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Room Temperature Direct β-Arylation of Thiophenes and Benzo[*b*]thiophenes and Kinetic Evidence for a Heck-type Pathway

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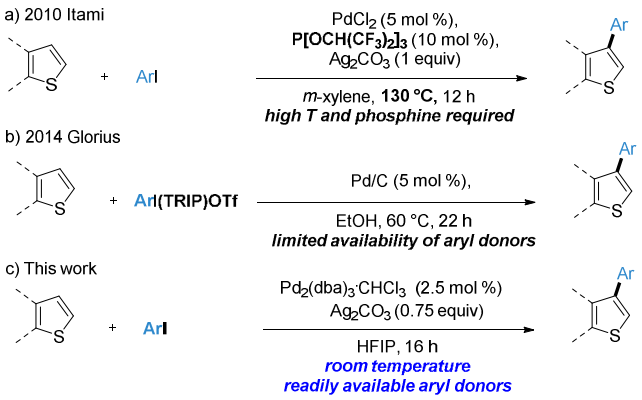
Supporting Information Placeholder

ABSTRACT: The first example of a regioselective β-arylation of benzo[*b*]thiophenes and thiophenes at room temperature with aryl iodides as coupling partners is reported. This methodology stands out for its operational simplicity: no prefunctionalization of either starting material is required, the reaction is insensitive to air and moisture, and proceeds at room temperature. The mild conditions afford wide functional group tolerance, often with complete regioselectivity and high yields, resulting in a highly efficient catalytic system. Initial mechanistic studies, including ^{13}C and ^{2}H KIEs, suggest that this process occurs via a concerted carbopalladation across the thiophene double bond, followed by a base assisted anti-elimination.

1. INTRODUCTION

Heterobiaryl scaffolds are common motifs in pharmaceuticals, natural products and organic electronic components. Methods for their efficient synthesis are of significant interest.[1] In recent years, direct C-H arylation of heteroarenes has emerged as an efficient approach to the synthesis of these heterobiaryls.[2] Major challenges in developing these methods involve the control of the regioselectivity of arylation[2,3] and achieving mild reaction conditions,[4] with most current methodologies requiring elevated temperatures, strong oxidants, and acids or bases. The direct arylation of thiophenes and benzo[*b*]thiophenes, which are widely present in biologically active molecules and organic electronic materials,[5] is a rapidly growing area of research. Over the last few years several methodologies allowing the direct arylation of thiophenes at the most acidic α position have been developed.[6] Direct β-arylation of thiophenes has proven a more challenging task with only a handful of examples in the absence of directing groups reported.[7,8] In 2010, Itami and co-workers reported a methodology for the selective β-arylation of thiophenes with iodoarenes (Scheme 1a), where a $PdCl_2/P[OCH(CF_3)_2]_3$ catalytic system was found essential for achieving high regioselectivity.[7a] This report was followed by examples using aryl boronic acids,[7b] aryltrimethyl silanes,[7c] aryl chlorides[7d] and benzensulfonyl chlorides[7e] as aryl donors. However, all of these methods require high temperatures (80–150 °C), or require TFA as solvent, thus limiting functional group compatibility. Furthermore, some of these methods provide low yields with electron-deficient aryl donors, require a large excess of this coupling partner, and/or provide moderate C-3/C-2 regioselectivity. Recently, Glorius and co-workers reported a milder method that uses diaryliodine(III) salts (Scheme 1b, TRIP = 2,4,6-triisopropylphenyl) as coupling partners, allowing the selective β-arylation to proceed at 60 °C.[7f] However, a mild methodology employing more readily available coupling partners would be of significant utility. Herein we report the first example of a methodology capable of performing β-arylation of thiophenes and benzo[*b*]thiophenes at room temperature. This method employs iodoarenes as coupling partners and proceeds in most cases with >99:1 regioselectivity. In addition, kinetic evidence implicating a Heck-type mechanistic pathway has been obtained for the first time.

