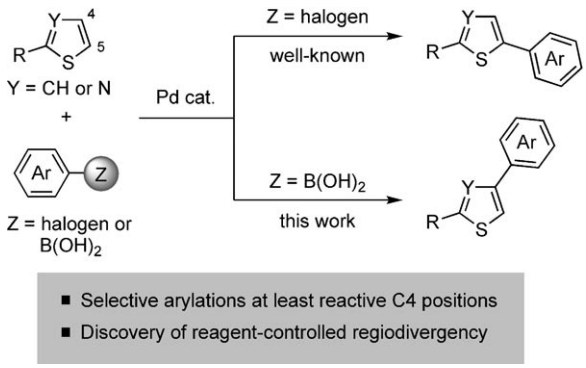
Heteroarenes equipped with aryl groups (heterobiaryls) are often found in biologically active compounds, organic materials, and pharmaceuticals. In recent years, the direct C–H arylation of heteroarenes catalyzed by a transition-metal complex[1,2] has emerged as a practical alternative to the well-established Pd-catalyzed cross-coupling reactions. Although tremendous efforts in the synthetic community including our groups[3–5] have culminated in a wealth of useful and highly active catalysts,[2] considerable room remains for further investigations. In particular, the development of a unique catalytic system that can preferentially activate and arylate an otherwise less reactive C–H bond on heteroarenes is critically important from both scientific and practical points of view.[6]

For example, the Pd-catalyzed arylation of C–H bonds of thiophenes with haloarenes is known to occur preferentially at the positions α to the sulfur atom (C2 and/or C5) following the typical reactivity profile of the thiophene ring (Scheme 1, top reaction).[6,7] Except for very rare cases,[4,8] selective and preferential arylation at the positions β to the sulfur atom (C3 and/or C4) does not take place. This is also true for the arylation of thiazoles, and a catalytic system that can preferentially arylate the least reactive C4 positions has not been forthcoming.[6,9] We herein report that the Pd-catalyzed oxidative C–H arylation of thiophenes and thiazoles with arylboronic acids manifests the otherwise difficult C4 regioselectivity (Scheme 1, bottom reaction).[10] The present finding is significant not only because the regioselective outcome is complementary to that of the arylation using haloarenes,[2] but also because it demonstrates the remarkable mechanistic difference between these two seemingly related Pd-catalyzed direct arylation processes.



Scheme 1. Reagent-controlled regiodivergency in the Pd-catalyzed C–H arylation of thiophenes and thiazoles.

In early experiments, we found that the C–H arylation of 2-ethylthiophene (**1a**) with phenylboronic acid (**2a**) took place in the presence of 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical[11] (TEMPO), $Pd(OAc)_2$, and 2,2′-bipyridyl (bipy) in 1,2-dichloroethane (DCE) at 80 °C (Table 1, entry 1). Very surprisingly, we identified 2-ethyl-4-phenylthiophene (**3aa**) to be the sole coupling product under these conditions (69 % yield). The corresponding C5-phenylation product (**4aa**) was not identified.

Based on these promising initial results we decided to further optimize the reaction conditions (Table 1). After we had found that the bipy is necessary for the reaction to occur (entry 2), we screened various nitrogen-based bidentate ligands such as bipy derivatives (**L1**–**L3**), phenanthrolines (**L4**–**L6**), and TMEDA (**L7**) in the reaction of **1a** with **2a** (entries 3–9). Although **L4** and **L6** were found to be equally effective ligands in terms of yield and regioselectivity, we selected bipy as the standard ligand for subsequent experiments in view of its efficiency, cost, and simplicity. With α,α,α-trifluorotoluene as a solvent, a slightly higher yield (76 %) was obtained (entry 10) and the reaction also proceeded at lower temperatures, remarkably even at room temperature (entry 11). Replacing TEMPO with other oxidants such as *p*-benzoquinone, (diacetoxyiodo)benzene, and copper(II) chloride resulted in a much lower reaction efficiency (entries 12–14). Higher concentrations of **1a** in α,α,α-trifluorotoluene resulted in higher yields while the high regioselectivity was maintained (entries 15 and 16). Reducing the catalyst loading to 5 or 2 mol % $Pd(OAc)_2$ led to a slight

