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Palladium-Catalyzed Desulfitative Heck-Type Reaction of Aryl Sulfinic Acids with Alkenes

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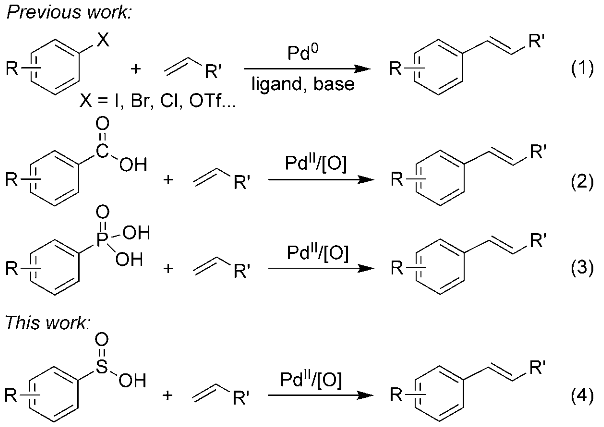
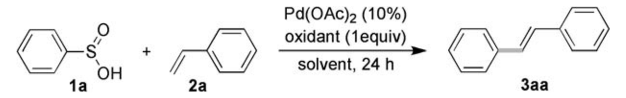
The Heck reaction is a powerful tool for the arylation of alkenes in organic synthesis[1–3] such as natural product total synthesis.[4] In the Heck reaction, the arylating reagents are traditionally aryl iodides and aryl bromides (Scheme 1, [Eq. (1)]).[1] A plethora of variants[2–4] for the aryl halides have emerged since its discovery in the early 1970s. Aryl triflates, aryl diazonium salts, diaryl iodonium salts, aroyl chlorides, and aroyl anhydrides as aryl palladium precursors have subsequently been developed.[2,4] The unreactive aryl chlorides can also be employed in the Heck reaction by using bulky, electron-rich phosphanes and carbenes as the ligands.[3] In contrast, aromatic organic acids have been seldom utilized in the Heck reaction, and until now only aryl carboxylic acids[5] and aryl phosphonic acids[6] have been described as the source of aryl groups in the Heck reaction (Scheme 1, [Eq. (2) and (3)]). The most striking difference in the reaction mechanisms for the conventional Heck reaction and the Heck-type reaction of aromatic organic acids lies in the different pathways leading to the aryl palladium(II) species. The former is generated by the oxidative addition of aryl halides or pseudohalide species to palladium(0),[2–4] whereas the latter is produced by the initiation of palladium(II) and decarboxylative C–C bond cleavage[5]/C–P bond cleavage.[6] Herein, we disclose the Pd-catalyzed Heck-type reaction of another kind of aromatic organic acid, that is, aryl sulfinic acids, with alkenes initiated by a palladium(II) species (Scheme 1, [Eq. (4)]).



Scheme 1. Various Heck-type reactions.

In our initial study, we investigated the Heck-type reaction of benzenesulfinic acid (**1a**) with styrene (**2a**) in the presence of a palladium catalyst (10 mol%) to optimize the reaction conditions with various oxidants and solvents. Silver salts were first chosen as the oxidant with dioxane as the solvent, and it was found that Ag_2CO_3 was more efficient than AgOAc, affording (*E*)-stilbene in 76% and 51% yield, respectively (entry 2 vs. entry 1, Table 1). In comparison, $K_2S_2O_8$ and O_2 were not proper oxidants and dramati-

Table 1. Heck-type reaction of benzenesulfinic acid with styrene under various conditions.[a]



