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Enantioselective Synthesis of Aryl Sulfoxides via Palladium-Catalyzed Arylation of Sulfenate Anions

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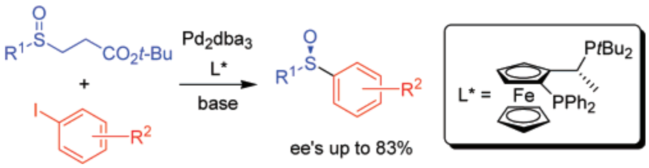
ABSTRACT



Arylation of various sulfenate anions generated from β-sulfinyl esters by retro-Michael reaction in the presence of palladium(0) and enantiopure ligands gave the corresponding aryl sulfoxides in enantio-enriched form. The Josiphos-type ligand (*R*)-(*S*)-PPF-*t*-Bu$_2$ turned out to be the best ligand tested, allowing ee's up to 83% in a predictable sense.

Enantiopure sulfoxides represent an important class of compounds because of their usefulness as chiral auxiliaries or as chiral ligands in asymmetric catalysis.[1] Moreover, a number of sulfoxides are known in the field of pharmaceutical and medicinal chemistry.[2] As a consequence, the synthesis of chiral nonracemic sulfoxides has been of high interest for several decades.[3] Two different methods are commonly employed for the preparation of this type of compounds: (a) the addition of organometallic nucleophiles, such as Grignard reagents, to enantiopure sulfinates having a stereogenic sulfur atom,[4,5] and (b) the enzymatic or catalytic asymmetric oxidation of unsymmetrical thioethers,[6] such as the modified Sharpless procedures described by Kagan or Modena's groups.[7] Despite their value, these two methods suffer from some limitations such as the use of a stoichiometric amount of chiral auxiliary in the preparation of enantiopure sulfinate precursors and high substrate-dependency of the asymmetric oxidation.

On the other hand, palladium-catalyzed arylation represents a primary synthetic tool to generate carbon-heteroatom bonds.[8] In particular, the use of sulfur-based nucleophiles[9]

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[2] For reviews, see: (a) Carrenõ, M. C. *Chem. Rev.* **1995**, *95*, 1717−1760. (b) Legros, J.; Dehli, J. R.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 19−31. (c) Bentley, R. *Chem. Soc. Rev.* **2005**, *34*, 609−624.

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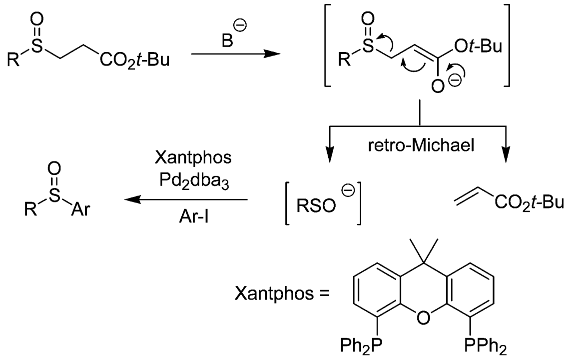
[7] (a) Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188−8193. (b) Pitchen, P.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 1049−1052. (c) DiFuria, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325−326. (d) Brunel, J. M.; Duetsch, M.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 8086−8088. (e) Brunel, J. M.; Kagan, H. B. *Synlett* **1996**, 404−406. (d) Kagan, H. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New-York, 2000; Chapter 6c.

10.1021/ol702343g CCC: $37.00

such as sulfinates[10] and thiolates[11] allows an easy generation of aryl sulfones and aryl sulfides, respectively. In this context, we recently described the synthesis of aryl sulfoxides[12] by palladium-catalyzed arylation of sulfenate anions.[13]

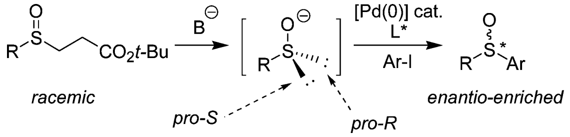
This original coupling reaction has been successfully achieved by generation of the desired sulfenate[14] anion via β-sulfinyl esters enolate elimination[15] under specifically developed biphasic conditions (Scheme 1).[16]

Scheme 1



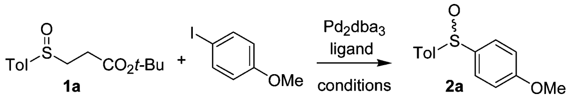
From this result, we reasoned that, if suitable enantiopure ligands were used for the coupling, the prostereogenic nature of the sulfenate anion could disclose a new route toward enantiomerically enriched aryl sulfoxides (Scheme 2).[17] Yet, such a strategy appeared non-obvious, as our previous study demonstrated that achiral Xantphos was the only ligand able to promote the coupling reaction.[12]

Scheme 2



The coupling reaction between the in situ generated p-tolyl sulfenate anion and p-iodoanisole was chosen as the model reaction, using toluene/H_2O biphasic conditions (Table 1).

