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The 2-(*N*,*N*-Dimethylamino)phenylsulfinyl Group as an Efficient Chiral Auxiliary in Intramolecular Heck Reactions

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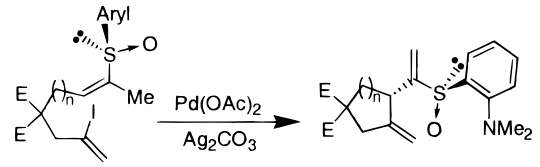
ABSTRACT



The synthesis, reactivity, and stereochemical behavior of differently substituted iodoalkenyl α,β-unsaturated sulfoxides in intramolecular Heck reaction is described. Particularly, the 2-(*N*,*N*-dimethylamino)phenylsulfinyl group is demonstrated to be an effective chiral auxiliary for the intramolecular Heck reaction of 2-iodo-1,6-(or 1,7)dienes. A desulfinylation sequence removes the auxiliary and yields cyclic compounds of high enantiopurity.

Discovered in the late 1960s,[1] the palladium-catalyzed arylation or vinylation of alkenes (the Heck reaction) has developed into one of the most versatile methods for C−C bond formation.[2] However, highly enantioselective examples of asymmetric Heck reactions are relatively rare and involve the use of enantiopure P,P or P,N bidentate ligands.[3] Despite the conceptual and practical advantages of chiral catalysts for asymmetric synthesis, it is surprising that the chiral auxiliary approach has not been investigated due to the possibility that it may be less substrate dependent.[4,5] In connection with our interest in sulfoxides as stereochemical controllers in intermolecular Heck reactions[5] and other metal-catalyzed processes,[6] we report a novel asymmetric methodology for the intramolecular Heck reaction of 2-iodo-1,6-(or 1,7)-dienes. The reactions rely upon the use of the 2-(*N*,*N*-dimethylamino)phenylsulfinyl group as an efficient chiral auxiliary.

To test the behavior of α,β-unsaturated sulfoxides in intramolecular Heck reactions, we synthesized the racemic

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(3) Reviews on the asymmetric Heck reaction: (a) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371. (b) Guiry, P. J.; Hennessy, A. J.; Cahill, J. P. *Top. Catal.* **1997**, *4*, 311. For some recent references, see: (a) Tietze, L. F.; Thede, K.; Schimpf, R.; Sannicolo, F. *Chem. Commun.* **2000**, 583. (b) Tietze, L. F.; Thede, K.; Sannicolò, F. *Chem. Commun.* **1999**, 1811. (c) Honzawa, S.; Mizutani, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 311. (d) Flubacher, D.; Helmchem, G. *Tetrahedron Lett.* **1999**, *40*, 3867. (e) Namyslo, C.; Kaufmann, D. E. *Synlett* **1999**, 804. (f) Tschoerner, M.; Pregosin, P. *Organometallics* **1999**, *18*, 670. (g) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500. (h) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488. (i) Miyazaki, F.; Votsu, K.; Shibasaki, M. *Tetrahedron* **1998**, *54*, 13073.

(4) To the best of our knowledge only a few examples using SAMP (or RAMP) as chiral auxiliaries in Heck reactions have been reported: Grigg, R.; Dorrity, M. J. R.; Malone, J. F.; Mongkolaussavaratana, T.; Norbert, W. D. J. A.; Sridharan, V. *Tetrahedron Lett.* **1990**, *31*, 3075. See also: Meyer, F. E.; Henniges, H.; de Meijere, A. *Tetrahedron Lett.* **1992**, *33*, 8039.

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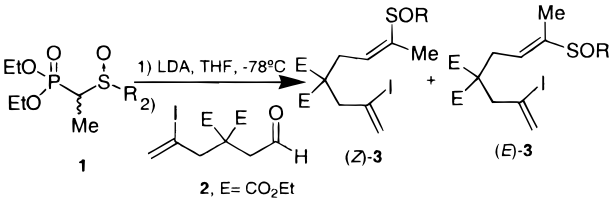
Scheme 1



sulfoxides **3** as model substrates due to the precedented Heck cyclizations of 2-halo-1,6-dienes.[2] Dienes **3** were readily prepared as *E*/*Z* mixtures by Wadsworth−Emmons olefination of the phosphonates **1**[7] with the aldehyde **2**[8] (Scheme 1, Table 1). The major *Z* isomers[9] were separated by flash

