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Pd-Catalyzed Desulfitative Heck Coupling with Dioxygen as the Terminal Oxidant

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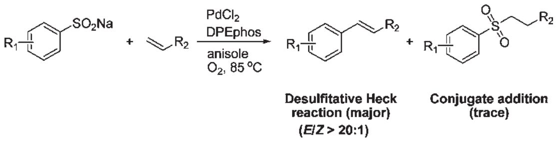
ABSTRACT



A Pd-catalyzed desulfitative Heck-type reaction of aromatic sulfinic acid sodium salts with various olefins is developed with O_2 as the terminal oxidant under mild conditions. The presence of phosphane ligand DPEphos in anisole can significantly enhance the reaction selectivity.

Transition metal-catalyzed C−C and C−heteroatom bond forming reactions are among the most powerful methods in organic synthesis and play a crucial role in medicinal chemistry, fine chemicals, and material science.[1] Among them, the palladium-catalyzed Mizoroki−Heck reaction has proven to be one of the most powerful and versatile processes for C−C double bond formation both in preparative laboratories and in industrial applications.[2] Traditionally, the Heck reaction was defined as the palladium-catalyzed coupling of an aryl halide with an olefinic substrate in the presence of phosphane ligand and base (Scheme 1, eq 1).[3] Other highly efficient catalyst systems have been developed using aryl triflates,[4] diazonium salts,[5] and aroyl halides and sulfonyl halides[6] as aryl sources rather than aryl halides. In recent years, other aryl sources for Mizoroki−Heck-type reactions have been widely studied. Pioneered by Fujiwara and Moritani,[7] oxidative olefination of C−H bonds using alkenes represents a potential atom-economy strategy to functionalize arenes directly (Fujiwara−Moritani reaction).[8] This process is highly attractive in that no prior functionalization of the arene is necessary (eq 2). Another important feature of

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(1) (a) de Meijere, A; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 2004. (b) Diederich, F.; Stang, P. T. *Metal-Catalyzed Cross-coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998. (c) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1998. (d) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004.

(2) Lawrence, N. J. In *Preparation of Alkenes: a Practical Approach*; Williams, J. M. J., Ed.; Oxford University Press: Oxford, UK, 1995.

(3) (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320. F or leading reviews, see:(c) Oestreich, M. *The Mizoroki-Heck Reaction*; Wiley: Chichester, UK, 2009. (d) Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed.* **1994**, *33*, 2379. (e) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (f) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (g) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (h) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449. (i) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (j) Hassan, J.; Sévignon, M.; Gozzi, C.; Schultz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (k) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553. (l) Littke, A. F.; Fu, G. C. *Org. Synth.* **2004**, *81*, 63. (m) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771. (n) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (o) Phan, N. T. S.; Van der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609. (p) Köhler, K.; Pröckl, S. S.; Kleist, W. *Curr. Org. Chem.* **2006**, *10*, 1585. (q) Schmidt, A. F.; Al Halaiqa, A.; Smirnov, V. V. *Synlett* **2006**, 2861. (r) McGlacken, G. P.; Fairlamb, I. J. S. *Eur. J. Org. Chem.* **2009**, 4011.

(4) (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (b) Cacchi, S.; Moreau, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 2271.

(5) (a) Knowles, J. P.; Whiting, A. *Org. Biomol. Chem.* **2007**, *5*, 31. (b) Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1977**, 159. (c) Kikakuwa, K.; Ikenaga, K.; Kono, K.; Toritani, K.; Wade, F.; Matsuda, T. *J. Organomet. Chem.* **1984**, *270*, 277. (d) Beller, M.; Fischer, H.; Kühlein, K. *Tetrahedron Lett.* **1994**, *35*, 8773.

(6) (a) Blaser, H. U.; Spencer, A. *J. Organomet. Chem.* **1982**, *233*, 267. (b) Andrus, M. B.; Liu, J.; Meredith, E. L.; Nartey, E. *Tetrahedron Lett.* **2003**, *44*, 4819. (c) Andrus, M. B.; Liu, J. *Tetrahedron Lett.* **2006**, *47*, 5811. (d) Miura, M.; Hashimoto, H.; Itoh, K.; Nomura, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, *8*, 2207.

(7) (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119. (b) Fujiwara, Y.; Moritani, I.; Matsuda, M. *Tetrahedron* **1968**, *24*, 4819.