Table 1. Optimization of Reaction Conditions[a]



entry	ligand	base	solvent	temp (°C)	yield (%)[b]	% ee[c] (config)
1	Xantphos[d]	KOH	tol/H_2O	70	84	
2	Binap[e]	KOH	tol/H_2O	70	0	
3	(+)-Diop[f]	KOH	tol/H_2O	70	42	8 (*R*)
4	**A**	KOH	tol/H_2O	70	13	29 (*R*)
5	**B**	KOH	tol/H_2O	70	55	83 (*R*)
6	**C**	KOH	tol/H_2O	70	0	
7	**D**	KOH	tol/H_2O	70	0	
8	**E**	KOH	tol/H_2O	70	0	
9	**F**	KOH	tol/H_2O	70	54	25 (*S*)
10	**G**	KOH	tol/H_2O	70	30	12 (*S*)
11	**H**	KOH	tol/H_2O	70	0	
12	**B**	Cs_2CO_3	tol	110	83	73 (*R*)

[a] Reagents and reaction conditions: p-iodoanisole (1.2 equiv), β-sulfinylester, Pd_2dba_3 (1 mol %), ligand (2 mol %), KOH (50% aqueous solution, 20 equiv), 1:1 toluene/H_2O, 70 °C or Cs_2CO_3 (4 equiv), at reflux of toluene. [b] Yields are given for isolated products. [c] Enantiomeric excess was determined by chiral supercritical fluid chromatography. [d] Xantphos: 4,5-bis(phenylphosphino)-9,9-dimethylxanthene. [e] Binap: 2,2′-bis(diphenylphosphino-1,1′-binaphthyl. [f] (+)-Diop: (+)-*O*-isopropylidene-*trans*-2,3-dihydroxy-1,4-bis(diphenyl-phosphino)butane.

Preliminary experiments performed with Binap and Diop ligands were disappointing. Indeed, with the former ligand no sulfoxide was observed (entry 2), whereas Diop allowed generation of the expected coupling product in a moderate (42%) yield and a poor (8%) ee (entry 3). After the beginning of our project, Hartwig and co-workers reported the palladium-catalyzed coupling reaction of aryl halides with thiols using enantiopure Josiphos **A** as the ligand.[11c] Although in Hartwig's paper asymmetric catalysis was not addressed, this result prompted us to test Josiphos-type ligands in our coupling reactions.

Encouragingly, use of Josiphos **A** as the ligand allowed access to p-tolylsulfinyl anisole with 29% ee albeit with a very poor yield (13%) (entry 4).

On the other hand, use of ligand **B** allowed generation of the corresponding sulfoxide[18] in 55% yield and a satisfactory 83% ee (entry 5). Replacement of Josiphos with the Josiphos-type ligands **C**−**E** or Mandiphos-, Taniaphos-, and Walphos-type ligands **F**−**H**, respectively (Figure 1), increased neither the yield nor the enantioselectivity (entries 6−11). Finally, optimized conditions were set with ligand **B** (Cs_2CO_3 as base

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(9) Kondo, T.; Mitsudo, T.-A. *Chem. Rev.* **2000**, *100*, 3205−3220.

(10) (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M.; Bernini, R. *J. Org. Chem.* **2004**, *69*, 5608−5614. (b) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M. *Org. Lett.* **2002**, *4*, 4719−4721.

(11) For pioneering 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 more 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.

(12) (a) Maitro, G.; Vogel, S.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* **2006**, *8*, 5951−5954. See also: (b) Colobert, F.; Ballesteros-Garrido, R.; Leroux, F. R.; Ballesteros, R.; Belén, A. *Tetrahedron Lett.* **2007**, *48*, 6896−6899.

(13) For reviews on the chemistry of sulfenate anions, see: (a) O'Donnell, J. S.; Schwan, A. L. *J. Sulfur Chem.* **2004**, *25*, 183−211. (b) Hogg, D. R. *Chemistry of Sulfenic Acids and Esters. The Chemistry of Sulfenic Acids and their Derivatives*; Wiley-Interscience: Toronto, 1990; pp 361−402. (c) Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. *The Chemistry of Sulfenic Acids, Esters and their Derivatives*; Patai, S., Ed.; John Wiley & Sons: New York, 1990; pp 351−429.

