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Aryl Sulfoxides via Palladium-Catalyzed Arylation of Sulfenate Anions

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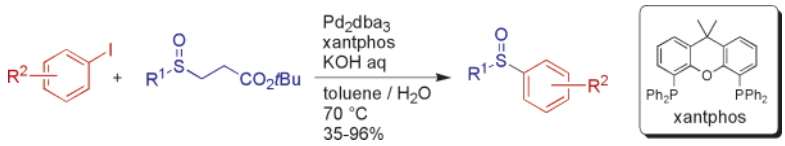
ABSTRACT



Palladium-catalyzed arylation of sulfenate anions generated from β-sulfinyl esters can take place under biphasic conditions. This hitherto unknown reaction provides a simple, mild, and efficient route to aryl sulfoxides in good yields. The development of a new pseudo-domino type I procedure involving a sulfinylation followed by a Mirozoki–Heck coupling is also described.

The palladium-catalyzed arylation reaction represents a primary synthetic tool to generate carbon−carbon and carbon−heteroatom bonds. In particular, the use of sulfur-based nucleophiles[1] such as sulfinates (RSO_2^-)[2] and thiolates (RS^-)[3] allows the easy generation of aryl sulfones and aryl thioethers, respectively. On the other hand, no related method allowing the generation of aryl sulfoxides via arylation of a sulfenate anion (RSO^-) has, to our knowledge, so far been reported. Although the sulfenate anion has been reported to be the precursor of sulfoxides, sulfenic acids, sulfenate esters, and thiols,[4] its use remains sporadic probably due to its nonstraightforward preparation.[5] In view of the importance of many aryl sulfoxides for medicinal[6] and pharmaceutical chemistry, we decided to test this previously unknown type of coupling.

We recently described the synthesis of allylic sulfoxides by palladium-catalyzed allylic alkylation of sulfenate anions (Scheme 1),[7] an original transformation that could be successfully achieved generating the desired sulfinate anion via β-sulfinyl ester enolate elimination[8] under specifically developed biphasic conditions.[9]

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(2) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Paris, L. M.; Bernini, R. *J. Org. Chem.* **2004**, *69*, 5608−5614.

(3) For precursor works, see: (a) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385−1389. (b) Foà, M.; Santi, R.; Garavalia, F. *J. Organomet. Chem.* **1981**, *206*, C29−C32. For recent examples, see: (c) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180−2181. (d) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *Chem.−Eur. J.* **2006**, *12*, 7582−7596. (e) Itoh, T.; Mase, T. *J. Org. Chem.* **2006**, *71*, 2203−2206. (f) Moreau, X.; Campagne, J.-M.; Meyer, G.; Jutand, A. *Eur. J. Org. Chem.* **2005**, 3749−3760. (g) Mispelaere-Canivet, C.; Spindler, J.-F.; Perrio, S.; Beslin, P. *Tetrahedron* **2005**, *61*, 5253−5259. (h) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587−4590. (i) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397−7403.

(4) (a) Hogg, D. R. *Chemistry of Sulfenic Acids and Esters. The Chemistry of Sulfenic Acids and their Derivatives*; Wiley-Interscience: Toronto, 1990; pp 361−402. (b) Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. *The Chemistry of Sulfenic Acids, Esters and their Derivatives*; Patai, S., Ed.; John Wiley & Sons: 1990; pp 351−429. (c) Katritzky, A. R.; Takahashi, I.; Marson, C. M. *J. Org. Chem.* **1986**, *51*, 4914−4920. (d) O'Donnell, J. S.; Schwan, A. L. *Tetrahedron Lett.* **2003**, *44*, 6293−6296. (e) Maezaki, N.; Yoshigami, R.; Maeda, J.; Tanaka, T. *Org. Lett.* **2001**, *3*, 3627−3629. (f) Maezaki, N.; Yagi, S.; Ohsawa, S.; Ohishi, H.; Tanaka, T. *Tetrahedron* **2003**, *59*, 9895−9906. (g) Maezaki, N.; Yagi, S.; Yoshigami, R.; Maeda, J.; Suzuki, T.; Ohsawa, S.; Tsukamoto, K.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 5550−5558. (h) Maezaki, N.; Yagi, S.; Maeda, J.; Yoshigami, R.; Tanaka, T. *Heterocycles* **2004**, *62*, 263−277. (i) Sandrinelli, F.; Perrio, S.; Beslin, P. *J. Org. Chem.* **1997**, *62*, 8626−8627. (j) Sandrinelli, F.; Perrio, S.; Averbuch-Pouchot, M.-T. *Org. Lett.* **2002**, *4*, 3619−3622. (k) Sandrinelli, F.; Fontaine, G.; Perrio, S.; Beslin, P. *J. Org. Chem.* **2004**, *69*, 6916−6919.

