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VIP

2-Pyridyl Sulfoxide: A Versatile and Removable Directing Group for the Pd^{II}-Catalyzed Direct C–H Olefination of Arenes

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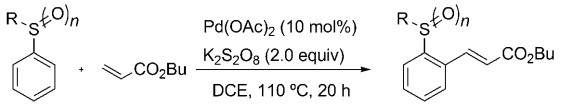
Dedicated to the memory of Professor Rafael Suau

The Mirozoki–Heck reaction, which couples aryl halides (or triflates) with olefins, ranks among the most powerful and reliable C–C bond-forming reactions.[1] As a very attractive alternative, from chemical efficiency and environmental impact aspects, the Pd^{II}-catalyzed oxidative direct C–H alkenylation (Fujiwara–Moritani reaction), in which the aryl halide is replaced by an unactivated arene, is receiving increasing attention.[2–8] Very efficient procedures for the Pd^{II}-catalyzed aryl C–H alkenylation of aniline derivatives,[2] pyridine *N*-oxides,[3] aromatic carboxylic acids,[4] alcohols,[5] and amines,[6] as well as heteroaromatic compounds,[7] have been recently reported.[9] Most of these protocols require a directing group that aids in the carbometallation of a proximal C–H bond, a common strategy in C–H functionalization.[10] However, the majority of such directing groups are not easily removable from the resulting products, thus compromising the generality of the reaction.

From a synthetic practicality viewpoint, directing groups that are not only easily attachable and removable but also chemically versatile are highly valuable, since they provide an additional handle to introduce diversity and complexity in the final product.[11] In spite of this progress, critical challenges still remain in this reaction, such as achieving high selectivity in the monoalkenylation product without affecting the second *ortho* C–H bond, thus enabling a sequential double olefination, and expanding the scope to include other types of substrates. In this regard, organosulfur compounds play an important role in biological systems and they serve as versatile reagents, ligands, and catalysts for organic synthesis. However, auxiliary directing groups for catalytic C–H carbometalation/cross coupling reactions leading to aromatic sulfur derivatives such as thiols, sulfides, or sulfoxides remain, to the best of our knowledge, undocumented. Herein, we describe a practical Pd^{II}-catalyzed *ortho* C–H alkenylation assisted by a 2-pyridyl sulfoxide group, a group that can be readily removed or transformed into other functionalities such as a thiol group.

We have previously reported the direct Pd^{II}-catalyzed C2–H alkenylation and oxidative homocoupling of indoles using a *N*-(2-pyridyl)sulfonyl group that functions as both directing and protecting group.[7f,h] In the pursuit of extending this C–H alkenylation strategy to non heteroaromatic compounds, our initial studies focused on phenyl 2-pyridyl sulfone (**1**) as substrate. However, the $Pd(OAc)_2$-catalyzed (10 mol%) *ortho* olefination of **1** with butyl acrylate in the presence of $K_2S_2O_8$ (2 equiv) as oxidant failed to provide the desired alkenylation product **7** in useful conversions (Table 1, entry 1). This low reactivity could be ascribed to the high electron-deficient character of the substrate **1** compared to *N*-sulfonyl indoles.

Table 1. Screening of a sulfur-based directing group for Pd^{II}-catalyzed aromatic *ortho* C–H alkenylation.



Entry	R (imine)	Substrate	Product	Yield [%][a]
1	2-pyridyl	**1** ($n=2$)	**7** ($n=2$)	<15
2	2-pyridyl	**2** ($n=0$)	**8** ($n=1$)	55[b]
3	2-pyridyl	**3** ($n=1$)	**8** ($n=1$)	100 (79)
4	Ph	**4** ($n=1$)		–[c]
5	Me	**5** ($n=1$)		–[c]
6	4-pyridyl	**6** ($n=1$)		–[c]

[a] Conversion yields (determined by ^{1}H NMR spectroscopy from the crude reaction mixture). In parenthesis, isolated yield after chromatography. [b] Phenyl 2-pyridyl sulfoxide (45%) was also detected in the mixture. [c] Oxidation to sulfone was only detected. DCE = 1,2-dicloroethane.

Therefore, we turned our attention to less electron-withdrawing sulfur-directing groups. Thus, both the phenyl 2-pyridyl sulfide (**2**) and the phenyl 2-pyridyl sulfoxide (**3**) were examined in the model reaction with butyl acrylate using

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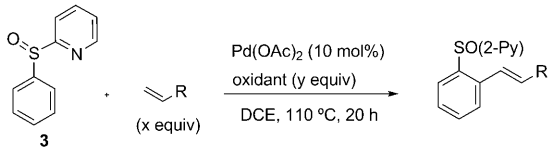
$K_2S_2O_8$ (2.0 equiv) as oxidant. The reaction of sulfide **2** (Table 1, entry 2) afforded a 45:55 mixture of the sulfoxide **3** and its *ortho*-alkenylation product (**8**). Pleasingly, the sulfoxide **3** served as a very effective directing group, leading to complete *ortho* alkenylation without detecting oxidation to sulfone. Under the optimized conditions [$Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (2.0 equiv), DCE, 110°C], the olefination product **8** was obtained with complete *ortho*-selectivity and very high mono-selectivity[12] in 79% isolated yield.

