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Palladium-Catalyzed Intermolecular Desulfinylative Cross-Coupling of Heteroaromatic Sulfinates

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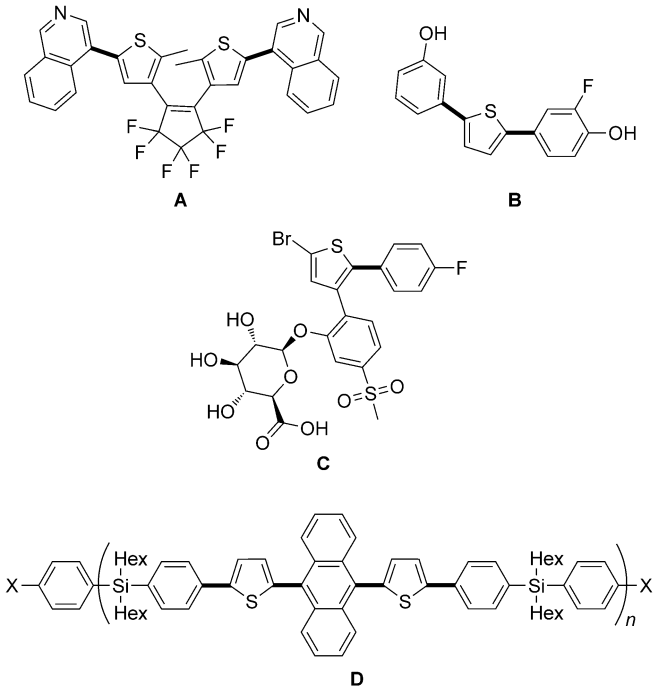
C2-arylated heteroaromatics are an important class of compounds with extensive use in diverse fields such as advanced materials,[1] organic light-emitting transistors (OLETs),[2] solar cells,[3] natural products,[4] and medicinal chemistry[5] (Scheme 1).



Scheme 1. Selected examples that show the importance of C2-arylated thiophenes. **A**) A photochromic DTE system (photoswitch),[1d] **B**) a 17ß-HSD1 inhibitor,[5b] **C**) a natural product,[4] and **D**) a hole-transporting material for multilayered EL devices.[1e]

The development of simple and sustainable chemistry is important as there continues to be an increasing demand on non-renewable resources. Annually the refinement of petroleum generates over 40000 gigagrams (Gg) of SO_2 waste worldwide.[6] Exploiting this untapped resource of SO_2 to access key motifs such as C2-arylated heteroaromatics using sulfinic acids would be environmentally beneficial. These C2-arylated heteroaromatic motifs are most commonly accessed by classical palladium-catalyzed cross-couplings,[7] such as the Suzuki–Miyaura[8] and Stille[9] couplings, amongst others[7b,10] that continue to attract attention.[11] An increasing amount of effort has been devoted to developing more sustainable alternatives, such as C–H-activated[12] and decarboxylative[13] cross-couplings. Direct C–H arylations are facile and do not require pre-functionalization, but can lead to regioselectivity issues when similarly reactive C–H bonds are present.[14] Although a broad range of C2-arylated heteroaromatics can be generated by decarboxylative cross-coupling, the procedure suffers certain challenges. Nonetheless, decarboxylative couplings continue to attract significant attention,[5a,15] leading to the development of elegant advances employing copper and/or silver as co-catalysts.[13c,d] Developing an alternative to carboxylic acids with analogous yet complementary reactivity led us to investigate sulfinic acids. The decarboxylative cross-coupling of 2-heteroaromatic carboxylic acids was postulated to generate a key C2-electrophilic palladation intermediate by a mechanism that is dependent on the π-nucleophilicity of the system.[13e] DFT calculations[16] demonstrate similarities between the HOMO of thiophene-2-sulfinic acid and thiophene-2-carboxylic acid (Figure 1).[17] However, the model suggests that the sulfinic

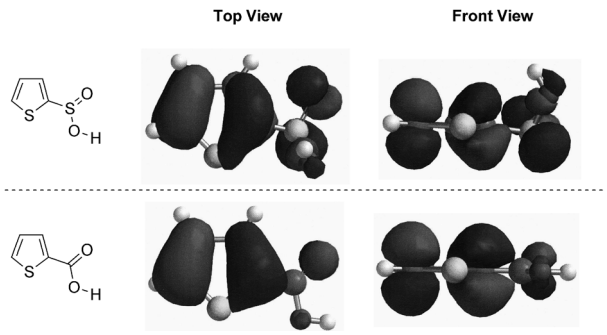


Figure 1. The HOMO of thiophene-2-carboxylic acid and of thiophene-2-sulfinic acid.

