C–H Functionalization

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Pd/C as a Catalyst for Completely Regioselective C–H Functionalization of Thiophenes under Mild Conditions**

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In memory of Berthold Beitz

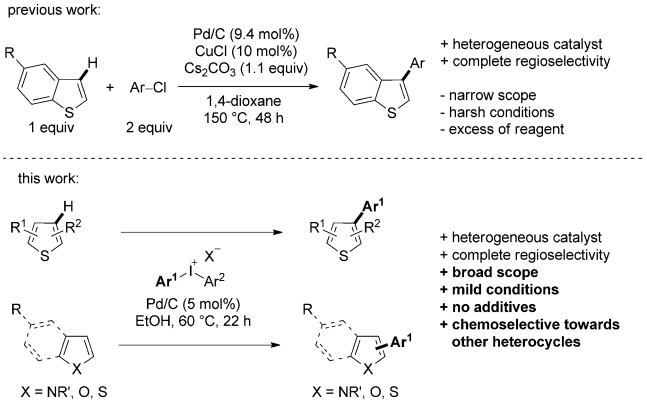
Abstract: *The completely C3-selective arylation of thiophenes and benzo[b]thiophenes was achieved by using Pd/C as a heterogeneous catalyst without ligands or additives under mild reaction conditions. The practicability of this transformation is demonstrated by notable functional group tolerance and the insensitivity of the reaction to H_2O and air. This method is also applicable to nitrogen- and oxygen-containing heterocycles, yielding the corresponding C2-arylated products. Three-phase tests along with Hg-poisoning and hot-filtration tests suggest that the catalytically active species is heterogeneous in nature.*

In view of the energy and commodity challenges facing society today, the development of mild, efficient, and sustainable chemical processes is required. In synthetic chemistry, the direct functionalization of C–H bonds in catalytic coupling reactions is considered to be a significant step towards achieving this goal and fantastic progress has already been made.[1] Of particular interest is the regio- and chemoselective transformation of heteroaromatic building blocks, which are prevalent in natural products,[2] biologically active molecules,[3] and organic materials.[4] Furthermore, environmentally benign, operationally simple, and robust reactions, particularly those employing heterogeneous catalysts are of significant interest to the chemical industry.[5–9]

Arylated thiophenes and benzo[*b*]thiophenes are prominent scaffolds in biologically active molecules[10] and in the field of organic materials.[4] Due to the inherent reactivity of (benzo[*b*]-)thiophenes, catalytic methods for the direct C2-arylation of unfunctionalized substrates have been widely explored.[1c,11] In contrast, only recently has notable success been achieved in mediating direct C3-selective arylation[12] without recourse to directing groups or employing substrates in which the C2-position is already substituted.[13]

In 2010, Itami and co-workers published the first method for the selective arylation of substituted thiophenes using a Pd–ligand system and an aryl iodide as a coupling partner.[12a] Following this seminal work, notable contributions were made by the groups led by Studer,[12b,c] Itami,[12a–c,g] and Doucet.[12h] These reports stand out due to either the mild reaction conditions[12b] or the broad substrate scope.[12h] However, despite the remarkable progress made, all methods to date are limited by either harsh reaction conditions, narrow substrate scope, incomplete selectivity, or the required large excess of coupling partners and/or reagents.[12]

Our group has recently presented the first completely C3-selective arylation of benzo[*b*]thiophenes, employing aryl chlorides and using a ligand-free catalyst system of Pd/C and CuCl (Scheme 1).[14] Despite the narrow scope and harsh reaction conditions, this reaction proved particularly intriguing: Studies identified the active catalyst as very likely to be heterogeneous in nature,[15] even though Pd/C is often considered to be a source of catalytically active, solution-phase Pd species,[16] especially under such forcing conditions.



Scheme 1. Heterogeneously catalyzed functionalization of heterocycles.

