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# Pd(II)-Catalyzed Direct Sulfonylation of Unactivated C(sp$^3$)−H Bonds with Sodium Sulfinates

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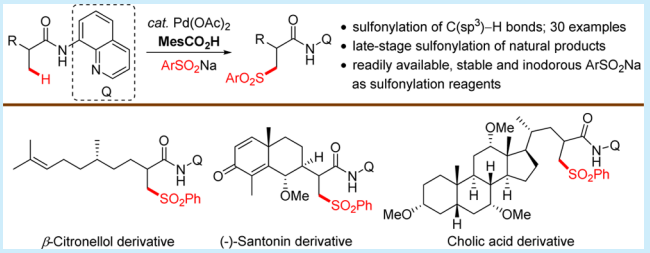
Supporting Information

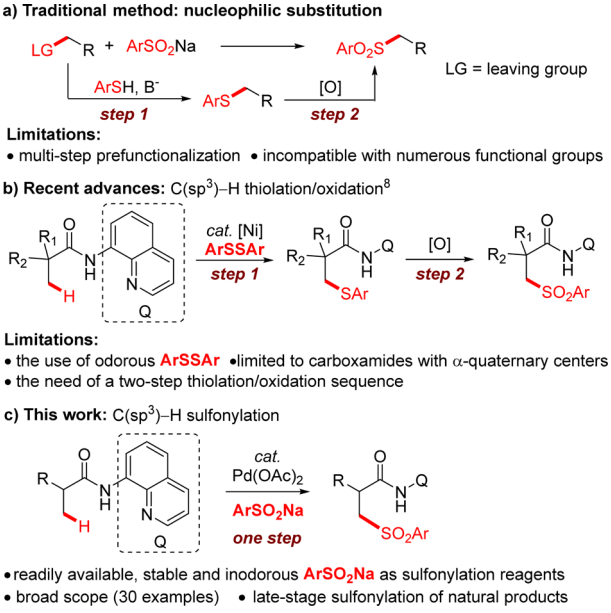
**ABSTRACT:** A Pd(II)-catalyzed sulfonylation of unactivated C(sp$^3$)−H bonds with sodium arylsulfinates using an 8-aminoquinoline auxiliary is described. This reaction demonstrates excellent functional group tolerance with respect to both the caboxamide starting material and the sodium arylsulfinate coupling partner, affording a broad range of aryl alkyl sulfones. Moreover, the late-stage modification of complex molecules was achieved via this sulfonylation protocol.




Aryl alkyl sulfones constitute an important class of compounds that find widespread use as pharmaceuticals and materials.[1] They are also versatile precursors in synthetic chemistry, including in fragment coupling and in Julia olefination.[2] Therefore, considerable efforts have been devoted to the synthesis of sulfones.[3] The most commonly used methods for aryl alkyl sulfone preparation are nucleophilic substitution of carbon electrophiles with sodium sulfinates or thiophenols followed by oxidation (Scheme 1a).[4] These methods have disadvantages in that they require multistep sequences to preinstall a leaving group and that they are incompatible with numerous functional groups. From the viewpoint of step and atom economy, an attractive and complementary alternative would be direct sulfonylation of C(sp$^3$)−H bonds.[5] In 2009, Dong and co-workers reported a pioneering study on Pd(II)-catalyzed *ortho*-C(aryl)−H sulfonylation with arylsulfonyl chlorides directed by a pyridine coordinating group.[6a] Shortly thereafter, mechanistic experiments from the same group showed the first direct evidence of C(sp$^2$)−$SO_2$ reductive elimination from high-valent Pd(IV) intermediates.[6b] Although these seminal studies demonstrated the strategic value of directed sulfonylation through a Pd(II)/Pd(IV) catalytic cycle, reactions of this type have generally been limited to C(sp$^2$)−H bonds with substrates that are unsuitable for further elaboration.[7] This, in turn, has significantly limited synthetic applications toward structurally complex molecules.