(8) For reviews on the Fujiwara−Moritani reaction, see: (a) Ferreira, E. M.; Zhang, H. M.; Sctoltz, B. M. In *The Mizoroki-Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, UK, 2009; p 377. (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (c) Fujiwara, Y.; Jia, C. *Pure. Appl. Chem.* **2001**, *73*, 319. (d) Moritani, I.; Fujiwara, Y. *Synthesis* **1973**, 524. (e) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

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Scheme 1. Transition Metal-Catalyzed Heck-Type Reactions

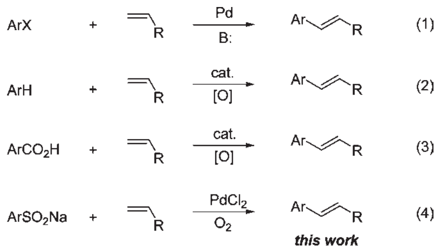
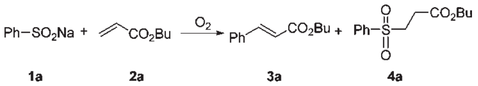


Table 1. Optimization of the Reaction Conditions[a]



				yield(%)[b]	
entry	catalyst	ligand	solvent	3a	4a
1	Pd(OAc)$_2$		DMF	25	22
2	Pd(acac)$_2$		DMF	13	8
3	Pd(COD)Cl$_2$		DMF	28	35
4	Pd(CH$_3$CN)$_2$Cl$_2$		DMF	30	35
5	PdBr$_2$		DMF	60	20
6	PdOI$_2$		DMF	80	18
7	PdCl$_2$	PPh$_3$	DMF	63	27
8	PdCl$_2$	dppe	DMF	50	30
9	PdCl$_2$	dppb	DMF	45	33
10	PdCl$_2$	DPEphos	DMF	88	10
11	PdCl$_2$	1,10-Phen	DMF	1	10
12	PdCl$_2$	L-phenylalanine	DMF	n.d.	60
13	PdCl$_2$	DPEphos	1,4-dioxane	77	22
14	PdCl$_2$	DPEphos	DMSO	70	28
15	PdCl$_2$	DPEphos	diglyme	90	1
16	PdCl$_2$	DPEphos	anisole	95	n.d.
17	PdCl$_2$	DPEphos	anisole/H$_2$O	90	n.d.
18[c]	PdCl$_2$	DPEphos	anisole	50	30

[a] Conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), catalyst (5 mol %), ligand (5 mol %), solvent (0.4 mL), 85 °C, 24 h under an atmosphere of oxygen unless otherwise noted. [b] GC yield based on **2a**. n.d. = not detected (below 1% yield), the *E*/*Z* ratio is > 20:1 as determined by ^{1}H NMR. [c] Under air.

this process is that water is the only waste when dioxygen is used as the terminal oxidant.[9]

In 2002, Myers and co-workers reported a Pd-catalyzed decarboxylative Heck coupling of benzoic acids with olefins, providing an attractive alternative to traditional Heck couplings.[10] Since then, this protocol has been widely investigated by using carboxylic acids as the aryl sources (eq 3).[11] Similarly, decarbonylative Heck-type reactions were also developed using carbonyl compounds such as carbonic acid chlorides,[12] anhydrides,[13] and esters[14] as substrates.

Arenesulfonyl chlorides are active compounds and are used as starting materials for preparing compounds containing a sulfonyl group. The sulfonyl group is common in organic materials, bioactive molecules, and pharmaceuticals.[15] Arenesulfonyl chlorides are also used as aryl sources for C−C bond forming reactions via desulfitative Heck-type reactions. The first palladium-catalyzed desulfitative C−C double bond-forming reactions with arenesulfonyl chlorides were developed by Kasahara et al. and Miura and co-workers under high reaction temperature (> 130 °C).[16] Compared to the active and moisture sensitive arenesulfonyl chloride, sulfinic acid sodium salts are stable and easy to handle. Thus, sulfinic acid sodium salts have the potential to serve as the ideal aryl sources for

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(9) For oxidative Heck-type reaction using oxygen as terminal oxidant, see: (a) Dams, M.; De Vos, D. E.; Celen, S.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3512. (b) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476. (c) Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2004**, *69*, 1221. (d) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (e) Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 337. (f) Wang, D.; Engle, K.; Shi, B.; Zhang, Y.; Lam, J.; Wang, D.; Yu, J. Q. *Science* **2010**, *327*, 315. (g) Zhang, Y.; Shi, B.; Yu, J. Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (h) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407. (i) Patureau, F.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982.