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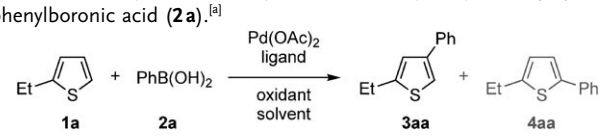
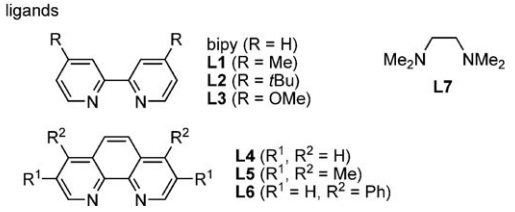
Table 1: Pd-catalyzed C–H arylation of 2-ethylthiophene (**1a**) with phenylboronic acid (**2a**).[a]



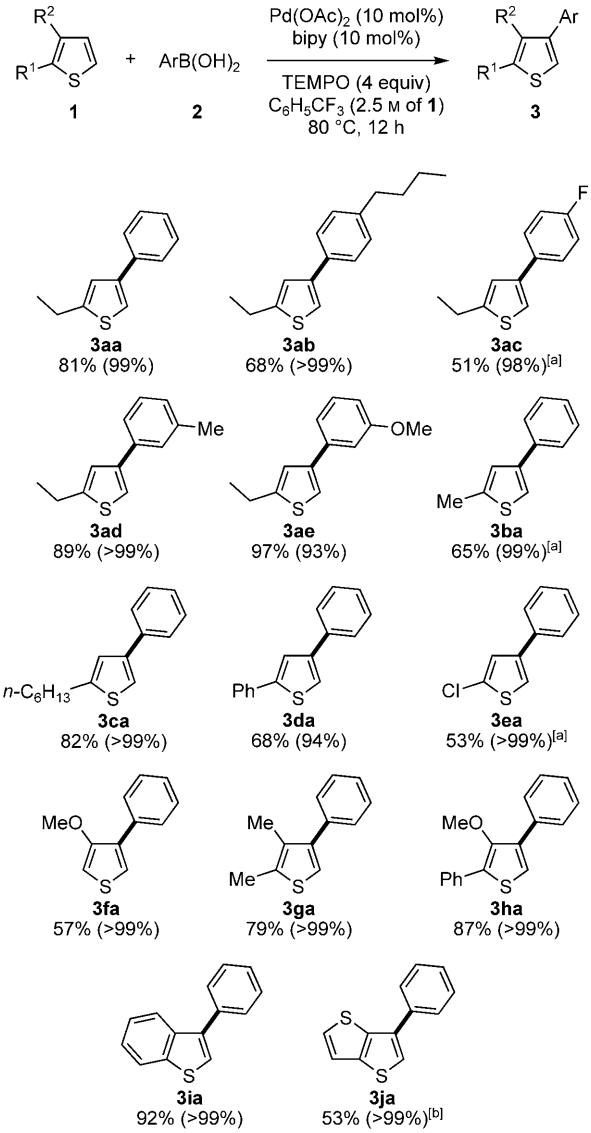
1a 2a 3aa 4aa

ligands



Entry	Ligand	Oxidant	Solvent	Yield [%][b]	**3aa**/**4aa**
1	bipy	TEMPO	DCE	69	>99:1
2	–	TEMPO	DCE	<1	n.d.[e]
3	**L1**	TEMPO	DCE	55	>99:1
4	**L2**	TEMPO	DCE	51	>99:1
5	**L3**	TEMPO	DCE	41	>99:1
6	**L4**	TEMPO	DCE	65	>99:1
7	**L5**	TEMPO	DCE	25	>99:1
8	**L6**	TEMPO	DCE	72	>99:1
9	**L7**	TEMPO	DCE	7	92:8
10	bipy	TEMPO	$C_6H_5CF_3$	76	>99:1
11[c]	bipy	TEMPO	$C_6H_5CF_3$	40	>99:1
12[d]	bipy	BQ	$C_6H_5CF_3$	16	96:4
13[d]	bipy	$PhI(OAc)_2$	$C_6H_5CF_3$	2	98:2
14	bipy	$CuCl_2$	DCE	1	90:10
15[f]	bipy	TEMPO	$C_6H_5CF_3$	84	99:1
16[g]	bipy	TEMPO	$C_6H_5CF_3$	88 (81)	99:1
17[g,h]	bipy	TEMPO	$C_6H_5CF_3$	76	99:1
18[g,i]	bipy	TEMPO	$C_6H_5CF_3$	63	99:1
19[j,k]	bipy	TEMPO	$C_6H_5CF_3$	81	99:1
20[j,l]	bipy	TEMPO	$C_6H_5CF_3$	34	96:4

[a] Conditions: **1a** (1 equiv), **2a** (4 equiv), $Pd(OAc)_2$ (10 mol%), ligand (10 mol%), oxidant (4 equiv), solvent (0.25 M of **1a**), 80 °C, 12 h. BQ = *p*-benzoquinone. [b] Yields were determined by GC analysis. The number in parenthesis for entry 16 is the yield of isolated product. [c] The reaction was carried out at room temperature. [d] 0.63 M of **1a**. [e] Not determined. [f] 0.83 M of **1a**. [g] 2.5 M of **1a**. [h] 5 mol% $Pd(OAc)_2$/bipy was used. [i] 2 mol% $Pd(OAc)_2$/bipy was used; the reaction time was 24 h. [j] 1.25 M of **1a**. [k] 2 equiv of TEMPO was used. [l] 2 equiv of **2a** was used.

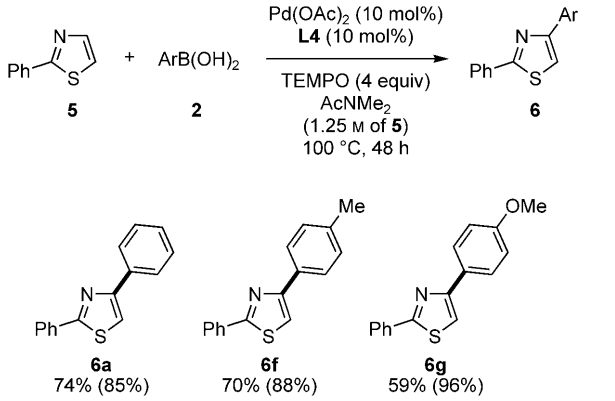


Scheme 2. Scope of thiophene and boronic acid coupling partners; yield of the isolated product and regioselectivity (in brackets) are given. [a] 1.25 M of **1** in DCE. [b] 3,6-Diphenylated product was obtained in 19% yield.

decrease in the yield without affecting the regioselectivity (entries 17 and 18). Lowering the amount of TEMPO to 2 equiv (entry 19) did not affect the yield, but decreasing the amount of **2a** led to lower yield and slightly lower regioselectivity (entry 20).

Under optimized reaction conditions (see Scheme 2), the scope with respect to thiophenes **1** and arylboronic acids **2** was investigated. As shown in Scheme 2 the optimized reaction conditions can be applied to a wide variety of substrates. A range of thiophene derivatives including 2-substituted (**1a**–**1e**), 3-substituted (**1f**), and 2,3-disubstituted thiophenes (**1g** and **1h**) as well as thiophene-containing fused arenes (**1i** and **1j**) underwent C–H bond arylation with very high regioselectivity (93 to >99%) at the position β to the sulfur atoms (C4 for 2-substituted thiophenes).[12]

