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Palladium-Catalyzed Domino Heck/Sulfination: Synthesis of Sulfonylated Hetero- and Carbocyclic Scaffolds Using DABCO–Bis(sulfur dioxide)

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Cite This: *Org. Lett.* 2021, 23, 2797–2801 Read Online

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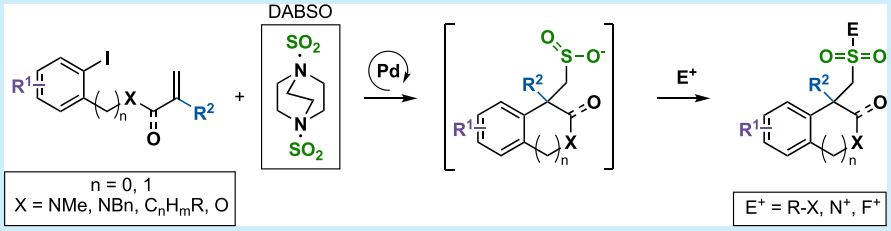


ABSTRACT: The synthesis of a broad variety of hetero- and carbocyclic scaffolds via a Pd-catalyzed domino Heck/SO_2 insertion reaction is reported. This reaction utilizes DABSO, a safe and easy-to-handle alternative to SO_2 gas. The reaction proceeds through a sulfinate intermediate, which can act as a lynchpin for the *in situ* generation of sulfones, sulfonamides, and sulfonyl fluorides. Good yields and scalability are demonstrated.

Small molecules incorporating sulfur-based functional groups represent a class of compounds which are known to possess valuable bioactive properties.[1] Numerous examples of pharmaceuticals and chemical reagents underscore sulfur-containing small molecules as highly important (Figure 1).

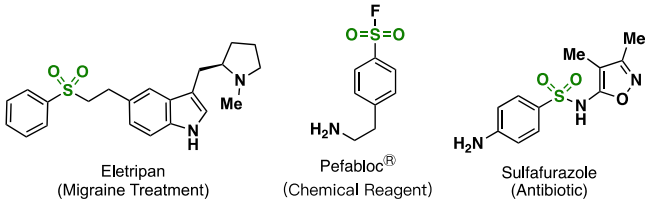


Figure 1. Small-molecule containing drugs and chemical reagents.

However, the synthesis of such compounds often necessitates the use of difficult-to-handle, toxic, and gaseous sulfur dioxide as a reagent, which has hindered progress into the broader applications of SO_2 in new reactions and catalytic processes.[2,3]

In search of alternatives, surrogate molecules such as the charge-transfer complex DABSO,[4a,5a−c] among others,[4b] have proven to be an attractive solution to safely supply SO_2 in syntheses. Methodologies using copper, iron, and iridium photocatalysts have been used in the synthesis of aryl and alkyl sulfones, sulfonamides, and sulfinates employing a variety of SO_2 surrogates.[5d−l] However, many of these reactions are frequently limited to the synthesis of specific heterocycles and sulfur-containing motifs. Recently, the Wu lab reported a sulfonylation reaction employing ultraviolet irradiation and alkene tethered aryl iodides.[6] The use of a radical acceptor appears to restrict this method to generating sulfones. Additionally, only oxindoles and benzofurans could be accessed.[6] In search of a method to construct a broad range of heterocycles that contain valuable sulfur-based functionalities, we turned to domino palladium catalysis.

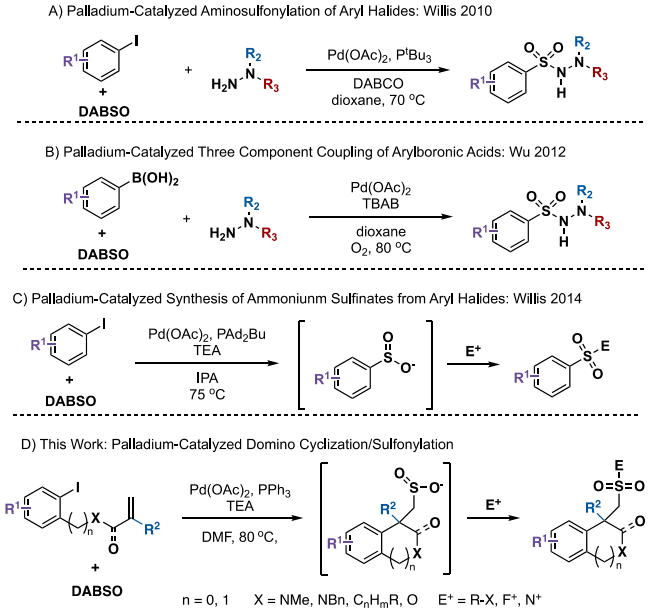
Palladium-catalyzed domino Heck reactions offer an efficient pathway to both construct and functionalize complex ring systems in a single step without isolating intermediates.[7,8] The resulting alkylpalladium(II) species, formed via carbopalladation of a tethered alkene, can be readily intercepted to install new functionality; however no examples incorporating SO_2 have been reported.[8−15]