Scheme 1. Approaches to β-Regioselective Arylation of Thiophenes and Benzo[*b*]thiophenes



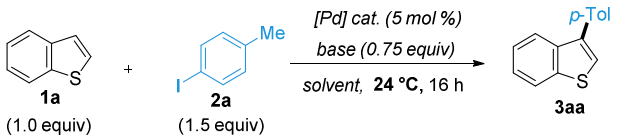
2. RESULTS AND DISCUSSION

2.1. Reaction Optimization and Scope

Research conducted in our group has previously highlighted the role of silver(I) carboxylate salts in enhancing the reactivity of a Pd/ArI system and enabling the direct arylation of indoles to proceed at room temperature.[9] We used this catalytic

system as our starting point for the investigation into the arylation of unsubstituted benzo[*b*]thiophene **1a** with 4-iodotoluene **2a** (Table 1, entry 1). Under these conditions, C-3 arylated adduct **3aa** was obtained as the major regioisomer, albeit with a yield of only 7%. Contrary to our experience with indoles, a screening of silver(I) carboxylates did not provide any improvement on the yield (entries 1-3 and Table S1 in the Supporting Information). A solvent screening revealed that replacing H_2O with the more acidic 1,1,1-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropan-2-ol (HFIP)[10] led to a marked increase in reactivity (Table 1, entries 4-6), with the latter solvent, in combination with Ag_2CO_3 as the base, affording **3aa** in 72% yield (Table 1, entry 6). However, significant amounts of the homocoupling product of benzo[*b*]thiophene **1a** were also observed. This undesired product could be formed upon reaction of **1a** with $Pd(OAc)_2$ while presumably forming the catalytically active Pd^0 species. A change of precatalyst to $Pd_2(dba)_3 \cdot CHCl_3$ was effective at preventing homocoupling of **1a**, affording the desired C-3 arylated compound in 92% yield (Table 1, entry 7) with >99:1 C3:C2 regioselectivity without making use of any additional ligand. Control experiments further outlined the need for both Pd catalyst and Ag_2CO_3 (entries 8-9).[11]

Table 1. Optimization of Reaction Conditions[a]