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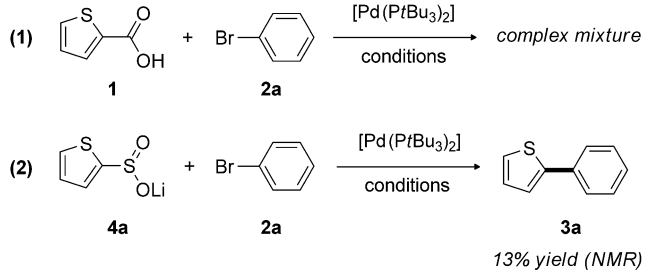
acid slightly bends the thiophene ring, disrupting aromaticity and consequently increasing the π-nucleophilicity. Additionally, the out-of-plane OH group of the sulfinic acid may direct the palladium to the C2-position more efficiently.

Examples of sulfinates that are used as electrophilic coupling partners in palladium-mediated cross-couplings has been demonstrated,[18] although their use as nucleophilic partners is rare.[19] A concern when utilizing sulfinic acids lies in their instability, which is partly due to their intermediate oxidation state.[20] Alternatively, sulfinate salts provide an important advantage owing to their bench stability and non-hygroscopic nature, making them easy to handle starting materials that reluctantly undergo redox chemistry.[20,21]

The hypothesis that heteroaromatic sulfinates can be used as nucleophilic coupling partners in a catalytic process was evaluated by subjecting thiophene-2-sulfinate to optimized decarboxylative cross-coupling conditions (Scheme 2). It

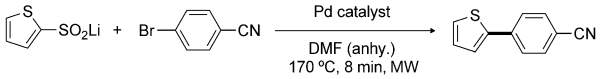


Scheme 2. Desulfinylative versus decarboxylative cross-coupling. Reaction conditions: Heteroaromatic species **1** or **4a** (0.20 mmol, 1.0 equiv), bromobenzene **2a** (0.40 mmol, 2.0 equiv), $[Pd(PtBu_3)_2]$ (0.01 mmol, 0.05 equiv), Cs_2CO_3 (0.20 mmol, 1.0 equiv), nBu_4NBr (0.30 mmol, 1.5 equiv) in anhydrous DMF (2 mL) at 170 °C for 8 min, microwave (MW) irradiation.

was previously established that thiophene-2-carboxylic acid did not yield the desired cross-coupling product under these conditions [Scheme 2, Eq (1)]. Rewardingly, the coupling of lithium thiophene-2-sulfinate [Scheme 2, Eq (2)] provided the corresponding product (13% yield by NMR spectroscopy), thus demonstrating that sulfinates are viable coupling partners in a catalytic palladium-mediated cross-coupling.

Lithium thiophene-2-sulfinate (**4a**) and 4-bromobenzonitrile (**2b**) were selected as coupling partners for the optimization of reaction conditions (Table 1) to facilitate product isolation. The initial conditions (entry 1) utilized $[Pd(PtBu_3)_2]$ catalyst with Cs_2CO_3 as base and nBu_4NBr additive.[13e,22] Rewardingly, an initial 72% yield of isolated product was obtained. Because sulfinate salts were utilized as the nucleophilic aryl source, the Cs_2CO_3 base was omitted, and the product was obtained in comparable yields (69%, entry 2). Subsequent removal of the nBu_4NBr additive yielded an identical result of 69% (entry 3), despite the fact this additive was an essential component for the decarboxylative cross-coupling. The advantage that heteroaromatic sulfinates present as nucleophilic coupling partners lies in the ability

Table 1. Optimization of reaction conditions.[a]