(5) For a review, see: O'Donnell, J. S.; Schwan, A. L. *Sulfur Lett.* **2004**, *25*, 183−211.

(6) For reviews, see: (a) Legros, J.; Dehli, J. R.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 19−31. (b) Bentley, R. *Chem. Soc. Rev.* **2005**, *34*, 609−624.

(7) Maitro, G.; Prestat, G.; Madec, D.; Poli, G. *J. Org. Chem.* **2006**, *71*, 7449−7454.

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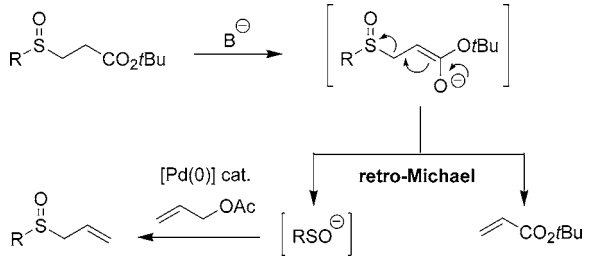
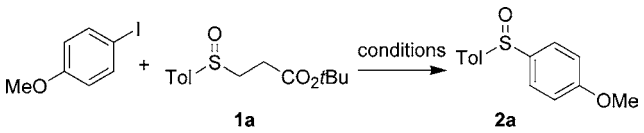
Scheme 1



From this result, we advanced the hypothesis that sulfenate anions could be suitable nucleophiles for palladium-catalyzed arylation reactions as well, so as to unveil a new route toward arylsulfoxides.[10] This proved to be the case, and we report herein our results.

The Pd-catalyzed arylation reaction between the in situ generated *p*-tolyl sulfenate anion and *p*-iodoanisole was chosen as the model reaction for preliminary experiments (Table 1).

Table 1. Optimization of the Reaction Conditions[a]

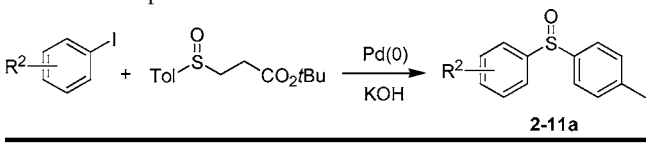


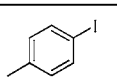
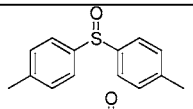
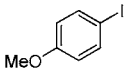
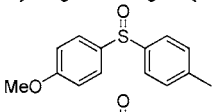
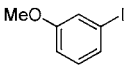
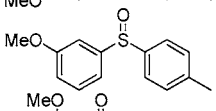
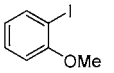
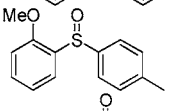
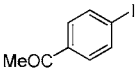
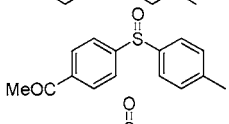
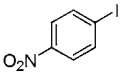
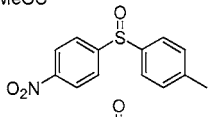
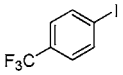
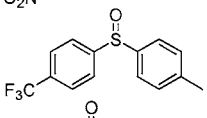
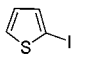
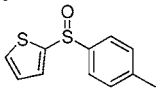
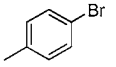
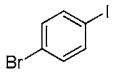
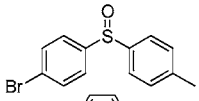
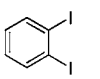
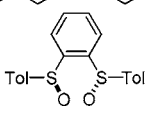
entry	catalytic system	base (equiv)	solvent	yield (%)[b]
1	Pd_2dba_3/xantphos	KOH (20)	toluene/H_2O	70
2	Pd_2dba_3/PPh_3[c]	KOH (20)	toluene/H_2O	–
3	Pd_2dba_3/dppe	KOH (20)	toluene/H_2O	–
4	Pd_2dba_3/binap	KOH (20)	toluene/H_2O	–
5	$Pd(OAc)_2$/xantphos	KOH (20)	toluene/H_2O	62
6	Pd_2dba_3/xantphos	Cs_2CO_3 (4)	toluene	42

[a] Reagents and reaction conditions: *p*-iodoanisole (1.2 equiv), *β*-sulfinyl ester, Pd_2dba_3 (5 mol %) or $Pd(OAc)_2$ (10 mol %), ligand (10 mol %), KOH (50% aqueous solution) in a 1:1 toluene/H_2O system or Cs_2CO_3 in toluene at 70 °C. [b] Yields are given for isolated products. [c] The reaction was carried out by using 20 mol % of PPh_3.

