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Oxidative Addition of Pd(0) to Ar–SO_2R Bonds: Heck-Type Reactions of Sulfones

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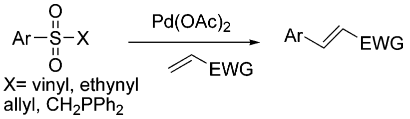
ABSTRACT



Phenyl vinyl sulfones and sulfoxides react with $Pd(OAc)_2$ to form styryl sulfoxides and sulfones according to the first Mizoroki–Heck reaction reported for these thio derivatives. Only sulfones are able to react by using catalytic amounts of Pd (up to 1 mol %) in the presence of Ag_2CO_3. 1,2-Diphenylsulfonyl ethenes, alkynylphenyl sulfones, and other sulfones, less prone to act as acceptors in the Heck-type reactions, can transfer the aryl group to alkyl acrylates forming cinnamic esters.

Transition-metal-catalyzed C−C bond-forming reactions are the most powerful methods of organic synthesis.[1] The Mizoroki−Heck reaction, first described in the 1970s,[2] is currently a well-documented and exploited process.[3] It consists of the reaction of aryl halides[4] with alkenes giving rise to styrenes with the formation of a Csp^2−Csp^2 bond. Aryl halides are usually iodides or bromides, but reactions with the less expensive and less reactive chlorides are also successful using Fu's catalyst[3h,5] or carbene ligands.[6] Vogel and co-workers have recently published the use of arene sulfonyl chlorides instead of aryl halides to achieve these reactions.[7] This contribution is conceptually interesting because it is the first general method involving the oxidative insertion of Pd(0) into the Ph−S bond[8] that increases the scope of the Mizoroki−Heck reaction, so far limited to aryl halides. However, to our knowledge, the use of other sulfur compounds such as aryl thioethers, aryl sulfoxides, and aryl sulfones as substrates of these reactions catalyzed with Pd in a Heck reaction has never been reported.[9] In this paper, we report our results concerning the behavior of thioethers,

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(7) (a) Dubbaka, S. R.; Vogel, P. *J. Am. Chem. Soc.* **2003**, *125*, 15292. (b) Dubbaka, S. R.; Vogel, P. *Org. Lett.* **2004**, *6*, 95. (c) Dubbaka, S. R.; Vogel, P. *Adv. Synth. Catal.* **2004**, *346*, 1793. (d) Dubbaka, S. R.; Vogel, P *Chem. Eur. J.* **2005**, *11*, 2633. (e) For a review on sulfur compounds as electrophilic reagents in metal catalyzed reactions, see: Dubbaka, S. R.; Vogel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 7674.

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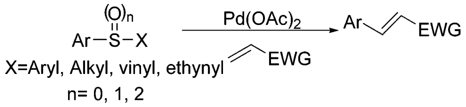
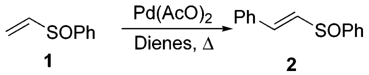
sulfoxides, and sulfones which demonstrate that some of the arylsulfinyl and arylsulfonyl derivatives are also able to undergo the oxidative addition of Pd in their Ar−S bond and therefore may be used in the Mizoroki−Heck reaction with deactivated olefins (Scheme 1).

Scheme 1



In the search for new conditions and catalysts to control the π-facial selectivity of the asymmetric Diels−Alder reactions of vinyl sulfoxides,[10] we found that compound **2** (Scheme 2) was formed as a byproduct in low but significant yield when vinyl phenyl sulfoxide was heated with dienes for long periods of time in the presence of $Pd(OAc)_2$.

Scheme 2

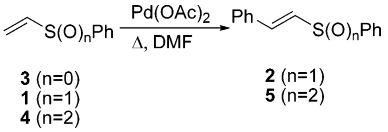


To rationalize this result, we assumed the oxidative addition of Pd into the C−S bond as the initial step in a Mizoroki−Heck- type process with the vinyl sulfoxide acting as an acceptor (Scheme 2). However, when we searched the literature for results which could support this explanation, we realized that such processes had never been reported for sulfoxides. This prompted us to investigate this reaction.

We first studied the reactions of vinyl phenyl thioether (**3**), vinyl phenyl sulfoxide (**1**), and vinyl phenyl sulfone (**4**) with 1 equiv of $Pd(OAc)_2$ under different conditions, obtaining the results indicated in Table 1.