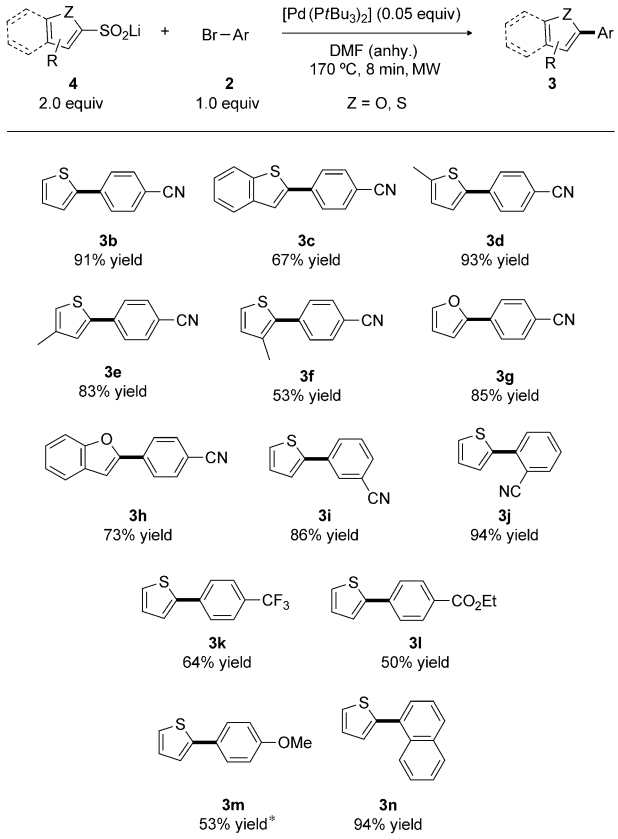
Entry	**4a** [equiv]	**2b** [equiv]	catalyst (Pd, 0.05 equiv)	[%] yield
1	1.0	2.0	$[Pd(PtBu_3)_2]$	72[b]
2	1.0	2.0		69[c]
3	1.0	2.0		69
4	1.0	1.0		59
5	1.5	1.0		84
6	1.5	1.0	$PdCl_2/HP(tBu)_3BF_4$ (1:2)[d]	66
7	1.5	1.0	$[Pd(PPh_3)_4]$	83
8	1.5	1.0	$[Pd(PPh_3)_4]$	87[e]
9	1.5	1.0	$PdCl_2/PPh_3$ (1:4)	70
10	2.0	1.0	$[Pd(PtBu_3)_2]$	91
11	2.0	1.0		93[f]

[a] Reactions were performed on a 0.20 mmol scale. [b] using nBu_4NBr (1.5 equiv), Cs_2CO_3 (1.0 equiv). [c] using nBu_4NBr (1.5 equiv). [d] Using Cs_2CO_3 (0.10 equiv). [e] Using wet DMF. [f] Utilizing 28 month old sulfinate, stored open to air.

to efficiently undergo cross-coupling in a very good yield without the need of additives, base,[13e] or co-catalyst.[23] Sulfinates are known to undergo homo-coupling when treated with a stoichiometric amount of palladium.[19a,24] Suspecting this may be occurring and reducing the yield of the product, excess sulfinate was employed, and the yield increased to 84% with 1.5 equiv (entry 5) and 91% with 2.0 equiv (entry 10). Utilizing the more widely available and less expensive $[Pd(PPh_3)_4]$ catalyst (83%, entry 7) provided similar results to $[Pd(PtBu_3)_2]$ (84%, entry 5). However, the reaction showed tolerance to water when using wet DMF (entry 8).[20] In situ generation of the catalysts from $PdCl_2$ yielded the cross-coupling product employing both $HP(tBu)_3BF_4$ (66%, entry 6) and PPh_3 (70%, entry 9) as the ligand. The bench-stable nature of the sulfinates was demonstrated by coupling a 28 month old sulfinate left open to the air, with little change in yield (93%, entry 11; vs. 91%, entry 10).