Herein, we describe the completely C3-selective arylation of thiophenes and benzo[*b*]thiophenes using aryliodonium salts mediated by Pd/C under mild conditions. Furthermore, our investigation suggests that the active catalyst is surprisingly heterogeneous in nature, despite the strongly oxidative reaction conditions.[16] In addition, a "robustness screen" as reported by Collins and Glorius[17] was undertaken, and for

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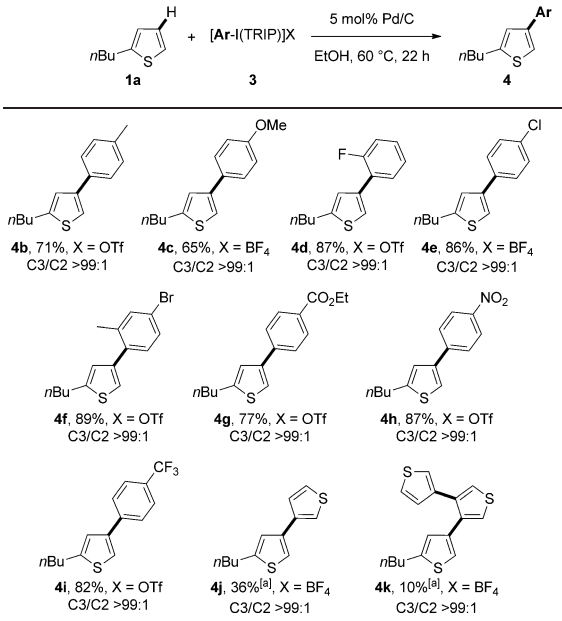
the first time the data obtained was used to rationally design a more complex molecule that predictably underwent a highly chemo- and regioselective reaction under the reported conditions.

Using our previously reported reaction conditions as a starting point,[14] we were delighted to discover that 2-*n*-butylthiophene (**1a**) and $[Ph_2I]BF_4$ (**2a**) gave 2-*n*-butyl-4-phenylthiophene (**4a**). Control experiments indicated that neither CuCl nor base were necessary and that reactivity was observed at room temperature. Of the heterogeneous catalysts screened, only Pd catalysts were reactive. Some homogeneous Pd catalysts also gave **4a**, though with much lower conversion. Standard screening of solvents, catalyst loading, temperature, and ratio of reagents established the optimized conditions to be 5 mol% Pd/C in EtOH at 60°C and **1a** and **2a** in a ratio of 1:1.4. No product formed in a control reaction conducted without Pd/C. Additional experiments showed that reaction with 2 mol% Pd/C gave similar conversion, though an elevated temperature of 80°C was required to avoid extended reaction time. Triflate counterions (**2b**) were tolerated, and the use of the unsymmetrical iodonium salt [PhI(TRIP)]OTf (**3a**) (TRIP = 2,4,6-triisopropylphenyl) gave **4a** in comparable yield without transfer of the TRIP group. Consequently, TRIP can be used as a cheap nontransferable dummy group instead of a potentially expensive second equivalent of arene as is the case with symmetrical aryliodonium salts. The yield did not change when absolute EtOH or an argon atmosphere were used. The addition of 50 equiv of water resulted in only a minor decrease in yield to 72%, which is likely due to poor dispersion of the catalyst.[18] We employed commercial Pd/C from Heraeus for our study, though Pd/C from other common suppliers was also reactive. See the Supporting Information for all optimization data.

Having established the reaction conditions, we explored the scope of unsymmetrical iodonium salts **3** (Table 1).[19] A broad range of functionalized arenes could be coupled with **1a** giving the expected products in good to excellent yields. Electron-poor, electron-rich, and sterically encumbered arenes were well tolerated. The coupling of heterocyclic iodonium salts (thiophene derivative) should be highlighted (**4j**, **4k**), and enabled the preparation of the all-C3-connected terthiophene **4k**.

