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Palladium(II)-Catalyzed *ortho*-Olefination of Arenes Applying Sulfoxides as Remote Directing Groups

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S *Supporting Information*

ABSTRACT: A novel palladium-catalyzed *ortho*-C(sp^2)−H olefination protocol has been developed by the use of sulfoxide as the directing group. Importantly, relatively remote coordination can be accessed to achieve the *ortho* olefination of benzyl, 2-arylethyl, and 3-arylpropenyl sulfoxide substrates, and the olefinated sulfoxide can be easily transformed to other functionalities.

The directing group strategy of transition-metal-catalyzed C−H activation has emerged as a powerful method for selective and efficient C−C and C−X bond formations.[1] The value of this strategy stems from its atom and step economic features and prevalence of diverse C−H bonds in the organic molecules. Currently, a wide variety of functional groups have been studied as the directing groups through monodentate and bidentate coordination[2] including hydroxyl groups,[3] amides,[4] amines,[5] carbonic acids,[6] esters,[7] ethers,[8] ketones,[9] N-containing heterocycles,[10,11] and others.[12] Significant success has been achieved in protocols for the construction of complex molecules.[13] Despite the tremendous progress made in this field, the development of simple and commonly encountered functional groups as directing groups is still highly desired, which will allow the successful conversion of diverse molecules to the requisite functionality for a given synthetic need via C−H activation.

Inspired by the coordination power of sulfur to metals in organic chemistry,[14] we have studied the *ortho*-olefination and arylation using thioether as DG.[15] However, related transformations of sulfoxide derivatives remain elusive within the synthetic community.[16] Sulfoxides are simple organic structures that allow expedient access to a diversity of synthetically useful architectures. In addition, they are prevalent in many natural products and pharmaceutical compounds.[17] Herein, we report a practical Pd-catalyzed *ortho*-olefination of C(sp^2)−H using sulfoxide as the directing group. It was demonstrated for the first time that both five- and six-membered palladacycles of sulfoxide could be formed, leading to the successful *ortho*-olefination of benzyl, 2-phenylethyl, and 3-phenylpropenyl sulfoxide substrates. The sulfoxide group can be transformed into useful functionalities through oxidation, Pummerer rearrangement, and reduction reactions.

Initially we optimized the reaction conditions and discovered that 1.1 equiv of Selectfluor efficiently promoted this Pd(II)-catalyzed alkenylation of benzyl *p*-tolyl sulfoxide with methyl acrylate at 100 °C after 24 h in DCE using 10.0 equiv of TFA as the additive (see Supporting Information (SI)). Under the optimal reaction conditions, a variety of olefins, including ethyl acrylate, *n*-butyl acrylate, phenyl acrylate, and benzyl acrylate, participated in the reaction smoothly to give the products in good yields (Scheme 1, **3aa**−**3ae**). It is notable that all of the products presented excellent regioselectivity at the *ortho*-position of the arenes with the *E*-configuration. This direct aromatic C−H olefination displayed good functional group tolerance with various arenes. For example, arenes bearing either electron-donating or -withdrawing groups could be olefinated, although the electron-rich arenes presented higher reactivity (Scheme 1, **3ba**−**3gc**). More Selectfluor (2 equiv) and a higher reaction temperature were required in order to obtain comparable yields for arenes with electron-withdrawing groups. In addition, hexafluoroisopropanol (HFIP) was a better solvent for the reaction of electronic-deficient arenes (Scheme 1, **3ha**−**ma**). Diverse functionalities such as methyl, *tert*-butyl, −F, −Cl, −Br, and −CF$_3$ groups were tolerated, assessing the generality of this catalytic olefination process. Substituents of the sulfoxide moiety were found to influence the reactivity of this *ortho*-olefination reaction considerably (**3pa**−**3ta**).

