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Enantioselective allylation of the α-sulfonyl radical controlled by coordination of a chiral Lewis acid to an enantiotopic sulfonyl oxygen

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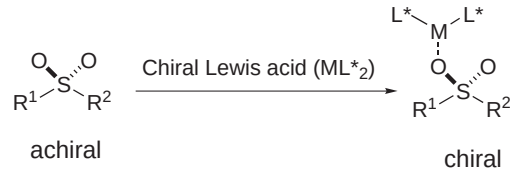
Abstract—Selective coordination of a chiral Lewis acid to an enantiotopic sulfonyl oxygen enabled enantioselective allylation of the α-sulfonyl radical. The addition–allylation products were obtained in low to good stereoselectivities (up to 84% ee).

Radical-mediated enantioselective C–C and C–H bond formation has become of great importance.[1] The sulfinyl groups have been shown to be attractive stereoinducers in diastereoselective radical reactions.[2] We reported excellent stereocontrol in the hydrogenation of the α-sulfinylated β-hydroxy radical generated from alkyl radical addition to the (α-hydroxyethyl)vinyl sulfoxide.[3] More recently, we reported that the reaction of the α-sulfonylated β-hydroxy radical with tributyltin hydride gave the hydrogenation product with excellent diastereoselectivity.[4] In both reactions, we demonstrated the significant role of intramolecular hydrogen bonding and the Lewis acid chelation between the hydroxyl group and the sulfinyl or the sulfonyl oxygen in the reactivity or diastereoselectivity. These results strongly suggested the possible discrimination of the diastereotopic sulfonyl oxygens by intramolecular hydrogen bonding as well as by chelation with a Lewis acid. Selective coordination of a chiral Lewis acid to one of the oxygens in the *prochiral sulfone* would realize a new methodology[5] for the asymmetric radical reaction using the achiral sulfonyl group as a stereoinducer[6] (Scheme 1). We report herein the enantioselective allylation of the α-sulfonyl radical controlled by discriminative coordination of a chiral Lewis acid to the enantiotopic sulfonyl oxygen.

A typical experimental procedure is as follows: A 0.01 M CH_2Cl_2 solution of 1 equiv. of $Zn(OTf)_2$[7] and 1 equiv. of the bisoxazoline **5**[8] was stirred at room temperature for 1 h, and then the vinyl sulfone **1** was added to this solution. After stirring for 1 h, the mixture was cooled to −78°C and an allyltin compound, an alkyl iodide, and triethylborane, as a radical initiator,[9] were added. The mixture was stirred for the appropriate time (Scheme 2 and Table 1).

First, allylation of the radical derived from 2-pyridyl vinyl sulfone **1a** with allyltributyltin in the presence of bisoxazolines **3** and **4** at −78°C afforded the addition–allylation product **2a** with low stereoselectivity (entries 1 and 2). Enantioselectivity was improved to 46% ee when the bisoxazoline **5** was used, although the yield of the product was lowered (entry 3). The 2-(benzimidazolyl) sulfone **1b** showed better enantioselectivity than the 2-pyridyl sulfone **1a**, due presumably to steric effects of the methyl substituent on the benzimidazolyl ring (entry 4). More sterically demanding *N*-benzylbenzimidazolyl sulfone **1c** gave **2c** with 80% ee, although the yield still remained low because of the formation of a considerable amount of a structurally unidentified side product (entry 5). This side product was formed only in the reaction using allyltributyltin. Thus, the



Scheme 1.

Keywords: enantioselective allylation; α-sulfonyl radical; vinyl sulfone; allyltin.