The chemoselectivity of the desulfinylative cross-coupling was demonstrated by utilizing various substituted thiophene-2-sulfinates, which generated the corresponding product (Scheme 3, **3e**–**f**) in good to excellent yields. Lithium benzo[*b*]thiophene-2-sulfinate led to substantially reduced yields (67%, **3c**), which is most likely due to the reduced electron richness of the benzo-fused aromatic system. Interestingly, lithium 3-methylthiophene-2-sulfinate led to a markedly reduced yield of 53% (**3f**). This is complementary to the analogous carboxylic acid examples previously observed, where the addition of the C3 methyl group allowed improved, rather than reduced, yields.[13e] The scope of the reaction was extended to other heteroaromatics, and very good yields of 85% (**3g**) and 73% (**3h**) were obtained when employing furan-2-sulfinate and benzo[*b*]furan-2-sulfinate, respectively.

Variation of the electronic and steric nature of the aryl bromides was subsequently evaluated. Altering the nitrile

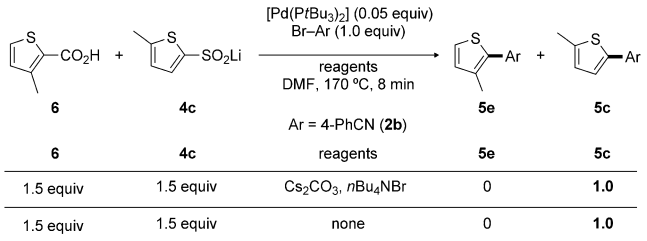


Scheme 3. Reaction scope. Reactions were performed on a 0.20 mmol scale; * using sodium thiophene-2-sulfinate salt.

position has a negligible impact on coupling yield (**3b**, **3i**,**j**). Other electron-withdrawing groups were employed at the *para* positions and provided the product in good yield (**3k** and **3l**). Electron-rich systems, such as 4-bromoanisole, underwent the cross-coupling less efficiently (53%, **3m**) than electron-deficient aryl bromides. Interestingly, electron-neutral 1-bromonaphthalene generated substantially larger amounts of cross-coupling product (94%, **3n**) than inductively activated aryl bromides (64%, **3k**).

It has been shown computationally that it should be easier to extrude SO_2 than CO_2.[25] To compare sulfinates and carboxylic acids as coupling partners with aryl bromides, two substrates known to undergo coupling efficiently were chosen. Towards this aim, 3-methylthiophene-2-carboxylic acid (**6**, Scheme 4) and lithium 5-methylthiophene-2-sulfinate (**4c**) were selected and subjected to optimized decarboxylative cross-coupling conditions. The desulfinylative cross-coupling product (**5c**) was detected exclusively by crude GC-MS and ^{1}H NMR spectroscopy. Importantly, no decarboxylative cross-coupling product (**5e**) was observed when omitting the additive and base, and the desulfinylative product (**5c**) was obtained exclusively. These results demonstrate the potential to selectively perform a desulfinylative cross-coupling in the presence of a carboxylic acid.

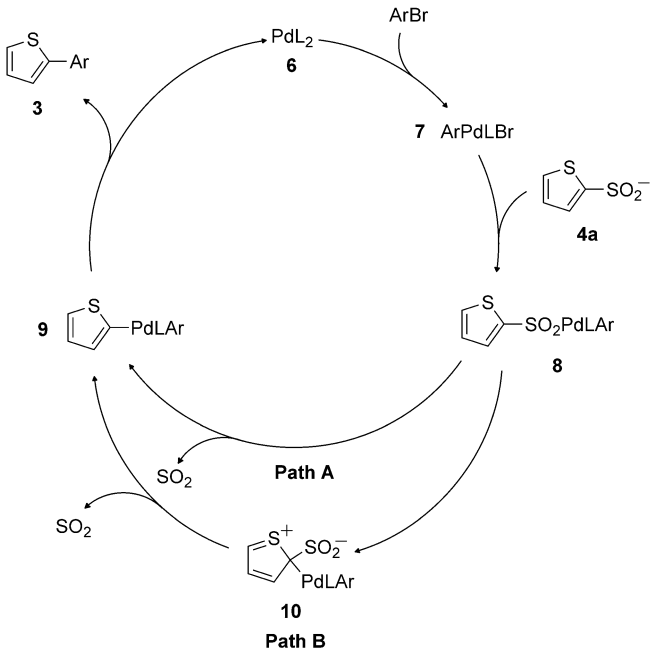
A mechanism (Scheme 5) that is similar to one previously proposed for the arylation of heteroaromatic carboxylic