Much to our satisfaction, treatment of the two substrates with Pd_2dba_3 (5 mol %), xantphos[11] as the ligand (10 mol %), and KOH (20 equiv) in 1:1 toluene/H_2O gave, after 4 h at 70 °C, the expected *p*-tolylsulfinyl anisole **2a** in 70% yield (Table 1, entry 1). The use of other ligands, such as PPh_3, dppe, or binap, did not allow generation of the corresponding sulfoxide (entries 2−4). Replacement of Pd_2dba_3 for $Pd(OAc)_2$ as the palladium source lowered the yield to 62% (entry 5), thereby confirming the major role of the Pd_2dba_3/xantphos combination for sulfur nucleophiles in palladium catalysis. Finally, an experiment performed in liquid−solid biphasic conditions, with Cs_2CO_3 as base, afforded the corresponding sulfoxide in a limited 42% yield (entry 6). It is interesting to note the absence of O-arylation products, despite the ambident nature of the sulfenate anion. With the optimized reaction conditions in hand, we investigated the scope and limitations of this transformation by treating the *p*-tolyl sulfenate precursor **1a** with a variety of substituted aryl iodides (Table 2).

Table 2. Scope of the Reaction[a]



entry	aryl halide	product		yield (%)[b]
1			**3a**	81
2			**2a**	70
3			**4a**	63
4			**5a**	79
5			**6a**	58
6			**7a**	82
7			**8a**	96
8			**9a**	82
9		no reaction	-	-
10			**10a**	61
11			**11a**	45[c]

[a] Reagents and reaction conditions: aryl halide (1.2 equiv), *β*-sulfinyl ester, Pd_2dba_3 (5 mol %), xantphos (10 mol %), KOH (50% aqueous solution) in 1:1 toluene/H_2O at 70 °C. [b] Yields are given for isolated products. [c] Diastereomeric *dl*/*meso* ratio of >90:10 determined by ^1H NMR.

(8) Caupène, C.; Boudou, C.; Perrio, S.; Metzner, P. *J. Org. Chem.* **2005**, *70*, 2812−2815.

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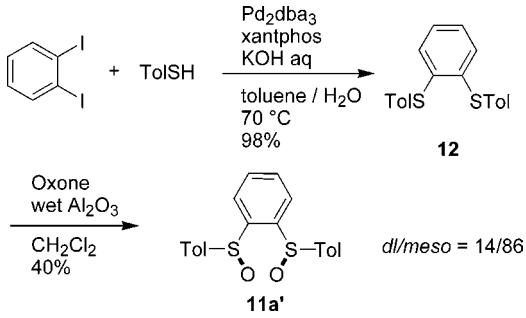
4-Iodotoluene reacted with **1a** to give the corresponding symmetrical sulfoxide **3a** in 81% yield (entry 1). *p*-, *m*-, and *o*-iodoanisoles afforded the corresponding isomeric sulfoxides **2a**, **4a**, and **5a** with 70%, 63%, and 79% yields, respectively (entries 2−4). Starting from *p*-iodoacetophenone, the reaction afforded sulfoxide **6a** in 58% yield (entry 5), whereas sulfoxide **7a** was isolated in 82% yield from *p*-iodonitrobenzene (entry 6). An excellent coupling yield (96%) was obtained using *p*-iodotrifluoromethyl benzene as the substrate (entry 7). Reaction of 2-iodothiophene produced the corresponding coupling product **9a** in 82% yield (entry 8). Conversely, under the same conditions, 4-bromotoluene did not allow generation of the expected sulfoxide **3a** (entry 9). This difference in reactivity between bromides and iodides was exploited in the reaction of 4-bromo-iodobenzene, which afforded the corresponding monosulfoxide **10a** without concomitant formation of the bis-sulfoxide product (entry 10). Reaction between 1,2-diiodobenzene and excess sulfenate precursor gave the bis-sulfoxide **11a** in 45% yield and ≥90:10 (*dl*/*meso*) ratio (entry 11).