Encouraged by the efficiency of the olefination via a five-membered sulfoxide palladacycle, we next tested the coupling of phenylethyl sulfoxide substrates (Scheme 2). To our delight, the coupling of phenylethyl sulfoxide **4a** with methyl acrylate proceeded effectively to give the olefinated product **6aa** in 67% yield in DCE at 100 °C for 24 h. Ethyl and phenyl acrylate were active as well in delivering the olefinated products in good yields (**6ba** and **6ca**). A wide range of phenylethyl sulfoxide substrates were found to be compatible with this reaction (**6da**−**6la**). The presence of electron-withdrawing substituents on the aromatic ring plays a negative effect on the olefination, leading to the lower yields (**6ga**−**6ja**). Products containing

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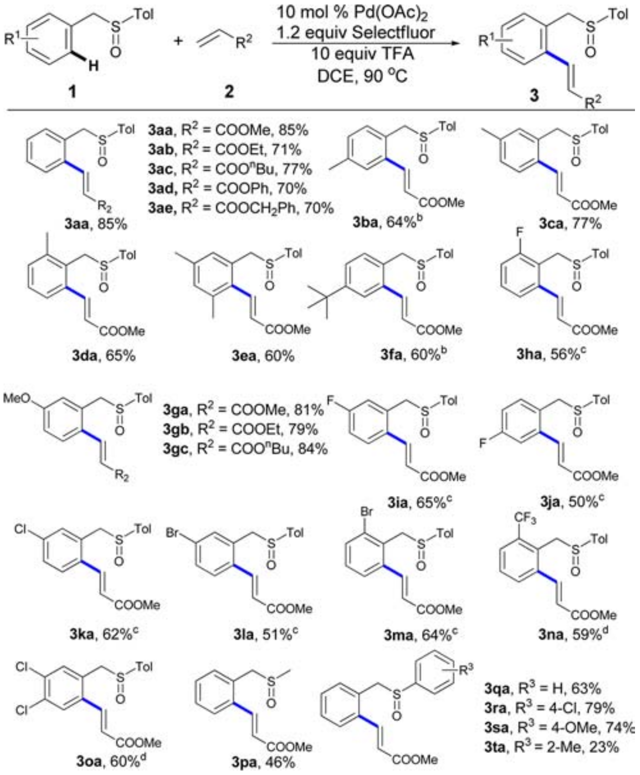
Scheme 1. Olefination of Benzyl Sulfoxide Substrates[a]



[a] Isolated yields are given. Reaction conditions: Sulfoxide **1** (0.2 mmol), acrylate **2** (0.4 mmol), $Pd(OAc)_2$ (4 mg, 0.02 mmol), CF_3COOH (200 mg, 2.0 mmol), and Selectfluor (84 mg, 0.24 mmol) in DCE (2 mL) at 90 °C for 24 h. [b] CH_3COOH was used instead of CF_3COOH. [c] HFIP was used as solvent at 110 °C, and 2.0 equiv of Selectfluor were used. [d] 130 °C.

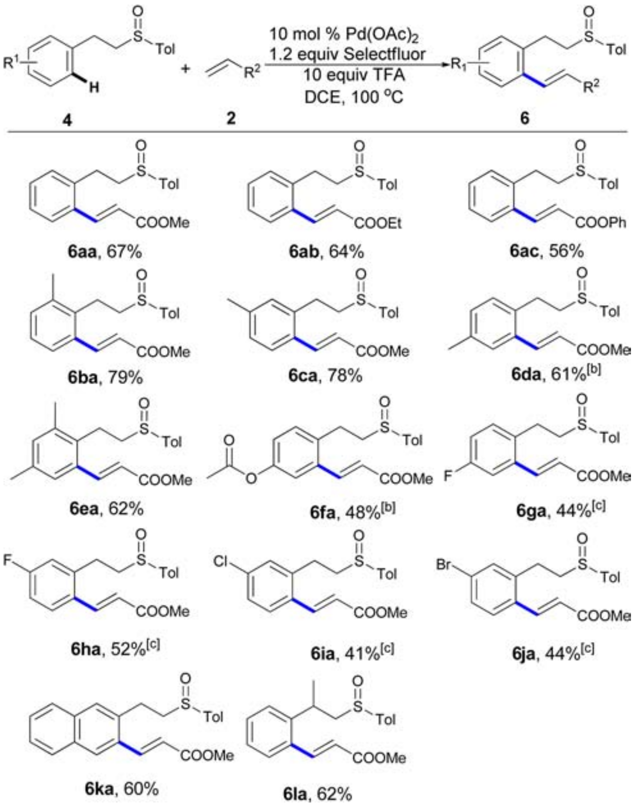
chloride (**6ia**), fluoride (**6ga** and **6ha**), and bromide (**6ja**) were obtained, which offered an opportunity for a subsequent cross-coupling reaction for the synthesis of complex molecules. In the case of *meta*-substituent arenes, the olefination occurred regioselectively at the less hindered position (**6ca**, **6ha**−**6ja**). 2-Naphthalenyl sulfoxide underwent the reaction smoothly, and a 60% yield was afforded (Scheme 2, **6ka**). Notably, the substitution pattern at the α-position was tolerated to give the product in 62% yield (**6la**).

