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Palladium-Catalyzed C−H Alkenylation of Arenes Using Thioethers as Directing Groups

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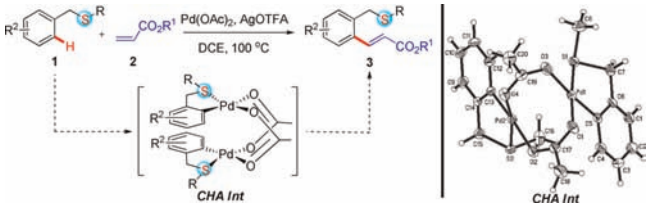
ABSTRACT



Thioethers have been proven to be reliable directing groups for palladium catalyzed alkenylation of arenes via C−H activation. Mechanistic investigation reveals that the C−H cleavage of arenes is the turnover-limiting step, and an acetate-bridged dinuclear cyclopalladation intermediate is involved. The alkenylated thioethers can be easily removed and transformed into a variety of useful groups.

Transition metal-catalyzed aromatic C−H activation arouses substantial interest currently for its step- and atom-economic advantages.[1] In particular, chelation-assisted C−H functionalization has emerged as a powerful method because of its excellent regioselectivity and reactivity.[2] The efficiency of these C−H activation transformations are profoundly influenced by chelation. The success of chelation-assisted C−H activation relies on the compatibility and synergism of metal and ligand. Strong binding between metal and ligand may quit the C−H activation process. Typical N- and O-based directing groups,[3] including anilides,[3a,b] ketones,[3c,d] esters,[3e] amines,[3f] oxazoline,[3g,h] carboxylic acid,[3i−k] alcohol,[3l] as well as silanol[4] and pyridylsulfoxide,[5−7] have been intensively investigated. Sulfur has received much attention by the chemists of organic synthesis, coordination chemistry, biomaterials, and functionl materials. However, there is an extremely rare example for utilizing

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sulfur as chelation groups in C−H activation,[8] possibly due to its strong coordination ability. Herein, we describe the first example of the use of thioether as the only directing group for the Pd-catalyzed olefination of arenes. The thioethers can be easily removed or engaged in a variety of useful transformations.[9,10] This result established that sulfur can be used as chelation group in C−H activation, which may lead to the creation of economical synthetic methods for sulfur containing compounds.

Thioether is an important structural motif in a wide range of molecules with numerous and important applications.[11] It has been widely used as coordination groups with various metals in many useful complexes.[12] The important applications of thioether derivatives in drug discovery and natural product synthesis[11] prompted us to develop a Pd-catalyzed *ortho*-alkenylation of aryl thioethers (Figure 1).[13] Initially, we examined a variety of S-involving groups as directing group for the palladium catalyzed direct alkenylation of aromatic C−H bond with methyl acrylate **2a**. It was found that the length of the tether group between arene and sulfur exerted a drastic effect on the reaction, and the benzyl thioethers showed the best efficiency. Smaller groups in thioether facilitate the transformation as shown when benzyl was replaced by methyl group, possibly due to the more efficient coordination. Arylthio presented better reactivity, although dialkenylated product was formed. Notably, the reaction of other S-containing groups such as sulfoxide, sulfone, and thioesters are sluggish, indicating that the properties of the sulfur play crucial role on the chelation with palladium. Analogous O-based groups such as phenylether had proven to be totally inactive.

After extensive screening the reaction conditions, we discovered that 2 equiv of Ag(OTFA) promoted efficiently

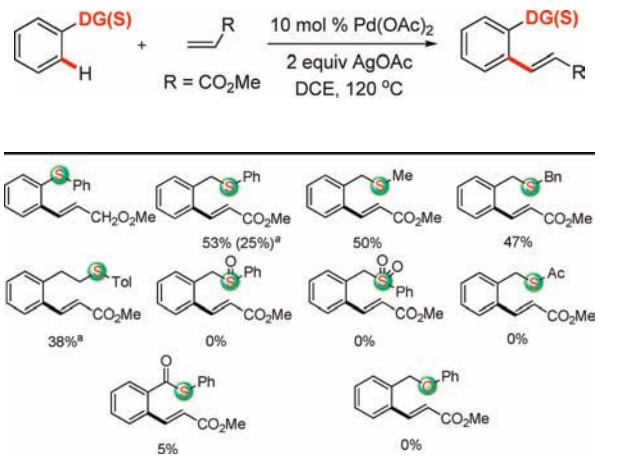

Figure 1. S-containing Directing Groups for Aromatic C-H Alkenylation. Reaction conditions: arenes (0.3 mmol), **2a** (51.6 mg, 0.6 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), and AgOAc (100.2 mg, 0.6 mmol) in DCE (2 mL) under air at 120 °C for 12 h. [a] AgOTFA was used instead of AgOAc.