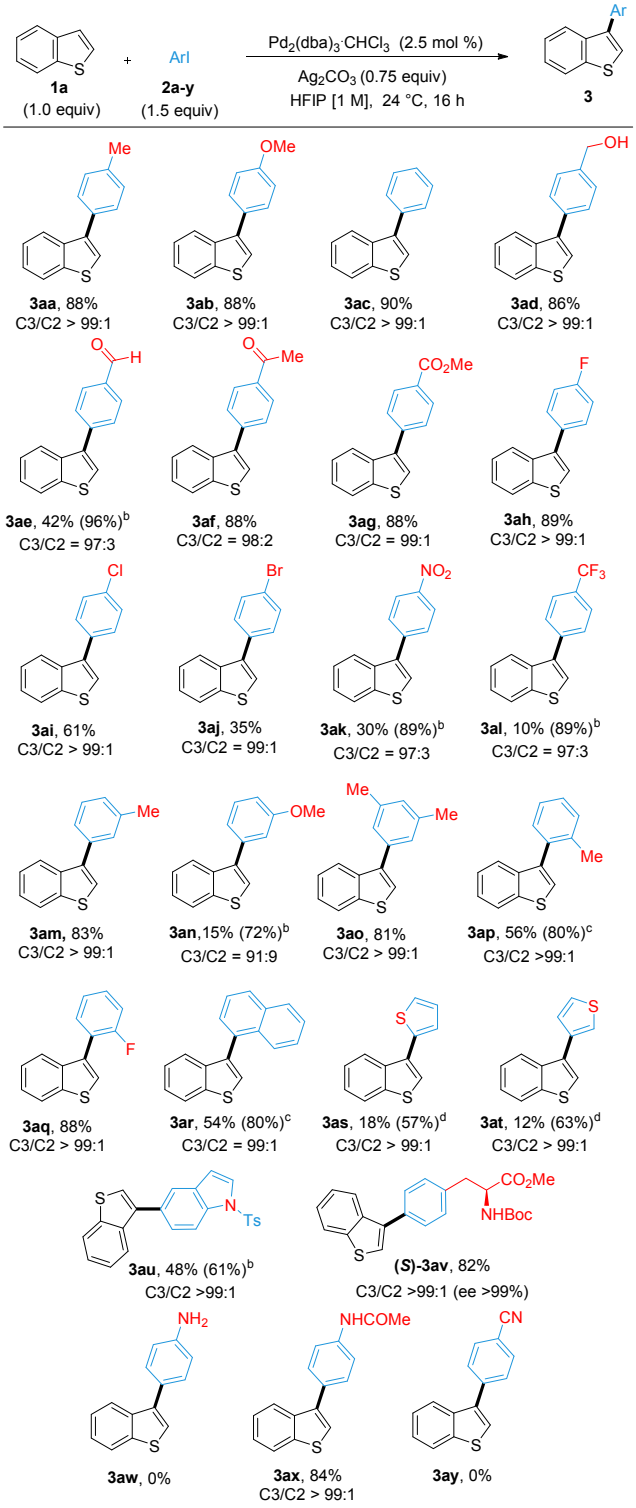


Entry	Base	[Pd] cat.	Solvent	Yield (%)[a]
1	*c*-$C_6H_{11}CO_2Ag$	$Pd(OAc)_2$	H_2O	7
2	*p*-NO_2-$C_6H_4CO_2Ag$	$Pd(OAc)_2$	H_2O	14
3	1-Ad-CO_2Ag	$Pd(OAc)_2$	H_2O	11
4	*c*-$C_6H_{11}CO_2Ag$	$Pd(OAc)_2$	TFE	15
5	Ag_2CO_3	$Pd(OAc)_2$	TFE	34
6	Ag_2CO_3	$Pd(OAc)_2$	HFIP	72
7	Ag_2CO_3	$Pd_2(dba)_3 \cdot CHCl_3$	HFIP	92
8	K_2CO_3	$Pd_2(dba)_3 \cdot CHCl_3$	HFIP	-
9	Ag_2CO_3	-	HFIP	-

[a] Yields were calculated by ^{1}H-NMR using an internal standard.

Having optimized the process, we then investigated the scope of the reaction (Table 2). Iodobenzene and iodoarenes bearing para electron-donating groups reacted efficiently (**3aa-3ad**). Electron-withdrawing para-substituents also provided **3ae-3aj** in good to excellent yields. Remarkably, this method is completely compatible with benzylic alcohol (**3ad**) and aldehyde (**3ae**) functionalities, both sensitive to oxidation under harsher conditions, and with ketones (**3af**), which often require protection. Chloro- and bromo- substitution was also tolerated (**3ai** and **3aj**), albeit with somewhat reduced yields despite no obvious side products being observed.[12] Highly electron-withdrawing para-substituents, such as nitro and trifluoromethyl (**3ak** and **3al**), resulted in low reactivity. Gratifyingly, adding 5 mol % tris(4-methoxyphenyl)phosphine to the catalytic system and raising the reaction temperature to 50 °C restored high yields for these less reactive iodoarenes, while maintaining high C3/C2 regioselectivity. Both of these observations contrast with Itami's methodology,[7a] where 1) electron-rich iodoarenes display lower reactivity and 2) addition of an electron-rich phosphine ligand switches the regioselectivity to C2. The diverse features shown by our system suggest

Table 2. Direct C-H Arylation of Benzo[*b*]thiophene 1a with Iodoarenes 2a-y[a]



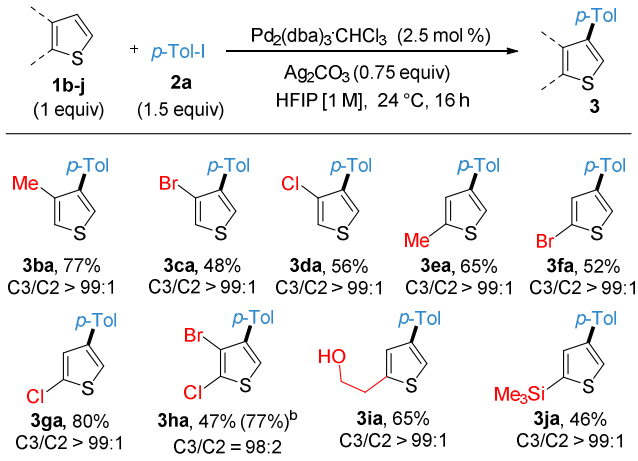
[a] Reactions carried out on a scale of 0.75 mmol of **1a**. Yields given are isolated. C3/C2 ratios were determined by GC-MS analysis of the crude reaction mixture. [b] Performed at 50 °C and in the presence of 5 mol % of P(*p*-$C_6H_4OMe)_3$. [c] Performed at 50 °C. [d] Performed with 3 equiv of **1a**, 1

equiv of ArI, 0.5 equiv of Ag_2CO_3, and 5 mol % of P(*p*-$C_6H_4OMe)_3$ at 50 °C.