We subsequently explored the scope of the thiophenes.[20] In general, alkyl-substituted thiophenes reacted irrespective of their substitution pattern to give the expected products in typically excellent yields (Table 2, **4a**, **4l**–**4n**). Notably, tetrasubstituted thiophenes (**4o**) can be prepared. The completely selective C3-arylation of unsubstituted thiophene is particularly noteworthy (**4p**), and when an excess of **2a** was used, only the 3,4-diarylated product was observed (**4q**). Substrates with aryl and halide substituents (no protodehalogenation observed) in the C2- or C3-position gave the desired products. Strongly electron-donating or electron-withdrawing groups (OMe, $C(O)NMe_2$, CO_2H) were tolerated only in the C3-position. A catalyst loading of 10 mol% Pd/C and a reaction temperature of 80°C were employed with non-alkyl C3-substituted thiophenes to maintain a reaction time of 22 h. Significantly, for the first time, unprotected alcohols, amides, and carboxylic acids (esterified in situ), were tolerated; these results extend the scope of our reaction beyond that of all other methods.[12]

Table 1: Substrate scope: variation of iodonium salts.



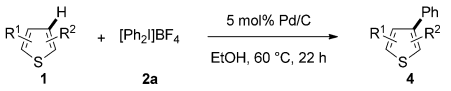
General conditions: **1a** (0.300 mmol), **3b–j** (1.4 equiv), Pd/C (5 mol%), EtOH (1.5 mL), 22 h. Yields refer to isolated products. C3/C2 ratios determined by GC–MS analysis of the crude reaction mixture.
[a] **1a**/**3j** = 3:1; **4j** and **4k** are products of the same reaction.

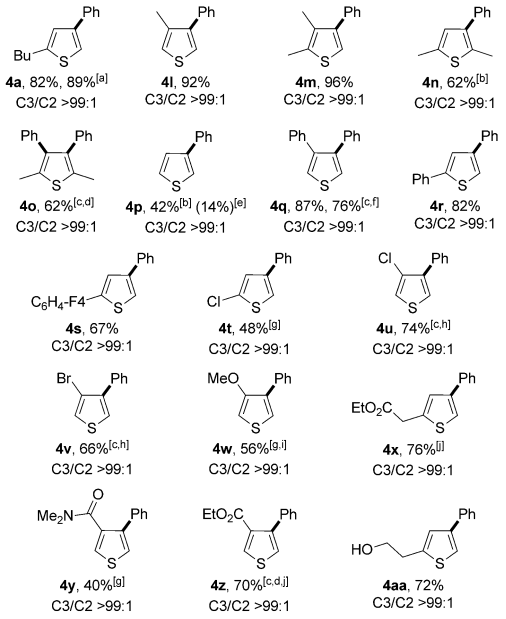
Our method also proved applicable to benzo[*b*]thiophenes, giving the desired products with complete selectivity (Table 3).[20] The reactivity of other heterocycles was also explored. The reactions of benzofuran and 1*H*-indole with **2a** gave the corresponding C2-arylated products in 77% and 40% yield, respectively (**6d** and **6e**). 2-*n*-Butylfuran was also found to be a suitable substrate when an electron-deficient aryliodonium salt was employed (**6f**). Reaction of 2-*n*-butylfuran with **2a** resulted in decomposition of the starting materials. To demonstrate the scalability of the reaction, the standard reaction was performed on a 5 mmol scale yielding **4a** in an excellent 89% yield. The recycling of Pd/C was also investigated, though a decrease in yield was observed for the second (64%) and third (48%) cycle. We used the surfactant Brij 35 so that reactions in both $EtOH/H_2O$ mixtures and pure H_2O proceeded with synthetically useful yields of up to 61% (see the Supporting Information).

Prior to exploring the substrate scope we applied the optimized reaction conditions in a robustness screen (see the Supporting Information).[17] The screen predicted the tolerance of the reaction to aryl and alkyl halides, aromatic esters, tertiary amides, and primary alcohols. Primary and aromatic amines, as well as alkenes and alkynes that are likely oxidized under the reaction conditions, were predicted to be unsuitable substrates. These results were validated when we explored the scope.