Over the past decade, transition-metal-catalyzed C(sp$^3$)−H functionalization has emerged as a powerful means of incorporating diverse functional groups into complex molecules.[7] However, direct sulfonylation of unactivated C(sp$^3$)−H bonds remained elusive, largely due to the difficulty of identifying proper sulfonylation reagents that are sufficiently reactive yet do not interfere with or inhibit the C−H activation process. Recently, our group and others have demonstrated the nickel-catalyzed thiolation of C(sp$^3$)−H bonds to form thioethers[8] and the corresponding sulfones could be synthesized followed by oxidation (Scheme 1b).[8c] These established methods, however, suffer from several limitations, including the use of odorous disulfides; a substrate scope restricted to carboxamides bearing $\alpha$-quaternary centers; and the need for a two-step thiolation/oxidation sequence to afford aryl alkyl sulfones. As part of our continuing efforts on Pd-catalyzed functionalization of unactivated C(sp$^3$)−H bonds,[9] we hypothesized that sodium sulfinates would be effective for this purpose for several reasons: (1) sodium sulfinates are

**Scheme 1. Synthesis of Aryl Alkyl Sulfones**

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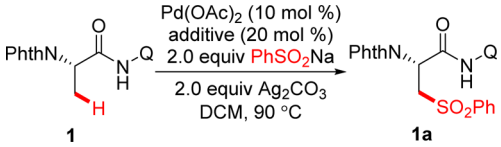
readily accessible and stable to air and moisture; (2) sodium sulfinates have been extensively used as sulfonyl nucleophiles in metal-catalyzed allylic substitution;[10] and (3) they prefer S-coordination to the palladium center over O-coordination because of the soft nature of sulfur. Inspired by the seminal work of Daugulis on Pd-catalyzed functionalization of unactivated C($sp^3$)−H bonds with *N*,*N*-bidentate directing groups,[11,12] we report herein a palladium-catalyzed direct sulfonylation of unactivated C($sp^3$)−H bonds with sodium sulfinates for the synthesis of diverse aryl alkyl sulfones (Scheme 1c). This protocol tolerates a wide range of functional groups and is compatible with the late-stage sulfonylation of complex molecules. Notably, this transformation represents the first example of transition-metal-catalyzed sulfonylation of unactivated C($sp^3$)−H bonds.

To test our hypothesis, we commenced our investigation by examining the reaction of alanine derivative **1** with $PhSO_2Na$ (Table 1). After extensive screening of various solvents and

**Table 1. Optimization of the Reaction Conditions**[a]




1 1a

| entry | additive | yield (%)[b] |
|---|---|---|
| 1 | / | 49 |
| 2 | Boc-Gly-OH | 55 |
| 3 | Boc-Phg-OH | 62 |
| 4 | Boc-Phe-OH | 60 |
| 5 | Boc-Val-OH | 65 |
| 6 | Boc-Tle-OH | 73 |
| 7 | Boc-Ile-OH | 63 |
| 8 | Ac-Ile-OH | 55 |
| 9 | $(BnO)_2PO_2H$ | 44 |
| **10** | **$MesCO_2H$** | **75(72)**[c] |
| 11 | 2,4-Dimethyl-BzOH | 54 |
| 12 | 2,6-Dimethyl-BzOH | 69 |
| 13 | 2-Ph-BzOH | 45 |
| 14 | 1-Ad$CO_2H$ | 35 |
| 15 | TsOH·$H_2O$ | 30 |

[a]Reaction conditions: **1** (0.1 mmol), $PhSO_2Na$ (0.2 mmol), $Pd(OAc)_2$ (10 mol %), additive (20 mol %), and $Ag_2CO_3$ (0.2 mmol) in DCM (1.0 mL) at 90 °C for 24 h under $N_2$. [b]Yield determined by $^1H$ NMR using $CH_2Br_2$ as the internal standard. [c]Isolated yield in parentheses.

oxidants, the desired product **1a** was obtained in 49% yield when the reaction was conducted in DCM at 90 °C using $Ag_2CO_3$ as the oxidant (entry 1; see the Supporting Information for further details). Recently, several elegant studies have shown that simple carboxylic acids,[13] amino acids,[14] and other types of organic acids[15] promote catalytic C($sp^3$)−H bond functionalization when used as additives. Encouraged by these precedents, we then surveyed the effect of a series of organic acids. To our delight, the sulfonylation reaction was facilitated by a variety of mono-*N*-protected α-amino acids (entries 2−8, 55−73% yields). Notably, $MesCO_2H$, a sterically bulky benzoic acid, proved to be the most effective additive, affording the desired product **1a** in 72% isolated yield without any detectable formation of the desulfinative arylation product (entry 10). Other organic acids were less efficient than $MesCO_2H$ (entries 11−15). The structure of sulfonylated product **1a** was confirmed by single-crystal X-ray analysis.[16]

With the optimized conditions in hand, the scope of sodium sulfinates was examined. As shown in Figure 1, a variety of