Table 1. Synthesis of Sulfinylated Dienes **3** by Wadsworth−Emmons Olefination

phosphonate	R	diene	*Z*:*E*[a]	yield (%)[b]
1a	*p*-Tol	**3a**	50:50	77
1b	*t*-Bu	**3b**	98:2	83 (83)[c]
1c	*o*-(Me_2N)C_6H_4	**3c**	85:15	88 (60)[c]

[a] Determined by ^{1}H NMR on the crude mixtures. [b] In pure products. [c] Yield in pure (*Z*) diene.

chromatography, and their Heck reactions were carried out in the presence of the couple $Pd(OAc)_2/Ag_2CO_3$ (Scheme 2,

Scheme 2

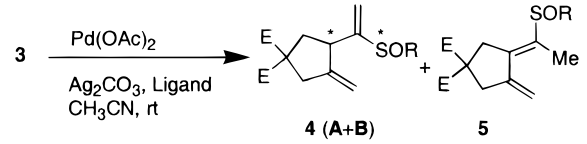


Table 2), which was found optimal in the case of the Heck reactions of sulfinyldihydrofurans.[5b]

Table 2. Intramolecular Heck Reaction of Sulfinylated Dienes **3**[a]

entry	diene	ligand	conv(%)[b]	**4**:**5** ratio[b]	**A**:**B** ratio[b]
1	(*Z*)-**3a**	PPh_3	>98	>98:<2	54:46[c]
2	(*Z*)-**3b**	PPh_3	60	>98:<2	83:17[c]
3	(*Z*)-**3c**	PPh_3	>98	86:14	>98:<2
4	(*Z*)-**3c**		14	>98:<2	>98:<2
5	(*Z*)-**3c**	dppp	35	>98:<2	>98:<2
6	**(*Z*)-3c**	**dppf**	**80**	**>98:<2**	**>98:<2**
7	(*E*)-**3c**	PPh_3	>98	40:60	20:80

[a] Reaction conditions: $Pd(OAc)_2$ (10 mol %), ligand (ratio P/Pd = 2:1), Ag_2CO_3 (200 mol %), CH_3CN, rt, 24 h. [b] Estimated by ^{1}H NMR on the crude mixtures. [c] The stereochemical assignment of both isomers has not been established.

A clean reaction was observed at rt using PPh_3 as the ligand (entries 1−3). The bulky *tert*-butyl sulfoxide **3b** (entry 2) was significantly less reactive than the aryl sulfoxides **3a** and **3c**. As expected, 1,6-dienes **3** reacted exclusively by a 5-*exo* cyclization mode. Furthermore, selectivity was observed between the two possible final β-hydride elimination pathways. The (*Z*) dienes afforded predominantly 1,4-diene **4** (entries 1−6), and the opposite regiochemical behavior was observed from the (*E*) dienes (entry 7). Interestingly, a remarkable dependence of the stereoselectivity with the substitution at sulfur was observed. The cyclization stereoselectivity of *p*-tolyl sulfoxide (*Z*)-**3a** was low (entry 1), and *tert*-butyl sulfoxide (*Z*)-**3b** gave moderate stereoselectivity (entry 2). In contrast, the Heck reaction of 2-(*N*,*N*-dimethylamino)phenylsulfoxide (*Z*)-**3c** occurred with complete diastereocontrol,[10] leading to the exclusive formation of **4cA** (entry 3), along with the minor formation of 1,3-diene **5c**. After a brief study of the effect of the ligand (entries 3−6), we found that in the presence of dppf the cyclization was completely regioselective and diastereoselective (entry 6). As optimal experimental conditions, the reaction of (*Z*)-**3c** with $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (200 mol %), and dppf (10 mol %) in acetonitrile at 60 °C for 5 h afforded **4cA** in 75% yield after chromatographic purification. Although we were unable to establish the relative configuration of isomers **4A** and **4B** by NMR, the configuration of **4cA** could be unequivocally deduced from that of its diol **6**, a crystalline derivative obtained by dihydroxylation of **4cA** (OsO_4, Me_3NO) whose configuration was determined by X-ray analysis[11] (Figure 1).

To determine the generality of this type of diastereoselective Heck reaction, the chain-unsubstituted substrate (*Z*)-**7**, the ethyl derivative (*Z*)-**8**, and the 1,7-diene (*Z*)-**9** were readily prepared,[12] and their Heck reactions were studied under the optimized conditions previously found for (*Z*)-**3c**.

