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Sulfinyl Group as a Novel Chiral Auxiliary in Asymmetric Heck Reactions

Nuria Díaz Buezo, Inés Alonso, and Juan C. Carretero*

Departamento de Química Orgánica
Facultad de Ciencias, Universidad Autónoma de Madrid
28049, Madrid, Spain

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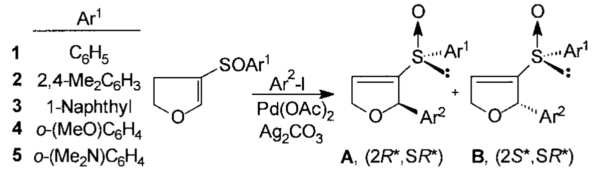
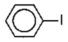
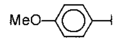
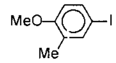
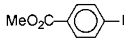
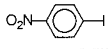
Despite the usefulness and widespread use of palladium-catalyzed arylation and alkenylation of olefins (Heck reaction),[1] successful examples of asymmetric Heck reactions are scarce and have been reported only in the past few years, mainly using enantiopure chelating diphosphines such as BINAP or (phosphinoaryl)-oxazolines as chiral ligands.[2] On the other hand, although sulfoxides have proved to be efficient chiral auxiliaries in asymmetric synthesis,[3] especially in other crucial C−C bond forming reactions such as Diels−Alder cycloadditions or nucleophile additions, very little is known about their use in asymmetric transition-metal-catalyzed reactions.[4] To the best of our knowledge we report here the first examples of asymmetric Heck reactions using sulfoxides as chiral auxiliaries and how the sense of the stereoselection can be controlled by appropriate choice of the substitution at the sulfinyl moiety.[5]

2,3-Dihydrofuran has been the most frequently used substrate in intermolecular asymmetric Heck reactions due to its cyclic structure and good reactivity.[6] In Table 1 are summarized the results obtained in the palladium-catalyzed arylations of the readily available (±)-4-arylsulfinyl-2,3-dihydrofurans **1**−**5**.[7]

After some experimentation, we found that the reactions proceeded cleanly in the presence of Ag_2CO_3 as base. Typical experimental conditions are as follows: ArI (3 equiv), $Pd(OAc)_2$ (10 mol %), and Ag_2CO_3 (2 equiv) in DMF at 100 °C for a few hours. These reactions took place similarly both in the absence and in the presence of phosphine ligands (PPh_3, dppp,[8] or dppf[8]), although in the latter case the processes were faster, giving in satisfactory yields a mixture of 2-aryl-3-sulfinyl-2,5-dihydrofurans **A** and **B**,[9] which in many cases could be separated by flash chromatography. However, the most interesting result concerns the dependence of the stereoselectivity with the substitution at the sulfoxide. Thus, regardless the electronic character of the substitution at the aryl iodide, sulfoxides **1**−**4** lead predominantly to the isomers **A** with moderate stereoselectivity (diastereomeric excess (de) = 34−56%), while the *o*-dimethylamino sulfoxide **5** affords the isomers **B** with a remarkable stereocontrol (de = 70−88%).[10]

Table 1. Heck Reactions of **1**−**5** with Iodoarenes[a]



Entry	Substrate	Ar^2-I	**A**:**B** ratio (%)[b]	Yield (%)[c]
1	**1**		**6A**:**6B** = 77:23	68
2	**2**		**7A**:**7B** = 78:22	80
3	**3**		**8A**:**8B** = 71:29	43
4	**4**		**9A**:**9B** = 75:25	47
5	**5**		**10A**:**10B** = 6:94	80
6	**1**		**11A**:**11B** = 69:31	70
7	**5**		**12A**:**12B** = 14:86	55
8	**1**		**13A**:**13B** = 75:25	60
9	**5**		**14A**:**14B** = 15:85	86
10	**1**		**15A**:**15B** = 71:29	61
11	**5**		**16A**:**16B** = 7:93	45[d]
12	**1**		**17A**:**17B** = 67:33	59
13	**5**		**18A**:**18B** = 6:94	64

[a] Reaction conditions : **1-5**, Ar^2-I (3 equiv), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2 equiv), dppp (10 mol %), DMF, 100 °C, 2-24 h. [b] Determined by ^{1}H-NMR on the crude mixtures. [c] In isolated products after chromatography. [d] In converted product (50% of **5** was recovered).