The Willis group demonstrated the utility of DABSO in the palladium-catalyzed synthesis of *N*-aminosulfonamides in 2010 (Scheme 1, A).[5a] Wu and co-workers later developed a three component, palladium-catalyzed coupling between DABSO, boronic acids, and amines, generating similar products (Scheme 1, B).[5b] More recently, the Willis group described the palladium catalyzed synthesis of ammonium sulfinates from

Received: March 1, 2021
Published: March 15, 2021

https://dx.doi.org/10.1021/acs.orglett.1c00716
Org. Lett. 2021, 23, 2797–2801

Scheme 1. Pd-Catalyzed SO_2-Insertion Strategies[a]



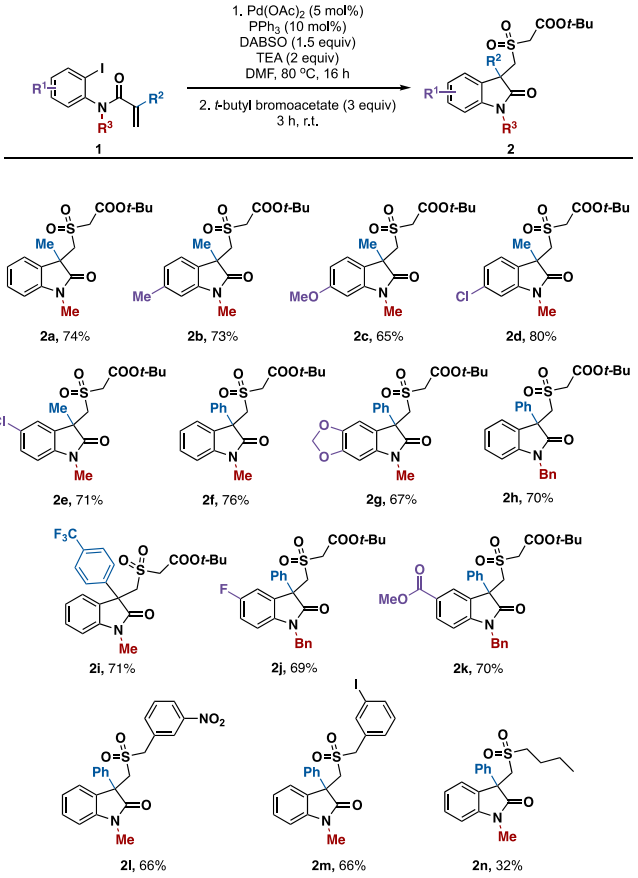
[a]Selected examples of Pd-catalyzed sulfonylation reaction strategies using DABSO as the SO_2 surrogate, and proposed work.

aryl halides—a useful methodology which avoids the isolation of the sulfinate intermediate.[5c] These reports highlight the potential to readily incorporate SO_2 using DABSO in conjunction with palladium catalysis; however, its application toward more complex frameworks has yet to be realized.[4,5] Therefore, we sought out to employ DABSO in a Pd-catalyzed domino-Heck process with the aim of developing a general method to access sulfur-containing hetero- and carbocycles.

Our optimal conditions employ aryl iodide **1a** and DABSO and resemble conditions similar to those previously reported.[8a] By employing $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), TEA (2 equiv), and DABSO (1.5 equiv) in DMF at 80 °C for 16 h (see the Supporting Information), the sulfinate intermediate was generated. Subsequent addition of *tert*-butyl bromoacetate (3 equiv) at room temperature gave the desired sulfonylated oxindole product **2a** in 74% yield (Scheme 2).

