



# Pd-catalyzed asymmetric sulfinylzincation of 1-alkynoates using 1-alkynyl sulfoxides bearing a chiral auxiliary

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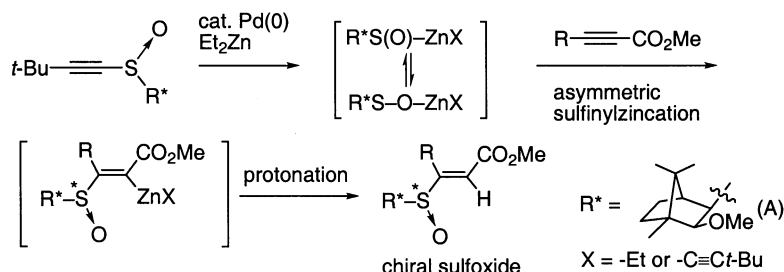
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**Abstract**—Stereoselective sulfinylzincation was accomplished by utilizing a 1-alkynylsulfoxide bearing an isborneol-type chiral auxiliary. The sulfinylzincation of various 1-alkynoates proceeded in a highly *syn*-selective manner and vinylic sulfoxides with (*S<sub>s</sub>*)-configuration were formed predominantly. Both (*R<sub>s</sub>*)- and (*S<sub>s</sub>*)-1-alkynyl sulfoxides **5** provided the same (*S<sub>s</sub>*)-alkenyl sulfoxide **8a**, although the yield from (*R<sub>s</sub>*)-**5** was better than that from (*S<sub>s</sub>*)-**5**. © 2002 Elsevier Science Ltd. All rights reserved.

Chiral vinylic sulfoxides are versatile building blocks and have been used for various asymmetric reactions. Recently, we have reported Pd-catalyzed sulfinylzincations of activated alkynes to produce vinylic sulfoxides using 1-alkynyl sulfoxide as the sulfinyl source, in which a sulfinylzinc (or zinc sulfenate) species is assumed to be generated by oxidative addition of the 1-alkynyl sulfoxide to the Pd(0)-catalyst followed by transmetalation with Et<sub>2</sub>Zn.<sup>1</sup> This methodology allows easy introduction of a sulfinyl group into activated alkynes in a highly *syn*-selective manner under very mild conditions, thereby providing a complimentary procedure to the *anti*-selective methodology, which involves conjugate addition of thiolate<sup>2</sup> followed by oxidation to the sulfoxide. However, a major drawback of this reaction is the loss of chirality at the sulfur atom during the reaction, which we attributed to a rapid sulfinyl–sulfenate tautomerization. In order to control the stereochemistry of the reaction, we planned to

employ the 1-alkynyl sulfoxide bearing a chiral substituent. Although a similar transformation has been accomplished in the addition of chiral sulfenic acid to alkynes,<sup>3</sup> the selectivity was moderate. The asymmetric addition of a sulfenate anion has not hitherto been investigated, to the best of our knowledge.<sup>4</sup> After investigation of appropriate chiral auxiliaries, we found that the chiral auxiliary (A) having an isborneol structure is suitable for the Pd-catalyzed asymmetric sulfinylzincation. Based on the previous results,<sup>1</sup> the 3,3-dimethylbutynyl group was employed as a substituent on the sulfoxide to prevent undesirable self-reaction of the resulting sulfinylzinc species with the substrate.

We report herein the synthesis of the chiral sulfinylzinc (or zinc sulfenate) precursor and Pd-catalyzed asymmetric sulfinylation of 1-alkynoates, including determination of the absolute configuration of the adducts (Scheme 1).



Scheme 1.

