Ag(I)–C–H Activation Enables Near-Room-Temperature Direct α-Arylation of Benzo[b]thiophenes

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Supporting Information

ABSTRACT: The first example of near-room-temperature α-arylation of benzo[b]thiophenes is reported. The discovery rests on the observation of a switch in α-/β-regioselectivity at different loadings of Pd2(dba)3·CHCl3 in the coupling between benzo[b]thiophene and 4-iodotoluene. We show that this unprecedented regioselectivity switch is driven by a Ag(I)-mediated C–H activation at the α-C–H position, which becomes the dominant mode of reactivity at low concentrations of Pd. Competition experiments, kinetic studies, KIE, and D/H scrambling experiments have been carried out supporting this mechanism.

1. INTRODUCTION
The widespread presence of arylated benzo[b]thiophenes and thiophenes in biological compounds, pharmaceuticals, and material sciences makes these scaffolds attractive targets for synthetic methodologies (Scheme 1). While conventional cross-couplings are still widely used, direct C–H arylation has emerged over the last two decades as a powerful approach that eliminates the need for prefunctionalization, thus leading to shorter synthetic routes. The direct C2-arylation of benzo[b]thiophene was first demonstrated by Ohta in 1990, and over the past decade several further examples have been reported using Pd, Cu, or Ir as catalysts. However, all the methodologies reported require the use of elevated temperatures (100–150 °C), which limits their functional group compatibility. Furthermore, high catalyst loadings are typically required with a few exceptions. The development of mild conditions for the C2-arylation of benzo[b]thiophenes is therefore a highly desirable synthetic target, which would allow a significant expansion of the functional group tolerance and applicability of the methodology. Herein we report studies leading to the discovery of a novel Ag(I)–C–H activation-based methodology that overcomes the aforementioned limitations and affords the first near-room-temperature C2-arylation of benzo[b]thiophenes. This new methodology offers wide functional group tolerance, operates at near room temperature, and requires only 0.4 mol % Pd-catalyst loading.

Our investigation began with an unexpected observation during the development of our recently reported C3-selective C–H arylation of benzo[b]thiophenes (1a) with aryl iodides (2a, Scheme 2). During optimization of the Pd-catalyst loading of this process we observed that the ratio C2/C3 showed a marked dependence on the concentration of Pd catalyst used in the experiment (Scheme 2). Indeed, while 1:>99 selectivity was obtained when using 2.5 mol % Pd2dba3·CHCl3 this ratio was eroded when decreasing the catalyst loading and eventually reversed at loadings as low as 0.05 mol %. To the best of our knowledge this is the first time a change in the regioselectivity of a C–H functionalization process has been shown to originate in a change in catalyst concentration. Driven by the potential mechanistic implications and the possibility to develop unprecedentedly mild conditions for C2-arylation, we proceeded to investigate the origin of this regioselectivity switch. Given that changes in catalyst loading of this process we observed that the ratio C2/C3 showed a marked dependence on the concentration of Pd catalyst used in the experiment (Scheme 2). Indeed, while 1:>99 selectivity was obtained when using 2.5 mol % Pd2dba3·CHCl3 this ratio was eroded when decreasing the catalyst loading and eventually reversed at loadings as low as 0.05 mol %. To the best of our knowledge this is the first time a change in the regioselectivity of a C–H functionalization process has been shown to originate in a change in catalyst concentration.

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concentration should not affect the ratios of the different in
cycle catalytic species in a typical catalytic cycle (Scheme 3, Path A), we hypothesized that this switch could originate in
the existence of an alternative pathway involving a cocatalyzed
process.

Through a combination of stoichiometric and kinetic
studies, we have recently demonstrated that Ag(I) salts are
able to carry out C−H activation of electron-deficient arenes. This allows for a C−H arylation process that occurs with very
low catalyst loadings of Pd (Scheme 4a). Concurrently,
Sanford and co-workers established the same prominent role
of Ag(I) salts on the C−H activation of both polyfluoroarenes
and thiophenes at 100 °C (Scheme 4b). Additionally, the
investigation of a selective allylation of aryl C−H bonds
catalyzed by Pd and mediated by AgOPiv led Hartwig and co-
workers to the isolation of the fi
rst phosphine-ligated arylsilver(I) complex, which was shown to react with an
allyl−Pd complex (Scheme 4c).

