EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201403211

Room-Temperature Direct Alkenylation of 3-Arylsydnones

Yiwen Yang*[a] and Chunxiang Kuang*[b]

Keywords: Synthetic methods / C–H activation / Alkenylation / Nitrogen heterocycles / Palladium

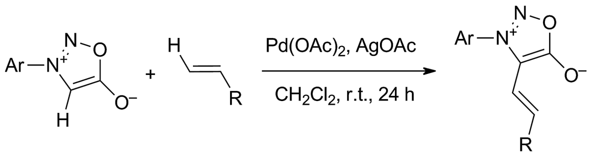
A new efficient method for the direct alkenylation of 3-arylsydnones by palladium-catalyzed C–H functionalization was developed. The reaction proceeded smoothly at room temperature and delivered the product in yields up to 83 %.

Introduction

In recent years, transition-metal-catalyzed C–H bond activation reactions have gained interest from academic and industrial chemists,[1] because they can significantly simplify and shorten a synthetic route and because they allow the utilization of affordable, readily available starting materials. The Pd-catalyzed direct cross-coupling of arenes and olefins, also called the oxidative Heck-type reaction or the Fujiwara–Moritani reaction,[2] is a representative of such reactions. The transformation has high atom economy because the formation of a C–C bond occurs from two C–H bonds. However, previous reports on these reactions indicated that the processes often require the use of elevated temperatures (80 to 180 °C),[3] which severely limits the compatibility of the substrates and their large-scale applications. Developing milder reaction conditions that can proceed at ambient temperature is necessary in widening the applicability of these transformations.

Sydnones are unique, dipolar, five-membered heterocycles that are part of an intriguing family of mesoionic compounds.[4] Over the years, sydnones have gained significant interest because of their biological value as antibacterial,[5] antiinflammatory,[6] antimalarial,[7] analgesic, antipyretic,[8] and antineoplastic[9] agents, in addition to their potential use as therapeutic agents,[9] liquid crystals,[10] and electrolytic solvents.[11] Previous research on the olefination of sydnones focused on the use of sydnones (or 4-halosydnones) and alkenyl halides (or alkenyl boronic acids) as the starting materials;[12] these processes often need preformation of the alkenyl halide, alkenyl boronic acid, or 4-halosydnone, which leads to low atom economy of these transformations. The direct alkenylation of 3-arylsydnones by alkenes offers a cleaner and more efficient method of meeting such goals; no example of such a transformation has been reported. Considering the great medicinal significance and applications of sydnones and inspired by the oxidative Heck-type reaction, we became interested in the use of new methods for the direct alkenylation of sydnones under mild and operationally simple conditions.

In this paper, we report a new and convenient method for the oxidative coupling of 3-arylsydnones with alkenes through Pd-catalyzed C–H bond functionalization. The direct alkenylation of 3-arylsydnones at room temperature by the oxidative Heck-type reaction is exploited (Scheme 1).



Scheme 1. Direct alkenylation of 3-arylsydnones.

Results and Discussion

To confirm the optimum reaction conditions, we selected the reaction of 3-*p*-tolylsydnone (**1a**) with styrene (**2a**) as a model reaction and conducted the experiment under various reaction conditions. Table 1 shows that upon treating **1a** with **2a** (2.0 equiv.) in the presence of $Pd(OAc)_2$ (10 mol-%) and $K_2S_2O_8$ (2.0 equiv.) in 1,2-dichloroethane (DCE) at 25 °C for 24 h, product **3a** was isolated in 35% yield (Table 1, entry 1). If the temperature was increased to 60, 90, and 120 °C, the yield decreased to 30, 32, and 28%, respectively (Table 1, entries 2–4). Different solvents were examined. If the DCE solvent was replaced by dichloromethane, ethoxyethane, acetone, or acetonitrile, product **3a** was obtained in 42, 33, 37, or 15% yield, respectively (Table 1, entries 5–8). Various oxidants were studied. Upon using O_2 (101.3 kPa), $Cu(OAc)_2$, benzoquinone (BQ), or no oxidant, the yield of product **3a** was 26, 24, 27, or 20%,