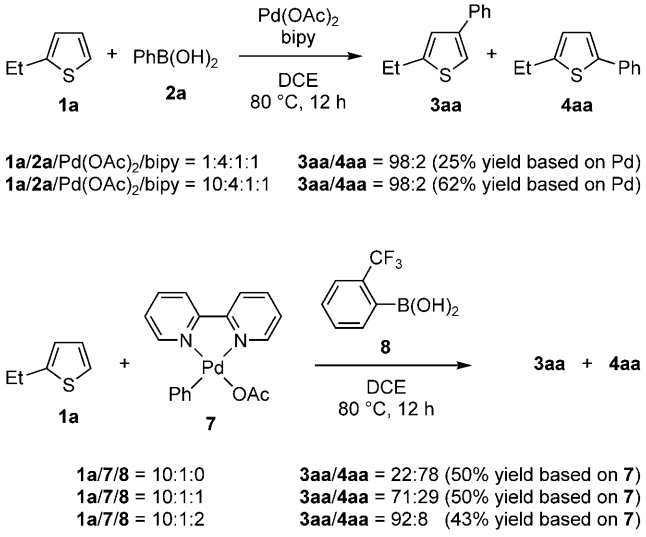
We next investigated whether also other heteroarenes undergo highly regioselective arylation. Although furans and indoles reacted with arylboronic acids under the optimized conditions, these heteroarenes manifested low reactivity (<20% yield) and the preferred reaction sites turned out to be the C2 positions. However, we were pleased to find that the C4-selective arylation of 2-phenylthiazole (**5**) occurred with $PhB(OH)_2$ (**2a**) using $Pd(OAc)_2$/bipy/TEMPO to give the coupling product **6a** in 43% yield with good regioselectivity (C4/C5 = 87:13). After optimization we found that regioselective C4-arylation of **5** is best conducted in dimethylacetamide (1.25 M) with phenanthroline (**L4**) as the ligand at 100 °C for 48 h. Various arylboronic acids **2** were reacted with **5** under these conditions to afford the C4-arylated thiazoles **6** in good yields and regioselectivity (selected examples are shown in Scheme 3).[13] To the best of our knowledge, these



Scheme 3. C4-selective arylation of 2-phenylthiazole (**5**); yield of the isolated product and regioselectivity (in brackets) are given.

are the first examples of C4-selective arylation of thiazoles catalyzed by a transition-metal complex.[6,9]

To determine the mechanism of C4-selective arylation of thiophenes and thiazoles, we carried out several control experiments (Scheme 4). The focal point in this study was to



Scheme 4. Roles of TEMPO and arylboronic acid.

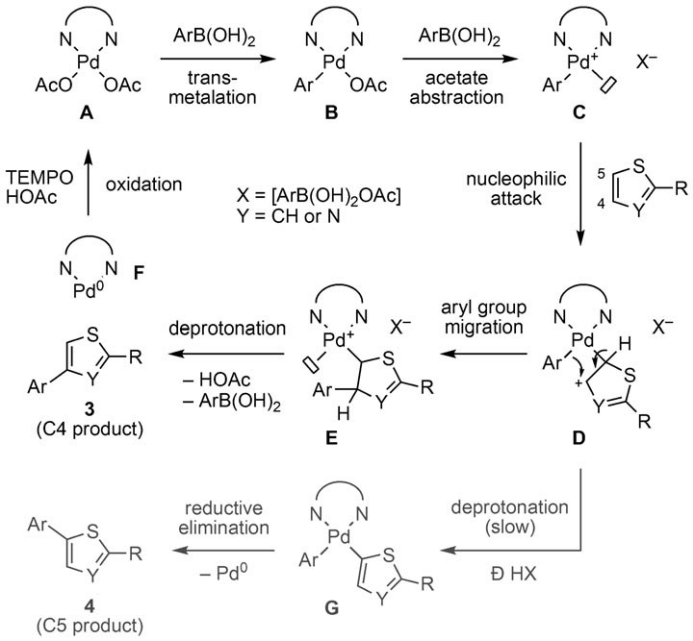
identify the critical elements (TEMPO or arylboronic acids) responsible for the unique C4 regioselectivity. In the first set of experiments, TEMPO was excluded from the reaction mixture. When the mixture of 2-ethylthiophene (**1a**), $PhB(OH)_2$ (**2a**), $Pd(OAc)_2$, and bipy in DCE was heated at 80 °C for 12 h (molar ratio, **1a**/**2a**/$Pd(OAc)_2$/bipy = 1:4:1:1), **3aa** and **4aa** were produced in 25 % combined yield with high C4 regioselectivity (**3aa**/**4aa** = 98:2). The low yield resulted from the competing formation of biphenyl as a result of the homocoupling of **2a**. Assuming that a high **1a**/Pd ratio might be important in suppressing the formation of biphenyl in the actual catalytic reactions, we increased the **1a**/Pd ratio to 10:1. Indeed, under these conditions, C4-selective arylation occurred with higher yield (62 % yield based on Pd). These TEMPO-free experiments clearly indicate that TEMPO is not responsible for the C4 regioselectivity but rather plays its primary role as an oxidant in the Pd^{II}/Pd^{0} redox catalytic cycle.[11]