Thioether **3** did not react under any of the conditions used. After 3 days at 120 °C in DMF it remains unaltered (entry 1, Table 1). By contrast, sulfoxide **1** slowly reacted into the desired derivative **2** (entries 2 and 3, Table 1). The starting material completely disappeared after 5 days at 110 °C. Sulfone **4** could also be transformed into **5** under similar conditions (entries 4−6, Table 1). The reactivity of the sulfone is higher than that of the sulfoxide (compare entries 2 and 3 with 5 and 6, respectively, Table 1). These results suggest that intramolecular Mizoroki−Heck reactions are only possible for sulfoxides and sulfones, whereas thioethers are not able to react under the same conditions.

Table 1. Reactions of Vinylthio Derivatives with Stoichiometric $Pd(OAc)_2$ under Different Conditions



entry	n	T (°C)	time (days)	product	conversion (isolated yield) (%)
1	0	120	3		
2	1	60	6	**2**	65
3	1	120	5	**2**	100 (57)
4	2	60	3	**5**	54
5	2	60	6	**5**	100 (51)
6	2	120	3	**5**	100 (55)[11]

We then tried the crossed reactions of ethyl acrylate and the aryl thio derivatives **1**, **3**, or **4**[12] with the aim of obtaining the cinnamyl esters resulting from the transfer of the phenyl group from these thio derivatives. The results were identical to those shown in Table 1, thus indicating that the sulfinyl and sulfonyl ethylenes are much more efficient as acceptors than the conjugated esters. The reactions of compounds such as $PhSO_nPh$ and $PhSO_nMe$ ($n = 0-2$), which do not exhibit acceptor properties, with ethyl acrylate and $Pd(OAc)_2$ under different conditions were unfruitful, showing that these thio derivatives cannot undergo oxidative addition onto the Ph−S bond.

Before exploring other substrates, it was necessary to look for conditions that allowed an efficient use of the $Pd(OAc)_2$ in catalytic amounts. Therefore, we investigated the influence of many additives and bases (Et_3N, AcONa, K_2CO_3, and Na_2CO_3). Finally, we found that only Ag_2CO_3 was efficient (AgOAc only provides 10% yield under catalytic conditions). Thus, compound **5** can be obtained in 59% isolated yield by heating **4** in DMF at 110 °C with Ag_2CO_3 (10 mol %) and 5 mol % of the $Pd(OAc)_2$. The complete conversion of **4** can also be achieved with 1 mol % of catalyst, but the reaction is not so clean, the isolated yield is lower (55%), and it required longer reaction time to be complete (4 days). Under catalytic conditions, sulfoxide **1** evolved into compound **2** but with very low conversion, which suggests that the process is not catalytic starting from sulfoxides.

A reasonable mechanism compatible with our data is indicated in Scheme 3. The first step would involve the coordination of the palladium to the double bond of the sulfone (thus explaining the absence of reactivity of diaryl and aryl alkyl sulfones), making easier (entropic reasons) the oxidative addition to the Ar−S bond (second step). Finally, coordination of palladium to the double bond of the acceptor molecule (easier for **1** and **4** than for acrylic esters), insertion, and β-elimination complete the catalytic cycle (Scheme 3).

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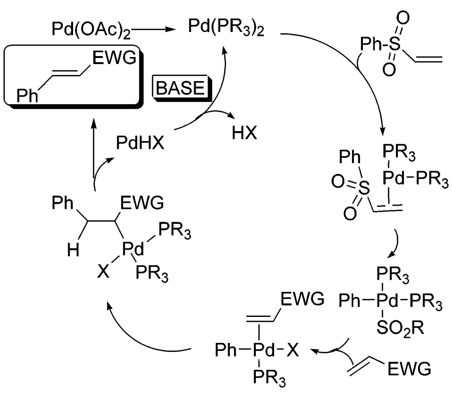
(9) A desulfonylative Kumada reaction catalyzed by $Ni(acac)_2$ was described in: (a) Clayden, J.; Cooney, J. J. A.; Julia, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 7. Suzuki and Negishi reactions have been carried out with vinyl sulfoxides: See: (b) Ma, S.; Ren, H.; Wei, Q. *J. Am. Chem. Soc.* **2003**, *125*, 4817.