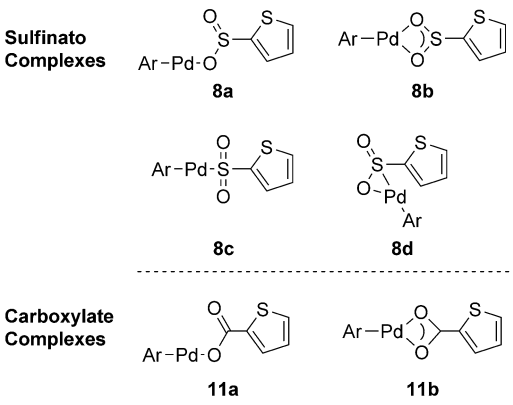
6	4c	reagents	5e	5c
1.5 equiv	1.5 equiv	Cs_2CO_3, nBu_4NBr	0	**1.0**
1.5 equiv	1.5 equiv	none	0	**1.0**

Scheme 4. Competition experiments. Reaction conditions: **6** (1.5 equiv), **4c** (1.5 equiv), **2b** (1.0 equiv), [Pd(P*t*Bu$_3$)$_2$] (0.05 equiv) in DMF at 170 °C for 8 min in μw.

acids is likely.[13e] The nucleophilic sulfinate may, similar to carboxylates, chelate palladium by attack onto the electrophilic palladium(II) intermediate X–PdL–Ar **7**. A direct desulfinylation (Path A) generating the Het(Ar)–Pd–Ar intermediate **9** is speculated to occur. However, bending of the thiophene ring owing to the sulfinic acid functionality implies a more nucleophilic π-system, perhaps facilitating a C2 electrophilic palladation (Path B), generating intermediate **10**. Subsequently, re-aromatization of the heteroaromatic ring **10** to generate intermediate **9** occurs by the extrusion of SO_2. In both cases, the catalytic cycle is completed by reductive elimination of intermediate **9**, generating the aryl-substituted heteroaromatic **3** exclusively at the sulfinate position. Although the sulfinato–palladium complex may bind similarly to that of the carboxylic acid (Scheme 6, **8a** and **8b** vs. **11a** and **11b**), evidence suggests that sulfinates preferentially form sulfinato-*S* (**8c** and **8d**) rather than sulfinato-*O* complexes owing to the softer nature of sulfur.[26] Nonetheless, further mechanistic investigations are required to better understand the mechanism.



Scheme 5. Proposed mechanism.



Scheme 6. Sulfinato versus carboxylate palladium complexes.

In summary, an atom-economical desulfinylative cross-coupling has been developed for the synthesis of aryl-substituted heteroaromatics in very good yields that does not require base, additive, or co-catalysts. Heteroaromatic sulfinate salts have been shown to be efficient nucleophilic coupling partners that are bench-stable and easily accessed with inexpensive materials. This cross-coupling provides new avenues as a simple, efficient, and environmentally benign method to access important materials, such as photoswitches, OLETs, and solar cells. Current efforts are ongoing to gain an understanding of the mechanism for this transformation.

Experimental Section

Heteroaromatic sulfinate **4a**–**g** (0.20–0.40 mmol, 1.0–2.0 equiv), aryl halide **2b**–**h** (0.20–0.40 mmol, 1.0–2.0 equiv), and $[Pd(PtBu_3)_2]$ (0.01 mmol, 0.05 equiv) were added to a 5 mL conical microwave vial equipped with a spin-vein. DMF (2 mL) was then added and the vial was pre-stirred for 30 s at 23 °C, followed by heating at 170 °C for 8 min with stirring. The crude cross-coupling solution was diluted with EtOAc (50 mL). The organic layer was washed with a saturated NaCl aqueous solution (2×50 mL), saturated $NaHCO_3$ aqueous solution (2×50 mL), distilled H_2O (1×50 mL), and saturated NaCl aqueous solution (1×50 mL). The combined aqueous phases were washed with EtOAc (50 mL). The combined organic phases were dried over Na_2SO_4 and after filtration the solvent was evaporated under reduced pressure and the solid residue was purified by flash column chromatography to obtain the pure product **3b**–**n**.

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Keywords: C–C bond formation · cross-coupling · heterocycles · palladium · sustainable chemistry

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