We next investigated whether the 2-pyridyl or the sulfinyl moiety was responsible for the directing ability of the 2-pyridylsulfinyl group. As shown in Table 1, neither the diphenyl sulfoxide (**4**, entry 4) nor the methyl phenyl sulfoxide (**5**, entry 5) led to even traces of the corresponding alkenylation products under the optimized conditions; only oxidation of the starting material to sulfone being observed after extended reaction times. Furthermore, the absence of the alkenylation reaction observed in the case of the phenyl 4-pyridyl sulfoxide (**6**, entry 6), an isomer of **3**, highlights the key role of the 2-pyridylsulfinyl group likely through stabilization of the cyclopalladated intermediate.

With a regioselective C–H alkenylation protocol in hand, the scope with regard to the alkene component was examined (Table 2). Monosubstituted electrophilic alkenes (2–3 equiv) cross coupled efficiently with substrate **3**, affording the corresponding monoalkenylated products in good yields (65–79%, Table 2, entries 1–4). The more challenging styrene derivatives showed, however, very low reactivity under these reaction conditions (less than 10% conversion). Gratifyingly, this low reactivity problem could be solved by using $PhI(OAc)_2$ as the oxidant. With the more reactive $PhI(OAc)_2$ (1.5 equiv), a variety of styrene derivatives (3.0 equiv) were found to be competent coupling partners regardless of the electronic nature of the substituents on the phenyl ring, although the yields were slightly lower (49–63%, Table 2, entries 5–8).

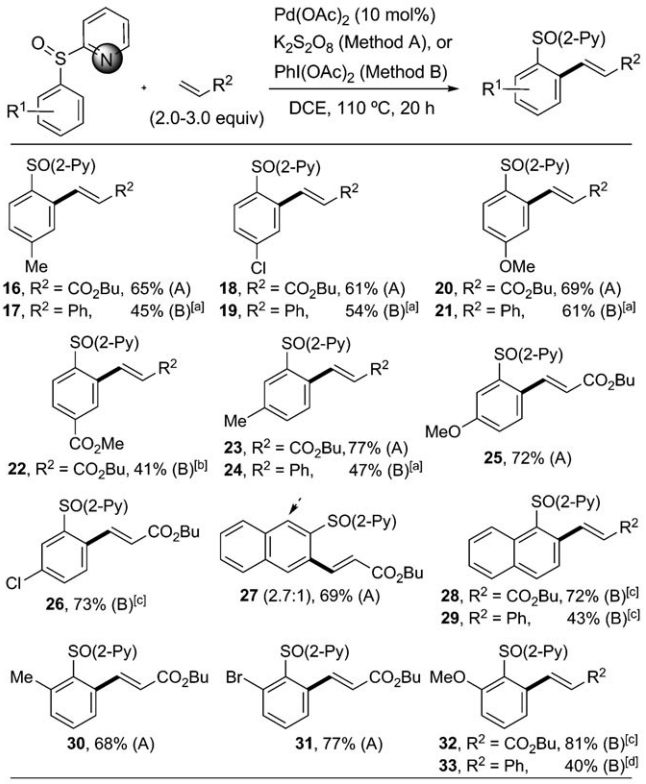
Table 2. Pd^{II}-catalyzed selective monoolefination of phenyl sulfoxide **3**.



Entry	R (*x*)	Oxidant (*y*)	Product	Yield [%][a]
1	CO_2Bu (2.0)	$K_2S_2O_8$ (2.0)	**8**	79
2	CO_2Me (2.0)	$K_2S_2O_8$ (2.0)	**9**	72
3	SO_2Ph (3.0)	$K_2S_2O_8$ (2.0)	**10**	65
4	$P(O)(OMe)_2$ (3.0)	$K_2S_2O_8$ (2.0)	**11**	70
5	Ph (3.0)	$PhI(OAc)_2$ (1.5)	**12**	63
6	4-$OAcC_6H_4$ (3.0)	$PhI(OAc)_2$ (1.5)	**13**	49
7	4-$OMeC_6H_4$ (3.0)	$PhI(OAc)_2$ (1.5)	**14**	62
8	4-BrC_6H_4 (3.0)	$PhI(OAc)_2$ (1.5)	**15**	57

[a] Yield of isolated product after chromatography.