The screen indicated that heterocycles including pyrroles, indoles, furans, and benzofurans are reactive under the standard conditions. As the screen determines the yield of

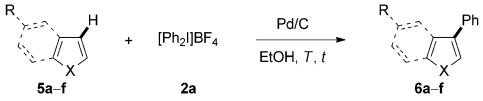
Table 2: Substrate scope: variation of thiophenes.[20,21]

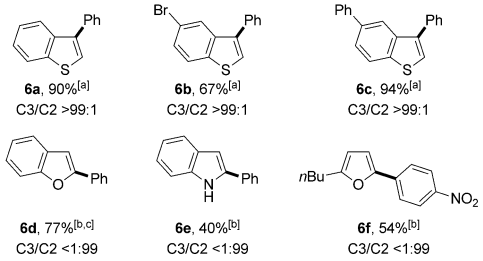




General conditions: **1** (0.300 mmol), **2a** (1.4 equiv), Pd/C (5 mol%), EtOH (1.5 mL), 22 h. Yields refer to isolated products. C3/C2 ratios determined by GC–MS analysis of the crude reaction mixture. [a] 5 mmol scale, reaction time 46 h, yield determined by GC analysis. [b] **1**/**2a** = 3:1. [c] 3 equiv of **2a**. [d] Reaction time 46 h. [e] 3,4-diarylated product. [f] Thiophene as starting material. [g] 10 mol% Pd/C, 80°C. [h] Yield determined by NMR analysis. [i] MeOH as solvent. [j] Carboxylic acid as starting material; esterification with solvent under reaction conditions.

Table 3: Substrate scope: reaction of different heterocycles.[20]

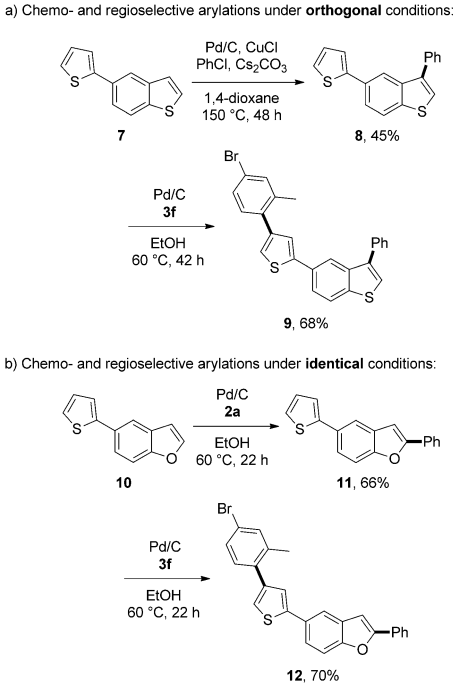




[a] General conditions: benzo[*b*]thiophene **5a–c** (0.300 mmol), **2a** (2.2 equiv), Pd/C (10 mol%), EtOH (1.5 mL), 80°C, 36 h. Yields refer to isolated products. C3/C2 ratios determined by GC–MS analysis of the crude reaction mixture. [b] General conditions: heterocycle **5d–f** (0.300 mmol), **2** or **3** (1.4 equiv), Pd/C (5 mol%), EtOH (1.5 mL), 60°C, 22 h. Yields refer to isolated products. C3/C2 ratios determined by GC–MS analysis of the crude reaction mixture. [c] 2,3-Diphenylbenzofuran was also isolated in 10% yield.

product, and the additive and starting material remaining after the reaction, it provided significant data relating to the relative rate of reaction of different substrates under the reaction conditions. Consequently, for the first time, we have utilized data generated by the robustness screen to design substrates that should demonstrate high chemoselectivity in sequential reactions under our standard conditions. This shows the utility of the screen beyond predicting simple functional group tolerance and stability.