Entry	Oxidant (equiv)	Solvent [°C]	Yield [%][b]
1	AgOAc (1)	dioxane (100)	51
2	Ag_2CO_3 (1)	dioxane (100)	76
3	$K_2S_2O_8$ (1)	dioxane (100)	46
4	O_2[c]	dioxane (100)	25
5	**$Cu(OAc)_2 \cdot H_2O$ (1)**	**dioxane (100)**	**85**
6	$CuCl_2 \cdot 2H_2O$ (1)	dioxane (100)	80
7	$CuBr_2$ (1)	dioxane (100)	83
8	$Cu(OAc)_2 \cdot H_2O$ (0.5)	dioxane (100)	55
9	$Cu(OAc)_2 \cdot H_2O$ (2)	dioxane (100)	78
10	$Cu(OAc)_2 \cdot H_2O$ (1)	NMP (100)	44
11	$Cu(OAc)_2 \cdot H_2O$ (1)	DMSO (100)	39
12	$Cu(OAc)_2 \cdot H_2O$ (1)	EtOH (78)[d]	51
13	$Cu(OAc)_2 \cdot H_2O$ (1)	AcOH (100)	78
14	$Cu(OAc)_2 \cdot H_2O$ (1)	CH_3CN (81)[d]	37
15	$Cu(OAc)_2 \cdot H_2O$ (1)	DCE (83)[d]	43
16	$Cu(OAc)_2 \cdot H_2O$ (1)	*o*-xylene (100)	56

[a] Unless otherwise specified, all reactions were carried out using 10 mol% of $Pd(OAc)_2$, 0.25 mmol of **1a**, 0.3 mmol of **2a**, and 1.5 mL of solvent under different conditions for 24 h. [b] Yield of isolated product. [c] Under an oxygen atmosphere. [d] Refluxing temperature of the solvent.

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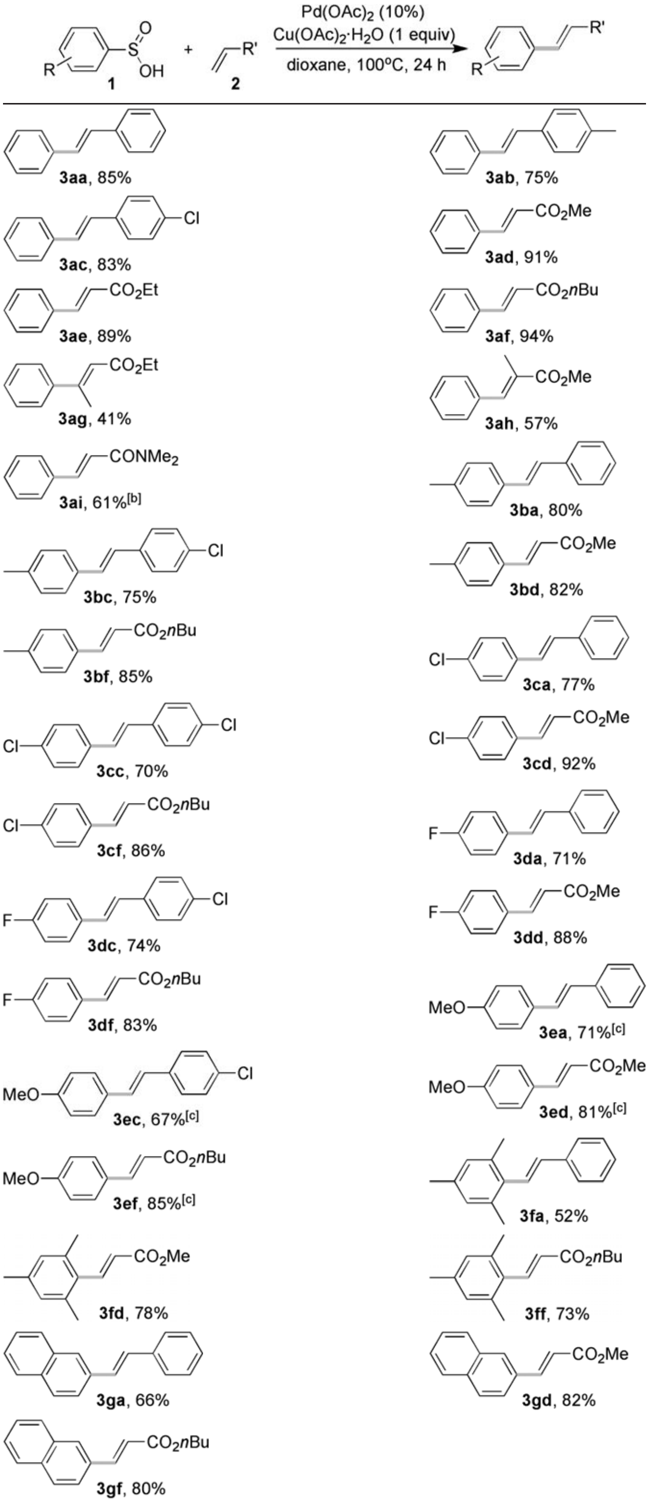
cally reduced the yield to 46 % and 25 %, respectively (entries 3 and 4, Table 1). Pleasingly, when copper sources were employed, (*E*)-stilbene was obtained in excellent yield (entries 5–7, Table 1). Copper(II) acetate proved to be more active than other copper sources, furnishing (*E*)-stilbene in 85 % yield (entry 5, Table 1). Reducing the oxidant loading decreased the yield significantly, while increasing the loading did not improve the yield (entries 8 and 9, Table 1). Further screening of solvents revealed that dioxane was the best solvent; other polar solvents such as *N*-methyl-2-pyrrolidone (NMP), ethanol, and DMF were harmful to this transformation (entries 10–12, Table 1). Interestingly, an isolated yield of 78 % was achieved when acetic acid was used as the solvent (entry 13, Table 1). Several low-polar solvents including acetonitrile, dichloroethane (DCE), and *o*-xylene were also examined under similar conditions, but all gave inferior results compared to dioxane (entries 14–16 vs. entry 5, Table 1). A palladium catalyst is indispensable, as the reaction did not proceed with only silver or copper salts. It is noteworthy that although aryl sulfonyl chlorides have been employed for the Pd-catalyzed desulfitative Heck-type reaction,[7] benzenesulfonic acid, instead of benzenesulfinic acid, proved unreactive towards styrene under our optimal conditions (entry 5, Table 1), and the desired cross-coupling product was not obtained. This result demonstrated the unique properties and privileges of aryl sulfinic acids over aryl sulfonic acids in this desulfitative Heck-type reaction.