During this investigation, we also discovered that phenylpropyl sulfoxide substrates could dramatically afford the *ortho*-olefination products under the reaction conditions with HFIP as the optimal solvent (Scheme 3). For example, using methyl acrylate, ethyl acrylate, and butyl acrylate, the corresponding olefinated products were obtained in 63%, 58%, and 65% yields, respectively. This synthetic flexibility stemmed from the special effect of the sulfoxide directing group expanding the range of core structures that can subsequently be accessed.

Fortunately, we obtained the two palladacycle complexes through a stoichiometric reaction of sulfoxides with $Pd(OAc)_2$ in the presence of 1 equiv of TFA in DCE at 80 °C for 8 h (Scheme 4). Single crystal XRD analysis of compounds **5** and **7** revealed that sulfur was indeed the anchoring atom in the palladacycles.[18] The corresponding olefination products **3aa** and **6aa** were delivered in good yields by the treatment of palladacycle **5** and **7** with methyl acrylate (see SI).

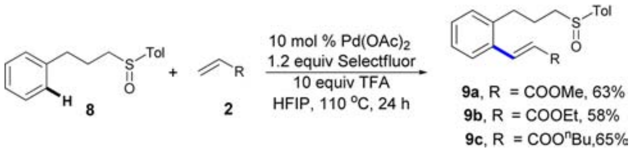
To gain insight into the mechanism, an intermolecular isotope kinetic experiment was performed. Benzyl *p*-tolyl

Scheme 2. Olefination of Phenylethyl Sulfoxide Substrates[a]



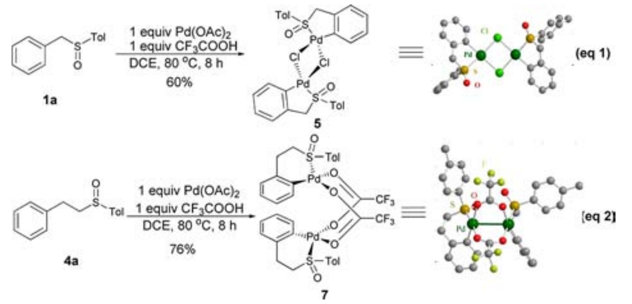
[a] Isolated yields are given. Reaction conditions: sulfoxide **5** (0.2 mmol), acrylate **2** (0.4 mmol), $Pd(OAc)_2$ (4 mg, 0.02 mmol), CF_3COOH (200 mg, 2.0 mmol), and Selectfluor (84 mg, 0.24 mmol) in DCE (2 mL) at 100 °C for 24 h, in a sealed tube. [b] CH_3COOH was used instead of CF_3COOH. [c] HFIP was used as solvent at 110 °C, and 2 equiv Selectfluor were used.