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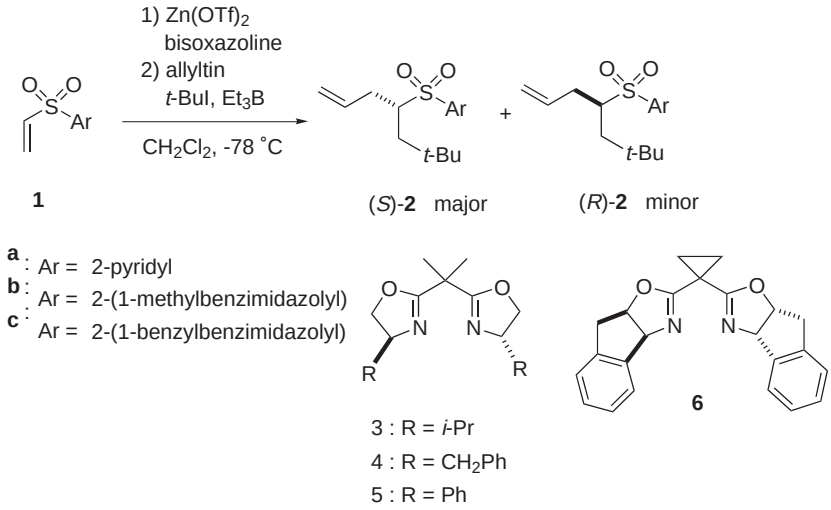
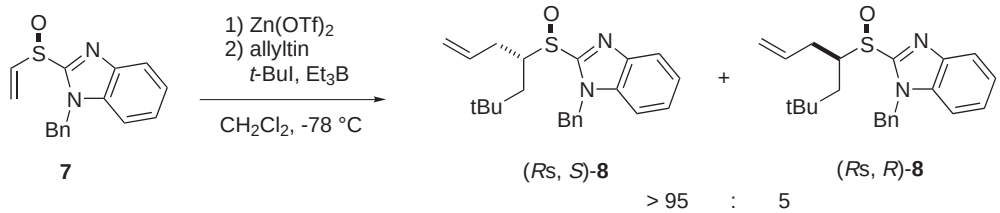


Scheme 2.

Table 1. Allylation of the α-sulfonyl radical generated from the reaction of the vinyl sulfones with a *tert*-butyl radical

Entry	Substrate	Ligand	Tin compound	Time (min)	Yield (%)	ee (%)[a]
1	**1a**	**3**	$AllylBu_3Sn$	30	60	10
2	**1a**	**4**	$AllylBu_3Sn$	120	47	4
3	**1a**	**5**	$AllylBu_3Sn$	120	36	46
4	**1b**	**5**	$AllylBu_3Sn$	120	35	62
5	**1c**	**5**	$AllylBu_3Sn$	120	35	80
6	**1a**	**5**	$AllylPh_3Sn$	90	82	50
7	**1b**	**5**	$AllylPh_3Sn$	90	88	24
8	**1c**	**5**	$AllylPh_3Sn$	180	49	16
9	**1c**	**5**	$Allyl_4Sn$	120	87	51
10	**1c**	**5**	$Allyl_2Bu_2Sn$	120	74	50
11	**1c**	**5**	$AllylBu_2SnCl$	180	85	17
12	**1c**	**5**	$Allyl_2Bu_2Sn$[b]	50	86	78
13	**1c**	**5**	$Allyl_2Bu_2Sn$[c]	20	80	84
14	**1c**	**6**	$Allyl_2Bu_2Sn$	15	18	4

[a] Enantiomer excess was determined by HPLC analysis using Chiralcel OD-H.
[b] Diallyldibutyltin (5 equiv.) was used.
[c] Diallyldibutyltin (10 equiv.) was used.



Scheme 3.

reaction of **1a** with allyltriphenyltin gave **2a** in 82% yield with 50% ee (entry 6), although the enantioselectivity dropped to 24 and 16% ee in the reaction of benzimidazolyl sulfones **1b** and **1c**, respectively (entries 7 and 8). The reaction of **1c** with tetraallyltin or diallyldibutyltin gave **2c** in 87% yield with 51% ee (entry 9) or in 74% yield with 50% ee (entry 10), respectively. We found that allyldibutyltin chloride also gave the allylation product in high yield but with low ee (entry 11). Allyldibutyltin chloride appears to act not only as a reactive allylating agent but also as a weak Lewis acid,[10] which would cause damage to the chelation and lower the enantioselectivity. Allyldibutyltin iodide is apparently produced during the reaction with diallyldibutyltin and it would reduce the enantioselectivity. In order to minimize the damage caused by allyldibutyltin iodide, we performed the reaction with an excess amount of diallyldibutyltin and found that both the enantioselectivity and the yield were improved up to 84% ee and 80%, respectively, with 10 equiv. of diallyldibutyltin (entry 13). Allylation using **6** showed only poor enantioselectivity (entry 14). The absolute