These optimized conditions for selective mono-olefination using butyl acrylate and styrene as model olefins [with either $K_2S_2O_8$ or $PhI(OAc)_2$ as oxidant] turned out to be applicable to a wide range of substituted aryl 2-pyridyl sulfoxides[13] (Scheme 1). Both electron-rich substrates bearing Me or OMe substituents and electron-deficient substrates containing Cl, Br, or CO_2Me groups were efficiently converted into the corresponding products with complete mono-selectivity in most cases. In general, butyl acrylate showed higher efficiency (typically 60–80% yield) than styrene (typically 40–60% yield). Substrates with *meta* substituents underwent alkenylation to form a single detectable regioisomeric product (with the new C–C bond installed at the less hindered *ortho* position), regardless of the electronic nature of the substituent (products **23**–**26**). The only exception to this trend was found with the 2-naphthyl 2-pyridyl sulfoxide, which provided a substantial amount of C1 alkenylation (C3/C1 = 2.7:1, products **27**).

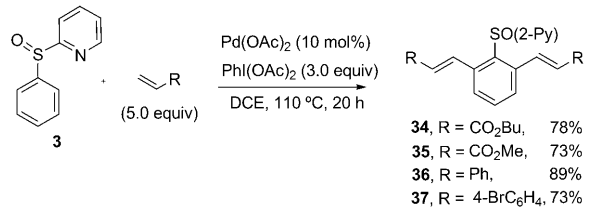


Scheme 1. Pd^{II}-catalyzed mono-olefination of sulfoxide **3**. Method A: alkene (2.0 equiv), $K_2S_2O_8$ (2.0 equiv). Method B: [a] alkene (3.0 equiv), $PhI(OAc)_2$ (1.5 equiv); [b] alkene (1.05 equiv), $PhI(OAc)_2$ (2.0 equiv); [c] alkene (3.0 equiv), $PhI(OAc)_2$ (2.0 equiv); [d] alkene (3.0 equiv), $PhI(OAc)_2$ (3.0 equiv).

Even substrates that contained an *ortho* substituent to the sulfinyl directing group proved to be suitable for this reaction (products **28**–**33**), although in some cases the reaction required 2–3 equivalents of the oxidant $PhI(OAc)_2$ for achieving good conversions (products **28**, **29**, **32**, and **33**).

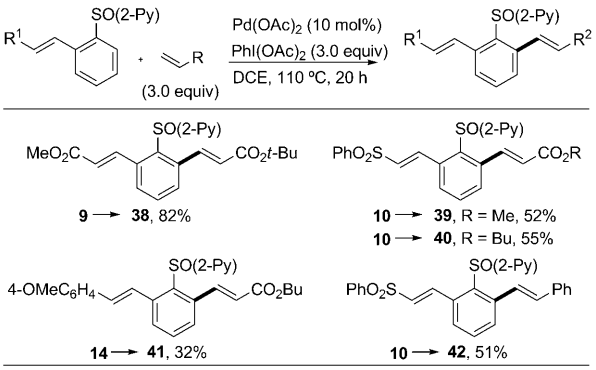
Interestingly, increasing the amount of alkene to five equivalents and the amount of $PhI(OAc)_2$ to three equiva-

lents resulted in a clean and high-yielding di-*ortho*-olefination with both Michael acceptor olefins and styrene-type substrates (products **34**–**37**, 70–89% yield, Scheme 2).



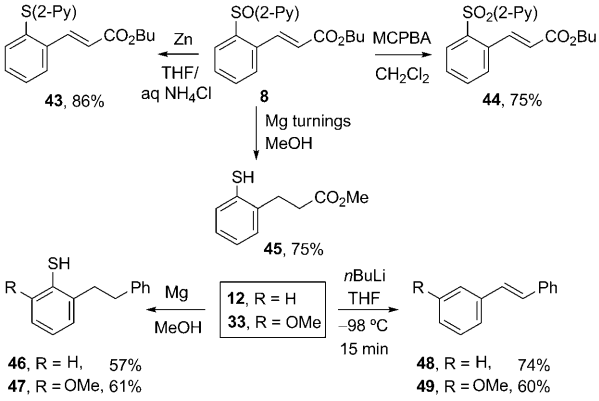
Scheme 2. Pd^{II}-catalyzed di-*ortho*-olefination of sulfoxide **3**.

Furthermore, the installation of two different alkenes at the two *ortho* positions of the arene by sequential double C–H alkenylation reactions is also feasible, as demonstrated in Scheme 3. The second *ortho*-olefination reaction was performed by using the more reactive catalyst system $Pd(OAc)_2$/$PhI(OAc)_2$ under the same reaction conditions. Products asymmetrically substituted with two orthogonally protected acrylates (e.g., product **38**), two different types of Michael acceptor olefins (vinyl sulfone/acrylate, products **39** and **40**), as well as two electronically dissimilar olefins (acrylate/styrene, products **41** and **42**) were obtained generally in acceptable yields.