this Pd(II)-catalyzed alkenylation of (2-methylbenzyl)-(phenyl)sulfane **1f** with butyl acrylate under 100 °C for 12 h in DCE (see the Supporting Information for details). The substrate scope of the reaction is summarized in Figure 2. Various acrylic esters had proven to be reliable substrates in the reaction, and the yields increased from 55 to 72% with the elevation of the boiling point of the acrylic ester (**3aa**, **3ab**, and **3ac**). When phenylthio **1b** and *p*-tolylthio **1c** were used as directing groups, dialkenylation product was observed (**3ba** and **3ca**). The electron-rich arenes were readily alkenylated to give the anticipated products fast in good yields (**3dc**−**3fc**). Notably, the reaction presented excellent regioselectivity with the alkenylation at the *ortho*-position of the less steric side of the arenes (**3dc**−**3ec**, **3ga**, **3gc**, and **3jc**). The *ortho*-substituent arylthioethers participated in the reaction smoothly to afford the desired alkenylated products in good yields (**3fa**−**3fc**). The electronic-deficient arenes furnished the alkenylated products in good yields as well, but longer reaction time was required (**3ga**−**3ia**). The arenes bearing a strong electron-withdrawing group such as CN showed lower reactivity to give low yield even after prolongation of reaction time (**3jc**).

Arenes bearing double electron-donating groups were also subjected to the reaction. It was surprising that no expected product was observed. After switching the oxidant to AgOAc, the reaction was smooth, with mono-alkenylation occurring on the less steric side of the arenes (**3ka** and **3lc**). In contrast, double electron-withdrawing group substituted arenes such as **3m** were compatible with AgOTFA, giving the regioselective alkenylaion product **3mc** in a 37% yield.

It should be pointed out that dialkenylation product was not detected in the reactions involving *meta*- and *ortho*-substituted arenes. However, in the case of unsubstituted

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(**1b** and **1c**) and *para*-substituted arenes (**1n** and **1o**), dialkenylation products were produced spontaneously under the reaction conditions. The absence of dialkenylated products might be attributed to the steric hindrance of *meta*-substituents. The dialkenylation could be avoided by the replacement of *p*-tolyl thioether with smaller methyl thioether, which selectively delivered the monoalkenylation products **3pa** and **3pc** in moderate yields.

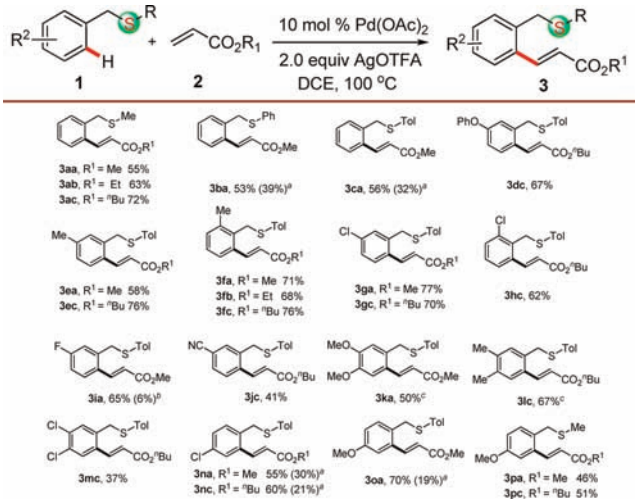
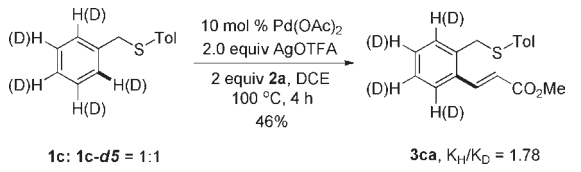


Figure 2. Reaction conditions: $ArCH_2SR$ **1** (0.3 mmol), alkenes **2** (0.36 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), and AgOTFA (132.0 mg, 0.6 mmol) in DCE (2 mL) under air at 100 °C for 12 h. [a] 0.6 mmol of alkenes **2** were used, and the dialkenylation product was isolated in the parentheses. [b] Regioselective product {(*E*)-methyl 3-[2-fluoro-6-(*p*-tolylthiomethyl)phenyl] acrylate} was obtained. [c] AgOTFA was replaced by AgOAc.

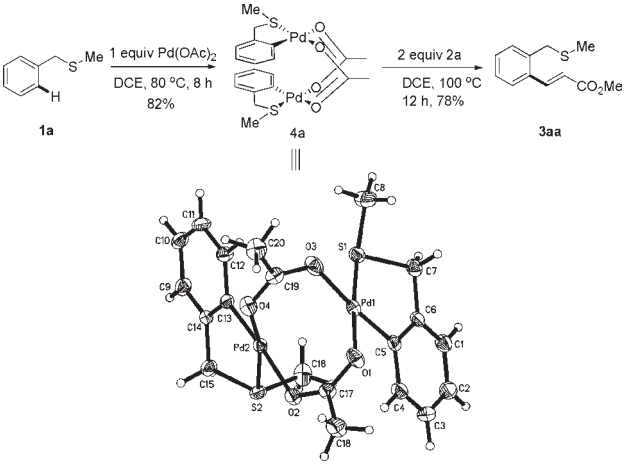
To probe the mechanism of this reaction, an intermolecular isotope kinetic experiment was performed. Benzyl(*p*-tolyl)sulfane **1c** and its deuterated analogue **1c**-d_5 were equivalently subjected to the reaction (Scheme 1). An isotope kinetic effect (KIE) of 1.78 was disclosed, implying that the palladium mediated C−H cleavage was the rate-determining step (RDS) in the catalytical cycle.