(10) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250.

(11) (a) Tanaka, D.; Myers, A. G. *Org. Lett.* **2004**, *6*, 433. (b) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323. (c) Maehara, A.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1159. (d) Hu, P.; Kan, J.; Su, W.; Hong, M. *Org. Lett.* **2009**, *11*, 2341. (e) Li, Z.; Zhang, S. L.; Fu, Y.; Shang, R.; Guo, Q. X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 8815. (f) Fu, Z. J.; Huang, S. J.; Su., W.; Hong, M. *Org. Lett.* **2010**, *12*, 4992. (g) Sun, Z.; Zhang, J.; Zhao, P. *Org. Lett.* **2010**, *12*, 992.

(12) (a) Sugihara, T.; Satoh, T.; Miura, M.; Nomura, M. *Adv. Synth. Catal.* **2004**, *346*, 1765. (b) Sugihara, T.; Satoh, T.; Miura, M. *Tetrahedron Lett.* **2005**, *46*, 8269.

(13) Stephan, M.; Teunissen, A.; Verzijl, G.; de Vries, J. *Angew. Chem., Int. Ed.* 1998, *37*, 662.

(14) (a) Goossen, L. J.; Paetzold, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1237. (b) Goossen, L. J.; Paetzold, J. *Synlett* **2002**, 1721. (c) Goossen, L. J.; Paetzold, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1095.

(15) (a) Page, P. *Organosulfur Chemistry: Stereochemical Aspects*; Academic Press, Inc.: San Diego, CA, 1998. (b) Dubbaka, S.; Vogel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 7674. (c) Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon Press: Oxford, UK, 1993.

(16) (a) Kasahara, A.; Izumi, T.; Kudou, N.; Azami, H.; Yamamato, S. *Chem. Ind.* **1988**, 51. (b) Kasahara, A.; Izumi, T.; Miyamoto, K.; Sakai, T. *Chem. Ind.* **1989**, 192. (c) Miura, M.; Hashimoto, H.; Itoh, K.; Nomura, M. *Tetrahedron Lett.* **1989**, *30*, 975. (d) Miura, M.; Hashimoto, H.; Itoh, K.; Nomura, M. *J. Chem. Soc., Perkin Trans.1* **1990**, *8*, 2207. For other desulfinylative C−C coupling with arylsulfonyl chlorides, see: (e) Dubbaka, S.; Steunenberg, P.; Vogel, P. *Synlett* **2004**, 1235. (f) Dubbaka, S.; Vogel, P. *Adv. Synth. Catal.* **2004**, *346*, 1793. (g) Dubbaka, S.; Vogel, P. *Chem.—Eur. J.* **2005**, *11*, 2633. (h) Zhang, S.; Zeng, X.; Wei, Z.; Zhao, D.; Kang, T.; Zhang, W.; Yan, M.; Luo, M. *Synlett* **2006**, 1891. (i) Rao, C. M.; Vogel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1305. (j) Zhao, X.; Dimitrijević, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466.

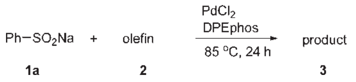
(17) For recent examples of sulfonylation with sodium sulfinates, see: (a) Sandrinelli, F.; Perrio, S.; Beslin, P. *Org. Lett.* **1999**, *1*, 1177. (b) Yang, W.; Berthelette, C. *Tetrahedron Lett.* **2002**, *43*, 4537. (c) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L.; Berning, R. *J. Org. Chem.* **2004**, *69*, 5608. (d) Zhu, W.; Ma, D. *J. Org. Chem.* **2005**, *70*, 2696. (e) Martin, C.; Sandrinelli, F.; Perrio, C.; Perrio, S.; Lasne, M. *J. Org. Chem.* **2006**, *71*, 210. (f) Guan, Z.; Zuo, W.; Zhao, L.; Ren, Z.; Liang, Y. *Synthesis* **2007**, 1465. (g) Drabowicz, J.; Kaiatkowska, M.; Kielbasinski, P. *Synthesis* **2008**, 3563. (h) Sreedhar, B.; Reddy, M.; Reddy, P. *Synlett* **2008**, 1949. (i) Kim, H.; Kasper, A.; Park, Y.; Wooten, C.; Hong, J.; Moon, E.; Dewhirst, M. *Org. Lett.* **2009**, *11*, 89. (j) Varela-Álvavez, A.; Marković, D.; Vogel, P.; Sordo, J. *J. Am. Chem. Soc.* **2009**, *131*, 9547. (k) Liu, C.; Li, M.; Cheng, D.; Yang, C.; Tian, S. *Org. Lett.* **2009**, *11*, 2543. (l) Reddy, M.; Reddy, P.; Sreedhar, B. *Adv. Synth. Catal.* **2010**, *352*, 1861. (m) Li, Y.; Cheng, K.; Lu, X.; Sun, J. *Adv. Synth. Catal.* **2010**, *352*, 1876. (n) Ueda, M.; Hartwig, J. F. *Org. Lett.* **2010**, *12*, 92. (o) Maloney, K.; Kuethe, J.; Linn, K. *Org. Lett.* **2011**, *13*, 102.