different mechanistic pathways (*vide infra*), and understanding these could lead to the development of new regioselective methodologies. meta-Substituted iodoarenes also showed good reactivity under our reaction conditions (**3am-3ao**). ortho-Substitution is tolerated, although a slightly higher temperature is required to achieve high yields (**3ap-3ar**). Heteroiodoarenes, such as 1- and 2-iodothiophene and *N*-tosyl-5-iodoindole could also be successfully employed as coupling partners (**3as-3au**). Furthermore, we examined the applicability of our methodology towards the synthesis of non-natural amino acids, which could be further incorporated into peptides leading to isosteric molecules with potential biological properties.[13,14] When we tested the coupling between benzo[*b*]thiophene (**1a**) and (*S*)-*N*-Boc-4-iodo-phenylalanine (**2v**) the corresponding product was obtained in high yield. Furthermore, we were pleased to discover that no racemization took place with **3av** obtained in >99% enantiomeric excess.[15] 4-Iodoaniline was not compatible with the reaction conditions (**3aw**), likely due to inactivation of the catalyst by coordination.[16] Protecting the amine functional group to a less strongly coordinating acetamide gave the desired product in 84% yield (**3ax**). Similarly, no reactivity was observed with 4-iodobenzonitrile (**3ay**).

The process can be also applied to the regioselective C-4 arylation of C-2 and C-3 substituted thiophenes (Table 3). In most examples, nearly complete regioselectivity was observed, with >99:1 of C-4 arylation versus all other regioisomers. Moderately electron-withdrawing and -donating substituents were found compatible with the reaction, but lower yields or decomposition were observed with stronger electron-donating or -withdrawing substituents. The reaction conditions tolerate free alcohols (**3ia**) and a $SiMe_3$ substituent (**3ja**).

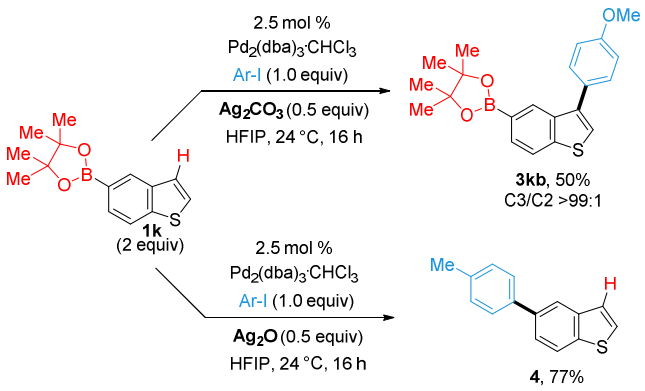
Table 3. Direct C-H Arylation of Thiophenes 1b-1j with Iodoarene 2a[a]



[a] Reactions carried out on a scale of 0.75 mmol of **1**. Yields given are isolated. Regioselectivity was determined by GC-MS of the crude reaction mixture. [b] Reaction performed at 50 °C.

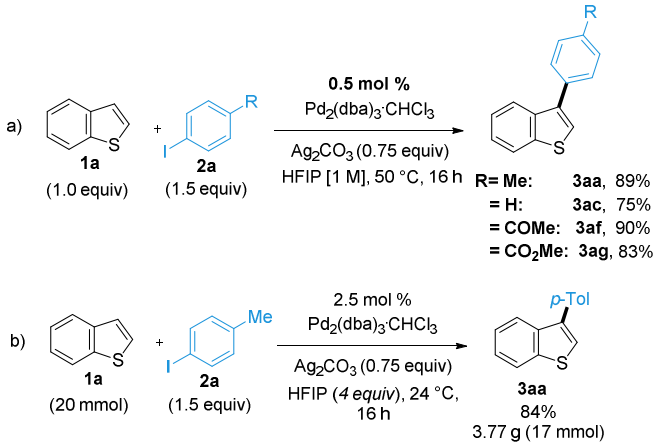
In order to further explore the compatibility of our room temperature conditions with sensitive functional groups, we tested a substrate containing a boronic ester substitution (Scheme 2). Remarkably, good yield, chemo- and regioselectivity towards the C-3 arylation product **3kb** was obtained under our standard conditions. Conversely, a simple change of base from Ag_2CO_3 to Ag_2O effected a complete switch in chemoselectivity, providing the Suzuki coupling adduct **4** in 77% yield.

Scheme 2. Chemoselectivity Towards C-H Activation in the Presence of Boronic Esters



The reaction set up is highly practical as the reagents can be weighed under air and the reaction is neither air nor moisture sensitive. We also explored whether further tailoring of the reaction would accommodate particular practical needs between concentration, catalyst loading and temperature of reaction. For example, in the reaction of **1a** with **2a** the catalyst loading could be reduced to only 0.5 mol %, affording **3aa** in 89% when reacting at 50 °C instead of room temperature (Scheme 3a). These conditions were applied to a selection of substrates which gave the corresponding arylated compounds in good to high yields (75%-90%). To our knowledge this is the lowest palladium catalyst loading reported for a C-3 arylation of (benzo)thiophenes. Furthermore, the amount of HFIP solvent can be significantly reduced to only 4 equiv, while maintaining the same high yields of **3aa** (86%, see Table S6 in the Supporting Information). Finally, the reaction is amenable to scaling up: the arylation of **1a** with **2a** using only 4 equiv of HFIP could be directly run at a 20 mmol of **1a** scale without any modifications, to afford 3.77 g (84%) of pure isolated adduct **3aa** (Scheme 3b).