(6) The use of sulfoxides as chiral auxiliaries in metal-catalyzed reactions has not been extensively explored. Recent references: (a) Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **1999**, *121*, 7411. (b) Henrich, M.; Delgado, A.; Molins, E.; Roig, A.; Llebaria, A. *Tetrahedron Lett.* **1999**, *40*, 4259. (c) Paley, R. S.; Estroff, L. A.; McCulley, D. J.; Martínez-Cruz, L. A.; Jiménez Sánchez, A.; Cano, F. H. *Organometallics* **1998**, *17*, 1841. (d) Paley, R. S.; Rubio, M. B.; Fernández de la Pradilla, R.; Dorado, R.; Hundal, G.; Martínez-Ripoll, M. *Organometallics* **1996**, *15*, 4672. For the use of sulfoxides as chiral ligands, see: Hiroi, K.; Suzuki, Y.; Abe, I. *Tetrahedron: Asymmetry* **1999**, *10*, 1173 and references therein.

(7) Racemic phosphonates **1** (as mixtures of both diastereomers) were readily prepared in two steps: initial phosphorylation of the α-sulfinyl carbanion of the corresponding methyl sulfoxide with diethyl chlorophosphate followed by methylation (LDA, THF, and then MeI).

(8) Aldehyde **2** was prepared from diethyl malonate by two sequential alkylations (bromoacetaldehyde diethyl acetal first and 3-bromo-2-iodo-1-propene second) and acid hydrolysis of the acetal moiety.

(9) The *E*/*Z* configuration of olefins **3** was clear from spectral evidence. For instance, the chemical shift of the olefinic proton is significantly higher in the *E* isomers than in the *Z* ones ($\Delta\delta$ = 0.47−0.53 ppm, $CDCl_3$) as a consequence of the deshielding *cis*-effect of the sulfinyl group. This assignment has also been corroborated by NOE experiments.

(10) With these preliminary results, it does not appear to be easy to determine unequivocally the origin of the high stereochemical control exerted by the 2-(*N*,*N*-dimethylamino)phenylsulfinyl group in the Heck reactions. At present, we are investigating if this effect could be mainly due to steric reasons, conformational preferences around the C−S bond in the reactants, or a chelation control directed by a previous coordination of the intermediate palladium cationic species with the dimethylamino moiety prior to the insertion step.

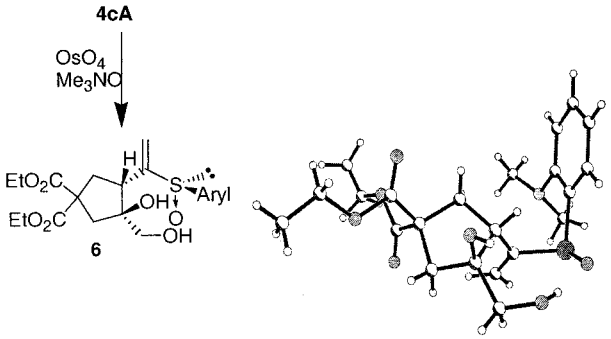


Figure 1. Structure of diol **6** in the crystal.

Again, the cyclizations took place without significant formation of 1,3-dienes and in a highly stereoselective manner to give the corresponding **A**[13] 1,4-dienes **10A**, **11A**, and **12A** in satisfactory yields (Scheme 3 and Table 3).

Scheme 3

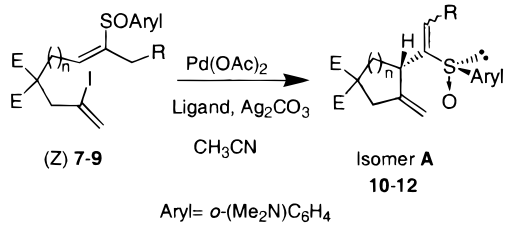


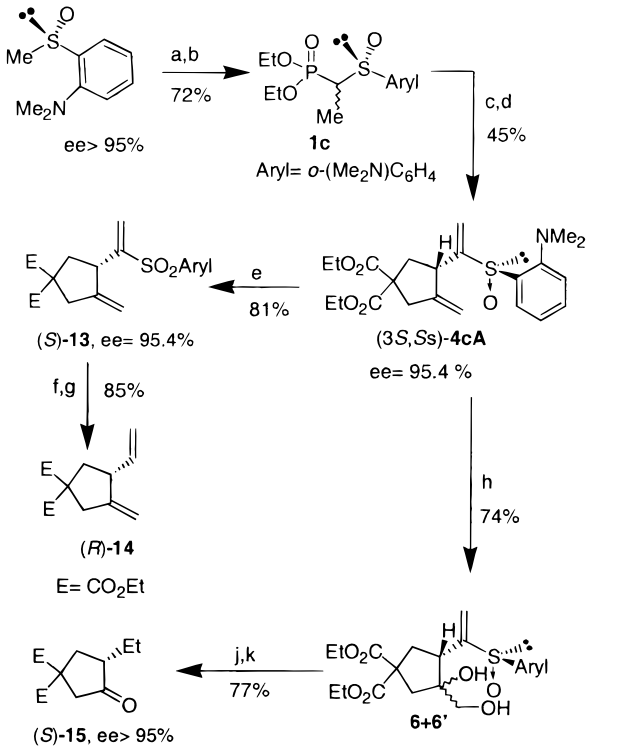
Table 3. Intramolecular Heck Reaction of Dienes (*Z*)-**7**−**9**[a]