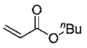
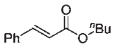
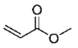
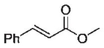
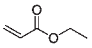
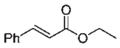
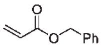
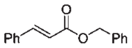
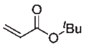
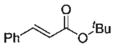
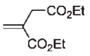
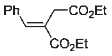
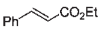
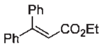
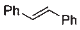
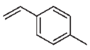
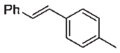
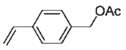
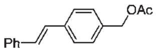
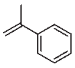
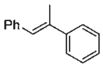
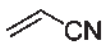
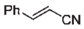
(18) Sato and Okoshi reported a palladium-catalyzed biaryl synthesis using sulfinic acid sodium salts and aromatic bromides (at 150 °C): Sato, K.; Okoshi, T. patent, US5159082, 1992.

C−C bond-forming reactions via release of SO_2. Currently, research has been mainly focused on using sodium arenesulfinates as sulfonylation reagents.[17] Research on desulfitative C−C bond formation is rare.[18] *Herein we report a palladium-catalyzed desulfitative Heck coupling of arenesulfinic aicd sodium salts with alkenes under mild reaction conditions using oxygen as the terminal oxidant (eq 4).*

We began our investigation by screening various palladium salts for desulfitative Heck coupling between benzenesulfinic acid sodium salt (**1a**) and *n*-butyl acrylate (**2a**), and the results are summarized in Table 1. When *n*-butyl acrylate reacted with 2 equiv of benzenesulfinic acid sodium salt in the presence of 5 mol % of $Pd(OAc)_2$, the desired product was observed in 25% yield along with 22% of conjugate addition product *n*-butyl 3-(phenylsulfonyl)-propanote (**4a**) as detected by GC-MS and ^1H NMR methods (Table 1, entry 1) using 1 atm of oxygen as oxidant.

Table 2. Desulfitative Heck Coupling of **1a** with Olefins[a]



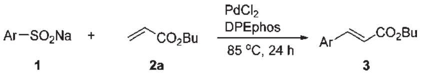
entry	olefin		product		yield(%)[b]
1		2a		3a	85
2		2b		3b	70
3		2c		3c	75
4		2d		3d	68
5		2e		3e	70
6		2f		3f	65
7		2g		3g	30
8		2h		3h	77
9		2i		3i	82
10		2j		3j	64
11		2k		3k	45
12		2l		3l	43

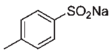
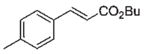
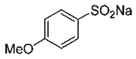
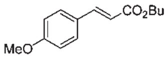
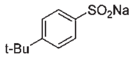
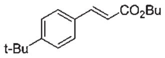
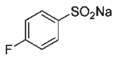
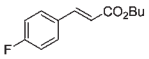
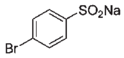
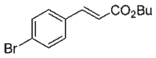
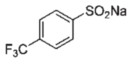
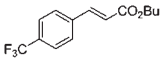
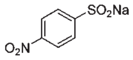
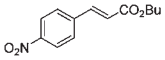
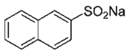
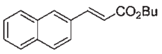
[a] Conditions: **1a** (0.4 mmol), **2** (0.2 mmol), $PdCl_2$ (5 mol %), DPEphos (5 mol %), anisole (0.4 mL), 85 °C, 24 h, under oxygen. [b] Isolated yield based on **2**, the *E*/*Z* ratio of product is >20:1.