To shed more light onto the mechanism, we next investigated the reactions of bipy-bound PhPdOAc complex **7**,[14] which could be produced within a catalytic cycle from [(bipy)$Pd(OAc)_2$] and **2a** by transmetalation (Scheme 4). Very surprisingly, we found that the "wrong" C5-arylated isomer **4aa** was preferentially formed when **7** (1 equiv) was treated with 2-ethylthiophene (**1a**; 10 equiv) in DCE at 80 °C (**3aa**/**4aa** = 22:78, 50 % combined yield). At this point, we became aware of the possibility that boronic acids might play a secondary role in catalysis for switching the regiochemical outcome (C5 to C4). In line with such an assumption, we observed complete recovery of the C4 regioselectivity when a "spectator" arylboronic acid such as *o*-$CF_3C_6H_4B(OH)_2$ (**8**)[15] was added in the reaction of **7** with **1a** (**3aa**/**4aa** = 71:29 (with 1 equiv of **8**) and 92:8 (with 2 equiv of **8**)). These results clearly showed the essential role of excess boronic acids in achieving the otherwise difficult C4 regioselectivity.

Based on these results, we propose a possible mechanism for the Pd-catalyzed C4-selective oxidative arylation of thiophenes and thiazoles with arylboronic acids (Scheme 5); 1) transmetalation of [(bipy)$Pd(OAc)_2$] (**A**) with $ArB(OH)_2$ followed by acetate abstraction from the resulting intermediate **B** with $ArB(OH)_2$ generates a cationic Ar–Pd species **C** having a boronate $[ArB(OH)_2OAc]^-$ as the counteranion; 2) nucleophilic attack of thiophene/thiazole to **C** (at the most nucleophilic C5 position) leads to cationic intermediate **D**; 3) aryl-group migration from Pd to the C4 position provides intermediate **E**; 4) deprotonation of **E** eventually produces C4-arylated product **3** and the Pd^0 species **F**; and 5) oxidation of **F** by two equivalents of TEMPO and subsequent ligand exchange with HOAc regenerates **A** to close the catalytic cycle.

In this mechanistic proposal, the reversal in the regioselectivity caused by the arylboronic acid could be explained as follows: the acetate anion that is expelled from reaction of **B** to give **C** is trapped by the excess arylboronic acid to generate the boronate $[ArB(OH)_2OAc]^-$. Since this boronate is less basic than the free acetate anion, the deprotonation of intermediate **D** would become significantly slower, thereby allowing the aryl group on Pd to irreversibly migrate onto the C4 position of thiophene/thiazole to give **E**. In the absence of excess $ArB(OH)_2$, the deprotonation from **D** (where X = OAc) would become the major pathway to afford diarylpalladium intermediate **G**, which should then provide the C5-arylated product **4** by reductive elimination. The control experiments shown in Scheme 4 are all in agreement with this mechanistic scenario. It should be noted that cationic intermediates similar to **D** have been often considered in the Pd-catalyzed C–H arylation of thiophenes and thiazoles with haloarenes. As these reactions are typically conducted under basic conditions, the direct deprotonation pathway from **D** should be rapid and thereby manifest C5 regioselectivity.