To demonstrate the potential application of our transformation to more complex molecules we prepared substrates **7** and **10**. Both comprise two heteroaromatic systems that are pervasive in biologically active molecules and reactive under our conditions. We present the consecutive arylation of the two heterocycles within one molecule in a highly chemo- and regioselective manner. In the first example we demonstrate the complete orthogonality of our previous reaction conditions with those reported herein (Scheme 2a). The reaction of **7** using our previously reported catalyst system of Pd/C and CuCl[14] enables the completely chemo- and regioselective arylation of the benzo[*b*]thiophene moiety with phenyl chloride to give **8**.[20] Subsequent arylation of the thiophene moiety of **8** with Pd/C and aryliodonium salt **3f** again proceeded with complete selectivity to give **9**. Intermediate **8** proved to be sparingly soluble in EtOH, and consequently a longer reaction time and increased amounts of **3f** were necessary for good conversion.[20] With knowledge of the relative rates of the reactions of benzofuran and thiophene obtained from the robustness screen, we demonstrated that it is possible to undertake sequential arylations of first the benzofuran of **10** to give **11**, and then the thiophene moiety of **11** under identical reaction conditions to give **12** (Sche-



Scheme 2. Consecutive chemo- and regioselective arylation of different fused heterocycles.

me 2b).[20] These two examples highlight the powerful selectivity of our method. Further functionalizations of the aryl bromide to give more sophisticated molecules can be envisaged.

The active catalyst for our reaction is of significant interest as Pd/C is widely reported to act as a reservoir for Pd species in solution,[16] though our previous studies using this reagent system surprisingly indicated a heterogeneous catalyst.[14] Consequently we have conducted a number of established studies[15] which strongly suggest the heterogeneous nature of our active catalyst species (see the Supporting Information):

1) Three-phase tests: Substrate **1a** was replaced by polymer-bound thiophene and no reactivity was observed, suggesting that active solution-phase Pd species are not formed. To exclude a synergistic effect of thiophenes and iodonium salts in the leaching of Pd from the support, we ran a second test in which the polymer-bound thiophene was added to the standard reaction containing non-polymer-bound **1a**. Despite reaction in solution, which indicates the formation of the active catalytic species, no reaction on the polymer-bound thiophene was observed. During our studies we demonstrated that the reaction could be mediated by $Pd(OAc)_2$, though with less efficiency than Pd/C. Consequently, we sought to employ this source of formally soluble Pd species in a three-phase test. The lack of product formation strongly suggests that $Pd(OAc)_2$ acts as a source of heterogeneous Pd species that mediate the reaction.
2) Hg-poisoning test: The introduction of mercury to the reaction mixture immediately inhibited the reaction, suggesting a heterogeneous catalytic species.
3) Hot-filtration test: The hot reaction mixture was filtered to remove all heterogenous components, and the reaction progress was subsequently monitored. No further reaction was observed, suggesting all active catalytic species were removed by filtration.

It is highly intriguing that these experiments suggest an active heterogeneous catalytic species, especially considering that the strongly oxidizing reaction conditions are likely to generate soluble Pd species.[16]

To evaluate possible reaction pathways, preliminary mechanistic experiments were undertaken (see the Supporting Information). 2-*n*-Butyl-4-deuterothiophene (**13**) and 2-*n*-butyl-5-deuterothiophene (**14**) showed negligible kinetic isotope effects (KIEs) in both kinetic (1.2, 1.5, respectively) and competition experiments (both 1.0), suggesting that cleavage of the C–H bond at either the C2- or C3-position is not rate determining.[22] To explore a potential radical pathway, the reaction was performed with an equimolar amount of 1,4-benzoquinone or 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) as radical scavengers. Both reactions proceeded with no notable decrease in yield, suggesting that a radical mechanism is unlikely. Considering these results, and that exclusive transfer of the less hindered aryl group in reactions with unsymmetrical iodonium salts **3b–j** is observed (Table 1), we tentatively propose an electrophilic reaction pathway which includes activation of the iodonium salt through oxidative addition of Pd to the C–I bond . Activation of the iodonium salt in this manner has extensive precedent.[23]