Scheme 3. Reactions at Low Catalyst Loading and 20 mmol Scale Up.

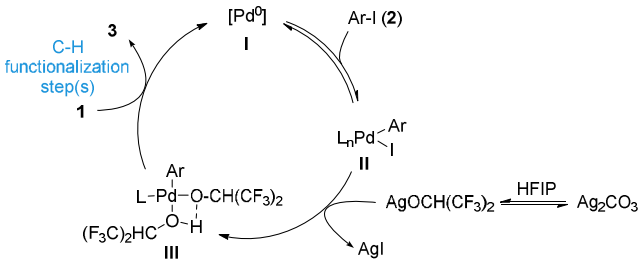


2.2. Mechanistic Considerations

2.2.1. Mechanistic Outline

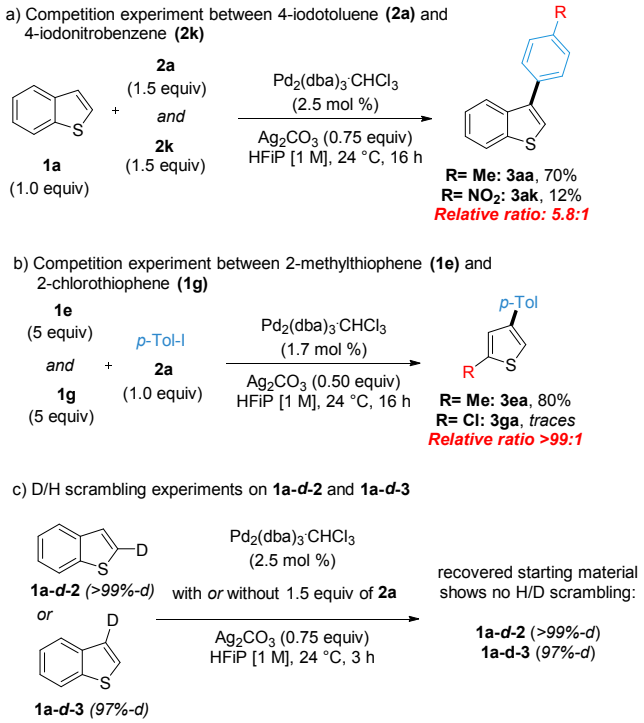
A plausible mechanistic pathway involving a $Pd^{0/II}$ catalytic cycle is outlined in Scheme 4. The cycle would start by oxidative addition of Ar-I **2** to Pd(0) (**I**) to form PdArI species **II**. HFIP is a mildly acidic solvent (pKa 9.3) which would react with Ag_2CO_3 in an acid-base equilibrium forming $AgOCH(CF_3)_2$, which can then transmetallate with **II** to form Pd alcoxyde **III**. These species may be further stabilized by H-bonding with another molecule of HFIP.[17] Pd-species **III** would then undergo the C-H arylation step or steps (*vide infra*) on the benzo[*b*]thiophene substrate **1**.

Scheme 4. Plausible Reaction Mechanism.



A competition experiment between 4-iodotoluene (**2a**) and 4-iodonitrobenzene (**2k**) was carried out, resulting in a relative reactivity of 5.8:1 (Scheme 5a).[18] If the oxidative addition was irreversible, coupling with the electron-poor iodoarene (albeit in low yield) would be the expected major product.[19] Instead, the result obtained suggests that oxidative addition is reversible and occurs before the rate limiting step, consistently with our mechanistic proposal in Scheme 4. Alternatively, a $Pd^{II/IV}$ pathway has also been proposed to explain a C–H arylation mediated by $Pd(OAc)_2$ and AgOAc displaying a similar reactivity trend.[20]

