

Completely Regioselective Direct C–H Functionalization of Benzo[*b*]thiophenes Using a Simple Heterogeneous Catalyst

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S Supporting Information

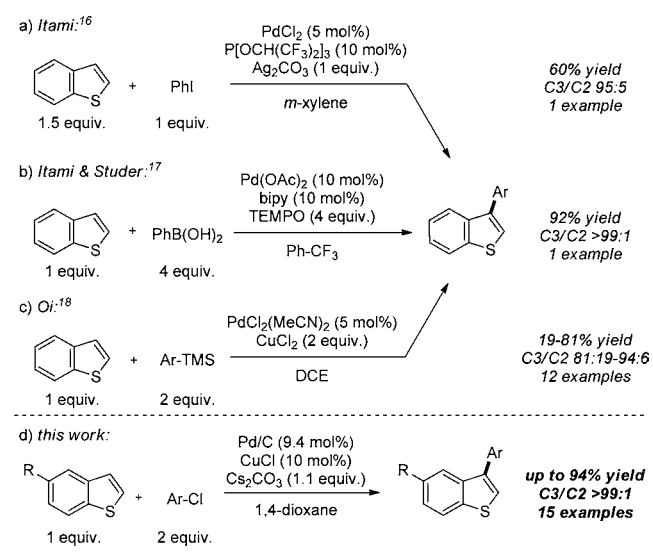
ABSTRACT: The first completely selective C3 C–H arylation of benzo[*b*]thiophenes is reported, demonstrating previously unexploited reactivity of palladium. Benzo[*b*]thiophenes are coupled with readily available aryl chlorides using a ligand-free, dual catalytic system of heterogeneous Pd/C and CuCl. The reaction is operationally simple and insensitive to air and moisture, and it provides valuable products with complete selectivity. Significant investigations into the nature of the active catalytic species and mechanistic considerations are discussed.

Despite significant recent advances in homogeneous catalysis, this knowledge has largely not been applied in an industrial environment, with the majority of industrial catalytic processes continuing to employ heterogeneous catalysts.¹ The high costs associated with homogeneous catalysis due to the use of unrecoverable metals and ligands, as well as practical limitations with regard to catalyst handling, recyclability, and separation of the catalyst from products, impede the transfer of advances in homogeneous catalysis to large-scale industrial processes. In contrast, many of these limitations can be obviated by use of heterogeneous catalysts; thus, the development of such processes is desirable.^{2–5}

Arylated heterocycles are valuable structural motifs present in many natural products and biologically active molecules.⁶ Commonly these are prepared via transition-metal-catalyzed cross-coupling of functionalized heterocycles and suitable coupling partners,⁷ though more sustainable methods are desirable. Recently, significant development of the field of C–H activation has enabled the direct arylation of heterocycles,⁸ circumventing the need for pre-functionalization. Unfortunately, multicomponent and expensive catalyst systems are often required, and directing groups to control regioselectivity are necessary. Alternatively, many metal-catalyzed direct C–H functionalizations exploiting the inherent reactivity of heterocycles are established,^{8c,9} providing viable alternatives, though methods that selectively functionalize the less reactive C–H bonds without recourse to directing groups,¹⁰ or exploiting the steric bulk of ligands,¹¹ substituents,¹² or additives,¹³ remain underdeveloped.

For valuable benzo[*b*]thiophene motifs,^{14,15} transition-metal-catalyzed direct arylation of the C2-position is well established;^{9c} efficient methods for the more challenging direct C3-arylation remain more elusive, with only three reports to date (Scheme 1a–c).^{16–18} Of the three reports, two provide a single example,

Scheme 1. C3-Selective Arylation of Benzo[*b*]thiophenes



and other limitations include expensive catalyst systems, large excesses of reagents or coupling partners, limited availability of coupling partners, and super-stoichiometric use of oxidants. Limitations in the C3/C2 selectivity of these methods are also apparent.

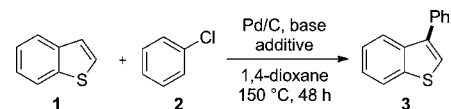
In the course of investigating novel reactivity of heterogeneous catalysts¹⁹ we have established an operationally simple, *completely* selective C3-arylation of unsubstituted benzo[*b*]thiophenes, addressing many of the limitations of existing methods. Here we describe the coupling of benzo[*b*]thiophenes with inexpensive and widely available aryl chlorides, using Pd/C with CuCl as co-catalyst (Scheme 1d). The reaction is ligand-free, scalable, and insensitive to air and moisture, and it represents reactivity for Pd/C beyond its typical application in cross-coupling and hydrogenation reactions.^{4,20} Furthermore, our investigations suggest the active catalytic species is likely to be heterogeneous in nature.