In summary, we have presented a mild, operationally simple, and completely C3-selective arylation of thiophenes and benzo[*b*]thiophenes. The reaction demonstrates high functional group tolerance, and represents a significant step forward for this challenging transformation. Other notable features are the absence of base and ligands, the employment of a widely available and comparatively cheap Pd source, the use of EtOH as the solvent, and the insensitivity of the reaction to the presence of air and water. The required iodonium salts limit the application of the method, though the use of the TRIP group as a cheap nontransferable surrogate is important. For the first time, relative reaction rate data generated from a robustness screen has been exploited to develop the highly chemoselective reaction of multifunctional substrates. Excellent orthogonality with existing methods is also demonstrated. Although strongly oxidizing conditions are in operation, experimental data suggests a heterogeneous active catalyst.

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[1] For most recent reviews on C–H activation, see: a) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; b) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; c) T. Newhouse, P. S. Baran, *Angew. Chem.* **2011**, *123*, 3422; *Angew. Chem. Int. Ed.* **2011**, *50*, 3362; d) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; e) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885; f) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; g) M. C. White, *Science* **2012**, *335*, 807; h) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; i) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem.* **2012**, *124*, 9092; *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; j) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936; k) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; l) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369; m) L. Ackermann, *Acc. Chem. Res.* **2013**, DOI: 10.1021/ar3002798.

[2] a) K. C. Nicolaou, C. R. H. Hale, C. Nilewski, H. A. Ioannidou, *Chem. Soc. Rev.* **2012**, *41*, 5185; b) G. P. McGlacken, L. M. Bateman, *Chem. Soc. Rev.* **2009**, *38*, 2447.

[3] *Bioactive Heterocyclic Compound Classes: Pharmaceuticals and Agrochemicals* (Eds.: C. Lamberth, J. Dinges), Wiley-VCH, New York, **2012**.

[4] For examples of organic materials containing (benzo[*b*]-)thiophenes, see: a) A. R. Murphy, J. M. J. Fréchet, *Chem. Rev.* **2007**, *107*, 1066; b) A. Seed, *Chem. Soc. Rev.* **2007**, *36*, 2046; c) I. McCulloch, M. Heeney, M. L. Chabinyc, D. DeLongchamp, R. J. Kline, M. Cölle, W. Duffy, D. Fischer, D. Gundlach, B. Hamadani, R. Hamilton, L. Richter, A. Salleo, M. Shkunov, D. Sparrowe, S. Tierney, W. Zhang, *Adv. Mater.* **2009**, *21*, 1091; d) Y. Liu, Y. Liu, X. Zhan, *Macromol. Chem. Phys.* **2011**, *212*, 428; e) C. Wang, H. Dong, W. Hu, Y. Liu, D. Zhu, *Chem. Rev.* **2012**, *112*, 2208.

[5] a) *Fine Chemicals through Heterogeneous Catalysis* (Eds.: R. A. Sheldon, H. van Bekkum), Wiley-VCH, Weinheim, **2001**; b) *Asymmetric Catalysis on Industrial Scale* (Eds.: H. U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2004**.

[6] A. Thayer, *Chem. Eng. News* **2005**, *83*, 55.

