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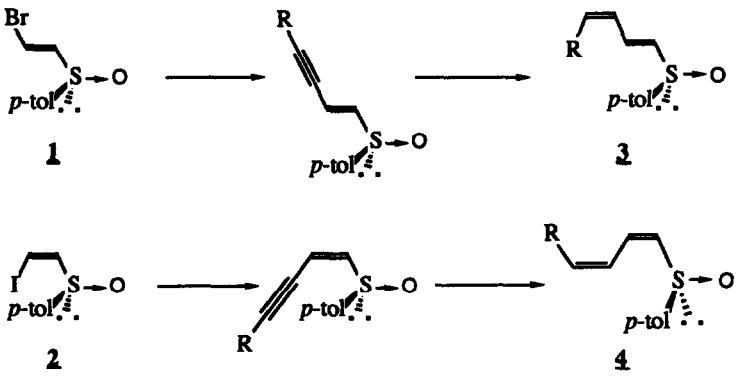
ENANTIOPURE ENYNYL SULFOXIDES VIA PALLADIUM-CATALYZED COUPLING REACTIONS

Robert S. Paley,* Jennifer A. Lafontaine, and Maria Paz Ventura

Swarthmore College, Dept. of Chemistry, Swarthmore, PA 19081, USA

Summary: Enantiomerically pure 1-sulfinyl-1-en-3-ynes are prepared from 2-halovinylsulfoxides via Sonogashira or Stille coupling procedures. The *trans*-enynyl sulfoxides may be hydrogenated to provide (1*E*, 3*Z*)-dienylsulfoxides.

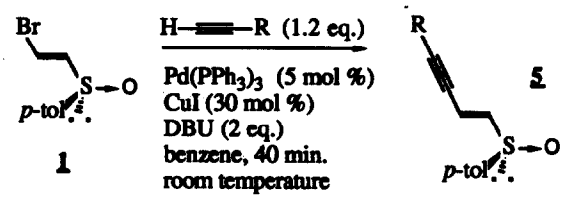
The use of chiral sulfoxides as an element of enantio- and diastereocontrol has ample precedent in a variety of synthetic processes.[1-4] In the context of a project examining the diastereoselectivity of transition metal catalyzed cycloisomerizations of enantiopure sulfoxides bearing multiple unsaturation, we required a general and flexible stereocontrolled method for the preparation of acyclic sulfinyl dienes under mild conditions. While exploring the feasiblity of employing Stille methodology to couple *trans*-vinyl stannanes with enantiopure (*E*)- or (*Z*)-2-halovinylsulfoxides (**1** and **2**, respectively) in order to prepare (1*E*, 3*E*)- or (1*Z*, 3*E*)-1-sulfinyl dienes,[5] we also examined approaches to the more challenging 3*Z* isomers, **3** and **4** (Scheme 1). Since, at the onset of this work there were no general, straightforward preparations for *cis*-vinyl stannanes,[6] we envisioned a solution to this problem which would involve *syn*-reduction of previously unknown enantiopure enynyl sulfoxides. Herein we present the results of our efforts to couple alkynes or 1-stannylalkynes with halovinylsulfoxides **1** and **2**. In addition, our successful preliminary attempts to reduce the resulting enynyl sulfoxides are also presented.



Scheme 1

We judged that the most direct approach to the synthesis of enantiopure (*E*)-1-sulfinyl-1-en-2-ynes would involve use of Sonogashira methodology[7] to couple an alkyne to enantiopure *trans*-2-bromovinylsulfoxide **1**. There was precedent, though limited, that electron-deficient vinyl halides could be used as partners in this context; for example, Schreiber's coupling of a terminal alkyne with methyl (*E*)-3-iodoacrylate[8] indicated that such a transformation was possible. Schreiber's modification of the "standard" conditions involved the use of a hindered amine base, presumably to suppress addition-elimination side

Table 1. Synthesis of (*E*)-1-Sulfinyl-1-en-3-ynes.[9]

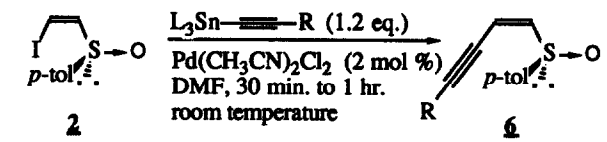


R	Product	% yield	$[\alpha]_D$ (*c*)[a]
CH_2OH	**5a**	84	+265.9 (0.47)
Bu	**5b**	84	+190.4 (1.04)
$(CH_2)_3OTBS$	**5c**	86	+155.0 (0.20)
$SiEt_3$	**5d**	87	+177.8 (1.67)

[a] All optical rotations were measured in $CHCl_3$.

reactions. Our results corroborate the requirement for the presence of a hindered base; attempts to couple propargyl alcohol with **1** under "standard" conditions[7] [$Pd(PPh_3)_4$ (5 mol%), CuI (30 mol%), benzene, room temperature] consistently gave disappointing yields (less than 30%) of the desired enynyl sulfoxide **5a**. The reaction completely failed when diethylamine was employed as the solvent. Use of triethylamine as a cosolvent improved the reaction somewhat (yields of 54% were obtained in 4:1 benzene/triethylamine), however, the use of 2 equivalents of the non-nucleophilic base DBU gave the optimal results. Under these latter conditions, the coupling of propargyl alcohol and bromovinylsulfoxide **1** was complete within 40 minutes (as judged by TLC), and enynyl sulfoxide **5a**[9] was isolated after chromatography in a yield of 84%. The reaction proved to be general for a number of functionalized alkynes; the results are summarized in Table 1.