Scheme 5. Competition and Deuteration Experiments

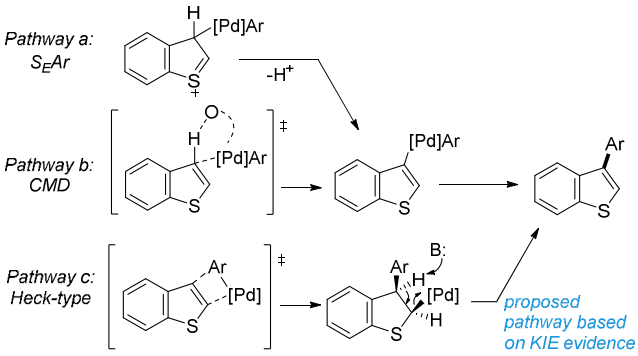


2.2.2. Studies on the C-H Functionalization Pathway

The C-H functionalization steps could proceed through: *a*) an electrophilic aromatic substitution (S_EAr) pathway; *b*) a concerted metalation-deprotonation (CMD); or *c*) a Heck-type process (Scheme 6).[2b,f] Pathway *a* involves an electrophilic attack by Ar-Pd^{II} at C-3 of benzo[*b*]thiophene followed by deprotonation and reductive elimination. This pathway is inconsistent with the regioselectivity of arylation observed for thiophenes, given that these are most nucleophilic in the α, not β position. For pathway *b*, an unusual C-H activation at the less acidic position needs to be invoked in order to explain the β-regioselectivity of the process. Pathway *c*, on the other hand, involves a carbo-palladation followed by an *anti*-β-hydride elimination or a more likely base assisted E2 elimination. Calculations by Fu have shown that a base assisted E2-type elimination may indeed be a viable process in certain cases.[21a] Itami and Studer have also reported calculations that favor the hypothesis of a carbo-palladation pathway on the C-3 arylation of thiophenes with arylboronic acids.[21b]

With the aim of obtaining experimental evidence supporting one of these mechanistic pathways for the C-C bond forming step, we set out a competition experiment between 2-methyl- (**1e**) and 2-chloro-thiophene (**1g**) showing that the more electron-rich **1e** reacts exclusively (>99:1, Scheme 5b). This suggests that the C-H activation step does not proceed via a concerted metalation-deprotonation (pathway *b*), where the electron-poor **1g** should react faster, or that the C-H activation step is not rate-determining.[22] Furthermore, a CMD process would be expected to occur at the most acidic α-position in the thiophene, rather than the observed β-arylation.[23] To test whether a reversible CMD process might be in operation in our system, H/D scrambling experiments were attempted by subjecting benzo[*b*]thiophene **1a**-*d*-3 and **1a**-*d*-2 to the reaction conditions in the presence and in the absence of ArI: in all cases recovered starting material **1** showed no D/H scrambling (Scheme 5c), suggesting that a non-rate determining reversible CMD process is also unlikely.

Scheme 6. Possible Mechanistic Pathways for the C-C Bond Formation Step



With the aim of obtaining supporting evidence for a Heck-type pathway we set to determine the $^{13}C/^{12}C$ and D/H KIEs for the process. Kinetic isotope effect (KIE) measurements have proven to be invaluable tools to assess mechanistic hypotheses in a wide variety of transition metal-catalyzed reactions.[24] Within the C-H functionalization arena, ^2H KIEs are often measured and can provide information on the nature of the C-H activation event. On the other hand, despite their potential for providing new and complementary information, ^{13}C

KIEs are rarely determined. This is likely due to the difficulty in preparing ^{13}C isotopically labeled substrates. Over the last two decades, Singleton and co-workers have demonstrated that ^{13}C natural abundance in substrates can be used to determine intermolecular competitive ^{13}C KIEs by quantitative ^{13}C NMR.[25,26] During the course of a reaction, the starting material will become more enriched in ^{13}C at those positions with a positive $^{13}C/^{12}C$ kinetic isotopic effect; therefore, an increase in the ratio of $^{13}C/^{12}C$ between the recovered starting material and the original starting material will result. This ratio (R/R_0) is directly related to the fractional conversion of reagents (F) and the KIEs by eq. 1 and 2.[25,27]

$$R/R_0 = (1-F)^{(1/KIE)-1} \quad (1)$$

$$KIE = \frac{\log(1-F)}{\log[(1-F)R/R_0]} \quad (2)$$

Importantly, the experimental KIEs on benzo[*b*]thiophene will reflect the first irreversible step between the catalyst and benzo[*b*]thiophene, regardless of what is the rate determinig step in the overall process.[28] Therefore, this is an ideal technique to directly probe the nature of the C-H arylation step. Following this procedure, we carried out two independent experiments which allowed the simultaneous measurement of ^{13}C KIE at C-2, C-3, and C-4. These experiments indicated the presence of a significant primary ^{13}C KIE at both C-3 and C-2 positions of benzo[*b*]thiophene: KIEs of 1.042±0.006 and 1.044±0.005 were obtained for C-3 position, while KIEs of 1.015±0.006 and 1.014±0.005 were determined for C-2 (Figure 1a, values in black). These KIEs are consistent with a Heck process (see discussion below).