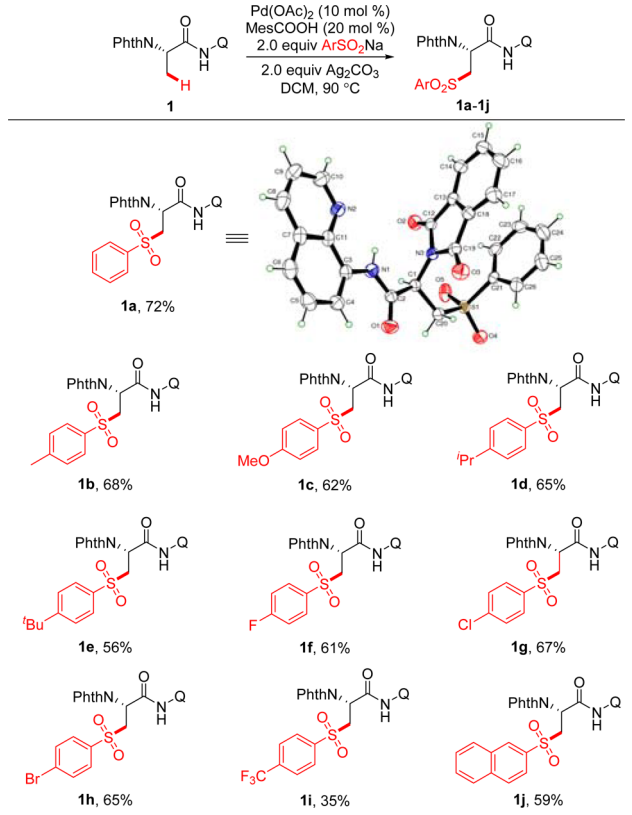



**Figure 1. Scope of sodium sulfinates.** Reaction conditions: **1** (0.2 mmol), $ArSO_2Na$ (0.4 mmol), $Pd(OAc)_2$ (10 mol %), $MesCO_2H$ (20 mol %), and $Ag_2CO_3$ (0.4 mmol) in DCM (2.0 mL) at 90 °C for 24 h. Isolated yields.

sodium arylsulfinates bearing both electron-donating (**1b**−**1e**, R = Me, OMe, $^i$Pr and $^t$Bu) and -withdrawing groups (**1f**−**1i**, R = F, Cl, Br, and $CF_3$) were tolerated and gave the desired sulfonylated products in good yields. It is noteworthy that halides, such as fluoride, chloride, and bromide, survived under the standard reaction conditions, giving the sulfonylated products in moderate to good yields (**1f**−**1h**). This offers the opportunity for further elaboration of these versatile functional groups by traditional cross-coupling. A more sterically hindered sodium sulfinate, sodium 2-naphthylsulfinate, also reacted smoothly with **1** to give the desired product in 59% yield. Unfortunately, no sulfonylation products were obtained when sodium alkyl sulfinates were used as the coupling partners.

The scope of aliphatic carboxamide substrates was next examined (Figure 2). Generally, the reaction preferentially functionalizes β-methyl C($sp^3$)−H bonds over other potential sites. The reaction was sensitive to steric hindrance; substrates with linear aliphatic chains at the α-position gave lower yields (**2a**−**4a**), while substrates bearing sterically bulky groups at the α-position afforded the desired products in higher yields (**7a** and **8a**). Notably, a TIPS-protected terminal alkyne, which could be used to attach biologically important fluorescent tags via click chemistry, was compatible with this protocol (**5a**). Substrates bearing aryl groups (**9a**−**17a**) were more reactive than those with aliphatic chains. A number of functional groups,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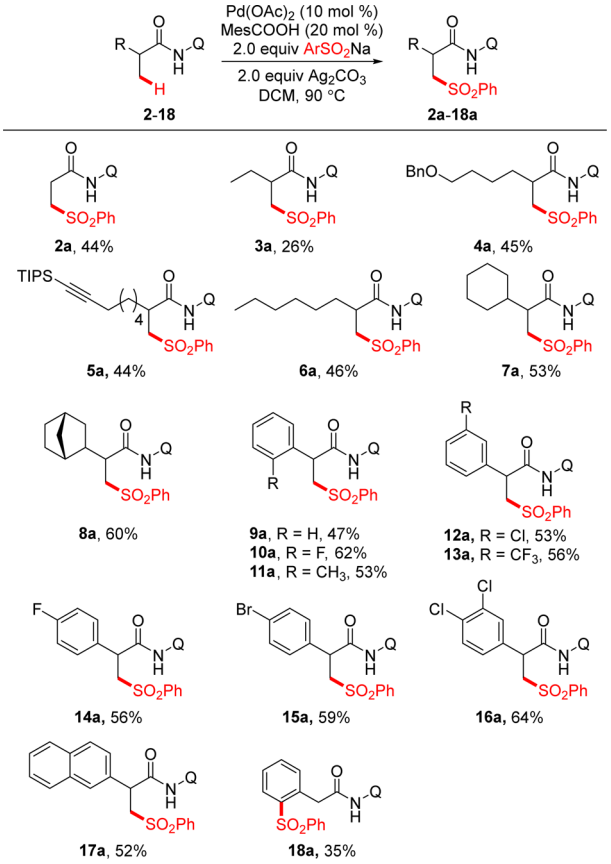
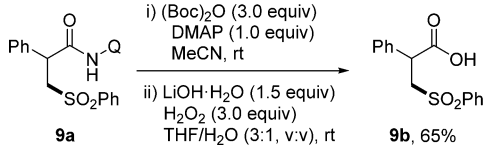