Scheme 1. Isotope Kinetic Experiment



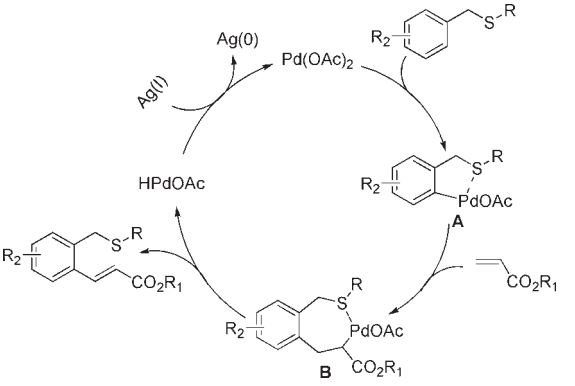
We succeeded in isolating an intermediate complex **4a** through the stoichiometric reaction of **1a** and $Pd(OAc)_2$. Single crystal XRD analysis of **4a** revealed a dinuclear bis-μ-acetatopalladium structure. The bond length between Pd and S was 2.243 Å, suggesting sulfur was indeed the anchoring atom in the palladium catalyzed olefination of the arenes. Direct subjection of **4a** to react with alkene **2a** provided the alkenylation product **3aa** in a 78% yield (Scheme 2). These results clearly indicated that **4a** was the key catalytic intermediate and responsible for the C−H activation reaction.

Scheme 2. ORTEP of the C−H Activation Intermediate **4a**[a]



[a] Selected bond lengths (Å): Pd1−C5, 1.983; Pd1−S1, 2.243; Pd1−O1, 2.061; Pd1−O3, 2.138; Pd1−Pd2, 2.948.

Scheme 3. Plausible Mechanism



Since the arylthioethers with electron-withdrawing substituents showed relatively less reactivity (**3ga**−**3ia**, **3jc**), the intermediate **A** is possibly formed through an electrophilic palladation process.[14] However, the proton abstract mechanism[15] can not be fully excluded at the moment. After that, the insertion of alkenes affords the carbopalladation intermediate **B**, which undergoes the β-hydrogen elimination to produce the alkenylated benzyl thioethers and liberate the species HPdOAc. The reductive elimination of HPdOAc gives Pd(0), which is oxidized Pd(II) in situ by Ag(I) (Scheme 3).

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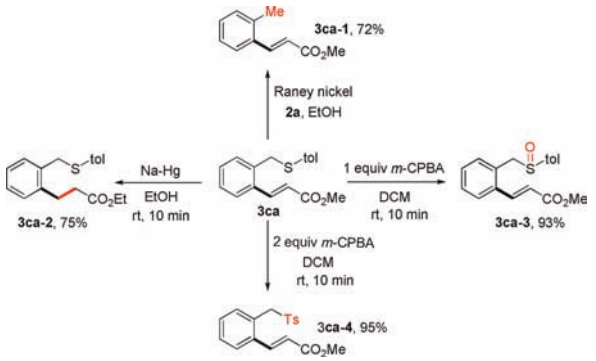
Scheme 4. Removal and Transformation of Thioethers



The *ortho*-alkenyl benzylsulfane **3ca** can be easily hydrogenated by Na−Hg to give the *ortho*-alkyl benzylsulfane **3ca**−**2** with a transesterification in a 75% yield. Changing the reductant to Renay Ni completely removed the phenylthio group, resulting in the formation of the 2-methyl cinnamic ester **3ca**−**1** in a 72% yield with no effect on the α,*β*-unsaturated ester moiety. By adjusting the loading of the oxidant *m*-CPBA, control oxidation of **3ca** could be fastly realized, producing the synthetically very useful sulfoxide **3ca**−**3** and sulfone **3ca**−**4** in high yields (Scheme 4).[5c]

In conclusion, we have demonstrated that thioethers are elegant directing groups in transition metal catalyzed C−H activation. A variety of alkenes can be selectively incorporated to arenes, leading to the economic synthesis of cinnamic esters in high efficiency. Mechanistic investigation reveals that the thioether-directed C−H cleavage is the turnover-limiting step, and the reaction proceeds through an acetate-bridged dinuclear Pd(II) intermediate. The directing group of the alkenylated arylthioethers can be easily removed or converted into a variety of useful functional groups. Further studies on the application of thioether directed C−H activation are currently ongoing in our laboratory.

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Supporting Information Available. Experimental procedures, characterization of all compounds, and crystal data **4a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.