Table 2. Heck-type reaction of aryl sulfinic acids with olefins.[a]



3aa, 85%
3ab, 75%
3ac, 83%
3ad, 91%
3ae, 89%
3af, 94%
3ag, 41%
3ah, 57%
3ai, 61%[b]
3ba, 80%
3bc, 75%
3bd, 82%
3bf, 85%
3ca, 77%
3cc, 70%
3cd, 92%
3cf, 86%
3da, 71%
3dc, 74%
3dd, 88%
3df, 83%
3ea, 71%[c]
3ec, 67%[c]
3ed, 81%[c]
3ef, 85%[c]
3fa, 52%
3fd, 78%
3ff, 73%
3ga, 66%
3gd, 82%
3gf, 80%

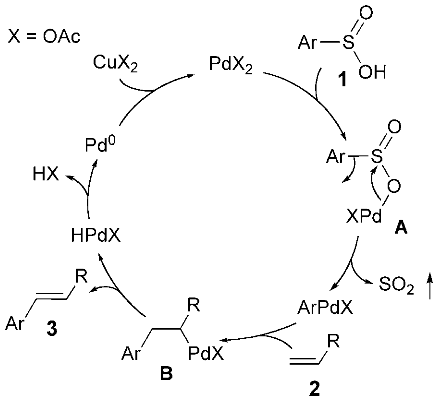
[a] Unless otherwise specified, all reactions were carried out using 0.25 mmol of **1**, 0.3 mmol of alkene **2**, 0.025 mmol (10 mol %) of Pd$(OAc)_2$, and 0.25 mmol of $Cu(OAc)_2 \cdot H_2O$ in dioxane (1.5 mL) at 100 °C for 24 h. [b] AcOH as the solvent at 80 °C for 24 h. [c] 15 mol % of Pd$(OAc)_2$ was used.