[7] For selected reviews on the application of nanocatalysts, see: a) D. Astruc, F. Lu, J. R. Aranzaes, *Angew. Chem.* **2005**, *117*, 8062; *Angew. Chem. Int. Ed.* **2005**, *44*, 7852; b) A.-H. Lu, E. L. Salabas, F. Schüth, *Angew. Chem.* **2007**, *119*, 1242; *Angew. Chem. Int. Ed.* **2007**, *46*, 1222; c) S. Shylesh, V. Schünemann, W. R. Thiel, *Angew. Chem.* **2010**, *122*, 3504; *Angew. Chem. Int. Ed.* **2010**, *49*, 3428; d) A. Schätz, O. Reiser, W. J. Stark, *Chem. Eur. J.* **2010**, *16*, 8950; e) K. V. S. Ranganath, F. Glorius, *Catal. Sci. Technol.* **2011**, *1*, 13; f) V. Polshettiwar, R. Luque, A. Fihri, H. Zhu, M. Bouhrara, J.-M. Basset, *Chem. Rev.* **2011**, *111*, 3036; g) E. Gross, J. H.-C. Liu, F. D. Toste, G. A. Somorjai, *Nat. Chem.* **2012**, *4*, 947.

[8] For reviews on asymmetric heterogeneous catalysis, see: a) M. Heitbaum, F. Glorius, I. Escher, *Angew. Chem.* **2006**, *118*, 4850; *Angew. Chem. Int. Ed.* **2006**, *45*, 4732; b) T. Mallat, E. Orglmeister, A. Baiker, *Chem. Rev.* **2007**, *107*, 4863; c) A. F. Trindade, P. M. P. Gois, C. A. M. Afonso, *Chem. Rev.* **2009**, *109*, 418; d) Z. Wang, G. Chen, K. L. Ding, *Chem. Rev.* **2009**, *109*, 322; e) E. Gross, J. H. Liu, S. Alayoglu, M. A. Marcus, S. C. Fakra, F. D. Toste, G. A. Somorjai, *J. Am. Chem. Soc.* **2013**, *135*, 3881.

[9] L. Yin, J. Liebscher, *Chem. Rev.* **2007**, *107*, 133.

[10] For examples of (benzo[*b*]-)thiophenes in biologically active molecules, see: a) T. Y. Zhang, J. O'Toole, C. S. Proctor, *Sulfur Rep.* **1999**, *22*, 1; b) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893; c) C. Bobbio, C. Corsi, S. A. M. Jean-Mart, S. V. Wendeborn, WO 2012/010567A1, **2012**; d) A. Kamboj, H. Randhawa, *J. Pharm. Res.* **2012**, *5*, 2676; e) http://cbc.arizona.edu/njardarson/group/sites/default/files/Sulfur%20Containing%20Pharmaceuticals2.pdf (07.10.2013).

[11] For selected reviews on direct arylation of (hetero)aromatics, see: a) L. Joucla, L. Djakovitch, *Adv. Synth. Catal.* **2009**, *351*, 673; b) F. Bellina, R. Rossi, *Tetrahedron* **2009**, *65*, 10269; c) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200.

[12] a) K. Ueda, S. Yanagisawa, J. Yamaguchi, K. Itami, *Angew. Chem.* **2010**, *122*, 9130; *Angew. Chem. Int. Ed.* **2010**, *49*, 8946; b) S. Kirchberg, S. Tani, K. Ueda, J. Yamaguchi, A. Studer, K. Itami, *Angew. Chem.* **2011**, *123*, 2435; *Angew. Chem. Int. Ed.* **2011**, *50*, 2387; c) K. Yamaguchi, J. Yamaguchi, A. Studer, K. Itami, *Chem. Sci.* **2012**, *3*, 2165; d) A. F. P. Biajoli, E. T. da Penha, C. R. D. Correia, *RSC Adv.* **2012**, *2*, 11930; e) K. Funaki, T. Sato, S. Oi, *Org. Lett.* **2012**, *14*, 6186; f) I. Schnapperelle, T. Bach, *ChemCatChem* **2014**, *6*, 392; g) K. Yamaguchi, H. Kondo, J. Yamaguchi, K. Itami, *Chem. Sci.* **2013**, *4*, 3753; h) K. Yuan, H. Doucet, *Chem. Sci.* **2013**, *5*, 3495.