On the basis of these precedents, we proposed that a Ag(I)-mediated C2-selective C−H activation process could be
responsible for the observed regioselectivity switch on the
arylation of benzo[b]thiophene, via competitive Path B
(Scheme 3). If the Ag(I)-mediated C−H activation is the
rate-determining step of the process leading to C2-arylation,
then a lowering of Pd catalyst loading could lead to the
observed switch by disproportionately slowing down the C3-
arylation process.

2. RESULTS AND DISCUSSION

2.1. Reaction Optimization and Scope. Inspired by this
mechanistic hypothesis, we decided to probe whether a low-
temperature Ag(I)-mediated C2-selective C−H activation would be feasible. We studied the D/H scrambling of 2-dbenzo[h]thiophene (d1-1a) in the presence of different silver
additives in hexafluoro-2-propanol (HFIP) (Table 1). Gratifyingly, 10% D/H scrambling was observed in the presence of
Ag2O (Table 1, entry 3), increasing to 34% when NaOAc was
added as an additive.

Table 1. D/H Scrambling Studies to Test for Ag(I)−C−H Activation

| silver additive | ratio d1-1a:1a |
|-----------------|----------------|
| Ag2CO3          | >99:1          |
| AgOAc           | >99:1          |
| Ag2O            | 99:10          |
| Ag2O + NaOAc    | 66:34          |

*aRatio determined by quantitative 1H NMR. *bNaOAc (0.5 equiv).

Encouraged by these results we then explored the development of a low-temperature C2-arylation protocol based on
the observed Ag(I)−C−H activation. Remarkably, reaction of
1a with 2a proceeded at near room temperature in 45% yield
carrying out in the presence of 0.75 equiv of Ag2O and 0.5
equiv of NaOAc and only 0.2 mol % Pd2dba3 · CHCl3 (Table 2,
entry 2). A switch of catalyst to 0.4 mol % Pd(OAc)2 further
increased the yield of product 3aa to 54% (Table 2, entry 3).
Inverting the stoichiometry of the two coupling partners
increased the yield to 73% (Table 2, entry 4), consistently with
the proposed rate-limiting C−H activation. Finally, increasing
the amount of Ag2O to 1 equiv afforded 3aa in 83% yield
(Table 2, entry 5).

With the optimized conditions in hand, we proceeded to
investigate the scope of the reaction (Table 3). Iodoarenes
bearing either electron-donating (2a−2d) or electron-with-
drawing groups (2e−2o) in para-position reacted in good to

Table 2. Optimization of Reaction Conditions

| entry | [Pd] | additive | 3aa (%) | 4aa (%) |
|-------|------|----------|---------|---------|
| 1     | Pd2(dba)3 · CHCl3 | - | 26 | 10 |
| 2     | Pd2(dba)3 · CHCl3 | NaOAc | 45 | 1 |
| 3     | Pd(OAc)2 | NaOAc | 54 | 6 |
| 4     | Pd(OAc)2 | NaOAc | 73 | 5 |
| 5     | Pd(OAc)2 | NaOAc | 83 | 3 |

*Yield determined by 1H NMR using 1,3,5-trimethoxybenzene as
internal standard. *a1a (0.25 mmol). *b1a (2 equiv), 2a (1 equiv, 0.25
mmol). *cAg2O (1 equiv).
excellent yields. Remarkably, the mild reaction conditions enabled compatibility with alcohol (3ad), aldehyde (3ae), and ketone (3af) substituents, which often suffer from issues of chemoselectivity when harsher conditions are employed.

Halogen substituents were also tolerated, giving the possibility to further functionalize the products through traditional cross-coupling (3ah−3aj).2 Highly electron-poor iodoarenes showed modest reactivity, although higher yields can be obtained by increasing the temperature to 50 °C (3ak−3al). While 4-iodoaniline was incompatible with the system, probably due to inhibiting coordination of the lone pair of the nitrogen (2m) to the catalyst,17 amide- and cyano-substituted iodoarenes reacted to generate the α-arylated products in yields of 38% (3an) and 63%, respectively (3ao). The methodology also exhibited compatibility with meta (3ap−3aq) and ortho-substituted iodoarenes (3ar−3ax), albeit with lower α/β regioselectivity in the latter case.18 The reactivity of heterocyclic iodoarenes was also investigated: in particular, 2,6-substituted pyridine 2y was found to react to a small extent (3ay), while N-tosyl-5-iodoindole generated the desired α-functionalized pyridine in excellent regioselectivity and 67% yield (3az). To further highlight the mild conditions afforded by this protocol, we tested the coupling between 1a and (S)-N-boc-4-iodophenylalanine 2aa’ obtaining the desired product 3aa’ in 83% yield without observing racemization at the chiral center.19 Finally, the reaction is amenable to scaling up: the arylation of 1a with 2a was performed on a 20 mmol scale, obtaining the desired arylated product in 71% yield and 97:3 (C2/C3) regioselectivity.