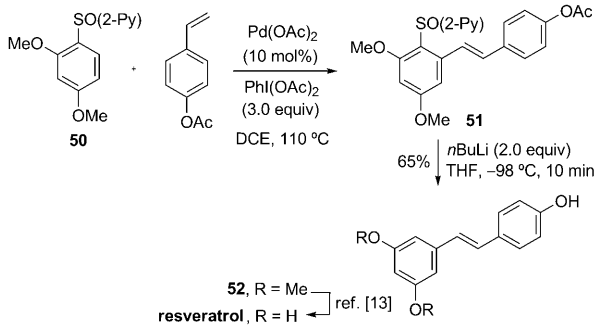
Scheme 3. Sequential dialkenylation process.

Finally, to fully demonstrate the synthetic potential of this methodology, we briefly explored both the removal of the directing group and its chemical versatility (Scheme 4). First, exploiting the ability of the sulfur atom to pass fairly readily from one oxidation state to another, the alkenylated sulfoxide **8** was converted into the corresponding sulfide (**43**) and sulfone (**44**). In addition, the 2-pyridyl sulfoxide **8** was found to undergo smooth conversion into the corresponding C2-alkylated thiophenol **45** by reduction with Mg (75% yield). In this reaction, the reduction of the carbon–carbon double bond of the acrylate moiety was also observed, along with transesterification to methyl ester. The same sulfoxide→thiol/double bond reduction sequence was cleanly attained with the *ortho*-styryl-substituted products **12** and **33**, affording the corresponding phenethyl-substituted products **46** and **47** in good yields.



Scheme 4. Transformations and removal of the directing group. MCPBA = *m*-chloroperbenzoic acid.

On the other hand, efficient cleavage of the 2-pyridylsulfinyl group was achieved by sulfoxide/lithium exchange[14] with *n*BuLi (2.0 equiv) in THF at −98 °C (products **48** and **49**).[15] Globally, considering installation of the sulfoxide–olefination-removal of the SOPy, compound **49** results from a three-step formal *meta* alkenylation of anisole. The practical utility of this sequence is illustrated in the formal synthesis of resveratrol,[16,17] a naturally occurring product of the phytoalexin family with important biological activities including anticancer properties (Scheme 5).[18]



Scheme 5. Application to the synthesis of resveratrol.

In conclusion, we have demonstrated the directing ability of the 2-pyridyl sulfinyl group in promoting the Pd^{II}-catalyzed *ortho* C–H olefination of arenes. Electron-deficient alkenes and styrene-type olefins serve as efficient coupling partners, providing access to either mono-alkenylated or asymmetrically di-*ortho*-alkenylated products (through a sequential double C–H alkenylation) in good yields and high selectivity. The 2-pyridylsulfinyl group can be readily removed from the products or transformed into a thiol group.

Experimental Section

Representative procedure for the *ortho*-alkenylation of 2-pyridyl sulfoxides: *Reaction of phenyl 2-pyridyl sulfoxide (**3**) with methyl acrylate to afford methyl 2-[2-(2-pyridyl)phenyl]acrylate (**9**)*: A glass tube with a septum was charged with the sulfoxide **3** (51 mg, 0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), and $K_2S_2O_8$ (135 mg, 0.5 mmol). The mixture was degassed with two vacuum-nitrogen cycles, before DCE (2.5 mL) and methyl acrylate (45 μL, 0.5 mmol) were added at room temperature. The septum was replaced by a teflon-lined screw cap and the tube was stirred at 110 °C for 20 h. The reaction mixture was then allowed to reach room temperature and it was treated with H_2O (2 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2×5 mL), and the combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane-EtOAc 7:3) to afford **9** as a white solid; yield: 52.1 mg (72%); m.p. 86–88 °C. See Supporting Information for spectroscopic data.

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Keywords: C–H activation · olefination · palladium · pyridine · sulfoxide

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[12] Traces of di-*ortho*-alkenylated product were detected in the crude reaction mixture (≤5%). Using $PhI(OAc)_2$ (2 equiv) as oxidant instead of $K_2S_2O_8$ a 70:30 mixture of mono- and di-alkenylated products was obtained.

[13] The aryl 2-pyridyl sulfoxides were readily prepared by oxidation of the corresponding sulfides which, in turn, were accessed either by reaction of 2-bromopyridine with arylthiolates, or by Cu^I-catalyzed cross-coupling of aryl iodides with 2-mercaptopyridine (see Supporting Information for details).

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