(10) García Ruano, J. L.; Alemparte, C.; Clemente, F. R.; González Gutierrez, L.; Gordillo, R.; Martín Castro, A. M.; Rodríguez Ramos, J. H. *J. Org. Chem.* **2002**, *67*, 2919 and references therein.

(11) Despite the fact that the yield (55%) is lower than the conversion (100%), no other byproduct was detected in the reaction mixture after the workup.

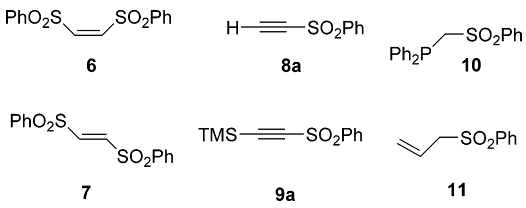
(12) All the reactions were carried out by using 2.20 mmol of the ester, 0.55 mmol of substrate and catalyst, and 2 mL of dried DMF.

Scheme 3



This mechanistic proposal suggests that the coordination of palladium to the double bond is required as a preliminary step to its oxidative addition into the Ar−S bond. Moreover, to achieve the cross-coupling reaction it would be necessary to decrease the acceptor character of the sulfones without altering their capability to undergo oxidative addition.

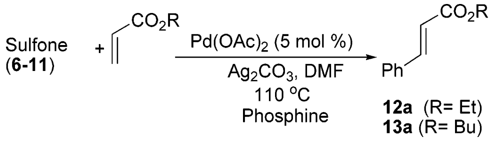
In this sense, we have studied the behavior of the sulfones depicted in Figure 1. The second sulfonyl group present in sulfones **6** and **7** should impose steric restrictions to the coupling process and thus decrease their reactivity and allow the reaction with other acceptors. Sulfones **10** and **11** cannot act as acceptors but support a functional group able to associate with Pd in the first step. Finally, the alkynyl sulfones **8a** and **9a** were chosen because the triple bonds are not common acceptors in Heck-type reactions. All of them were found to give cross-coupling with acrylic esters. A summary of the most significant results is given in Table 2. Starting from the (*Z*)-sulfone **6**, we found that the use of butyl esters provides better yields than ethyl esters (compare entries 1 and 2, Table 2). The addition of phosphines improved the yields in some cases. We have studied the influence of several phosphines on the reactivity. Many of them have a negative influence (PPh$_3$, dppf, dppp, and P^t-Bu$_3$),[13] but the addition of tricyclohexyl phosphine, PCy$_3$ (10%), improves the isolated yield of compound **12a** (68%) and reduces the required time for completion of the reaction (1 day, entry 3, Table 2).



6 **8a** **10** **7** **9a** **11**

Figure 1. Other sulfones used in this study.

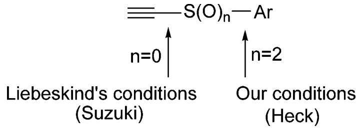
Table 2. Reactions of the Sulfones **6**−**11** with Alkyl Acrylates and Pd(OAc)$_2$ (5 mol %) under Different Conditions



entry	phosphine	sulfone	R	time	yield (%)
1		**6**	Et	3 d	42
2		**6**	Bu	3 d	53
3	P(Cy)$_3$ (10%)	**6**	Bu	24 h	68
4		**7**	Bu	3 d	53
5	P(Cy)$_3$ (10%)	**7**	Bu	30 h	56
6		**8a**	Bu	3 d	41
7	P(Cy)$_3$ (10%)	**8a**	Bu	3 d	53
8	P(Cy)$_3$ (10%)	**9a**	Bu	4 d	45
9		**10**	Bu	2 d	25
10		**11**	Bu	4 d	65

The use of the (*E*)-sulfone **7** gave similar results (entries 4 and 5, Table 2) but lower yields when the reactions were conducted under PCy$_3$ (compare entries 3 and 5, Table 2). The reactions with the alkynyl sulfones **8a** and **9a** were also efficient, with slightly better results when using the silylated compounds (entries 5−8, Table 2). At this point, it is remarkable that Liebeskind and co-workers [14] had found that the oxidative addition occurrs at the C(sp)−S bond for alkynyl arylthioethers, [CuTC, Pd(PPh$_3$)$_4$, THF at 45−50 °C], whereas in the case of the sulfones **8** and **9** it takes place at the Ar−S bond, which reveals the influence of the oxidation state at sulfur on the course of the reaction (Scheme 4).