Although from these preliminary results it is not possible to establish a precise mechanistic explanation about the opposite stereochemical outcome obtained from substrates **1**−**4** and **5**, we speculate that this different behavior could be attributed to either a steric or a chelation control in the insertion step, respectively. After oxidative addition, the coordination of the cationic arylpalladium species[1] $[ArPdL_2]^+$ with the double bond of vinyl sulfoxides **1**−**4** in their *s-trans* conformations[11] would occur preferably from the least hindered face, that opposite to the Ar^1 group, to give the complex **C**[12] (Figure 1). Further insertion on the double bond and β-hydrogen elimination steps would lead to the isomer **A**. In contrast, due to the excellent ability of the palladium atom to coordinate amino groups, it can be assumed that the initial coordination of $[PhPdL_2]^+$ to the NMe_2 unit of **5**

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[1] Recent reviews: (a) Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447. (b) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *36*, 2379. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.

[2] For a review on the asymmetric Heck reaction, see: (a) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371. See also: (b) Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* **1997**, 1338.

[3] Recent reviews: (a) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Gianneto, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1339. (b) Carreño, C. *Chem. Rev.* **1995**, *95*, 1717. (c) Walker, A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 961.

[4] (a) Paley, R. S.; Rubio, M. B.; Fernández de la Pradilla, R.; Dorado, R.; Hundal, G.; Martínez-Ripoll, M. *Organometallics* **1996**, *15*, 4672. (b) Tokunoh, R.; Sodeoka, M.; Aoe, K.-I.; Shibasaki, M. *Tetrahedron Lett.* **1995**, *36*, 8035. (c) Villar, J. M.; Delgado, A.; Llebaria, A.; Moretó, J. M. *Tetrahedron: Asymmetry* **1995**, *6*, 665. (d) Allen, J. V.; Bower, J. F.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1994**, *5*, 1895. (e) Khiar, N.; Fernández I.; Alcudia, F. *Tetrahedron Lett.* **1993**, *34*, 123. (f) Carreño, C.; García Ruano, J. L.; Maestro, M. C.; Martín Cabrejas, L. M. *Tetrahedron: Asymmetry* **1993**, *4*, 727.

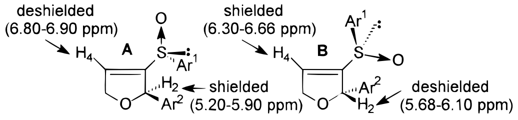
[5] For the use of *p*-tolyl vinyl sulfoxide in a palladium-catalyzed arylation, see: Somei, M.; Yamada, F.; Ohnishi, H.; Makita, Y.; Kuriki, M. *Heterocycles* **1987**, *26*, 2823.

[6] Very recent references: (a) Hii, K. K.; Claridge, T. D. W.; Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 984. (b) Hillers, S.; Sartori, S.; Reiser, O. *J. Am. Chem. Soc.* **1996**, *118*, 2087. (c) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200.

[7] Compounds (±)-**1**−**5** were prepared by oxidation of the corresponding thioethers (MCPBA), which were readily prepared by sulfenylation of 2,3-dihydrofuran with methyl aryl sulfoxides: Jain, S.; Shukla, K.; Mukhopadhyay, A.; Suryawanshi, S. N.; Bhakuni, D. S. *Synth. Commun.* **1990**, *20*, 1315.

[8] dppp = 1,3-bis(diphenylphosphino)propane. dppf = 1,1′-bis(diphenylphosphino)ferrocene.

[9] The configurational assignment of stereoisomers **A** and **B** was first established by NMR studies. Particularly, the chemical shifts of H_2 and H_4 were found to be excellent diagnostic criteria. H_4 appears significantly more deshielded in isomers **A** than in isomers **B** (δ_4**A**−δ_4**B** = 0.1−0.5 ppm, $CDCl_3$) whereas the opposite behavior is observed for δH_2 (δ_2**B**−δ_2**A** = 0.1−0.5 ppm, $CDCl_3$). These remarkable spectroscopic effects might be explained on the basis of the highly deshielding effect induced by the sulfinylic oxygen on its hydrogen in 1,3-parallel relationship: H_4 in isomers **A** and H_2 in isomers **B** in their presumed most stable conformations around the C−S bond, those avoiding important 1,3-parallel interactions between substituents at sulfur and at C-2 (see figures below). For NMR effects of the sulfinyl group, see: Lett, R.; Marquet, A. *Tetrahedron* **1974**, *30*, 3379.