We initially found that reaction of benzo[*b*]thiophene **1** and chlorobenzene **2** in the presence of Pd/C (K-0219 from Heraeus) gave 3-phenylbenzo[*b*]thiophene **3** in 30% GC yield with excellent C3/C2 selectivity (Table 1, entry 1). Solvent screening and standard optimization of catalyst loading, temperature, ratio of reagents, etc. gave a maximum yield of 60% (entry 5), though complete C3/C2 selectivity was

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Table 1. Optimization of Reaction Conditions



entry	additive (amount, mol%)	yield ^a (%)	C3/C2 ^b
1	–	30	>98:2
2	PivOH (10)	22	>99:1
3	Ag ₂ CO ₃ (5)	n.r.	–
4	AgSbF ₆ (5)	trace	>99:1
5 ^c	–	60	>99:1
6 ^c	AuCl ₃ (5)	64	>99:1
7 ^c	CuCl (5)	78	>99:1
8 ^c	CuCl (10)	88	>99:1
9 ^c	CuCl (15)	69	>99:1
10 ^c	CuBr (5)	77	>99:1
11 ^c	CuI (5)	n.r.	–
12 ^{c,d}	CuCl (10)	n.r.	–
13 ^{c,d}	–	n.r.	–
14 ^{c,e}	CuCl (10)	n.r.	–

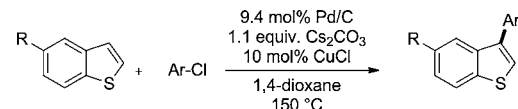
General conditions: **1** (0.300 mmol), **2** (1.0 equiv), Cs₂CO₃ (1.1 equiv), Pd/C (9.4 mol %), 1,4-dioxane (1.5 mL), 150 °C, 48 h. ^aYields determined by GC of crude reaction mixture; mesitylene as internal standard. n.r. = no reaction. ^bC3/C2 ratios determined by GC-MS of crude reaction mixture. ^c**1** (0.300 mmol), **2** (2.0 equiv), 1,4-dioxane (1.5 mL). ^dWithout Pd/C. ^eWithout base.

maintained. In an attempt to increase the yield of reaction further, we proposed a number of additives to enhance reactivity. Pivalic acid, a common additive in C–H activation chemistry,⁸ proved detrimental to reactivity (entry 2), as did silver salts which were proposed by Itami and Studer to facilitate the potential formation of cationic Pd species (entries 3 and 4).^{16,17} Pleasingly, in attempts to facilitate reaction by Lewis acid activation of **1**, we established that a number of zinc, iron, gold, and copper salts enhanced reactivity, with CuCl most efficacious. A catalyst loading of 9.4 mol% was determined to be optimal. Interestingly, CuBr gave a similar result, whereas CuI retarded the reaction completely (entries 10 and 11). Control experiments demonstrated that base is essential for reactivity, Cu did not catalyze the reaction in the absence of Pd, and no reaction was observed in the absence of Cu and Pd (entries 12–14). We also assessed numerous Pd/C sources and observed significant variation in activity, though “standard” Pd/C from both Heraeus and Sigma-Aldrich showed excellent reactivity. See Supporting Information (SI) for all experimental data.

In addition to Pd/C, the reactivity of several alternative heterogeneous catalysts under identical conditions was also investigated. Several supported Pd systems were investigated, as well as other transition metals. In all instances no appreciable reactivity was observed, highlighting the unique catalytic activity of Pd/C with respect to this transformation (see SI).