The reactivity of substituted benzo[b]thiophenes was then tested with 4-iodotoluene 2a as the coupling partner (Table 4). In general, 4- and 5-substituted benzo[b]thiophenes afforded high yields and regioselectivities of the corresponding α-
arylated products (3ba−3fa). Consistently with the scope of the iodoarene coupling partner, the methodology showed compatibility with alcohols (3ea) among other functional groups. Substituents at C7 were also found to be compatible, albeit with decreased α:β regioselectivity (3ga). Finally, the methodology could be successfully applied to the synthesis of α,β-bisarylated benzo[b]thiophenes (5aa−5ab). Substituents at C7 were also found to be compatible, albeit with decreased α:β regioselectivity (3ga). 3-Substituted benzo[b]thiophenes could be coupled with 4-iodotoluene (2a) generating the α-arylated products in remarkably high yields (5aa and 5ca). Even compound 5cr was obtained in a noteworthy yield of 87% considering that both the bromine atom and the methyl group at the ortho-position of the iodoarene are considerably sterically hindered. Moreover, the methodology could be successfully applied to the synthesis of α,β-bisarylated benzo[b]thiophenes (5aa−5ab). Finally, the same protocol was applied to substituted thiophenes 6a−e obtaining the α-arylated products 7aa−7ea in moderate to good yields and selectivity (Table 4).20,21

### 2.2. MECHANISTIC CONSIDERATIONS

#### 2.2.1. Competition Experiments.

With the aim of gaining information on the mechanism, we carried out a competition experiment between 4-iodotoluene (2a) and 1-iodo-4-nitrobenzene (2k) (Scheme 5a). The higher reactivity of the more electron-rich iodoarene 2a suggests that the oxidative addition is reversible and happening before the rate-limiting step.9,22 A competition experiment between 3-bromobenzo[b]thiophene (4c) and 3-methylbenzo[b]thiophene (4b) was also tested (Scheme 5b). The similar steric size of CH3 and Br (van der Waals radii of 1.85 and 1.97 Å (average), respectively)22,23 allows extracting conclusions on the electronic effects of these substituents. Thus, the much higher reactivity of the more acidic 4c suggests that the C−H activation is rate limiting.24,25 Further evidence was obtained by measuring a H/D KIE of 3.0 for this system, suggesting a rate-limiting C−H activation that is likely proceeding via a concerted metalation deprotonation-like process (Scheme 5c).11,12,26 This is in contrast to the KIE of 1.0 measured for the C3-arylation protocol.9

Under the standard conditions, the same “excess” reaction analyzed with the time-adjusted method reveals that the reaction was not affected by these issues (Scheme 6a). We began the analysis with an investigation on the order of the Pd catalyst. Similarly to our previously reported discovery of Ag(I)-mediated C−H activation,11 an order of zero was obtained for Pd(OAc)2 at loadings between 0.4 and 0.8 mol %. Given that the Pd species are fully soluble in the reaction conditions, these results imply that a process external to the Pd-catalytic cycle is rate limiting (Scheme 6b),11,30 in agreement with our proposal of a Ag-mediated C−H activation of benzo[b]thiophene 1a (Scheme 3, path B). An order of 1 in 1a and an order 0 in iodoarene 2a (Scheme 6c,d) provide further support for this hypothesis. The order of 1 in benzo[b]thiophene together with the order of 0 in Pd catalyst suggests that Pd is not involved in the C−H activation step. An

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**Scheme 5. Competition Experiments**

**Scheme 6.** (a) Same “Excess” Experiment Where VTNA Enables the Determination of the Order in (b) Pd Catalyst, (c) Benzo[b]thiophene 1a, (d) ArI 2a, (e) NaOAc, and (f) Ag2O