[10] In the absence of phosphines the stereoselectivity of the Heck reactions of **5** was somewhat lower. For instance in the reaction with iodobenzene the **A**:**B** ratio was 12:88 in the absence of phosphines, 8:92 in the presence of PPh_3 (20 mol %), and 6:94 in the presence of dppp or dppf (10 mol %).

[11] For conformational aspects in vinyl sulfoxides, see: Arai, I.; Takayama, H.; Koizumi, T. *Tetrahedron Lett.* **1987**, *28*, 3689.

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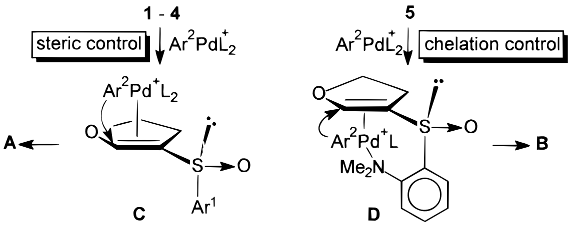
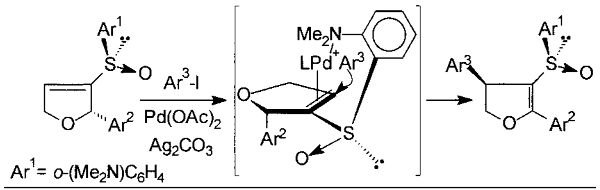


Figure 1. Proposed models for the insertion step in the Heck reaction of **1**−**4** and **5**.

Table 2. Heck Reaction of **10B** and **12B** with Iodoarenes[a]



Entry	Substrate	Ar^3-I	Product	Yield (%)[b]
1	**10B**	C_6H_5I	**19**	83
2	**10B**	p-$(MeO)C_6H_4I$	**20**	69 (80)[c,d]
3	**10B**	p-$(NO_2)C_6H_4I$	**21**	46 (84)[c]
4	**12B**	C_6H_5I	**22**	78
5	**12B**	p-$(MeO)C_6H_4I$	**23**	70[d]

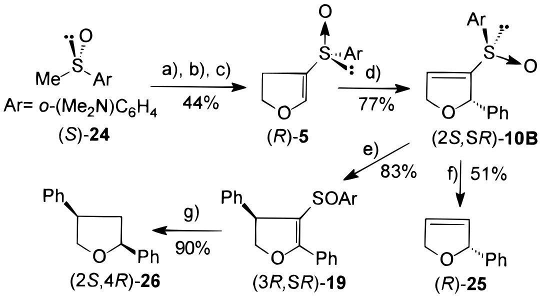
[a] Reaction conditions : **10B** or **12B**, Ar^3-I (3 equiv), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2 equiv), dppf (10 mol %), DMF, 100 °C, 20h. [b] In pure product. [c] Yields in parentheses are conversion yields. [d] dppp as ligand.

would lead to the amino complex **D**,[13] which would direct intramolecularly the insertion of the aryl group (Ar^2) from the same side of the (*N*,*N*-dimethylamino)phenyl moiety to afford finally the isomer **B**.

Having developed a stereoselective approach to the preparation of 2-aryl-3-(arylsulfinyl)-2,5-dihydrofurans (**A** and **B**), it was interesting to know if these new vinyl sulfoxides could undergo a second Heck reaction to afford diaryl substituted dihydrofurans. We were pleased to find that the major isomers **B** obtained from dihydrofuran **5** reacted cleanly and in a fully stereoselective manner under similar conditions to that described for **5**, but using longer reaction times (20 h instead of 2−6 h).[14] The reaction appears to be general (Table 2), and the resulting 3,5-diaryldihydrofurans (**19**−**23**) were isolated as single isomers in good yields (70−84%). This complete asymmetric induction might be rationalized assuming a chelated model similar to that proposed for dihydrofuran **5**, in which both the steric effects associated to the substitution at C-2 and the coordination Pd/NMe_2 in the *s-trans* conformation of the unsaturated sulfoxide (**10B** or **12B**) would favor the insertion step from the face of the double bond opposite to the aryl substituent at C-2.