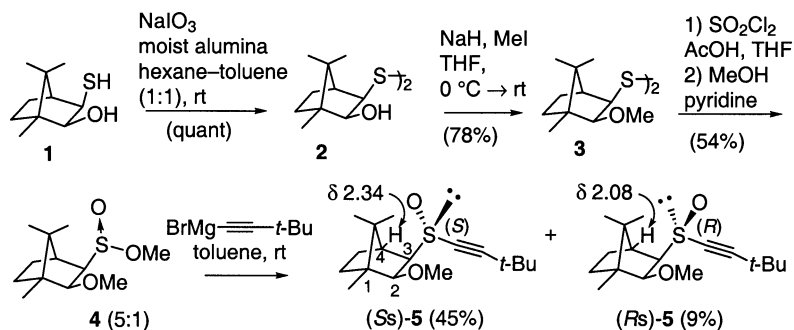
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The chiral 1-alkynyl sulfoxide was prepared from 3-mercaptoisoborneol<sup>5</sup> as shown in Scheme 2. Upon treatment with NaIO<sub>3</sub> and moist alumina,<sup>6</sup> the thiol **1** was converted into disulfide **2** quantitatively. Two hydroxy groups in the disulfide **2** were methylated on treatment with MeI and NaH in 78% yield. Then, the disulfide was transformed into a methyl sulfinato in the reaction with SO<sub>2</sub>Cl<sub>2</sub> in AcOH followed by methanolysis in pyridine,<sup>7</sup> giving **4** as a 5:1 diastereomeric mixture in 54% yield in two steps.<sup>8</sup> Finally, the mixture was treated with 3,3-dimethyl-1-butyne/magnesium bromide to give the (*S<sub>s</sub>*)-alkynylsulfoxide (*S<sub>s</sub>*)-**5** in 45% yield along with 9% of its diastereoisomer (*R<sub>s</sub>*)-**5**.

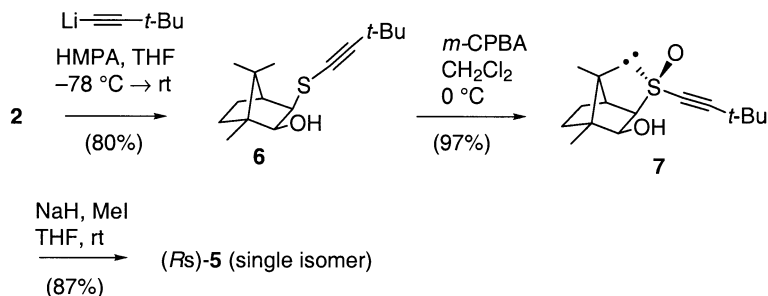
Since the yield of the final step was moderate, we investigated another synthetic route via oxidation of the sulfide (Scheme 3). The disulfide **2** was allowed to react with *t*-butyl acetylide in the presence of HMPA to give **6** in 80% yield. The adduct **6** was oxidized with *m*-CPBA, giving the sulfoxide **7** in 97% yield as a single isomer, which was methylated (MeI, NaH) to afford enantiomerically pure (*R<sub>s</sub>*)-**5** in 87% yield.<sup>9</sup> These two procedures afforded 1-alkynyl sulfoxides with opposite absolute configuration. The absolute configuration on the sulfur atom in (*R<sub>s</sub>*)- and (*S<sub>s</sub>*)-**5** was assumed by an empirical rule reported by Goodridge and co-workers.<sup>5</sup> They reported that, due to proximity of the sulfinyl oxygen to the H<sub>4</sub>-proton in the (*R<sub>s</sub>*)-isomer, the H<sub>4</sub>-proton signal of (*R<sub>s</sub>*)-isomers of 3-*exo*-(alkylsulfinyl)-isoborneols appears at lower field than that of the corresponding (*S<sub>s</sub>*)-isomers. Since the stereochemistry of the sulfoxides in the 3-*exo*-(alkynylsulfinyl)-

isoborneol derivatives is opposite to that in the 3-*exo*-(alkylsulfinyl)isoborneols due to the change in priority groups, the isomers having the H<sub>4</sub>-proton at 2.34 and 2.08 ppm were assigned as (*S<sub>s</sub>*)- and (*R<sub>s</sub>*)-isomers, respectively.