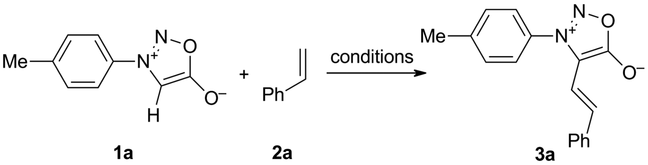
---

[a] Department College of Biological, Chemical Sciences and Engineering, Jiaxing University,
118 Jiahang Road, Jiaxing 314001, P. R. China
E-mail: yangyiwen@mail.zjxu.edu.cn
http://cbcse.zjxu.edu.cn/home/article/article/id/144/model/teachers
[b] Department of Chemistry, Tongji University,
1239 Siping Road, Shanghai 200092, China
E-mail: kuangcx@tongji.edu.cn
http://chemweb.tongji.edu.cn/Teachers/Details/a1a31ffb-88aa-4733-8fa5-8db01611b440

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403211.

respectively (Table 1, entries 9–12). Surprisingly, if Ag_2CO_3 or AgOAc was used as the oxidant, product **3a** was obtained in 76 or 81% yield, respectively (Table 1, entries 13 and 14). Upon reducing the dosage of $Pd(OAc)_2$ to 0.05 and 0.02 equiv., the yields decreased to 65 and 52% (Table 1, entries 15 and 16). The effects of different catalysts on the formation of **3a** were also remarkable. Upon using CuI, $Cu(OAc)_2$, or $FeCl_3$ as the catalyst, product **3a** was not obtained (Table 1, entries 17–19). Ultimately, the optimized reaction conditions were determined to include $Pd(OAc)_2$ (0.1 equiv.) as the catalyst and AgOAc (2.0 equiv.) as the oxidant in dichloromethane as the solvent at 25 °C with a **1a**/**2a** molar ratio of 1:2 in air for 24 h (Table 1, entry 14).

Table 1. Screening for optimal reaction conditions.[a]



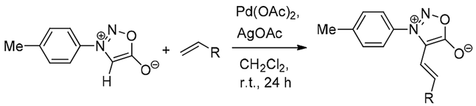
1a **2a** **3a**

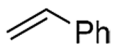
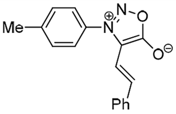
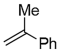
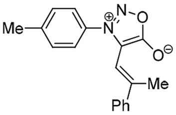
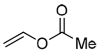
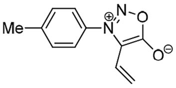
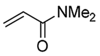
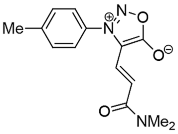
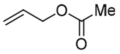
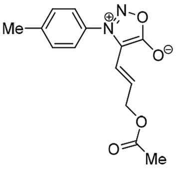
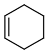
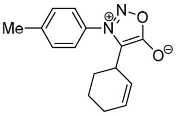
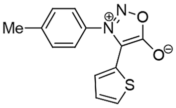
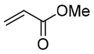
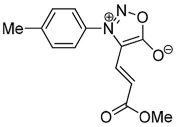
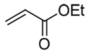
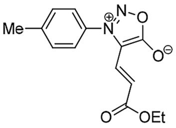
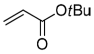
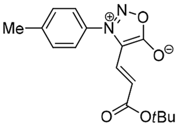
Entry	Catalyst	Oxidant	Solvent	T [°C]	Yield[b] [%]
1	$Pd(OAc)_2$	$K_2S_2O_8$	DCE	25	35
2	$Pd(OAc)_2$	$K_2S_2O_8$	DCE	60	30
3	$Pd(OAc)_2$	$K_2S_2O_8$	DCE	90	32
4	$Pd(OAc)_2$	$K_2S_2O_8$	DCE	120	28
5	$Pd(OAc)_2$	$K_2S_2O_8$	CH_2Cl_2	25	42
6	$Pd(OAc)_2$	$K_2S_2O_8$	Et_2O	25	33
7	$Pd(OAc)_2$	$K_2S_2O_8$	acetone	25	37
8	$Pd(OAc)_2$	$K_2S_2O_8$	CH_3CN	25	15
9	$Pd(OAc)_2$	O_2[c]	CH_2Cl_2	25	26
10	$Pd(OAc)_2$	$Cu(OAc)_2$	CH_2Cl_2	25	24
11	$Pd(OAc)_2$	BQ	CH_2Cl_2	25	27
12	$Pd(OAc)_2$	none	CH_2Cl_2	25	20
13	$Pd(OAc)_2$	Ag_2CO_3	CH_2Cl_2	25	76
14	$Pd(OAc)_2$	AgOAc	CH_2Cl_2	25	81
15	$Pd(OAc)_2$[d]	AgOAc	CH_2Cl_2	25	65
16	$Pd(OAc)_2$[e]	AgOAc	CH_2Cl_2	25	52
17	CuI[f]	none	CH_2Cl_2	25	0
18	$Cu(OAc)_2$[f]	none	CH_2Cl_2	25	0
19	$FeCl_3$[g]	none	CH_2Cl_2	25	0

