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PREPARATION OF CHIRAL SULFONES BY ASYMMETRIC ADDITION OF ARENESULFONYL CARBANIONS TO ACETONE

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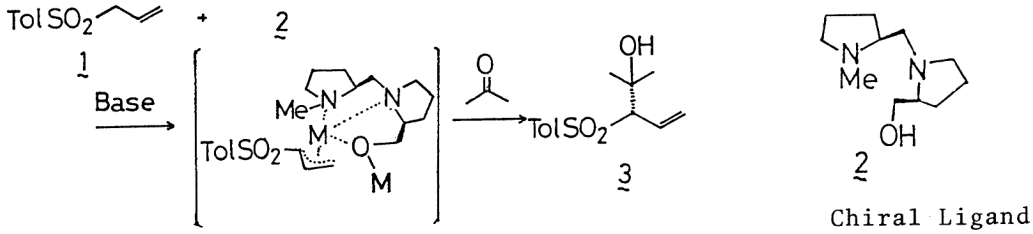
In the presence of a chiral diamine, the magnesium salt of tolyl sulfone reacts with acetone at the α-carbon to afford the corresponding β-hydroxy adduct in good optical purity.

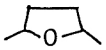
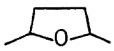
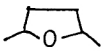
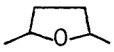
Recent advances in asymmetric synthesis have brought about several interesting transformations previously mediated mostly by enzymatic process. However, there still remain several important problems, e.g., development of highly chiral induction method by the interaction of the chiral auxiliary groups bounded in a non-covalent way. In other words, it appears to be very difficult to achieve asymmetric carbon-carbon bond forming reactions controlled by the coordination of chiral ligand to substrates.[1] Our continuing efforts on devising highly enantioselective reaction based on non-covalent bonded chiral ligands led us to consider the possible chirality creation at the α-carbon of allyl sulfone. Although sulfonyl group stabilized allylic carbanions have been studied extensively on organic synthesis and employed successfully on a variety of carbon-carbon bond forming reactions,[2] their application to asymmetric synthesis has not been reported.

We have now found that the magnesium salt of allyl tolyl sulfone undergoes asymmetric addition to acetone under the influence of chiral ligand derived from L-proline and wish to describe herein a first example of ligand controlled chiral induction to the α-carbon of allyl sulfone by the electrophiles.



As described in the above equation, allyl tolyl sulfone was converted to the lithium salt by addition of n-BuLi in the presence of (2S, 2'S)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine[1a] 2 in THF at -78 °C followed by addition of acetone to give 2-methyl-3-toluenesulfonyl-4-penten-2-ol[3] in 91% yield but in poor optical purity (entry 1 of Table 1).

Table 1. Preparation of Chiral Sulfones by Asymmetric Addition of Allyl p-Tolyl Sulfone Carbanion to Acetone [a]

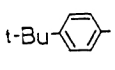
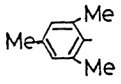
Entry	Base	Solvent	Temperature/°C	Yield/%	e.e./%
1	BuLi	THF	- 78	91	15
2	EtMgBr	THF	- 78	58	50
3	EtMgBr	THF	-100	47	60
4	EtMgBr	THF + 	-100	66	80[b]
5	EtMgBr	THF + 	-100	74	77
6	*i*-PrMgBr	THF + 	-100	89	74
7	*i*-PrMgCl	THF + 	-100	72	56

a) The reaction was carried out with allyl sulfone, diamine, and base (1: 1.5: 2.2). Reaction period was 20 min.
b) Reaction period was 10 min.

In this reaction the nature of the center metals and the kind of the reaction solvents seem to influence greatly on optical purity of the product. For example, by changing the center metal from lithium to magnesium, enantioselectivity was improved up to 50% e.e. (see, entry 2). It was also found that the use of a 1 : 1 mixture of THF and 2,5-dimethyltetrahydrofuran was crucial. Thus, the best result was obtained when ethylmagnesium bromide was used as base and the reaction was carried out in THF-2,5-dimethyltetrahydrofuran (1 : 1/v : v) at -100 °C (entry 4).

Next, a variety of sulfonyl moieties was examined and the results are summarized in Table 2.

Table 2. Effect of Arene Group [a]

Entry	1	2	3	4	5
Ar-					
Yield/%	66	quant.	98	38	72
e.e./%	80	76	72	50	33
$[\alpha]_D$/°	-74.9	-53.0	-54.5	35.4	-33.1

a) Absolute configuration was R in the case of entry 1. Though absolute configurations were not determined in other cases, the stereochemical course of this reaction is thought to be the same in all entries.

A bulky p-substituent on the aromatic ring appears to have little effect on increasing optical purity of the product, whereas an electron withdrawing group

decreased enantioselectivity presumably because of the decreased reactivity of the anion toward carbonyl addition.

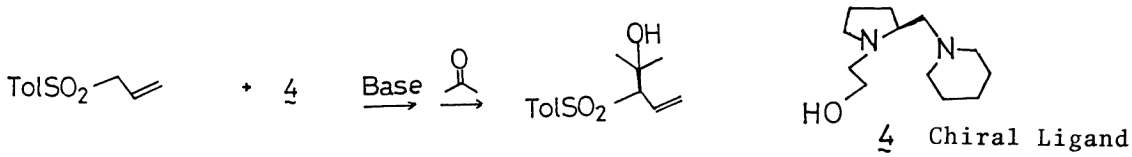
Reactions of other allyl sulfones were also carried out under the optimum reaction conditions shown in the case of allyl tolyl sulfone, and the results are summarized in Table 3.

