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 $\alpha_{n}\beta$ -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 reactions⁵ and other metalcatalyzed 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,Ndimethylamino)phenylsulfinyl group as an efficient chiral auxiliary.

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

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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* isomers⁹ were separated by flash

Table 1. Synthesis of Sulfinylated Dienes 3 byWadsworth-Emmons Olefination								
phosphonate	R	diene	Z:E ^a	yield (%) b				
1a	<i>p</i> -Tol	3a	50:50	77				
1b	t-Bu	3b	98:2	83 (83) ^c				

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

30

85:15

88 (60)^c

o-(Me₂N)C₆H₄

1c

chromatography, and their Heck reactions were carried out in the presence of the couple Pd(OAc)₂/Ag₂CO₃ (Scheme 2,



Table 2), which was found optimal in the case of the Heck reactions of sulfinyldihydrofurans.^{5b}

(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, CDCl₃) as a consequence of the deshielding *cis*-effect of the sulfinyl group. This assignment has also been corroborated by NOE experiments.

Table 2. Intramolecular Heck Reaction of Sulfinylated Dienes 3^a

entry	diene	ligand	conv(%) ^b	4:5 ratio ^b	A:B ratio ^b
1	(<i>Z</i>)- 3a	PPh ₃	>98	>98:<2	54:46 ^c
2	(<i>Z</i>)- 3b	PPh_3	60	>98:<2	83:17 ^c
3	(<i>Z</i>)-3c	PPh_3	>98	86:14	>98:<2
4	(<i>Z</i>)- 3c		14	>98:<2	>98:<2
5	(<i>Z</i>)- 3c	dppp	35	>98:<2	>98:<2
6	(<i>Z</i>)-3c	dppf	80	> 98: < 2	> 98: <2
7	(<i>E</i>)- 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 ¹H NMR on the crude mixtures. ^{*c*} The stereochemical assignment of both isomers has not been established.

A clean reaction was observed at rt using PPh₃ 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 %), Ag₂CO₃ (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 (OsO4, Me3-NO) whose configuration was determined by X-ray analysis¹¹ (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.

⁽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).

Table 3. Intramolecular Heck Reaction of Dienes (Z)-7-9 a								
diene	Е	n	R	product	A:B ratio ^b	yield (%) ^c		
(<i>Z</i>)-7	Н	1	Н	10	92:8	54		
(<i>Z</i>)- 8	CO ₂ Et	1	Me	11	>98:<2	70^d		
(Z)- 9	CO_2Et	2	Η	12	>98:<2	61		

^{*a*} Reaction conditions: Pd(OAc)₂ (10 mol %), dppp or dppf (10 mol %), Ag₂CO₃ (200 mol %), CH₃CN, 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 enantio-

(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.

selective 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



^{*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, Ag₂CO₃, dppf, CH₃CN, 60 °C. (e) i: MCPBA, CH₂Cl₂, 0 °C; ii: Zn, AcOH, THF, H₂O, rt. (f) *n*-Bu₃SnLi, THF, −78 °C. (g) SiO₂, CHCl₃, 50 °C. (h) OsO₄ (4 mol %), Me₃NO, acetone/H₂O, rt. (j) Ra Ni, EtOH, rt. (k) NaIO₄, CH₂Cl₂/H₂O, rt.

follows: deprotonation of (*S*)-2-(*N*,*N*-dimethylamino)phenyl methyl sulfoxide^{5b} (ee \geq 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*,*S*s)-**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.

⁽¹¹⁾ Crystal structure analysis of **6** (C₂₂H₃₁NO₇S): monoclinic, space group *C*2/*c*; *a* = 28.7179 (15), *b* = 8.0842 (3), *c* = 22.1820 (9) Å; *V* = 4802 Å³; *Z* = 8; *M*_{calcd} = 453.54; ρ_{calcd} = 1.255 mg/m³. Crystals were obtained from dichloromethane/*n*-hexane, with crystal dimensions 0.20 × 0.30 × 0.30 mm, θ_{max} = 57.14°, Cu K α 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 F². Automatic treatment of H atoms. Parameters refined: 287. Final *R* indices [*I* > 2*o*-(*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 Å³⁻³. Crystallographic data of **6** have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 138255.

⁽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, CHCl₃), (6Z,S_s)-**3c** $[\alpha]^{25}_{D} = +135.0$ (*c* = 1.0, CHCl₃), (3S,S_s)-**4cA** $[\alpha]^{25}_{D} = -29.0$ (*c* = 1.0, CHCl₃), **6** $[\alpha]^{25}_{D} = -31.0$ (*c* = 1.0, CHCl₃), (S)-**13** $[\alpha]^{25}_{D} = +74.3$ (*c* = 0.7, CHCl₃), (*R*)-**14** $[\alpha]^{25}_{D} = +13.7$ (*c* = 0.8, CHCl₃), (S)-**15** $[\alpha]^{25}_{D} = +95.8$ (*c* = 1.2, CHCl₃).

⁽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 (3S.Ss)-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*-Bu₃SnLi 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 (OsO4, Me3NO) of 4cA furnished a 1:1 mixture of diols $\mathbf{6} + \mathbf{6}'$ (74% yield),¹⁹ which was transformed into the cyclopentanone (S)-15^{14,20} (77%) yield, ee > 96%, NMR¹⁵) by treatment with Raney Ni followed by oxidative cleavage of the 1,2-diol moiety with $NaIO_4$ (Scheme 4).

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.

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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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⁽¹⁶⁾ **4cA** or its thioether was treated with Al–Hg; Mg–HgCl₂; Na– Hg; Raney Ni; NICRA, Ni₂B; Li/NH₃; Li/naphthalene; and 'PrMgBr/Pd-(acac)₂. Lack of reactivity 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 (\pm) -**14** was observed by NMR in the presence of chiral shift reagents or by chiral HPLC or GC].

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