[13] For recent reports, see: a) S. Yanagisawa, K. Ueda, H. Sekizawa, K. Itami, *J. Am. Chem. Soc.* **2009**, *131*, 14622; b) J. Roger, A. L. Gottumukkala, H. Doucet, *ChemCatChem* **2010**, *2*, 20; c) I. Schnapperelle, S. Breitenlechner, T. Bach, *Org. Lett.* **2011**, *13*, 3640; d) K. Si Larbi, H. Y. Fu, N. Laidaoui, K. Beydoun, A. Miloudi, D. El Abed, S. Djabbar, H. Doucet, *ChemCatChem* **2012**, *4*, 815.

[14] a) D.-T. D. Tang, K. D. Collins, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 7450; See also: b) K. Yuan, H. Doucet, *ChemCatChem* **2013**, *5*, 3495.

[15] For application and limitations, see: a) J. A. Widegren, R. G. Finke, *J. Mol. Catal. A* **2003**, *198*, 317; b) R. H. Crabtree, *Chem. Rev.* **2012**, *112*, 1536, and references therein. Although they are not completely definitive, these experiments represent the gold standard methods to determine whether an active catalyst is of homo- or heterogeneous nature.

[16] a) L. Huang, P. W. Wong, J. Tan, T. P. Ang, Z. Wang, *J. Phys. Chem. C* **2009**, *113*, 10120; b) M. Lamblin, L. Nasser-Hardy, J.-C. Hierso, E. Fouquet, F.-X. Felpin, *Adv. Synth. Catal.* **2010**, *352*, 33.

[17] a) K. D. Collins, F. Glorius, *Nat. Chem.* **2013**, *5*, 597; b) K. D. Collins, F. Glorius, *Tetrahedron* **2013**, *69*, 7817. For first applications, see: c) N. Kuhl, N. Schröder, F. Glorius, *Org. Lett.* **2013**, *15*, 3860; d) H. Wang, B. Beiring, D.-G. Yu, K. D. Collins, F. Glorius, *Angew. Chem.* **2013**, *125*, 12657; *Angew. Chem. Int. Ed.* **2013**, *52*, 12430; e) H. G. Lee, P. J. Milner, S. L. Buchwald, *Org. Lett.* **2013**, *15*, 5602.

[18] In H_2O, agglomeration of Pd/C was observed.

[19] Different counterions were introduced as a consequence of the synthesis routes employed.

[20] For reactions with incomplete conversion the respective hetero-aromatic compound remained after the reaction.

[21] For compound **4w** MeOH was used as the solvent due to transetherification under reaction conditions.

[22] E. M. Simmons, J. F. Hartwig, *Angew. Chem.* **2012**, *124*, 3120; *Angew. Chem. Int. Ed.* **2012**, *51*, 3066.

[23] a) M. Ochiai, T. Shu, T. Nagaoka, Y. Kitagawa, *J. Org. Chem.* **1997**, *62*, 2130; b) C. H. Oh, J. S. Kim, H. H. Jung, *J. Org. Chem.* **1999**, *64*, 1338; c) B. Xiao, Y. Fu, J. Xu, T.-J. Gong, J.-J. Dai, J. Yi, L. Liu, *J. Am. Chem. Soc.* **2009**, *131*, 468; d) B. Wang, J. W. Graskemper, L. Qin, S. G. DiMagno, *Angew. Chem.* **2010**, *122*, 4173; *Angew. Chem. Int. Ed.* **2010**, *49*, 4079; e) C.-L. Ciana, R. J. Phipps, J. R. Brandt, F.-M. Meyer, M. J. Gaunt, *Angew. Chem.* **2011**, *123*, 478; *Angew. Chem. Int. Ed.* **2011**, *50*, 458; f) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 4260; g) T. B. Petersen, R. Khan, B. Olofsson, *Org. Lett.* **2011**, *13*, 3462; h) S. R. Neufeldt, M. S. Sanford, *Adv. Synth. Catal.* **2012**, *354*, 3517.