Scheme 4



Reactions of sulfone **10** with butyl acrylate also yielded compound **13a** (entry 9). Despite the low yield obtained in this reaction, this result is highly significant because it supports the suggested need of the existence of a group able to fix the palladium as a preliminary step to the oxidative coupling. Finally, reaction of ethyl acrylate and the allyl sulfone **11** under Pd(OAc)$_2$ catalysis (entry 10, Table 2), yielding compound **13a**, pointed out that the coordination to the palladium catalyst is once more an essential step in this Heck reaction.

The last part in this research has been to study the influence of the electronic effects of the substituents at the aryl ring on the relative ease of the oxidative addition. We have chosen alkynyl aryl sulfones **8** and **9** as they were

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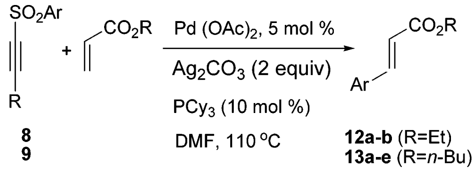
(13) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

(14) Savarin, C.; Srogl, J.; Liebeskind L. S. *Org. Lett.* **2001**, *3*, 91.

obtained readily from alkynes.[13] Their reaction with butyl acrylate afforded cinnamic esters **12** and **13** (Table 3) exclusively. This confirms that triple bonds exhibit poorer acceptor character than the double bond of the butyl acrylate (Table 3) in this oxidative addition.

Table 3. Different Reactions to Aryl Ethynyl Sulfones



entry	Ar	R′	R	time	product	yield (%)
1	*p*-MeO-C_6H_4 (**9b**)	TMS	Bu	3 d	**13b**	30
2	Ph (**8a**)	H	Bu	3 d	**13a**	53
3	Ph (**9a**)	TMS	Et	3 d	**12a**	40
4	Ph (**9a**)	TMS	Bu	3 d	**13a**	45
5	*p*-NO_2-C_6H_4 (**9c**)	TMS	Bu	3 d	**13c**	55
6	*p*-Cl-C_6H_4 (**9d**)	TMS	Bu	3 d	**13d**	25
7	*p*-Cl-C_6H_4 (**8d**)	H	Bu	3 d	**13d**	35
8	*p*-CF_3-C_6H_4 (**8e**)	H	Bu	30 h	**13e**	47
9	*p*-Me-C_6H_4 (**8f**)	H	Bu	3 d	**13f**	41

The only moderate yield (40%) obtained in the transfer of the phenyl group (entry 4, Table 3) is worse (30%) when electron-donating groups, such as methoxy group, are present on the ring (entry 1, Table 3). Analogously, the transfer of the *p*-Tol group is slightly less efficient than that of the Ph group (compare entries 9 and 2, Table 3). On the contrary, the electron-withdrawing effect of the *p*-NO_2 and *p*-CF_3 groups improves the yields (compare entries 5 and 8 with 3 and 4, respectively). The presence of chlorine in the aryl group had a negative effect on the yield (compare entries 6 and 7 in Table 3 with 4 and 2, respectively). Finally, as occurred for phenyl derivatives **8a** and **9a** (entries 2 and 4), lower yields were obtained starting from the TMS-protected acetylene **9d** than from the unprotected acetylene **8d** (compare entries 6 and 7). Therefore, the use of *n*-butyl esters instead of ethyl esters (entries 3 and 4) also improves the yields. It is remarkable that under these conditions only compounds **12d** and **13d**, resulting in the C−S oxidative addition, were identified in the reactions of chloro derivatives **8d** and **9d**. We could not detect the presence of the products corresponding to the C−Cl oxidative addition in the crude reaction.

In conclusion, the desulfonative Mizoroki−Heck-type arylation of alkenes can be carried out using a sulfone bearing an additional coordinating group, such as a conjugated or allylic double bonds, triple bond, and methylphosphine attached to the sulfur function. Maximum oxidation of the sulfur atom (SO_2) was necessary to obtain the best yields.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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