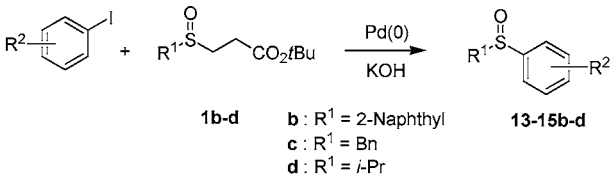
The above diastereomeric ratio assignment was evaluated on the basis of the spectroscopic data previously reported for the *dl* diastereomer[12] and confirmed by the synthesis of the corresponding and hitherto unknown *meso* product **11a′**. This was achieved by double palladium-catalyzed coupling between 1,2-diiodobenzene and excess *p*-thiocresol, followed by oxone-mediated thioether−to−sulfoxide oxidation[13] (Scheme 2).

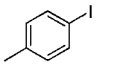
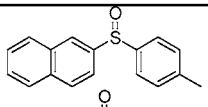
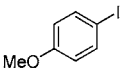
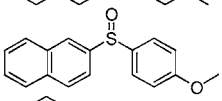
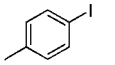
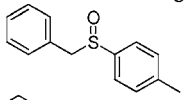
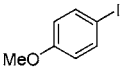
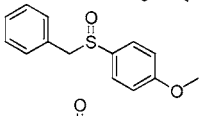
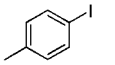
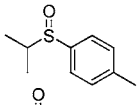
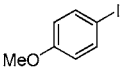
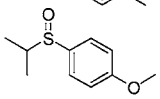
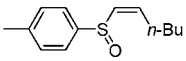
Scheme 2



The reaction was next studied on various β-sulfinyl esters (Table 3). Starting from 2-naphthylsulfenate precursor **1b**, reaction with *p*-iodotoluene or *p*-iodoanisole afforded the corresponding diaryl sulfoxides **13b** or **14b** in 79% and 45% respective yields (entries 1 and 2). Benzyl sulfenates could also be satisfactorily coupled (entries 3 and 4). It should be noted that the modest yields of the couplings involving *p*-iodoanisole (entries 2 and 4) were due to the formation of coupling byproducts (28% and 37% yields, respectively) carrying a phenyl ring instead of the *p*-methoxy moiety. These formally demethoxylated byproducts are very likely the result of phenyl transfer from xantphos, due to phosphonium ion mediated aryl scrambling of the arylpalladium(II) complex.[14]

Table 3. Scope of the Reaction[a]



entry	aryl halide	product		yield (%)[b]
1			**13b**	79
2			**14b**	45[c]
3			**13c**	70
4			**14c**	46[d]
5			**13d**	42
6			**14d**	35
7			**15a**	33

[a] Reagents and reaction conditions: aryl halide (1.2 equiv), β-sulfinyl ester substrate, Pd_2dba_3 (5 mol %), xantphos (10 mol %), KOH (50% aqueous solution) in 1:1 toluene/H_2O at 70 °C. [b] Yields are given for isolated products. [c] The corresponding formally demethoxylated byproduct was isolated in 28% yield. [d] The corresponding formally demethoxylated byproduct was isolated in 37% yield.

More disappointingly, alkyl sulfenates afforded the corresponding alkyl sulfoxides **13d** and **14d** in moderate 42% and 35% yields, respectively (entries 5 and 6). Finally, the use of (*Z*)-1-iodohex-1-ene gave the (*Z*)-vinyl-sulfoxide **15a** in 33% yield (entry 7); the same reaction starting from the (*E*)-isomer afforded only degradation products.

To take advantage of the chemoselectivity of the sulfinylation of 4-bromo-iodobenzene (Table 2, entry 10) and of the *tert*-butyl acrylate concomitantly released during sulfenate generation, the possible enchainment of a pseudo-domino type I[15] sulfinylation/Mirozoki−Heck sequence was envisioned. After some experimentation, we found that perform-

(12) Tokunoh, R.; Sodeoka, M.; Aoe, K.-I; Shibasaki, M. *Tetrahedron Lett.* **1995**, *36*, 8035−8038.

(13) Greenhalgh, R. P. *Synlett* **1992**, 235−236.