To apply this methodology to the preparation of optically pure compounds, enantiopure sulfoxides **1**−**5** were required. Compound (*R*)-**5** (enantiomeric excess (ee) > 96%) was readily prepared in 44% overall yield from (*S*)-*o*-(*N*,*N*-dimethylamino)-phenyl methyl sulfoxide[15] [(*S*)-**24**] as follows: reaction of the α-sulfinyl anion of (*S*)-**24** with ethylene oxide, formylation at α-position with ethyl formate to give a mixture of hemiacetals stereoisomers, and dehydratation with MsCl/Et_3N (Scheme 1). The Heck reaction of (*R*)-**5** with iodobenzene under the usual conditions afforded a 6:94 mixture of (2*R*,*SR*)-**10A** and (2*S*,*SR*)-**10B**. After flash chromatography (2*S*,*SR*)-**10B** was obtained in 77% yield and its further desulfinylation by treatment with activated powdered zinc[16] led to the known (*R*)-2-phenyl-2,5-dihydrofuran [(*R*)-**25**, 51% yield, ee > 96%[17]] whose optical rotation was identical to the previously reported,[18] proving otherwise the stereochemical assignments previously established by NMR for compounds **A** and **B**.[9] In a similar manner, the treatment of (2*S*,*SR*)-**10B** with iodobenzene yielded (3*R*,*SR*)-**19** (83%), which was cleanly transformed in one-step (90%) into enantiopure (2*S*,4*R*)-2,4-diphenyltetrahydrofuran [(2*S*,4*R*)-**26,** [α] = −52.5 (c = 1.40, $CHCl_3$), ee > 96%[17]] by reaction with Raney nickel. (2*S**,4*R**)-**26**, called Calyxolane B, has been recently isolated from a marine sponge.[19]

Scheme 1[a]



[a] Key: (a) (i) LDA, Et_2O, −78 °C; (ii) ethylene oxide; (b) (i) LDA, −78 °C, THF; (ii) ethyl formate, −78 °C; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C; (d) PhI, $Pd(OAc)_2$, Ag_2CO_3, dppp, DMF, 100 °C, 4 h; (e) PhI, $Pd(OAc)_2$, Ag_2CO_3, dppf, DMF, 100 °C, 20 h; (f) Zn, sat. NH_4Cl, THF, rt; (g) Raney Ni, H_2, EtOH, 0 °C.

In conclusion, it has been demonstrated that the sulfinyl group can be used as a novel and efficient chiral auxiliary in asymmetric Heck reactions of dihydrofurans. The best results have been obtained using *o*-(*N*,*N*-dimethylamino)phenyl sulfoxides, in which the presumed coordination of the Pd atom with the nitrogen determines a high asymmetric induction in the key insertion step.

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Supporting Information Available: Experimental procedures and spectral data of the new compounds (10 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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[12] Taking into account the moderate palladium-coordinating ability of the sulfinyl group (see for instance ref 4b), a prior complexation of the aryl palladium cation with either the sulfinylic oxygen or the sulfur lone pair of sulfoxides **1**−**4**, followed by π-complexation directed by the Pd atom, cannot be ruled out as a feasible alternative mechanism.

[13] For somewhat related Pd−N coordinated complexes proposed in the Heck reaction of acyclic nitrogen-containing vinyl ethers, see: (a) Larhed, M.; Andersson, C.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285. (b) Andersson, C.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757. See also: Krafft, M. E.; Wilson, A. M.; Fu, Z.; Procter, M. J.; Dasse, O. A. *J. Org. Chem.* **1998**, *63*, 1748.

[14] On the contrary, no reaction was observed after treatment of **6A** and **10A** with iodobenzene (3 equiv), $Pd(OAc)_2$ (10 mol %), dppf (20 mol %), and Ag_2CO_3 (2 equiv) in DMF at 100 °C for 20 h.

[15] Compound (*S*)-**24** was prepared using the DAG methodology: Fernández, I.; Khiar, N.; Llera, J. M.; Alcudia, J. *J. Org. Chem.* **1992**, *57*, 6789.

[16] Holton, R. A.; Crouse, D. J.; Williams, A. D.; Kennedy, R. M. *J. Org. Chem.* **1987**, *52*, 2317.

[17] The optical purities were determined by ^1H NMR in the presence of $Pr(hfc)_3$ [Praseodymium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate].

[18] [α] = +282 (c = 0.50, $CHCl_3$, 24 °C); [α] lit.[2b] = +280 (c = 1.06, $CHCl_3$, 24 °C, ee = 97%).

[19] Rodríguez, A. D.; Cóbar, O. M.; Padilla, O. L. *J. Nat. Prod.* **1997**, *60*, 915.