[a] Reaction conditions: A mixture of **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (0.1 equiv., unless otherwise noted), oxidant (2 equiv.), and solvent (4 mL) was stirred in a sealed tube for 24 h. [b] Yield of isolated product. [c] 101.3 kPa. [d] 0.05 equiv. [e] 0.02 equiv. [f] 0.2 equiv. [g] 0.3 equiv.

To extend the present reaction, we allowed **1a** to react with various alkenes under the optimized reaction conditions. These results are presented in Table 2. Alkenes such as α-menthylstyrene (**2b**), acetates **2c** and **2e**, acrylamide (**2d**), cyclohexene (**2f**), thiophene (**2g**), and acrylates **2h** and **2i** reacted with **1a** to provide the coupled products in moderate to good yields, whereas α-menthylstyrene (**2b**) and thiophene (**2g**) resulted in slightly lower yields (Table 2, entries 2 and 7). This may be caused by steric hindrance of **2b** or the low conversion of **2b** and **2g** at room temperature. Interestingly, the use of vinyl acetate (**2c**) and cyclohexene (**2f**) as the coupling partner led to the formation of terminal alkene **3c** and 4-(cyclohex-2-enyl) product **3f**, respectively (Table 2, entries 3 and 6). The latter may undergo double-

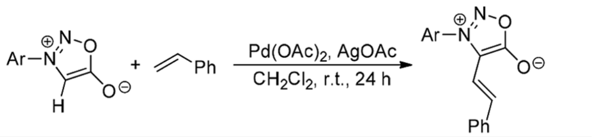
Table 2. Direct alkenylation of 3-*p*-tolylsydnone with various alkenes.[a]

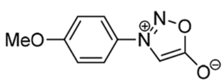
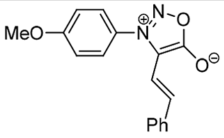
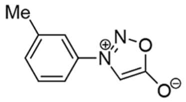
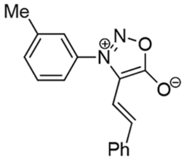
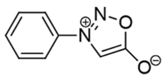
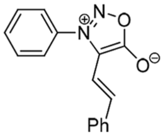
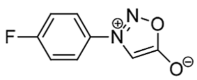
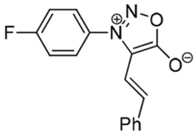
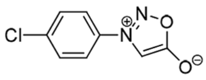
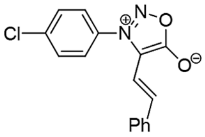
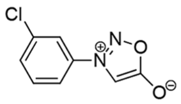
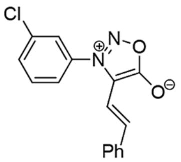
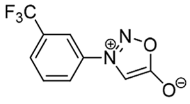
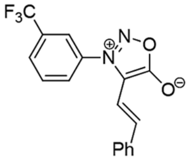
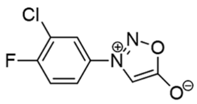
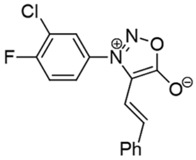


Entry	Alkene **2**	Product **3**	Yield[b] [%]
1	 **2a**	 **3a**	81
2	 **2b**	 **3b**	22
3	 **2c**	 **3c**	75
4	 **2d**	 **3d**	66
5	 **2e**	 **3e**	44
6	 **2f**	 **3f**	53
7	 **2g**	 **3g**	20
8	 **2h**	 **3h**	61
9	 **2i**	 **3i**	56
10	 **2j**	 **3j**	40

[a] Reaction conditions: A mixture of **1a** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), AgOAc (0.4 mmol), and CH_2Cl_2 (4 mL) was stirred in a sealed tube at 25 °C for 24 h. [b] Yield of isolated product.