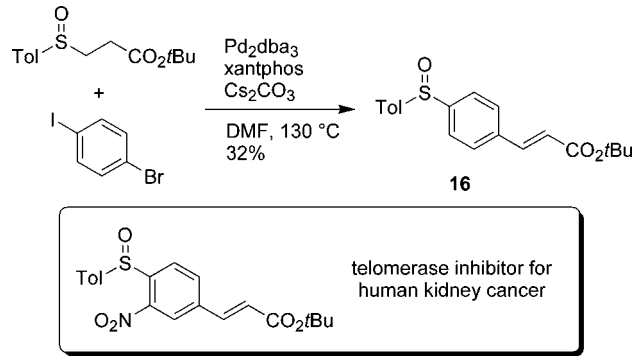
(14) This side reaction is known to plague Pd-catalyzed cross-couplings when electron-rich aryl halides and/or nucleophiles are used. (a) Kong, K.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313−6315. (b) Kwong, F. Y.; Lai, C. W.; Yu, M.; Chan, K. S. *Tetrahedron* **2004**, *60*, 5635−5645 and references cited therein.

(15) (a) Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, *67*, 9456−9459. (b) Lemaire, S.; Prestat, G.; Giambastiani, G.; Madec, D.; Pacini, B.; Poli, G. *J. Organomet. Chem.* **2003**, *687*, 291−300. (c) Prestat, G.; Poli, G. *Chemtracts - Org. Chem.* **2004**, *17*, 97−103.

(16) Kanda, H.; Nakatsu, R.; Asai, A.; Yamashita, N. Patent JP 2003137861, 2003.

ing the reaction in DMF at 130 °C, and in the presence of Cs_2CO_3 as the base, allowed isolation of the desired sulfinyl-substituted cinnamate **16** in 32% yield (Scheme 3). Despite

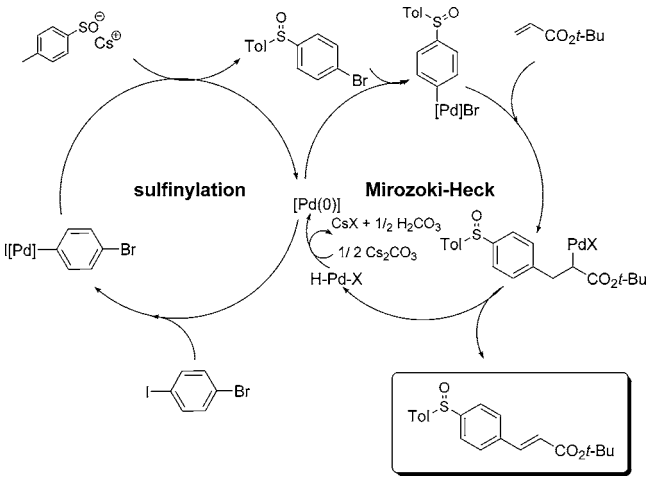
Scheme 3



its moderate yield, this new arylation reaction could be a straightforward method for the preparation of a telomerase inhibitor for human kidney cancer.[16]

We propose for this new one-pot, two C−C bond forming coupling the following mechanism (Scheme 4). Base-mediated deprotonation of the β-sulfinyl ester first gives the corresponding ester enolate. The following retro-Michael reaction generates the sulfenate anion and the acrylate ester, which are ready to enter the first (sulfinylation) and the second (Mirozoki−Heck) catalytic cycles, respectively. Transmetalation between the sulfenate anion and the arylpalladium(II) complex generated from oxidative addition of Pd(0) to the aryl iodide gives, after reductive elimination, the corresponding bromoaryl sulfoxide and releases Pd(0). Oxidative addition of Pd(0) to the bromoaryl sulfoxide expelled from the first catalytic cycle starts the second one. Then, carbo-palladation of the acrylate ester by the newly formed arylpalladium(II) complex, followed by dehydropalladation, generates the final sulfinyl cinnamate.

Scheme 4



In conclusion, we have reported the first palladium-catalyzed arylation of sulfenate anions under biphasic conditions, thereby disclosing a new synthetic route toward aryl sulfoxides. This methodological work was further enriched by the development of a pseudo-domino type I sulfinylation/Mirozoki−Heck sequence wherein the Pd(0) catalyst is formally shared by the two mechanistically independent catalytic cycles.

Enantioselective Pd-catalyzed sulfinylation reactions are presently under investigation and will be reported in due course.

Acknowledgment. The support and sponsorship concerted by CNRS and COST Action D24 "Sustainable Chemical Processes: Stereoselective Transition Metal-Catalysed Reactions" are kindly acknowledged.

Supporting Information Available: General 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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