**Figure 2. Scope of aliphatic amides.** Reaction conditions: **2**−**18** (0.2 mmol), $PhSO_2Na$ (0.4 mmol), $Pd(OAc)_2$ (10 mol %), $MesCO_2H$ (20 mol %), and $Ag_2CO_3$ (0.4 mmol) in DCM (2.0 mL) at 90 °C for 24 h. Isolated yields.

such as fluoro, chloro, bromo, and trifluoromethyl substituents, were tolerated on the aromatic ring. In addition, the electron-rich naphthyl group (**17a**) remained intact under the optimized conditions. However, the protocol can only be applied to the sulfonylation of $\beta$-methyl C($sp^3$)−H bonds under the optimized reaction conditions. Notably, the sulfonylation of $\gamma$-C($sp^2$)−H bond was also feasible, albeit in lower yield (**18a**, 35%).

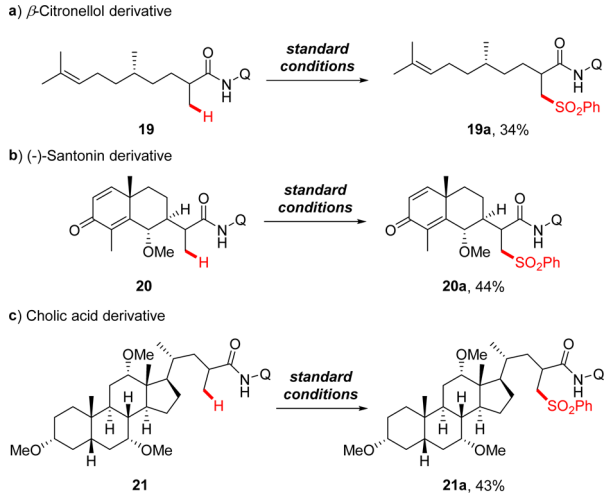
Next, we demonstrated the viability of this C($sp^3$)−H sulfonylation protocol in the late-stage modification of natural products. Carboxamide **19**, a derivative of $\beta$-citronellol, was successfully converted into the corresponding sulfone **19a** in 34% yield (Scheme 2a). Moreover, derivatives of (−)-santonin (**20**) and cholic acid (**21**) were also reacted smoothly with sodium sulfinate to afford the corresponding products **20a** and **21a** in moderate yields (Schemes 2b and 2c).

To further demonstrate the practicality of this protocol, the removal of the quinolinyl auxiliary was conducted as shown in eq 1. The corresponding carboxylic acid **9b** was easily obtained from the sulfonylated product **9a** through a mild, two-step sequence in 65% yield.[17]




(1)

**Scheme 2. Late-Stage C($sp^3$)−H Sulfonylation of Natural Products**




In conclusion, we have reported the first example of Pd(II)-catalyzed sulfonylation of an unactivated C($sp^3$)−H bond with sodium sulfinates. The reaction is characterized by a broad substrate scope, excellent functional group tolerance, and high regioselectivity. This transformation has been successfully applied to the late-stage sulfonylation of complex molecules and thus provides a powerful tool for the synthesis of aryl alkyl sulfones.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details, CIF information, and spectral data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01634.

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### Notes

The authors declare no competing financial interest.

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(16) CCDC 1040925 (**1a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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