Table 3. Effect of Allyl Moieties

Entry	1	2	3	4
Sulfone	$TolSO_2$	$TolSO_2$	$TolSO_2$ Ph	$PhSO_2CH_2Ph$
Yield/%	66	90	62	47
e.e./%	80	76	16	33
$[\alpha]_D$/°	-74.9	-42.2	29.0	46.5

The substituents at γ-position to the sulfonyl group decreased enantioselectivity (entries 2 and 3), especially in the case of phenyl substituent.

Interestingly, when the chiral diamine 4 was substituted for 2, prepared from L-proline, the other enantiomer was obtained in a good optical purity (69% e.e.).



4 Chiral Ligand

The following example represents a typical experimental procedure: To a THF solution (1.5 mL) of allyl tolyl sulfone 1 (71.8 mg, 0.36 mmol) and 2 (53.8 mg, 0.27 mmol) at 0 °C was added ethylmagnesium bromide (0.40 mL, 0.66 M solution in ether). After stirring at 0 °C for 30 min, 2,5-dimethyltetrahydrofuran (1.5 mL) was added and the mixture cooled to -100 °C. Then acetone (38 mg, 0.66 mmol) in THF-2,5-dimethyltetrahydrofuran (1.0 mL, 1 : 1/v : v) was added dropwise, and the stirring was continued at that temperature for 20 min. The reaction mixture was quenched by adding 2 M HCl in THF and then extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give an oil. Purification on silica-gel TLC (Hexane - AcOEt/4 : 3) gave 2-methyl-3-(p-tolylsulfonyl)-4-penten-2-ol (41.5 mg, 66%). The optical purity was determined by the NMR spectrometry to be 80% by examining the relative intensity of the two methyl groups separated by the chiral shift reagent, $Eu(hfc)_3$.

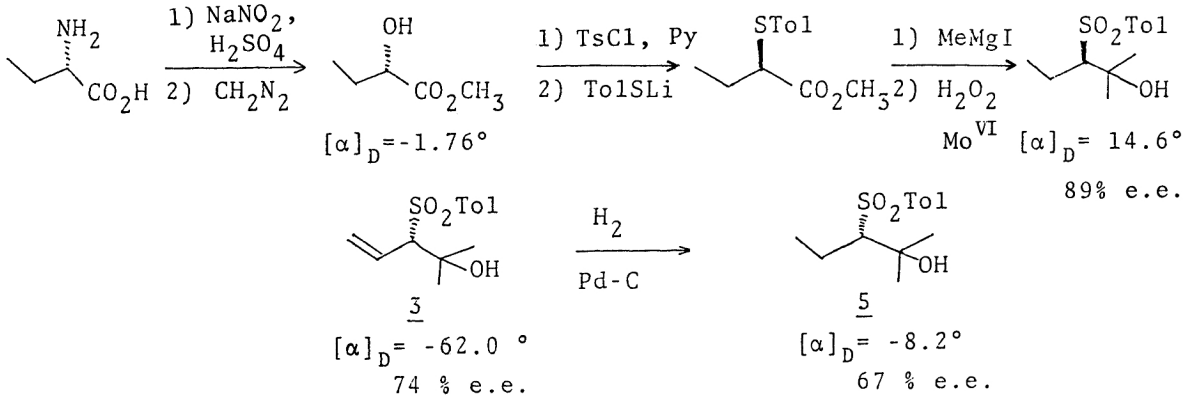
It is noted that according to the present study, each enantiomer of the allyl tolyl sulfone-acetone adduct could be prepared in good optical purity by choosing L-proline based ligand 2 or 4. Since allyl sulfones are important building blocks and can be transformed into a variety of compounds via alkylation mediated by π-allyl complex,[4] desulfonylation[5] and so on, the allyl tolyl sulfone-acetone adduct obtained by the present procedure is a possible intermediate for a variety of useful chiral compounds.

References

1) a) T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, and K. Suzuki, J. Am. Chem. Soc., 101, 1455 (1979); b) N. Iwasawa and T. Mukaiyama, Chem. Lett., 1983, 297; c) R. W. Stevens and T. Mukaiyama, *ibid.*, 1983, 1799; d) D. Seebach, G. Crass, E-M, Wilka, D. Hilbert, and E. Brunner, Helv. Chim. Acta, 62, 2695 (1979); e) T. D. Inch, G. D. Jewis, G. L. Sainsburg, and D. J. Sellers, Tetrahedron Lett., 1969, 3657; f) M. Guett, J. P. Guette, and J. Capillon, *ibid.*, 1971, 2863; g) T. Hayashi, M. Konishi, M. Fukushima, T. Mise, M. Kagotani, M. Tajika, and M. Kumada, J. Am. Chem. Soc., 104, 180 (1982).

2) For a review, see J. F. Bielmann and J. B. Ducep, Org. React., 27, 1 (1982).

3) The absolute configuration of this compound was determined by comparison of the hydrogenated compound with the authentic sample prepared according to the following procedure. Commercially available L-2-amino-n-butyric acid was transformed into 1-methyl-2-(p-tolylsulfonyl)penten-1-ol. Its optical rotation was positive, whereas 3 was hydrogenated to give 5 which showed a negative rotation. Thus, the configuration of 3 is assigned to be S.



4) B. M. Trost, N. R. Schmuff, and M. J. Miller, J. Am. Chem. Soc., 102, 5979 (1980).

5) B. M. Trost, H. C. Arndt, P. E. Strege, and T. R. Verhoeven, Tetrahedron Lett., 1976, 3477; Y. Ueno, S. Aoki, and M. Okawara, J. Am. Chem. Soc., 101, 5414 (1979); H. Kotake, T. Yamamoto, and H. Kinoshita, Chem. Lett., 1982, 1331.

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