After establishing the optimal conditions, we explored the scope of the oxindole products that could be produced (Scheme 2). Substrates incorporating substituents in the *para*-position relative to the iodide had a minimal impact of the yield. Product **2b** bearing a *p*-methyl was isolated in 73% yield along with *p*-methoxy and chloro products **2c** and **2d** in 65% and 80% yield, respectively. Moving the chloro substituent to the *meta*-position produced product **2e** in 71% yield. Tethering a phenyl ring to the alkene in the place of a methyl group was tolerated and gave product **2f** in 76% yield. These phenyl derivatives could tolerate various substituents such as the methylenedioxy backbone found in **2g** (67% yield) and substituents on the tethered phenyl ring such as a *p*-CF_3 group found in product **2i** (71% yield). An oxindole, bearing a benzyl group on the nitrogen atom, was successfully synthesized giving product **2h** in 70% yield. The benzyl derivatives were also able to tolerate fluoro and ester substituents in the *meta*-position, furnishing **2j** and **2k** in 69% and 70% yield, respectively. An example of *m*-nitrobenzyl bromide and *m*-iodobenzyl bromide acting as the alkyl halide electrophile gave product **2l** and **2m** both in 66% yield. While

Scheme 2. Scope of Sulfonylated Oxindoles[a]



[a]Reaction scope of selected accessible oxindoles (0.2 mmol scale). All reported yields are after isolation.

unactivated alkyl bromides gave lower yields at room temperature, as seen with product **2n** (32%), this example highlights the variety of functionalized dialkylated sulfones accessible.

Other hetero- and carbocyclic products could be accessed using this methodology including sulfonylated dihydrobenzofurans, indanes, isochromans, and tetrahydronaphthalenes (Scheme 3). The dihydrobenzofuran **4a** was isolated in 75% yield. At 1 mmol, **4a** was isolated in a somewhat reduced yield of 68%. Introducing a *m*-chloro substituent lowered the yield slightly to 65% of **4b**. Similarly, the yield of **4c** was considerably lower (41%) when a methoxy group was present *ortho* with respect to the tethered alkene substituent. Isochroman **4d** and Indane **4e** were successfully generated in the reaction, being isolated in 77% and 75%, respectively. These results led us to then attempt to synthesize a six-membered carbocyclic product **4f**, which was isolated in 67% yield.

The majority of previous reports of cyclization/SO_2 incorporation are limited to the generation of sulfones. By exploiting the sulfinate lynchpin, we aimed to explore the versatility of this methodology. We prepared sulfonamides in a one-pot, two-step fashion following procedures reported by Fier and Maloney (Scheme 4).[16] Following generation of the sulfinate, introduction of piperidine (1.5 equiv) and I_2 (1 equiv) at room temperature led to the formation of dihydrobenzofuran sulfonamide **5a** and oxindole-based sulfonamide **5b** which were isolated in 52% and 59% yield,

https://dx.doi.org/10.1021/acs.orglett.1c00716
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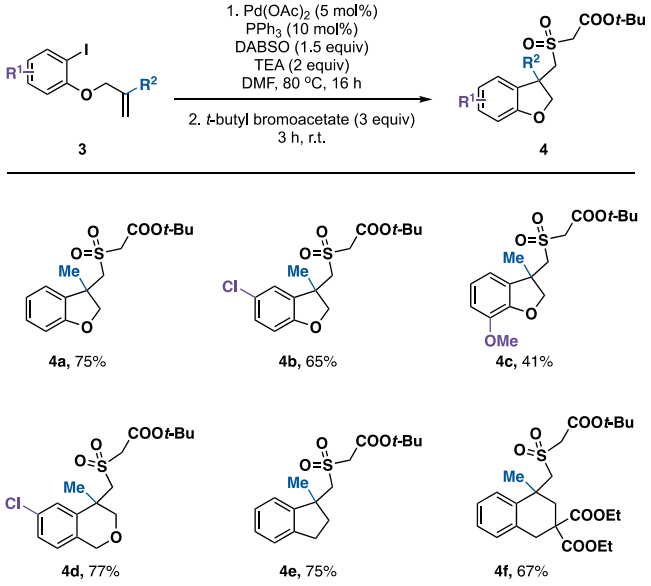
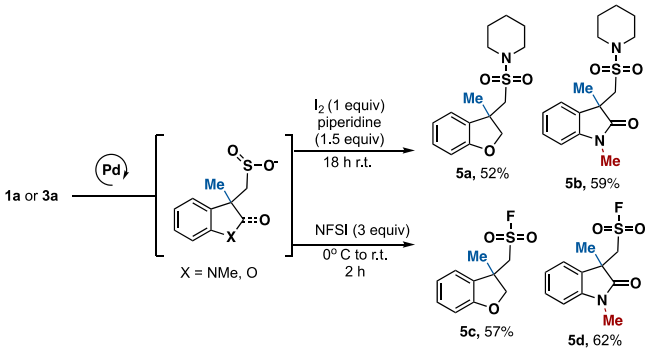
Scheme 3. Scope of Oxygen-Containing Heterocycles and All-Carbon Scaffolds[a]



[a]Reaction scope of selected additional hetero- and carbocyclic scaffolds accessible (0.2 mmol scale). All reported yields are after isolation.