diene	E	*n*	R	product	**A**:**B** ratio[b]	yield (%)[c]
(*Z*)-**7**	H	1	H	**10**	92:8	54
(*Z*)-**8**	CO_2Et	1	Me	**11**	>98:<2	70[d]
(*Z*)-**9**	CO_2Et	2	H	**12**	>98:<2	61

[a] Reaction conditions: $Pd(OAc)_2$ (10 mol %), dppp or dppf (10 mol %), Ag_2CO_3 (200 mol %), CH_3CN, 60 °C. [b] Estimated by ^1H NMR on the crude mixtures. [c] In purified product. [d] Obtained as a 5:1 mixture of *E*:*Z* isomers.

Finally, to utilize these reactions in asymmetric synthesis, two additional requirements had to be met. An enantioselective preparation of the starting dienes and a method to remove the chiral auxiliary must be developed. The enantiopure phosphonate **1c** (Scheme 4) was readily prepared as follows: deprotonation of (*S*)-2-(*N*,*N*-dimethylamino)phenyl methyl sulfoxide[5b] (ee ≥ 95%) with LDA and subsequent reaction with diethyl chlorophosphate afforded the corresponding sulfinylmethyl phosphonate, which was deprotonated (LDA) and methylated (MeI) to give the required enantiopure phosphonate **1c** as a 1:1 mixture of C-epimers.[14] Reaction of **1c** with aldehyde **2** yielded enantiopure diene (*Z*)-**3c**[14] (ee > 95%, NMR),[15] and its further Heck reaction led to the isomer (3*S*,*Ss*)-**4cA** with preservation of the starting optical purity (ee = 95.4%, HPLC, Chiralcel OD). This result indicates that no racemization at sulfur occurs during the olefination or in the palladium-catalyzed step.

Scheme 4[a]



[a] (a) i: LDA, THF, −78 °C; ii: $ClPO(OEt)_2$. (b) i: LDA, THF, −78 °C; ii: MeI, 0 °C. (c) i: LDA, −78 °C; ii: aldehyde **2**, 0 °C. (d) $Pd(OAc)_2$, Ag_2CO_3, dppf, CH_3CN, 60 °C. (e) i: MCPBA, CH_2Cl_2, 0 °C; ii: Zn, AcOH, THF, H_2O, rt. (f) *n*-Bu_3SnLi, THF, −78 °C. (g) SiO_2, $CHCl_3$, 50 °C. (h) OsO_4 (4 mol %), Me_3NO, acetone/H_2O, rt. (j) Ra Ni, EtOH, rt. (k) $NaIO_4$, CH_2Cl_2/H_2O, rt.

(11) Crystal structure analysis of **6** ($C_{22}H_{31}NO_7S$): monoclinic, space group *C*2/*c*; a = 28.7179 (15), b = 8.0842 (3), c = 22.1820 (9) Å; V = 4802 Å^3; Z = 8; M_{calcd} = 453.54; ρ_{calcd} = 1.255 mg/m^3. Crystals were obtained from dichloromethane/*n*-hexane, with crystal dimensions 0.20 × 0.30 × 0.30 mm, θ_{max} = 57.14°, Cu Kα radiation (λ = 1.54178 Å). The scan mode was Omega. T = 293 K. Reflections collected: 4027. Independent reflections: 3222 (R_{int} = 0.0254). Empirical Absorption Correction. The structure was solved with the program Shelxtl, version 5.1, Bruker AXS. Refinement method full-matrix least-squares on F^2. Automatic treatment of H atoms. Parameters refined: 287. Final *R* indices [$I > 2\sigma(I)$]: R1 = 0.0487, wR2 = 0.1376. *R* indices (all data): R1 = 0.0559, wR2 = 0.1459. Residual electron density: 0.392 and −0.328 e Å^{-3}. Crystallographic data of **6** have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 138255.