Table 3. Direct alkenylation of 3-arylsydnones with styrene.[a]



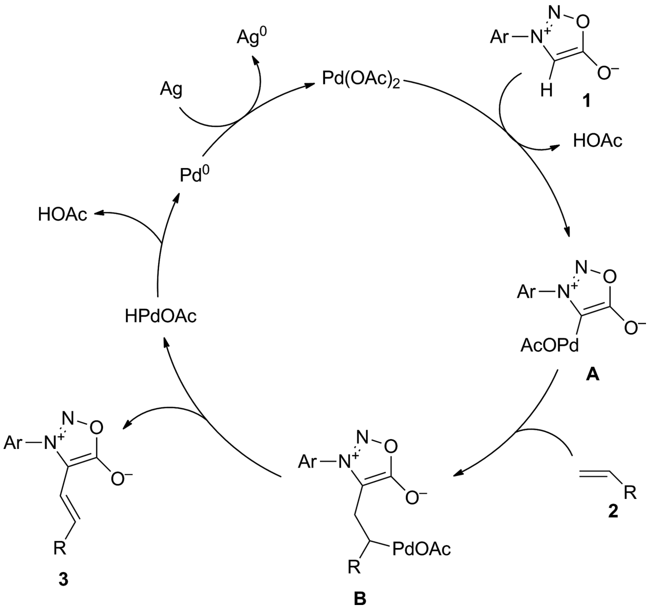
Entry	3-Arylsydnone **1**	Product **3**	Yield[b] [%]
1	 **1b**	 **3k**	83
2	 **1c**	 **3l**	60
3	 **1d**	 **3m**	50
4	 **1e**	 **3n**	44
5	 **1f**	 **3o**	37
6	 **1g**	 **3p**	41
7	 **1h**	 **3q**	36
8	 **1i**	 **3r**	24

[a] Reaction conditions: A mixture of **1** (0.2 mmol), **2a** (0.4 mmol), Pd(OAc)$_2$ (0.02 mmol), AgOAc (0.4 mmol), and CH$_2$Cl$_2$ (4 mL) was stirred in a sealed tube at 25 °C for 24 h. [b] Yield of isolated product.

bond isomerization,[13] and the cause of the former may be β-OAc elimination.[14]

The scope of the 3-arylsydnones was also examined, and the results are summarized in Table 3. 3-Phenylsydnone (**1d**) and its derivatives with electron-donating groups, such as methoxy (see compound **1b**) and methyl (see compound **1c**), or electron-withdrawing groups, including halo (see compounds **1e–g** and **1i**) and trifluoromethyl (see compound **1h**), on their aryl rings were smoothly alkenylated with styrene in moderate to good yields (Table 3, entries 1–8). Compared with **1d**, the presence of an electron-donating group in the aryl ring of 3-arylsydnone (see compounds **1b** and **1c**) remarkably increased the reaction yield (Table 3, entries 1–3). By contrast, the presence of one or two electron-withdrawing substituents on the aryl ring of 3-arylsydnone (see compounds **1e–i**) led to reactions that provided relatively low yields of product **3** (Table 3, entries 4–8). Generally, substrates **1** consisted of electron-donating groups that exhibited stronger electron-donating effects, and this resulted in higher yields; substrates **1** with electron-donating substituents in the *para* position provided higher yields than those with substituents in the *meta* position. These observations are in contrast to the behavior of substrates **1** containing electron-withdrawing groups.

On the basis of the typical mechanism for Pd-catalyzed dehydrogenative Heck reactions,[1a,3c] a possible reaction mechanism is shown in Scheme 2. Initially, electronic attack of Pd^{II} on 3-arylsydnone **1** and subsequent deprotonation form species **A**,[15] which inserts into the alkene to provide intermediate **B**. This step is followed by β-hydride elimination, which results in palladium hydride and product **3**. Reductive elimination of HPdOAc results in Pd^0 and acetic acid. Pd^{II} is regenerated from the oxidation of Pd^0 by silver acetate.



Scheme 2. Possible mechanism for the formation of **3**.

Conclusions

In summary, a mild and efficient method for the direct palladium(II)-catalyzed alkenylation of 3-arylsydnones was developed. The reaction was conducted at room temperature and provided the coupled product in moderate to good yields. These products are important heterocyclic compounds that are used in medicinal and biological research.

Experimental Section

General Procedure for the Synthesis of Product 3: A mixture of 3-arylsydnone **1** (0.2 mmol), alkene **2** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), AgOAc (0.4 mmol), and dichloromethane (4 mL) was stirred in a sealed tube at room temperature for 24 h. After the reaction was complete (as monitored by TLC), the solvent was evaporated in vacuo. The resulting residue was purified by preparative TLC (petroleum ether/ethyl acetate, 4:1 *v*/*v*) to yield **3**.