With the optimized reaction conditions ($Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2 \cdot H_2O$ (1 equiv), dioxane (1.5 mL), 100 °C, 24 h) in hand, this Pd-catalyzed desulfitative Heck-type reaction was then extended to a wide array of aryl sulfinic acids and styrenes/acrylic derivatives to explore the scope and limitations of the reaction (Table 2). Benzenesulfinic acid (**1a**) reacted efficiently with both electron-rich and -deficient styrenes (**2b** and **2c**), affording the coupling products **3ab** and **3ac** in 75–83 % yields. Acrylic esters such as methyl acrylate (**2d**), ethyl acrylate (**2e**), and *n*-butyl acrylate (**2f**) were better substrates than styrenes, and reacted with **1a** to give products **3ad**, **3ae**, and **3af**, respectively, in higher yields (89–94 %). Intriguingly, **1a** could also react with disubstituted olefins such as (*E*)-ethyl crotonate (**2g**) and methyl methacrylate (**2h**) to generate products **3ag** and **3ah** with high regioselectivity and stereoselectivity, albeit in expectedly lower yields (41–57 %). Although the reaction with acrylic amide (**2i**) under our optimized conditions gave a disappointingly low yield, the desired product **3ai** could be obtained in 61 % yield when the reaction was carried out in acetic acid at 80 °C for 24 h under otherwise the same conditions. To further expand the scope of this reaction, we next examined the coupling reaction of several other aryl sulfinic acids such as 4-methylbenzenesulfinic acid (**1b**), 4-chlorobenzenesulfinic acid (**1c**), 4-fluorobenzenesulfinic acid (**1d**), 4-methoxybenzenesulfinic acid (**1e**), 2,4,6-trimethylbenzenesulfinic acid (**1f**), and 2-naphthylsulfinic acid (**1g**) with different olefin substrates. Aryl sulfinic acids bearing methyl, chloro, and fluoro groups provided the cross-coupling products with either styrene or acrylic esters in high yields (71–92 %). Aryl sulfinic acid **1e** containing the strong electron-donating methoxy group decreased the reactivity, but good yields (67–85 %) could still be achieved with slightly higher catalyst loading. When the 2,4,6 positions of benzenesulfinic acid were substituted with methyl groups, that is, **1 f**, the product yield with styrene was reduced dramatically to 52 %, probably due to the steric hindrance. However, the reaction of **1 f** proceeded smoothly with acrylic esters, producing **3 fd** and **3 ff** in yields of 78 % and 73 %, respectively. Moreover, the reaction of 2-naphthylsulfinic acid was also effective to give the corresponding cross-coupling products **3 ga**, **3 gd**, and **3 gf** in good yields (66–82 %).

As seen from Table 2, only one isomer with *trans*-configuration was identified in each case, reflecting the extremely high regioselectivity and stereoselectivity of our Heck-type reaction. In a conventional Heck reaction, a base and a ligand are usually required for the conversion of the hydridopalladium(II) complex to the active palladium(0) catalyst and the stabilization of the regenerated palladium(0) species, respectively.[1–4] In sharp contrast, our Heck-type reaction did not require any base or ligand.

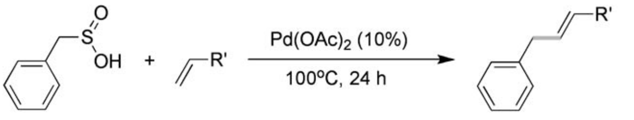
Pioneering work by the Myers group on the Pd-catalyzed decarboxylative Heck reaction is certainly a landmark. Nevertheless, at least one *ortho* substituent for aryl carboxylic acids was necessary for the successful decarboxylative palladation to occur.[5] It was found that a high loading of palladium and silver, excess acid additive, or carbene ligand for the C−C bond fission,[5] and the unusual oxidant Me_3NO with TBAF as the activator for the C−P bond cleavage[6] were crucial in the previous work. Therefore, our protocol, which employed aryl sulfinic acids with catalytic $Pd(OAc)_2$ and inexpensive $Cu(OAc)_2$, has its own merits and is complementary to the existing methodologies.[5,6] Notably, the reaction of sodium *p*-toluenesulfinate with alkenes in the presence of a stoichiometric amount of a palladium(II) salt has been reported,[8] yet our catalytic version is much more efficient.