With optimized conditions established we explored the scope of the reaction (Table 2). Electron-rich and electron-neutral aryl chlorides gave reaction products in typically excellent yield. Sterically encumbered aryl chlorides also proceeded in excellent yield, though extended reaction times were required; the reaction of 2-chloro-*m*-xylene is of particular note. Reaction with electron-deficient aryl halides including nitro- and ester-substituted systems proceeded, though the rate of reaction was significantly reduced.²¹ Interestingly, electron-deficient systems bearing only fluoride heteroatoms proceeded in high yield and acceptable

Table 2. Reaction Scope



3 (89%, 81% ^a) C3/C2 >99:1	4 (89%) C3/C2 >99:1	5 (85%) ^b C3/C2 >99:1	6 (71%) C3/C2 >99:1
7 (94%) ^c C3/C2 >99:1	8 (85%) C3/C2 >99:1	9 (75%) C3/C2 >99:1	10 (83%) C3/C2 >99:1
11 (24%) C3/C2 >99:1	12 (21%) ^c C3/C2 >99:1	13 (73%) C3/C2 >99:1	14 (69%) ^c C3/C2 >99:1
15 (41%) ^d C3/C2 >99:1	16 (74%) C3/C2 >99:1	17 (90%) C3/C2 >99:1	

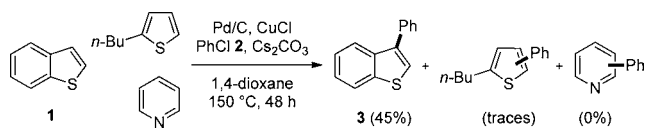
General conditions: **1** (0.300 mmol), ArCl (2.0 equiv), Pd/C (9.4 mol %), Cs₂CO₃ (1.1 equiv), 1,4-dioxane (1.5 mL), 48–72 h. Yields given are isolated. C3/C2 ratios determined by GC-MS of crude reaction mixture. ^a3 mmol scale, reaction time 72 h, GC yield. ^bProduct isolated as mixture with corresponding homo-coupled ArCl. Yield given refers to denoted compound. ^cReaction time 96 h. ^dArCl (0.300 mmol), **1** (3.0 equiv).

reaction time, indicating that the electron-deficient nature of the aryl chloride alone is not significantly detrimental to reactivity. Furthermore, C5-substituted benzo[*b*]thiophenes were amenable to the reaction conditions and were coupled in very high yield, and pleasingly, reaction of **1** with 1,4-dichlorobenzene gave the bis-benzo[*b*]thiophene adduct **15** in 41% yield. The scalability of the reaction was also demonstrated, with reaction to give **3** undertaken on a 3 mmol scale. Unfortunately, efficient recycling of the catalyst has not been established.

Application of this method to other heterocycles has provided limited success to date. Only thiophenes have demonstrated any notable reactivity, though poor C3/C2 selectivity is observed. Pleasingly, though, we have demonstrated the selective nature of this reaction in an intermolecular competition experiment. Using standard reaction conditions, a 1:1:1 mixture of **1**, 2-*n*-butylthiophene, and pyridine showed almost exclusive reactivity for **1**, suggesting this method is appropriate for application to more complex substrates (Scheme 2).

The hetero- or homogeneous nature of the active catalyst in many reactions is often highly contentious, and specifically with regard to Pd/C the active species is often thought to be homogeneous following leaching of Pd into solution.²²

Scheme 2. Intermolecular Competition Experiment



Consequently, we have undertaken significant effort to determine the nature of the active species in our system. Considering both the high temperature of the reaction and the presence of aryl chlorides—which in given examples are known to leach Pd from carbon supports via an oxidative addition process²³—it is highly notable that we have demonstrated that the active catalyst is very likely to be heterogeneous in nature.

Although *no current methods* evaluating the homo/heterogeneous nature of an active catalyst can be considered completely definitive,²² the results of numerous experimental tests and literature precedent for the conclusions drawn have led us to propose that the active catalytic species is highly likely to be heterogeneous in nature. Key experiments include the following: (i) Four 3-phase tests,²² whereby one reagent (the aryl chloride or benzo[*b*]thiophene) is immobilized on a solid support, show that active homogeneous catalytic species are not generated under these reaction conditions. (ii) Standard Hg(0) poisoning and hot filtration tests are positive for heterogeneous catalysis.²² (iii) The introduction of PPh₃ (10 mol%), an established poison for heterogeneous catalysts, results in significant inhibition of reactivity. Complete inhibition of the catalyst is typically expected with sub-stoichiometric quantities of PPh₃ (with respect to the catalyst) due to irreversible binding of the phosphine to the surface, though in this instance we propose that the high reaction temperature results in dynamic rather than irreversible binding of the phosphine, and thus trace reaction is observed. (iv) Numerous comparable homogeneous Pd catalysts show no reactivity. Reactivity of PdCl₂(PPh₃)₂ and Pd(PPh₃)₄ was observed, though they resulted *exclusively* in C2-arylation. (v) Analysis of the reaction mixture by X-ray fluorescence spectroscopy (XRF) after filtration shows Pd present at a concentration of <4 ppm, corresponding to 0.01% of the initial Pd loading. Additional experiments, clarification of results, and further circumstantial evidence are in the SI.