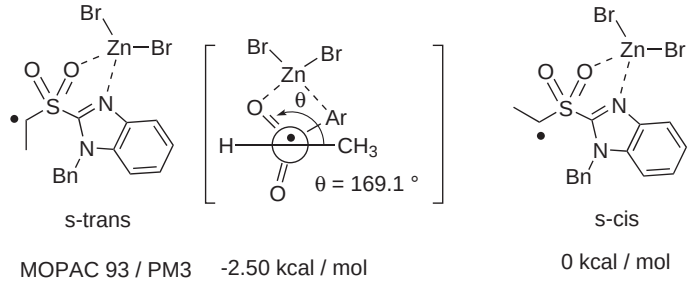


Figure 1.

stereochemistry of the major product **2c** was determined to be *S* by comparison of the HPLC data using Chiralcel OD-H with those of (*S*)-**2c** prepared by a different route. (*R*)-2-(1-Benzylbenzimidazolyl) vinyl sulfoxide **7** (85% ee) was allowed to react with 2 equiv. of allyltributyltin, *tert*-butyl iodide, and triethylborane in the presence of 1 equiv. of $Zn(OTf)_2$ at −78°C to give the addition–allylation product **8** in 96% yield in a diastereomer ratio of >95:5 (Scheme 3). The stereochemistry of the major isomer **8** was determined to be (*R*s,*S*) by the ^{1}H NMR spectral analyses.[11] The sulfoxide **8** was oxidized with OXONE® to afford (*S*)-**2c** in 81% yield with 85% ee.

Stereoselectivity observed in the reaction of **1** depends on the difference in energy between the s-*cis* and s-*trans* α-(arylsulfonyl)alkyl radical intermediates, as well as the discriminative coordination to the enantiotopic sulfonyl oxygen. Calculation of simplified radical intermediates by MOPAC 93/PM3[12] showed that the s-*trans* conformation is more stable than the s-*cis* by 2.50 kcal/mol (Fig. 1). A similar result was obtained by MOPAC/PM3 calculations of a simplified model for the radical intermediates derived from the vinyl sulfoxide **7**; (*R*s,*S*)-**8** would be formed via the more stable s-*trans* radical intermediate.[13] We performed further calculation of the radical intermediates using MM/DREIDING 2.21,[14] assuming the formation of a tetrahedral 1:1:1 complex[15] of a central zinc, the bisoxazoline and the sulfone. The s-*trans* pro-(*R*) radical intermediate (Fig. 2) was shown to have the lowest energy among other s-*cis* pro-(*R*), s-*trans* pro-(*S*), and s-*cis* pro-(*S*) complexes (not shown). The selective coordination to the enantiotopic pro-(*R*) oxygen would be realized by a combination of the steric effects of the two phenyl, the benzyl, and the *tert*-butyl groups, where the *tert*-butyl group is placed away from both the benzyl and phenyl groups.[16] In this intermediate, the stereoselective allylation occurs preferentially from the less hindered side to give the (*S*)-isomer predominantly.

In conclusion, selective coordination of a chiral Lewis acid to one of the enantiotopic oxygens in the sulfonyl group has realized a new entry to asymmetric induction in radical allylation. We are currently engaged in further application and extension of the methodology using the sulfonyl group in asymmetric induction.

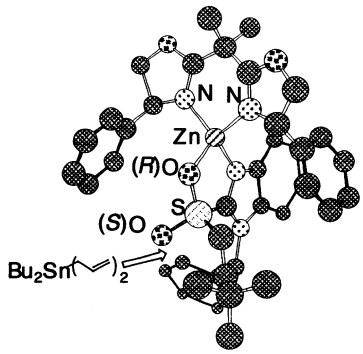


Figure 2.

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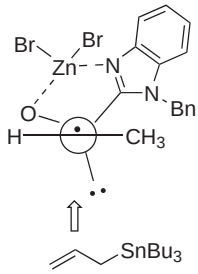

Figure 3.

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