

## Stereocontrolled Synthesis of Enantiomerically Pure Dienyl Sulfoxides via Palladium-Catalyzed Coupling Reactions

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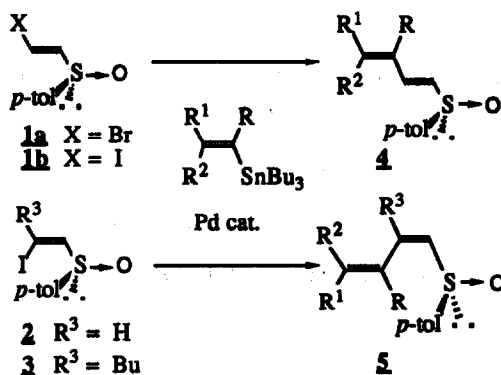
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**Summary:** The palladium-catalyzed coupling of enantiopure 2-halovinylsulfoxides and (*E*)-vinyl stannanes proceeds in an efficient, stereospecific manner to afford enantiopure 1-sulfinyldienes.

The use of chiral sulfoxides as a element of enantio- and diastereocontrol has ample precedent in a variety of synthetic processes.<sup>2-5</sup> In the context of a project examining the diastereoselectivity of transition metal catalyzed cycloisomerizations of enantiopure sulfoxides bearing multiple unsaturation, we required a general and flexible stereocontrolled method for the preparation of acyclic 1-sulfinyl dienes under mild conditions. Despite several recent reports<sup>6</sup> of selective dienyl sulfoxide syntheses, a stereochemically versatile method which would facilitate the preparation of any desired dienyl sulfoxide isomer was not available. In this paper, we report an approach to the synthesis of two of the four possible stereoisomers that is based on the coupling of halovinylsulfoxides with vinyl stannanes, using the methodology pioneered by Stille.<sup>7</sup>

Judging from the availability of enantiopure *trans* and *cis*-2-halovinylsulfoxides<sup>8</sup>, we reasoned that the desired 1-sulfinyldienes could be constructed, in a stereocontrolled manner, by taking advantage of well-established palladium-catalyzed coupling reactions with vinylic metal species. Because of the expected oxophilicity of boron, aluminum, or zirconium reagents, and their potential incompatibility with the sulfoxide group, we decided to focus our efforts on coupling vinylstannanes to halovinylsulfoxides **1a** and **1b**. After screening several ligand/catalyst combinations (as well as different reaction solvents and temperatures) for the reaction of *trans*-2-bromovinylsulfoxide **1a** with one equivalent of vinyltributylstannane, it was found that treatment with Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (2 mol %) and PPh<sub>3</sub> (8 mol %), in refluxing THF, (Method A), cleanly produced the desired dienylsulfoxide **4a** in excellent yield. Examination of the <sup>1</sup>H NMR spectrum of the crude reaction mixture at 300 MHz revealed that the product (Table I, entry 1) was stereochemically homogeneous; furthermore, its enantiomeric purity was judged to be 100% after analysis of the <sup>1</sup>H NMR spectrum of the purified material in the presence of Eu(hfc)<sub>3</sub>. The generality of the new methodology was tested by performing the coupling reaction with a variety of vinyl stannanes<sup>10</sup> (Table I, entries 2 and 3). It is significant to note that the optical rotations of products **4b** and **4c** are virtually identical to those reported by Solladié and co-workers<sup>6c</sup> for these compounds, synthesized by a different route; this additional evidence is confirmation that the optical purity of the sulfoxide is not compromised by the coupling process reported here.

After successfully demonstrating the feasibility of this approach with a *trans*-bromovinylsulfoxide, we turned our attention towards effecting an analogous transformation using the *cis* isomers and thus establish a stereocontrolled route to the challenging 1*Z*-1-sulfinyl dienes.<sup>9</sup> Unfortunately, an initial attempt to couple vinyl-

Table I. Palladium-Catalyzed Synthesis of Enantiomerically Pure Diaryl Sulfoxides<sup>11</sup>