Table 2. Synthesis of (*Z*)-1-Sulfinyl-1-en-3-ynes.[9]



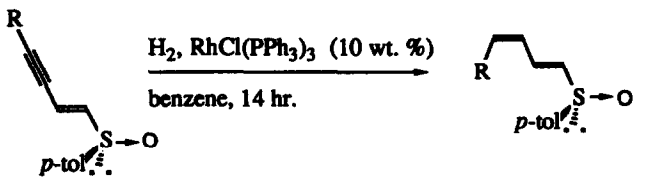
R	Product	% yield	$[\alpha]_D$ (*c*)[a]
Bu	**6a**	77[b]	-373.1 (1.08)
$(CH_2)_4O$-*t*-Bu	**6b**	74[b]	-598.4 (0.62)
CH_2OTBS	**6c**	75	-484.6 (0.39)
$SiEt_3$	**6d**	87	-885.1 (0.47)
$CH(OEt)_2$	**6e**	82	-738.6 (0.44)

[a] All optical rotations were measured in $CHCl_3$.

[b] Reactions carried out in 95:5 DMF/THF.

We next turned to the possibility of preparing (Z)-1-sulfinyl-1-en-2-ynes by employing this Sonogashira methodology to couple alkynes to *cis*-2-iodovinylsulfoxide **2**. Unfortunately, all attempts, regardless of choice of palladium catalyst or amine base, led to complete decomposition of the sulfoxide **2**. A different approach proved to be far more fruitful; we began to investigate if the required carbon-carbon bond could instead be formed by using Stille methodology[10] to couple readily available stannylalkynes to *cis*-2-iodovinylsulfoxide **2**. Indeed, treatment of **2** with 1-tributylstannyl-1-hexyne (1.3 equiv.) in the presence of $Pd(CH_3CN)_2Cl_2$ (2 mol %) (DMF/THF, 95:5, RT) rapidly afforded the desired enynyl sulfoxide **6a** in a 77% yield; ^1H NMR experiments on **6a** with Eu(hfc)$_3$ confirmed our earlier finding[5] that the optical purity of the sulfoxide is not compromised by Stille coupling processes. Again, this transformation proved to be general for a number of different stannylalkynes; the results are summarized in Table 2. In some cases, the use of THF as a cosolvent was found to improve the yield, due to the increased solubility of the stannylalkyne in the reaction medium.

That dienyl sulfoxides can be prepared from reduction of enynyl sulfoxides was also demonstrated. In preliminary, unoptimized experiments, enynyl sulfoxides **5a** and **5b** were hydrogenated[11] (1 atm.) with $RhCl(PPh_3)_3$ (10 wt. %) in benzene at room temperature for 14 hr. to afford (1*E*, 3*Z*)-1-sulfinyl dienes **3a** and **3b** in yields of 63% and 84%, respectively (Scheme 2). The *cis* stereochemistry of the new double bond in each dienyl sulfoxide was confirmed by analysis of the individual ^1H NMR spectra. After performing the required decoupling experiments, $J_{H3\text{-}H4}$ was determined to be 11.0 Hz and 10.8 Hz for each compound, indicative of *cis* stereochemistry.[12]



5a R = CH_2OH **3a** R = CH_2OH 63 %
5b R = Bu **3b** R = Bu 84 %

Scheme 2

Unfortunately, the enynyl sulfoxides (**6**) derived from *cis*-iodovinylsulfoxide **2** have proven to be far more resistant to hydrogenation than the *trans* analogs. All attempts to prepare (1Z, 3Z)-dienyl sulfoxides **4** have been unsuccessful, resulting in the recovery of **6** (Lindlar's catalyst/benzene, or Pd/$BaSO_4$/pyridine) or in the formation of a complicated mixture of **6** and overreduced products. It would seem that synthesis of this elusive dienyl sulfoxide isomer would depend on the success of a Stille coupling between *cis*-iodovinylsulfoxide **2** and a (Z)-vinylstannane.[6]

We have now demonstrated that three of the four possible 1-sulfinyldiene stereoisomers can be prepared stereo- and enantiospecifically by utilizing Pd(0)-catalyzed coupling methodology. Future reports from this laboratory will focus on the chemistry of these compounds, namely, transition metal mediated cycloisomerizations of enantiopure dienylsulfoxides with pendent unsaturation.

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