Although the mechanism of this reaction is not clear right now, we propose a possible pathway compatible with our data (Scheme 2). The first step is presumably a ligand exchange between $Pd(OAc)_2$ and the aryl sulfinic acid providing complex **A**. This step is mechanistically distinct from the first step in the Pd-catalyzed desulfitative Heck-type reaction of aryl sulfonyl chlorides, in which the oxidative addition of Pd^0 to $ArSO_2Cl$ is involved.[7] Elimination of SO_2 from complex **A** generates ArPdX, which inserts into the olefin to give intermediate **B**. A β-H elimination from intermediate **B** furnishes the final coupling product **3** and Pd^0 species. Oxidation of Pd^0 by $Cu(OAc)_2$ regenerates $Pd(OAc)_2$. A palladium(II)-catalyzed pathway with $Cu(OAc)_2$ as an oxidant has also been described for the Heck-type reaction of aryl boronic acids with alkenes.[9]



Scheme 2. Proposed reaction mechanism.

In the conventional Heck reaction, organic halides usually cannot contain β-hydrogens because they are easily eliminated to give olefins.[1] Therefore, the use of aliphatic halides as coupling partners in the Heck reaction is rare and challenging; aliphatic carboxylic and phosphonic acids as the alkyl source have not been described.[5,6] We attempted the Pd-catalyzed reaction of benzylsulfinic acid with 4-chlorostyrene and that with butyl acrylate under our standard conditions, and obtained the desired coupling products **4 ac** and **4 af** only in 6 % yield and in trace amounts, respectively. When tricyclohexylphosphine as ligand was added to and $Cu(OAc)_2$ was removed from the reaction systems, the yields were improved to 22 % and 17 %, respectively (Scheme 3).[10] Although the yields were still low, our results demonstrated the feasibility of the SO_2 extrusion from aliphatic sulfinic acids to form alkyl palladium and subsequent coupling with alkenes.



4ac (R' = 4-Cl-Ph): 6% (22%)
4af (R' = CO2*n*Bu): trace (17%)

Scheme 3. Palladium-catalyzed reaction of benzylsulfinic acid with alkenes.

In conclusion, we have developed an efficient protocol for the desulfitative Heck-type reaction of aryl sulfinic acids with a variety of alkenes in the presence of a catalytic amount of $Pd(OAc)_2$ and cheap $Cu(OAc)_2$ as oxidant. Our method doesn't require a ligand or a base, broadening the scope of Pd-catalyzed coupling reactions. The investigation of aryl sulfinic acids as the aryl source in other coupling reactions is underway.

Experimental Section

General procedure for the Heck-type reaction of aryl sulfinic acids with alkenes catalyzed by $Pd(OAc)_2$: Alkene (**2a–i**, 0.30 mmol) was added to a suspension of aryl sulfinic acid (**1a–g**, 0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), and $Cu(OAc)_2 \cdot H_2O$ (50.0 mg, 0.25 mmol) in dioxane (1.5 mL) with magnetic stirring. The mixture was stirred at 100 °C for 24 h. After completion of the reaction, the solvent was evaporated to dryness in vacuo. The residual was separated on a silica gel column with petroleum ether/ethyl acetate 15/1 as the eluent to get the desired product **3aa–3gf**.

Acknowledgements

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Keywords: alkenes • arylation • cross-coupling • desulfitation • palladium

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[10] The presence of $Cu(OAc)_2$ was detrimental when a ligand was added.

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