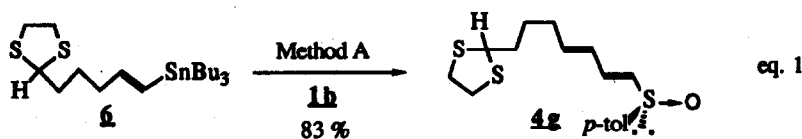
entry	sulfoxide	vinylstannanes				ref.	method <sup>a</sup>	1-sulfinyldienes		
		R	R <sup>1</sup>	R <sup>2</sup>	product			% yield <sup>b</sup>	[α] <sub>D</sub> (c) <sup>c</sup>	
1	1a	H	H	H		A	4a	87	+ 283.8 (0.68)	
2	1a	H	Ph	H	10a	A	4b	87	+ 168.9 (0.87) + 225.0 (0.44) <sup>d</sup>	
3	1a	H	Me	Me	10c	A	4c	80	+ 218.6 (1.06) <sup>d</sup>	
4	2	H	H	H		B	5a	91	- 438.5 (0.52)	
5	2	Me	H	H	10c	B	5b	80	- 329.5 (0.78)	
6	2	H	Me	Me	10c	B	5c	91	- 503.7 (1.08)	
7	3	H	Ph	H	10a	B	5d	92	- 663.2 (0.98)	
8	1b	Me	H	H	10c	B	4d	83	+ 207.6 (0.66)	
9	1b	EtO	H	H		B	4e	90	+ 382.8 (0.87)	
10	2	EtO	H	H		B	5e	83	- 623.8 (0.98)	
11	1a	H	CH(OEt) <sub>2</sub>	H	10b	A	4f	85	+ 142.9 (1.05)	
12	2	H	CH(OEt) <sub>2</sub>	H	10b	B	5f	76	- 244.0 (0.25)	
13	1a	H	e	H	10c	A	4g	83	+ 78.3 (0.97)	

<sup>a</sup> Reaction conditions: Method A: Vinyl stannane (1.0 eq), Pd<sub>2</sub>dba<sub>3</sub>-CHCl<sub>3</sub> (2 mol %), PPh<sub>3</sub> (8 mol %), refluxing THF, 30 min. Method B: Vinyl stannane (1.0 eq), Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub> (2 mol %), DMF, RT, 3 min to 1 h. <sup>b</sup> Unoptimized yields of pure products isolated by chromatography. <sup>c</sup> Optical rotations measured in CHCl<sub>3</sub> unless otherwise noted. <sup>d</sup> Optical rotation measured in acetone; see text and ref. 6e. <sup>e</sup> Vinyl stannane **g**; See text.

tributylstannane to iodovinylsulfoxide **2** using Method A was nonstereoselective. However, we were pleased to discover that milder reaction conditions, Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub> (2 mol %), in DMF at room temperature<sup>7b</sup>, cleanly and rapidly effected the desired transformation. Again, the coupling proceeded stereospecifically, with complete retention of double bond stereochemistry (Table I, entry 4). In addition to coupling various vinyl stannanes to **2** (entries 5 and 6), this procedure (Method B), could also be used with trisubstituted iodovinylsulfoxide **3** to produce an excellent yield of diene **5d** (entry 7), stereochemically homogeneous as determined by NOESY experiments. Not unexpectedly, Method B also proved to be practical for couplings with *trans*-2-

iodovinylsulfoxide **1h** (entries 8 and 9). Also, the straightforward preparation of oxygenated dienes **4e** and **5e** (entries 9 and 10) illustrates the versatility of our methodology.

After establishing the generality of these procedures, we sought to prepare dienyl sulfoxides which could be elaborated in subsequent operations. To this end, dienyl sulfoxides **4f**, **4g**, and **5f** (entries 11-13), each possessing a latent aldehyde, were efficiently prepared from the corresponding vinyl stannanes. Of particular interest is that the precursor of **4g**, vinyl stannane **6**, was prepared from the corresponding vinyl bromide by standard halogen-metal exchange methodology<sup>10c</sup>, in an 80 % yield, despite the possibility of lithiation of the dithiane ring. The coupling of this new vinyl stannane to bromovinylsulfoxide **1a** proceeded uneventfully to produce **4g** (eq. 1); the chemistry of the deprotected dienylsulfoxide (i.e., the corresponding  $\omega$ -oxo-1-sulfinyldiene) is currently being explored in our laboratories.



To summarize, enantiopure dienyl sulfoxides are now readily available by virtue of an efficient Stille-type coupling process. In a significant improvement over previous methods, the (*E, E*) and (*Z, E*)-1-sulfinyldienes presented here can now be prepared in excellent yield, and in a stereochemically reliable manner, through the use of stereodefined vinyl stannanes. The possibility of extending this methodology to include the preparation of the (*E, Z*) and (*Z, Z*)-1-sulfinyldienes is presently being examined, as is the synthesis of the related 2-sulfinyldienes.<sup>6c</sup> These results, and those pertaining to the chemistry of the sulfinyldienes in the present study, will be reported in due course.

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  11. All new compounds have been satisfactorily characterized.

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