With the chiral 1-alkynyl sulfoxides (*R<sub>s</sub>*)- and (*S<sub>s</sub>*)-**5** in hand, we examined the asymmetric sulfinylzincation of various 1-alkynoate derivatives with Et<sub>2</sub>Zn in the presence of catalytic Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (Table 1). The sulfinylation of 1-alkynoates using (*R<sub>s</sub>*)-**5** proceeded in moderate to good yields, except for the addition to the methyl propiolate (entry 6). In all cases, the adducts with an (*S*)-sulfoxide were obtained preferentially with ca. 9:1 dr, except that **8e** and **8g** exhibit lower selectivities, with dr of ca. 6:1. When the 1-alkynyl sulfoxide (*S<sub>s</sub>*)-**5** was used as a sulfinyl source, the yield was lower (entry 2), but the selectivity was almost the same as that obtained using (*R<sub>s</sub>*)-**5**. The results support the speculation that the same zinc sulfenate (or sulfinylzinc) intermediate was generated from both epimers of the 1-alkynylsulfoxide (*S<sub>s</sub>*)- and (*R<sub>s</sub>*)-**5**. The olefins were assigned *E*-geometry based on our preliminary results,<sup>1</sup> and this assignment was confirmed by lactone formation on treatment of two isomers of **8c** with TFA (Scheme 4). The chemical shifts of the H<sub>4</sub>-proton in the isoborneol substituent vary, ranging from 2.27 to 2.48 for (*S<sub>s</sub>*)-**8** and (*S<sub>s</sub>*)-**9**, and ranging from 1.59 to 1.86 for (*R<sub>s</sub>*)-**8**<sup>†</sup> and (*R<sub>s</sub>*)-**9**. These results indicate that the sulfoxide sulfur of the major products possesses (*S<sub>s</sub>*)-configuration by the above-mentioned empirical rule. This speculation was confirmed by X-ray single-crystal

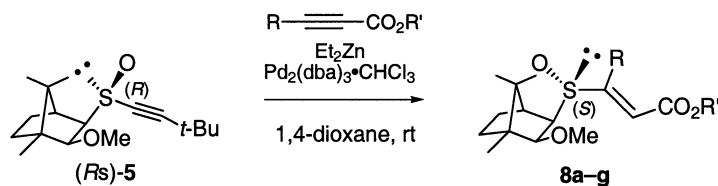


Scheme 2.



Scheme 3.

<sup>†</sup> The signal for the H<sub>4</sub>-proton for the minor products (*R<sub>s</sub>*)-**8e** and (*R<sub>s</sub>*)-**8f** could not be assigned due to overlap with other signals.

**Table 1.** Asymmetric sulfinylation of 1-alkynoates<sup>a</sup>

Entry	Product	R	R'	Yield (%)	<i>S<sub>s</sub></i> : <i>R<sub>S</sub></i> <sup>b</sup>
1	<b>8a</b>	BnOCH <sub>2</sub>	Me	99	91:9
2	<b>8a</b>	BnOCH <sub>2</sub>	Me	67	90:10 <sup>c</sup>
3	<b>8b</b>	AcOCH <sub>2</sub>	Me	51	92:8 <sup>d</sup>
4	<b>8c</b>	TBSOCH <sub>2</sub>	Me	98	90:10
5	<b>8d</b>	BnSCH <sub>2</sub>	Me	100	89:11 <sup>d</sup>
6	<b>8e</b>	H	Me	30	85:15 <sup>d,e</sup>
7	<b>8f</b>	Me	Et	100	90:10 <sup>d,e</sup>
8	<b>8g</b>	BnOCH <sub>2</sub>	4-NO <sub>2</sub> Bn	72	86:14

<sup>a</sup> The reactions were carried out using 1-alkynoate (3 equiv.), Et<sub>2</sub>Zn (2 equiv.), and Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (2 mol%) in dioxane overnight under Ar.

<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopic data.

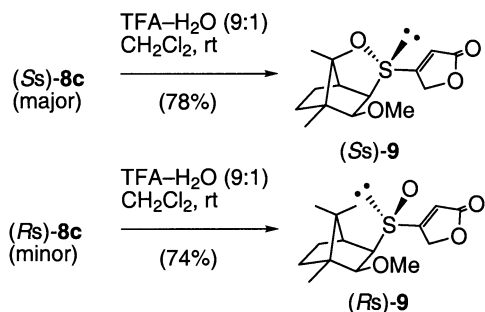
<sup>c</sup> (*S<sub>s</sub>*)-**5** was used.

<sup>d</sup> Diastereomeric isomers were inseparable.