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In the graphs, equiv are referred to the amounts of reactants whose orders are determined. For experimental details and unmodified temporal reaction profiles, see Supporting Information. The kinetic run was performed with 4c instead of 1a, to give product 5ca.
order of 0 was obtained for NaOAc, suggesting that this species is not involved in the rate-limiting step (Scheme 6e). We speculate that NaOAc helps the reaction by lowering the rate of insertion of the aryl–Pd complex III to the double bond of benzo[b]thiophene (to IV in Scheme 3) in the path to C3 formation, thus favoring the C2 pathway; * on the other hand, the rate from III to VI remains controlled by the Ag(I)−C−H activation rate-limiting step and therefore unaffected by NaOAc. Demonstrating the involvement of Ag in the C−H activation step of the catalytic process proved to be nontrivial. Two practical issues were faced: (1) the low solubility of Ag2O in HFIP and (2) when lowering the rate of the C2-arylation process, C3-arylation becomes competitive again, producing a mixture of C2 and C3 which is extremely difficult to deconvolute into mechanistic information (Supporting Information, Figure S7). These issues were overcome by changing the substrate to 3-bromobenzo[b]thiophene 4c. This allowed us to measure an order of 0.5 in Ag2O at concentrations between 0.6 and 0.4 M (Scheme 6f). This order in Ag is consistent with an inactive dimeric resting state of the type Ag2Xn, in equilibrium with the active monomeric AgX species. We speculate that AgOCH(CF3)2 could form in situ in low concentrations by acid−base reaction of Ag2O with HFIP and could be responsible for the observed reactivity.32,33 Taken together, these kinetic data point to a mechanism involving a rate-limiting Ag-mediated C−H activation of 1a consistent with our proposal in Scheme 3 (path B).

3. CONCLUSION

In conclusion, we have developed the first protocol for the near-room-temperature α-arylation of benzo[b]thiophenes, which also found application to the α-arylation of substituted thiophenes. The excellent regioselectivity and mild conditions of this methodology are derived from a novel approach that utilizes Ag(I) to carry out C2-selective C−H activation before transmetalation to Pd and subsequent C−C bond formation. The use of very low concentrations of the Pd catalyst is possible due to the key role played by Ag. D/H scrambling, competition experiments, KIE, and kinetic studies support a mechanism involving Ag(I)−C−H activation.

4. EXPERIMENTAL SECTION

**General Procedure.** Pd(OAc)2 (0.4 mol %), silver oxide (1.0 equiv), NaOAc (0.5 equiv), aryl iodide 2 (1.0 equiv), and (substituted)-benzo[b]thiophene 1 or 4, or (substituted)-thiophene 6 (2.0 equiv) were stirred in hexafluoro-2-propanol (1 M) at 30 °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 washed with EtOAc (30 mL), and the filtrate was evaporated to dryness under reduced pressure. Purification via column chromatography afforded the desired arylded (benzo)thiophenes 3, 5, or 7. **Representative Example.** 2-(p-Tolyl)benzo[b]thiophene (3aa; 0.75 mmol Scale Reaction: Table 3). Benzo[b]thiophene 1a (205 mg, 1.5 mmol, 2.0 equiv), 4-iodotoluene 2a (165 mg, 0.75 mmol, 1.0 equiv), Pd(OAc)2 (0.20 mg, 0.4 mol %), silver oxide (174 mg, 0.75 mmol, 1.0 equiv), and NaOAc (31 mg, 0.375 mmol, 0.5 equiv) were stirred in hexafluoro-2-propanol (HFIP) at 30 °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 washed with EtOAc (30 mL), and the filtrate was evaporated to dryness under reduced pressure. Product 3aa was then isolated by column chromatography (hexane) as a white solid in 84% yield (141 g, 0.63 mmol). Rf (hexane): 0.47. 1H NMR (500 MHz, CDCl3): δ (ppm) 7.82 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.51 (s, 1H), 7.37−7.27 (m, 2H), 7.24 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H). 13C NMR (101 MHz, CDCl3): δ (ppm) 144.7, 141.1, 140.0, 138.6, 131.8, 130.0, 126.7, 124.8, 124.4, 123.7, 122.6, 119.2, 21.6. HRMS: calcd for C19H12S (M+)/2, 224.0654; found, 224.0654. Mp: 166−168 °C.

**ASSOCIATED CONTENT**

Supporting Information
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Notes

The authors declare no competing financial interest.

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