Finally, we applied our regioselective C–H arylation reaction to the synthesis of the pharmacologically important structure **14** (Scheme 6).[16] Merck recently discovered that 4-

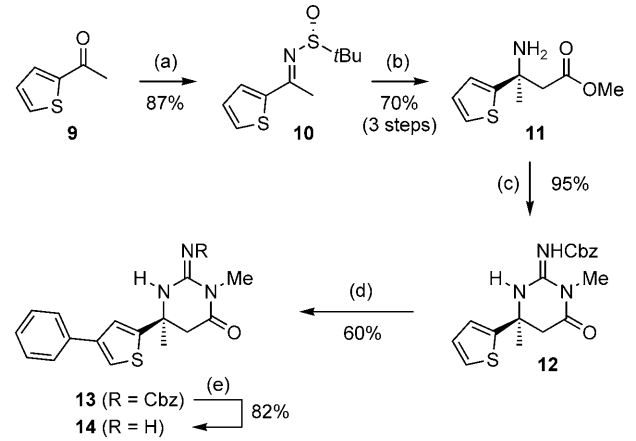


Scheme 5. Proposed catalytic cycle for Pd/TEMPO-mediated C–H arylation of thiophenes and thiazoles with arylboronic acids.

arylated thiophenes such as SCH-785532 belong to a class of small-molecule inhibitors of β-secretase (BACE), which are potential drug candidates for treatment of Alzheimer's disease. Prominent structural features of these pharmacologically interesting compounds are an iminopyrimidinone moiety and a 4-arylthiophene unit.

In our enantioselective synthesis of the core framework **14**, commercially available 2-acetylthiophene (**9**) was converted to the corresponding chiral sulfinyl imine **10**[17] using Ellman's Ti-mediated condensation reaction (Scheme 6).[18] The imine **10** formed was reacted with the titanium enolate[19] of methyl acetate to furnish β-amino ester **11** after a deprotection/protection sequence. This aminoester was then treated with CbzNHC(=S)NHMe[20] in the presence of EDCI to afford thiophene-appended iminopyrimidinone **12**. Applying our $Pd(OAc)_2$/bipy/TEMPO catalysis to the reaction of **12** and phenylboronic acid afforded the desired 4-phenylthiophene derivative **13** in 60% yield with virtually complete regioselectivity. It is important to mention that this reaction tolerates the sensitive guanidine moiety. Finally, removal of the Cbz group in **13** afforded **14** in 82% yield. We believe that the late-stage C–H functionalization presented herein will find use in the rapid generation of molecular libraries related to the structure of **14**.

In summary, we have developed a new method for the C4-selective C–H arylation of thiophenes and thiazoles with arylboronic acids under Pd/TEMPO catalysis. The reactions presented herein mostly occurred in high yields and excellent regioselectivities. Mechanistic studies revealed that the presence of excess boronic acid is the key in achieving the otherwise difficult C4 regioselectivity. Furthermore, we applied our arylation methodology to a concise synthesis of the key pharmacological structure **14**, which has potential for treatment of Alzheimer's disease. The previously inaccessible regioselectivity and the previously unrecognized regiocontrol elements that have been uncovered in this study should provide tremendous opportunities for these important processes. Further work is in progress to bolster the proposed mechanism of the C4-selective arylation of thiophenes/thiazoles; we are examining the role of arylboronic acids by supplemental experimentation and computational work.



Scheme 6. Application of the C4-selective thiophene arylation to the synthesis of **14**. Conditions: a) (*R*)-*t*BuSONH$_2$, Ti(OEt)$_4$, THF, 70°C. b) 1) $H_2C{=}C(OLi)OMe$, $TiCl(OiPr)_3$, THF, −78°C; 2) Me_3SiCl, MeOH, RT; 3) Me_3SiCHN_2, MeOH/CH_2Cl_2, RT. c) CbzNHC(=S)NHMe, EDCI (*N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide), iPr_2NEt, DMF, RT. d) $PhB(OH)_2$, $Pd(OAc)_2$, bipy, TEMPO, $C_6H_5CF_3$, 80°C. e) Pd/C, CF_3CO_2H.

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