Scheme 3. Olefination of Phenylpropyl Sulfoxide Substrates[a]



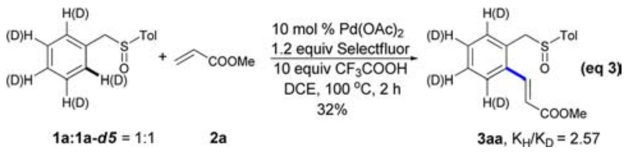
[a] Reaction conditions: sulfoxide **8** (0.2 mmol), acrylate **2** (0.4 mmol), $Pd(OAc)_2$ (4 mg, 0.02 mmol), CF_3COOH (200 mg, 2.0 mmol), and Selectfluor (84 mg, 0.24 mmol) in HFIP (2 mL) at 100 °C for 24 h in a sealed tube.

Scheme 4. Preparation and ORTEP of the C−H Activation Intermediates



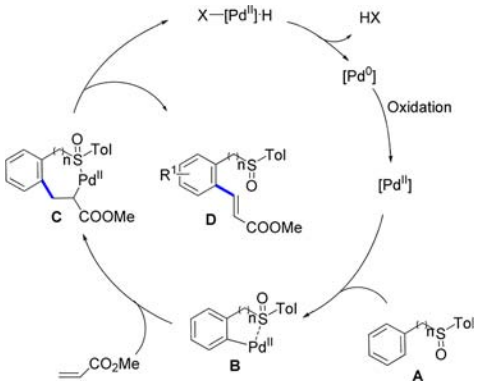
sulfoxide **1a** and its deuterated analogue **1a-*d5*** were equivalently subjected to the reaction (Scheme 5, eq 3). An isotope kinetic effect (KIE) of 2.57 was observed, indicating that the C−H cleavage might be the rate-determing step in the catalytic cycle.

Scheme 5. Intermolecular Isotope Kinetic Experiment



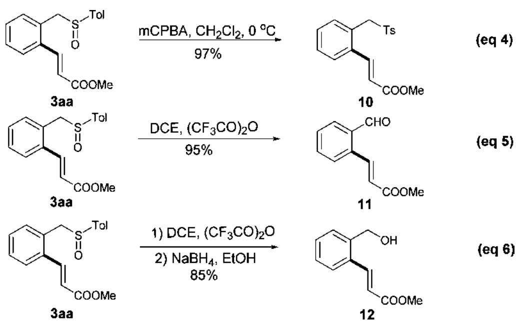
A possible pathway leading to the olefination is proposed (Scheme 6). The initial sulfoxide assisted *ortho*-palladation leads to the formation of five- or six-membered palladacycle **B**, which has been verified partially by the preparation and reaction reactivity of complex **5** and **7**. The sulfoxide palladacycle species **B** undergoes 1,2-migratory insertion with olefin to give the intermediate **C**. The subsequent β-hydride elimination generates the olefinated products and Pd(II) species, which undergoes the reduction elimination to liberate Pd(0). Pd(II) is regenerated by oxidation of Pd(0) to re-enter the catalytic cycle.

Scheme 6. Plausible Mechanism



The transformation of the sulfoxide moiety was also investigated. Oxidation of the olefinated benzylsulfoxide **3aa** by *m*-CPBA at 0 °C produced the corresponding sulfone **10** in high yields (Scheme 7, eq 4). The sulfoxide moiety can be almost quantitatively transformed into aldehyde **11** in the presence of acetic anhydride through Pummerer rearrangement (eq 5).[19] Without separation, the aldehyde could be reduced by NaBH$_4$ in the subsequent step to afford benzyl alcohol **12** in 85% yield (eq 6).

Scheme 7. Transformation of Sulfoxide Moiety



In conclusion, we have shown that sulfoxide can be successfully used as a directing group in Pd-catalyzed olefination through C(sp^2)−H activation. A variety of alkenes can be selectively incorporated to arenes, leading to economic synthesis of sulfoxide containing compounds in high efficiency. The ability of sulfoxide to activate the *ortho* C−H bond with different tether lengths (n = 1, 2, 3) is a distinctive feature of this process. In addition, the advantage of using sulfoxide as the directing group for C−H activation also lies in its extraordinarily easy transformation to other functionalities. Further studies toward broadening the scope of sulfoxide directed C−H activation are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data (^{1}H NMR, ^{13}C NMR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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