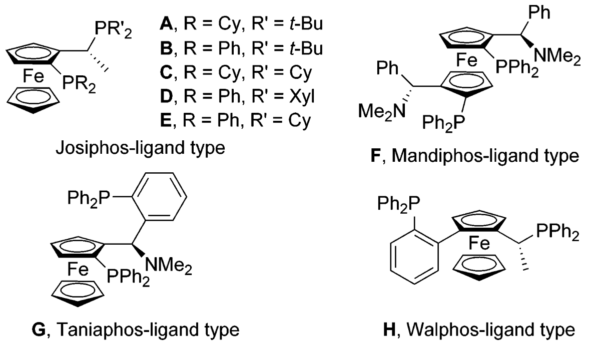
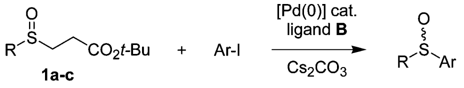
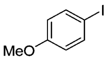
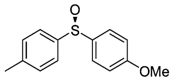
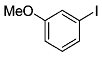
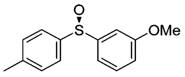
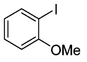
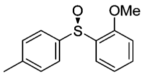
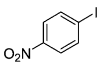
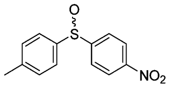
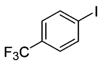
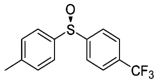
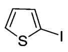
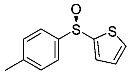
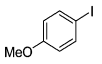
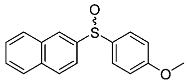
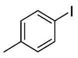
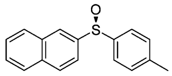
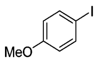
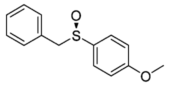
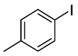
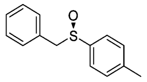


Figure 1. Enantiopure ligands tested.

Table 2. Scope of the Reaction[a]



a : R = Tol, **b** : R = 2-Naphthyl, **c** : R = Bn

entry	aryl halide	product		yield (%)[b]	% ee[c] (config)
1			**2a**	83	73 (R)
2			**3a**	90	68 (R)
3			**4a**	78	0
4			**5a**	67	66 (nd)
5			**6a**	98	80 (R)
6			**7a**	85	49[d] (R)
7			**2b**	75	72 (nd)
8			**3b**	93	65 (S)
9			**2c**	67	40 (R)
10			**3c**	71	47 (R)

[a] Reagents and reaction conditions: aryl iodide (1.2 equiv), β-sulfinylester, Pd_2dba_3 (1 mol %), ligand **B** (2 mol %), Cs_2CO_3 (4 equiv) at reflux of toluene. [b] Yields are given for isolated products. [c] Enantiomeric excess was determined by chiral supercritical fluid chromatography. Absolute configuration was determined by comparison of $[\alpha]_D$ with literature values. [d] ee% was determined by comparison of $[\alpha]_D$.

at reflux of toluene), which led to the desired sulfoxide in 83% yield, with only limited % ee erosion (entry 12).

With the optimized reaction conditions in hand, the scope and limitations of this enantioselective transformation were investigated by treating the β-sulfinyl esters **1a**−**c** with a variety of substituted aryl iodides (Table 2). *p*-Tolyl sulfenate precursor **1a** reacted with *p*- and *m*-iodoanisoles to afford the corresponding isomeric sulfoxides **2a** or **3a**[19] in 83% or 90% yields and in 73% or 68% ee's, respectively (entries 1 and 2). On the other hand, starting from *o*-iodoanisole, the coupling product **4a** was isolated in 78% yield in racemic form (entry 3). *p*-Iodonitrobenzene gave the sulfoxide **5a** in 67% yield and 66% ee (entry 4), whereas an excellent coupling yield (98%) and an interesting 80% ee were obtained using *p*-iodotrifluoromethyl benzene as the substrate (entry 5).[20] Reaction of 2-iodothiophene produced the corresponding coupling product **7a**[21] in 85% yield and 49% ee (entry 6). Starting from the β-sulfinylester **1b** (R = 2-naphthyl), reaction with *p*-iodoanisole and *p*-iodotoluene afforded the corresponding 2-naphthylsulfoxides **2b** or **3b**[22]

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in 75% or 93% yields and in 72% or 65% ee's, respectively (entries 7 and 8). Finally, benzylsulfenate precursor **1c** gave the aryl benzylsulfoxides **2c**[23] or **3c**[24] in 67% or 71% yields and 40% or 47% ee's, respectively (entries 9 and 10). It is noteworthy for predictive assignment that ligand **B** constantly favors sulfur-carbon bond formation via the *pro-S* sulfenate anion lone pair (Scheme 2).

In conclusion, we have reported the first asymmetric transition-metal-catalyzed arylation of sulfenate anions, thereby disclosing a new synthetic route toward enantiomerically enriched aryl sulfoxides. The Josiphos-type ligand **B** turned out to be the best ligand tested, allowing ee's up to 83% and in a predictable sense. Studies to elucidate the details of reaction mechanism as well as the origin of the enantioselectivity are currently in progress.

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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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