Due to the low sensitivity of ^{2}H NMR, measuring ^{2}H KIEs using the same analytical technique is generally very time consuming or results in too large an error. In order to overcome this problem we carried out a modification on Singleton's procedure: we partially deuterated the benzo[*b*]thiophene starting material at C-2 and C-3 (*ca* 1% each) and used an internal standard.[29] This allowed for an extremely accurate measurement of the ^{2}H KIEs. Two independent experiments (Figure 1b, black) showed an inverse KIE at C-3 (0.87±0.01, 0.88±0.01) and no KIE at C-2 (1.02±0.01, 1.00±0.01). The presence of an inverse kinetic isotope effect is consistent with a change in the hybridization at the carbon atom during the rate-determining step from sp^2 to sp^3. These values contrast with the positive ^{2}H KIEs measured by Glorius and coworkers (1.5 for C3 and 1.2 for C2) where a heterogeneous catalytic process is proposed.[7f]

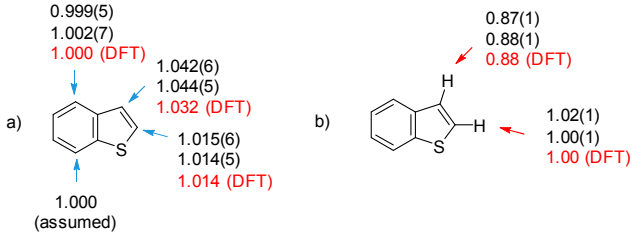


Figure 1. Determination of KIEs. Values in black correspond to the experimentally determined ^{13}C (a) and ^{2}H (b) intermolecular KIEs (two repeats). Figures in brackets correspond to the standard deviation in the last digit as determined from six measurements. Values in red correspond to the DFT predicted KIEs for the proposed olefin insertion step (Scheme 6, pathway c).

Taken together, the ^{13}C and ^{2}H KIE values are consistent with a carbopalladation step onto the C2-C3 double bond of the benzo[*b*]thiophene (Scheme 6c). On the other hand, these values are inconsistent with both the CMD and the electrophilic-metalation pathways (Scheme 6a and b), where a significant ^{13}C KIE should be only be observed at C-3 (not at C-2). Furthermore, a large primary ^{2}H KIE would be expected at C-3 for the CMD process.[30] For a rate limiting carbopalladation step, it would be expected that ^{13}C KIEs would be observed for both C-2 and C-3 carbon atoms along with inverse ^{2}H KIEs at both positions. Here, we observed both ^{13}C KIEs and an inverse KIE at the C-3 proton of benzo[*b*]thiophene. However, no ^{2}H KIE at C-2 was observed. Computational experiments (*vide infra*) revealed that, in this specific case, a ^{2}H KIE would not be expected at C-2.

To further probe the mechanism of the reaction, DFT modelling of a plausible carbopalladation step between benzo[*b*]thiophene and the likely active intermediate Pd[Ph(OCH(CF$_3$)$_2$)(HOCH(CF$_3$)$_2$)] (**III**, Scheme 4) was performed (Figure 2). The calculation in the gas phase showed the initial formation of an exergonic C2,C3-olefin π-complex (ΔG = –4.9 kcal/mol). The subsequent carbopalladation step afforded a free energy barrier of 22.4 kcal/mol, which is consistent with a room temperature process.[31,32] Furthermore, based on these calculated structures ISOEFF was used to predict the ^{13}C and ^{2}H KIEs corresponding to this step.[33,34]The predicted values are strikingly close to the experimentally observed ones (Figure 1a and b, values in red), highlighting the usefulness of combined ^{13}C and ^{2}H KIE studies to distinguish between the proposed mechanistic pathways. Conversely, DFT modelling of a plausible CMD pathway[21a,23] in the gas phase (see Supporting Information) leads to a higher free energy barrier of 24.7 kcal/mol and a predicted H/D KIE of 5.2 at C3.[35]