Scheme 4. Diversification of the Sulfinate Intermediate[a]

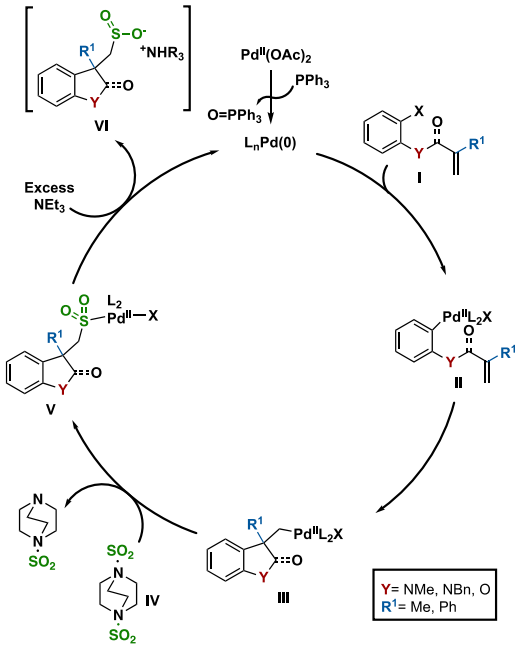


[a]Synthesis of sulfonamides and sulfonyl fluorides. All reactions performed on a 0.2 mmol scale. All yields reported are after isolation.

respectively. Furthermore, the analogous sulfonyl fluorides **5c** and **5d** were also isolated in 57% and 62% yield, respectively, by the addition of NFSI (3 equiv) at 0 °C.[17]

Previous reports of Pd-catalyzed C−SO_2 bond formation using DABSO required the use of a reducing agent, such as IPA or sodium formate.[5c,18] In contrast, the domino reaction worked without the addition of a reducing agent. A proposed mechanism for the formation of the ammonium sulfinate is shown in Scheme 5. Reduction of the Pd(II) precatalyst by PPh_3 yields the active Pd(0) species.[19,20] Oxidative addition of the Pd(0) catalyst into the aryl−X bond of **I** gives complex **II**. Carbopalladation across the tethered alkene gives complex **III**, proceeding before SO_2 insertion facilitated by DABSO (**IV**). Excess NEt_3 may play a dual role as both a hydride donor, regenerating the Pd(0) catalyst after SO_2 insertion, and as a base in the formation of the sulfinate intermediate **VI**.[20−24] Sulfinate **VI** then goes on to react with various electrophiles introduced to the reaction mixture.

Scheme 5. Proposed Mechanism of Sulfinate Formation



In summary, we have developed a palladium-catalyzed domino Heck/sulfination reaction which employs DABSO as the SO_2 surrogate, successfully forming reactive sulfinate intermediates in situ. These sulfinates can act as synthetic lynchpins, which readily react with alkyl halides, amines, or electrophilic fluorine sources to overall generate sulfones, sulfonamides, and sulfonyl fluorides in a one-pot, two-step fashion. This methodology gives access to new, sulfur-containing hetero- and carbocyclic scaffolds by using a simple SO_2 surrogate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00716.

Experimental procedures, characterization data, and $^1H/^{13}C$ NMR spectra for new compounds (PDF)

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https://dx.doi.org/10.1021/acs.orglett.1c00716
Org. Lett. 2021, 23, 2797−2801

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Toronto, the Natural Science and Engineering Research Council (NSERC), and Kennarshore, Inc. for financial support. A.G.D. and J.L.R. thank the Ministère de la Recherche et des Nouvelles Technologies, Normandie Université, CNRS, Region Normandie, and the LABEX Syn Org (ANR-11-LABX-0029). A.W. thanks the Walter C. Sumner Memorial Fellowship and the Province of Ontario (QEII) for funding. We thank Dr. Darcy Burns and Dr. Jack Sheng (University of Toronto) for their assistance in NMR experiments. Additionally, we thank Egor M. Larin (University of Toronto), Timothy McTiernan (University of Toronto), and Austin Marchese (University of Toronto) for insightful discussions and proofreading.

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