The results of our investigation strongly suggest a heterogeneously catalyzed reaction. The 3-phase tests and experiments demonstrating that site-selectivity is reversed when employing active homogeneous Pd(0) are particularly compelling. This change in selectivity highlights the unique reactivity possible when employing a heterogeneous catalyst. It should be noted a short induction period was observed when investigating the kinetic progress of the reaction. We propose this could be accounted for by the initial reduction/modification of the catalyst surface, to generate the active catalyst. Alternatively, leaching of Pd into solution could account for the induction period, though should this be the case, our results suggest likely agglomeration of leached Pd, and formation of a new heterogeneous active species rather than generation of a homogeneous active species.^{22a}

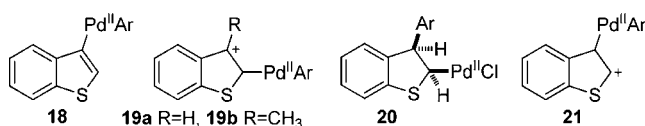


Figure 1. Hypothetical intermediates for refuted homogeneous reaction mechanisms.

In addition to our empirical investigation into the physical nature of the active catalyst, we have also evaluated possible mechanistic pathways. A number of viable homogeneous mechanistic pathways have been considered, though none is satisfactory (Figure 1, see SI for associated experimental data): (i) Direct C–H activation/palladation at C3 to give **18** followed by reductive elimination. As described by Hartwig, homogeneous C–H activation mechanisms are highly amenable to investigation using kinetic isotope studies.²⁴ In this instance, a “homogeneous-type” C–H activation mechanism is directly refuted by the absence of a KIE in the appropriate kinetic and competition experiments proposed by Hartwig. Furthermore, palladation at the more acidic C2-position would be expected for typical C–H activation mechanisms.⁸ (ii) Palladation at C2 generating cationic species **19**, followed by aryl migration and elimination of Pd as proposed by Itami.¹⁶ This mechanism was deemed improbable as unlike in the report of Itami, when silver salts were employed to promote formation of cationic Pd species via sequestering of halides, retardation of reaction was observed. Furthermore, no reaction of 3-methylbenzo[*b*]thiophene **22** under identical reaction conditions was observed. We suggest it is likely arylation at C2 would be expected in this instance via the reductive elimination of **19b**, as the migratory pathway is shut down. We appreciate subtle steric effects may also account for the lack of reactivity. (iii) A Heck-type mechanism. This was ruled out due to the mechanistic requirement for *syn* β -hydride elimination, thus requiring C–C bond rotation of cyclic intermediate **20** which is not possible. Alternatively, base-catalyzed elimination of the Pd driven by re-aromatization may be considered, though the selectivity observed in the hypothetical migratory insertion to benzo[*b*]thiophene is contrary to that expected.²⁵ (iv) Electrophilic palladation at C3 to give **21**, followed by reductive elimination and re-aromatization. Reaction of 2-methylbenzo[*b*]thiophene **23** and **22** under the standard reaction conditions gave 11% and 0% yield, respectively. Although electrophilic arylation in a manner analogous to that with indole would give preferential reactivity at C3, the complete inhibition of reactivity with **22** rather than a shift in selectivity is unlikely; additionally, the relatively small and electronically neutral substitution at C2 as present in **22**, would not be expected to inhibit reactivity to such an extent using such simple catalytic systems.²⁶ As a result of the discussed mechanistic considerations, we propose that traditional mechanisms associated with homogeneous catalysis are not *directly* applicable in this instance, and consequently that the supported nature of the catalyst may have a direct impact on the regioselectivity of the reaction.

In summary, we have described the first heterogeneously catalyzed C–H arylation of benzo[*b*]thiophenes, demonstrating novel reactivity mediated by a simple palladium catalyst. The reaction appears intrinsically selective for the typically less reactive C3-position, requiring no additional ligands or directing groups. Cheap and widely available catalysts and coupling partners are employed, and the reaction is both operationally simple, and tolerant of air and water. Our mechanistic investigation suggests typical homogeneous reaction mechanisms are unlikely to be in operation. Further studies relating to the interaction of the substrate and catalyst, the mechanism of reaction, and the role of CuCl are ongoing within our laboratory.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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