Subsequently, various palladium(II) salts were tested for this desulfitative Heck coupling reaction using oxygen as the terminal oxidant. Similar yields were observed when $Pd(acac)_2$, $Pd(COD)Cl_2$, and $Pd(CH_3CN)_2Cl_2$ were used as the catalysts (entries 2−4). A moderate yield was obtained when $PdBr_2$ was used (entry 5). The yield was further improved by using $PdCl_2$, and the desired product was obtained in 80% yield along with 18% of **4a** (entry 6). To improve the selectivity, various ligands were investigated for this transformation. Phosphine ligands such as PPh_3, dppe [1,2-bis(diphenylphosphino)ethane], and dppb [1,4-bis(diphenylphosphino)butane] all decreased the reaction selectivity (entries 7−9). The combination of $PdCl_2$ with DPEphos [bis(2-diphenylphosphinophenyl) ether] could slightly improve the selectivity (entry 10). Other nitrogen-containing ligands such as 1,10-phenanthroline and L-phenylalanine were not efficient ligands for this reaction and only a trace amount of the desired product was observed (entries 11 and 12). The effect of solvents on this reaction was investigated. The reaction was efficient in 1,4-dioxane and DMSO (entries 13 and 14). The reaction in diglyme gave the desired product in 90% yield along with a trace amount of **4a** (entry 15). The best yield and selectivity were obtained in anisole. The desired product was obtained in 95% yield and no conjugate addition product was detected (entry 16, the *E*/*Z* ratio >20). To our delight, in contrast to decarboxylative reactions, the reaction is not sensitive to water, and a 90% yield was obtained in the presence of 10 equiv of water (entry 17). The reaction is less efficient in air (entry 18).

The desulfitative Heck coupling of benzenesulfinic acid sodium salt **1a** with various olefins was conducted under optimized conditions, and the results are summarized in Table 2. For the scope of electron-poor olefin substrates, methyl-, ethyl-, benzyl-, and *tert*-butyl acrylate reacted with **1a** to give desulfitative Heck−Mizoroki products **3b**, **3c**, **3d**, and **3e** in good yields and with high selectivities

Table 3. Desulfitative Heck Coupling of **2a** with Various Sodium Sulfinates[a]



entry	sodium sulfinate		product		yield(%)[b]
1		1b		3m	85
2		1c		3n	84
3		1d		3o	77
4		1e		3p	50
5		1f		3q	78
6		1g		3r	75
7		1h		3s	49
8		1i		3t	71

[a] Conditions: **1** (0.4 mmol), **2a** (0.2 mmol), $PdCl_2$ (5 mol %), DPEphos (5 mol %), anisole (0.4 mL), 85 °C, 24 h, under oxygen. [b] Isolated yield based on **2a**, the *E*/*Z* ratio of product is >20:1

over conjugate addition (Table 2, entries 2−5). When itaconic acid diethyl ester (**2f**) was employed, the desired product was obtained in 65% yield (entry 6). However, a much lower yield was obtained when ethyl cinnamate (**2g**) was used as substrate (entry 7). Simple olefins were also investigated for this kind of transformation. Styrene, 4-methystyrene, and 4-vinylbenzyl acetate were successfully coupled with **1a** and gave the desired products in 77%, 85%, and 64% yield, respectively (entries 8−10). Only moderate yields were obtained when α-methylstyrene (**2k**) and acrylonitrile (**2*l***) were used (entries 11 and 12).

The reaction results of arylsulfinic acid sodium salts with *n*-butyl acrylate **2a** are presented in Table 3. A series of functional groups including methyl, methoxy, fluoro, bromo, and trifluoromethyl were tolerated under the optimal reaction conditions, and the desired products were obtained in moderate to good yields (entries 1−6). A moderate yield was obtained when (4-nitrophenyl)sulfinic acid sodium salt reacted with **2a** (entry 7). More steric substrates such as 2-naphthylsulfinic acid sodium salt also efficiently reacted with *n*-butyl acrylate and gave the product in 71% yield (entry 8). In all cases, *E*-1,2-disubstituted alkenes were the major products as determnined by a ^{1}H NMR method.

In summary, we have developed a new Pd-catalyzed method for the desulfitative Heck coupling of various aromatic sulfinic acid sodium salts with a wide range of olefins by using dioxygen as the terminal oxidant under mild conditions. The loss of SO_2 occurred at 85 °C, which is much lower than the loss of CO_2 (usually >150 °C). Ligands and solvents played an important role in the selectivity of the reaction, and the combination of $PdCl_2$/DPEphos in anisole gave the desired product in very high yield and selectivity. No conjugate addition byproducts were detected under the optimized conditions. A very high reaction yield still could be achieved in the presence 10 equiv of water. Studies into the mechanism and further application of the reaction will be the focus of our future work.

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Supporting Information Available. General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.