(12) In a manner similar to that described for the preparation of (*Z*)-**3c**, (*Z*)-**7**, (*Z*)-**8**, and (*Z*)-**9** were obtained by a highly (*Z*)-stereoselective Wadsworth−Emmons olefination of their corresponding aldehydes.

(13) The configurations of **10A**, **11A**, and **12A** were assigned by chemical analogy with the case of **4cA**. Accordingly, all these compounds show similar NMR parameters for the protons of the 1,4-diene moiety.

(14) Specific rotations: **1c** $[\alpha]^{25}_D$ = −258.0 (*c* = 1.0, $CHCl_3$), (6*Z*,*S*$_s$)-**3c** $[\alpha]^{25}_D$ = +135.0 (*c* = 1.0, $CHCl_3$), (3*S*,*S*$_s$)-**4cA** $[\alpha]^{25}_D$ = −29.0 (*c* = 1.0, $CHCl_3$), **6** $[\alpha]^{25}_D$ = −31.0 (*c* = 1.0, $CHCl_3$), (*S*)-**13** $[\alpha]^{25}_D$ = +74.3 (*c* = 0.7, $CHCl_3$), (*R*)-**14** $[\alpha]^{25}_D$ = +13.7 (*c* = 0.8, $CHCl_3$), (*S*)-**15** $[\alpha]^{25}_D$ = +95.8 (*c* = 1.2, $CHCl_3$).

(15) Determined in the presence of (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol.

In contrast, the removal of the sulfinyl chiral auxiliary proved to be more difficult than expected. All attempts to cleave the C−S bond in sulfoxide **4cA** were unsuccessful.[16] Finally, an indirect method for the conversion of (3*S*,*S*s)-**4cA** into the desired diene (*R*)-**14**[14,17] was found. The sequence consists of oxidation of **4cA** to its sulfone (*S*)-**13**[14] (81% yield, ee = 95.4%, HPLC, Chiralcel OD) and a two-step desulfonylation according to Fujita's procedure:[18] nucleophilic addition of *n*-Bu_3SnLi to the vinyl sulfone followed by thermal β-elimination of the resulting β-stannyl sulfone to yield cyclopentadiene (*R*)-**14** in 85% yield. Alternatively, dihydroxylation (OsO_4, Me_3NO) of **4cA** furnished a 1:1 mixture of diols **6** + **6′** (74% yield),[19] which was transformed into the cyclopentanone (*S*)-**15**[14,20] (77% yield, ee > 96%, NMR[15]) by treatment with Raney Ni followed by oxidative cleavage of the 1,2-diol moiety with $NaIO_4$ (Scheme 4).

(16) **4cA** or its thioether was treated with Al−Hg; Mg−$HgCl_2$; Na−Hg; Raney Ni; NICRA, Ni_2B; Li/NH_3; Li/naphthalene; and ^{i}PrMgBr/Pd(acac)$_2$. Lack of reactiviy or formation of complex mixtures of alkenes and/or sulfur containing products was observed depending on the reagent used.

(17) We were unable to find appropriate conditions to confirm the high enantiomeric composition of the diene (*R*)-**14** [no peak separation of (±)-**14** was observed by NMR in the presence of chiral shift reagents or by chiral HPLC or GC].

(18) Ochiai, M.; Ukita, T.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1983**, 619.

(19) Both diastereomers **6** + **6′** can be easily separated by flash chromatography.

In summary, the intramolecular Heck reaction of (*Z*) 2-iodo-1,6- and 1,7-dienes bearing a 2-(*N*,*N*-dimethylamino)-phenylsulfinyl group as a chiral auxiliary occurs stereoselectively. Because of the availability of the starting dienes in optically pure form and the development of procedures for the cleavage of the chiral auxiliary, this methodology constitutes an alternative to the enantioselective Heck reaction based on the use of chiral ligands.

Acknowledgment. This work was supported by the Ministerio de Educación y Cultura (DGES, project PB96-0021). N.D. also thanks the Ministerio de Educación y Cultura for a predoctoral fellowship.

Supporting Information Available: Representative experimental procedure and characterization data of compounds **1**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The sign of the specific rotation of 2-ethylcyclopentanone (*S*)-**15** [ref 14] is in agreement with that of related α-alkylated cyclopentanones: (a) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532. (b) Lacote, E.; Delouvrié, B.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2116.