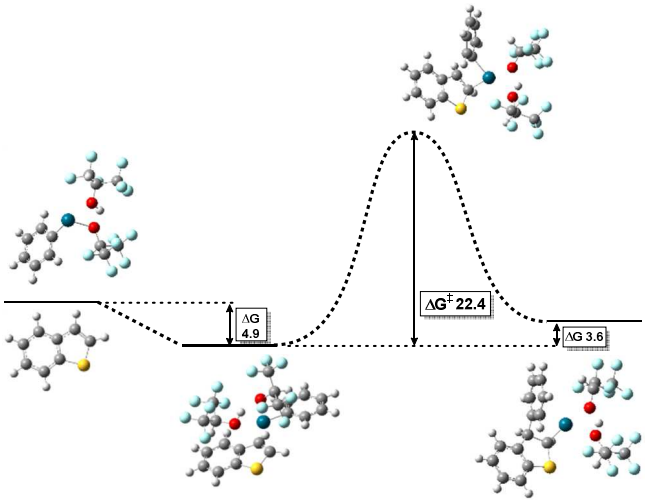


Figure 2. Computational studies for a plausible carbopalladation step of the Heck-type pathway in the gas phase. Structure and energies calculated by DFT (B3LYP/ LanL2Dz for Pd, 6-31G(d) for other atoms). Gibbs free energies (G) in kcal·mol^{-1}.

3. CONCLUSION

In summary, we have described the first catalytic system capable of β-arylation of benzo[*b*]thiophenes and thiophenes at room temperature. This system delivers very high regiose-

lectivities, presents broad functional group tolerance, can be carried out in an open flask and in the absence of phosphine ligands (with the exception of highly electron-poor iodoarenes). Preliminary mechanistic studies have provided the first experimental kinetic evidence supporting a Heck-type reaction pathway in C-H arylations of heteroarenes. Further investigations on the mechanism are ongoing in our laboratories and will be reported in due course.

4. EXPERIMENTAL SECTION

General procedure: $Pd_2(dba)_3{\cdot}CHCl_3$ (19.5 mg, 2.5 mol %), Ag_2CO_3 (155 mg, 0.56 mmol, 0.75 equiv), aryl iodide **2** (1.12 mmol, 1.5 equiv) and (benzo)thiophene **1** (0.75 mmol, 1.0 equiv) were stirred in hexafluoro-2-propanol (0.75 mL) at 24 °C for 16 h. After this time, the resultant mixture was diluted with EtOAc (5 mL) and filtered through a plug of silica. The silica plug was flushed with EtOAc (30 mL) and the filtrate was evaporated to dryness under reduced pressure. Purification via automated column chromatography afforded the desired arylated (benzo)thiophenes **3**.

Representative example: *3-(p-tolyl)benzo[b]thiophene (***3aa***; 20 mmol scale reaction: Scheme 3b*). Benzo[*b*]thiophene **1a** (2.74 g, 20 mmol, 1.0 equiv), 4-iodotoluene **2a** (6.67 g, 30 mmol, 1.5 equiv), Ag_2CO_3 (4.1 g, 15 mmol, 0.75 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (518 mg, 0.5 mmol, 2.5 mol %) were stirred in 8.4 mL of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) at 24 °C for 16 h. After this time, the resultant mixture was diluted with EtOAc (15 mL) and filtered through a plug of silica. The silica plug was flushed with EtOAc (50 mL) and the filtrate was evaporated to dryness under reduced pressure. Product **3aa** was then isolated by column chromatography (hexane) as a colorless oil in 84% yield (3.77 g, 17 mmol). $\mathbf{R_f}$ (hexane): 0.48; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ (ppm) 8.02-7.97 (m, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.47-7.44 (m, 2H), 7.42 (s, 1H), 7.36 (d, J = 8.0 Hz, 2H), 2.50 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ (ppm) 140.9, 138.2, 138.2, 137.4, 133.3, 129.6, 128.7, 124.5, 124.4, 123.1, 123.1, 123.0, 21.2; **HRMS**: calcd for $C_{15}H_{12}S$, 225.0660 ($M+H^+$); found, 225.0730.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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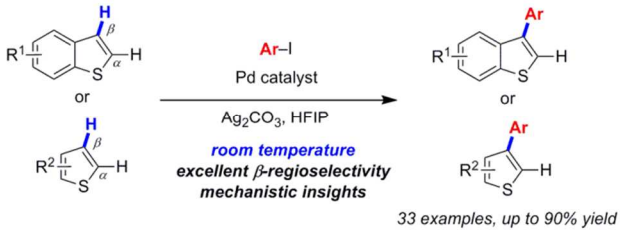
H
β
α
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or
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Ar–I
Pd catalyst
Ag2CO3, HFIP
room temperature
excellent β-regioselectivity
mechanistic insights
Ar
33 examples, up to 90% yield