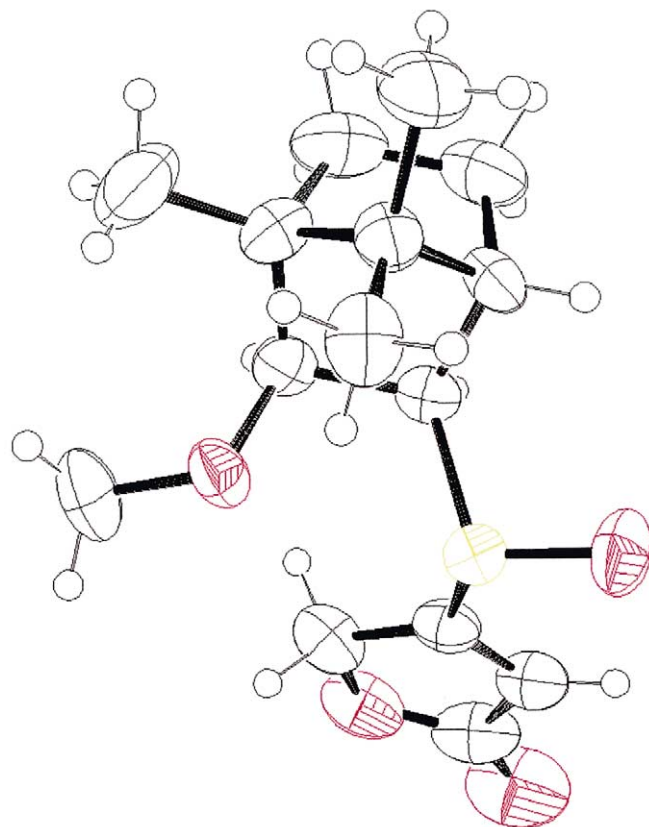
<sup>e</sup> 10 equiv. of 1-alkynoates were used.

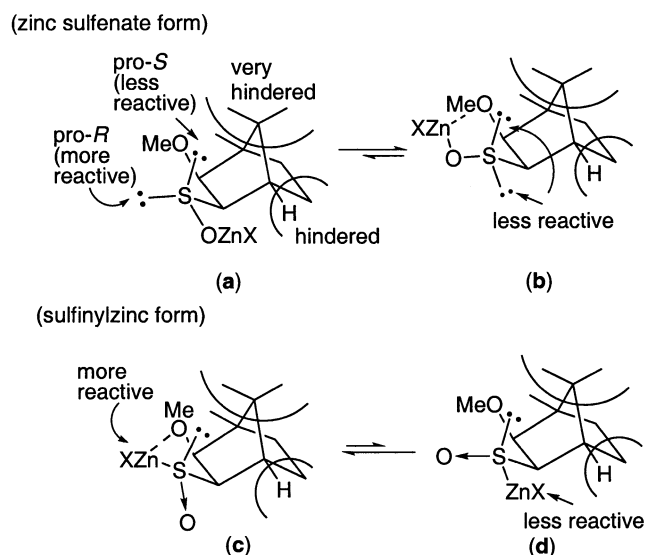
analysis of the  $\gamma$ -lactone (*S<sub>s</sub>*)-**9** derived from the major (*S<sub>s</sub>*)-**8c** (Fig. 1). In the ORTEP drawing, the direction of the sulfinyl oxygen locates close to the H<sub>4</sub>-proton and nicely explains the deshielding effect observed in the <sup>1</sup>H NMR data. Interestingly, the configuration of the sulfur was reversed via the sulfinylation reaction.

The observed diastereoselectivity was interpreted as follows. In the preferred conformers of the zinc sulfonate and sulfinylzinc species, the smallest group, a lone pair of electrons, would occupy the most crowded space near one of the C<sub>7</sub>-Me and C<sub>2</sub>-MeO groups (Fig. 2). The X-ray crystal structure of (*S<sub>s</sub>*)-**9** supports this speculation. Although intermediate **b** seems to be more stable than intermediate **a** by the coordination of the methoxy group, both lone pair electrons on the sulfur atom are shielded by the isborneol moiety in the intermediate **b**. Therefore, the reaction occurs at the pro-*R* lone pair electrons in the intermediate **a** having the least steric demand (Fig. 2 **a** and **b**). In comparison with the sulfinylzinc intermediates **c** and **d**, the intermediate **c** with an unshielded zinc anion would react preferentially with 1-alkynoates rather than the intermediate **d** (Fig. 2 **c** and **d**). Thus, the reactions would proceed preferentially via intermediate **a** or **c** to give sulfoxides with (*S<sub>s</sub>*)-configuration.

**Scheme 4.**

In conclusion, we have developed a novel method for asymmetric sulfinylzincation using the 3-*exo*-[(1-alkynyl)sulfinyl]isborneol derivative, and also established the stereochemistry. Further investigation will be reported in due course.

**Figure 1.** ORTEP drawing of (*S<sub>s</sub>*)-**9**



**Figure 2.** Plausible reaction mechanism for the asymmetric sulfinylzincation reaction (only relevant protons are shown).

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