Supporting Information (see footnote on the first page of this article): Spectral data and copies of the ^{1}H NMR and ^{13}C NMR spectra for all products **3**.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (NSFC) (grant number 21272174), the Key Projects of Shanghai in Biomedicine (grant number 08431902700), and the Scientific Research Foundation of the State Education Ministry for Returned Overseas Chinese Scholars. The authors also thank the Center for Instrumental Analysis at Tongji University, China.

---

[1] a) X. Chen, K. M. Engle, D. Wang, J. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; *Angew. Chem.* **2009**, *121*, 5196; b) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879.

[2] S. Moritani, Y. Fujiwara, *Tetrahedron Lett.* **1967**, *8*, 1119.

[3] a) H. Weissman, X. Song, D. Milstein, *J. Am. Chem. Soc.* **2001**, *123*, 337; b) C. Ying, S. Yan, W. Duan, *Org. Lett.* **2014**, *16*, 500; c) J. Wu, X. Cui, L. Chen, G. Jiang, Y. Wu, *J. Am. Chem. Soc.* **2009**, *131*, 13888; d) C. Wang, H. Chen, Z. Wang, J. Chen, Y. Huang, *Angew. Chem. Int. Ed.* **2012**, *51*, 7242; *Angew. Chem.* **2012**, *124*, 7354.

[4] a) F. H. C. Stewart, *Chem. Rev.* **1964**, *64*, 129; b) D. L. Browne, J. P. A. Harrity, *Tetrahedron* **2010**, *66*, 553.

[5] M. A. Moustafa, M. M. Gineinah, M. N. Nasr, W. A. H. Bayoumi, *Arch. Pharm.* **2004**, *337*, 427.

[6] J. B. Hill, R. E. Ray, H. Wagner, R. L. Aspinall, *J. Med. Chem.* **1975**, *18*, 50.

[7] D. J. McCaustland, W. H. Burton, C. C. Cheng, *J. Heterocycl. Chem.* **1971**, *8*, 89.

[8] K. Satyanarayana, M. N. A. Rao, *J. Pharm. Sci.* **1995**, *84*, 263.

[9] C. S. Dunkley, C. Thoman, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2899.

[10] W. Chan, W. Zhang, Y. Szeto, *Mater. Lett.* **2000**, *42*, 280.

[11] Y. Sasaki, O. Hirobomi, M. Handa, *Nippon Kagaku Kaishi* **1993**, *11*, 1217.

[12] a) V. N. Kalinin, P. M. Se, *J. Organomet. Chem.* **1988**, *352*, C34; b) A. Rodriguez, R. V. Fennessy, W. J. Moran, *Tetrahedron Lett.* **2009**, *50*, 3942; c) C. Wu, Y. Fang, R. C. Larock, F. Shi, *Org. Lett.* **2010**, *12*, 2234; d) D. L. Browne, J. B. Taylor, A. Plant, J. P. A. Harrity, *J. Org. Chem.* **2009**, *74*, 396.

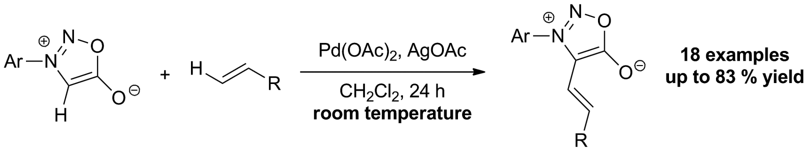
[13] X. Wu, J. Zhou, *Chem. Commun.* **2013**, *49*, 4794.

[14] J. Lindh, J. Saevmarker, P. Nilsson, P. J. R. Sjoeberg, M. Larhed, *Chem. Eur. J.* **2009**, *15*, 4630.

[15] a) H. Ge, M. J. Niphakis, G. I. Georg, *J. Am. Chem. Soc.* **2008**, *130*, 3708; b) Z. Lu, F. Luo, L. Wang, G. Zhu, *J. Org. Chem.* **2013**, *78*, 10894.

Received: September 13, 2014

C–H Activation



A new efficient method for the direct alkenylation of 3-arylsydnones by palladium-catalyzed C–H functionalization is developed. The reaction proceeds smoothly at room temperature and delivers the products in yields up to 83%.

Y. Yang,* C. Kuang* **1–5**

Room-Temperature Direct Alkenylation of 3-Arylsydnones

Keywords: Synthetic methods / C–H activation / Alkenylation / Nitrogen heterocycles / Palladium