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HIGHLY ENANTIOSELECTIVE MICHAEL ADDITION OF THIOLS TO 2-CYCLOHEXENONE BY USING (2S,4S)-2-(ANILINOMETHYL)-1-ETHYL-4-HYDROXYPYRROLIDINE AS A CHIRAL CATALYST

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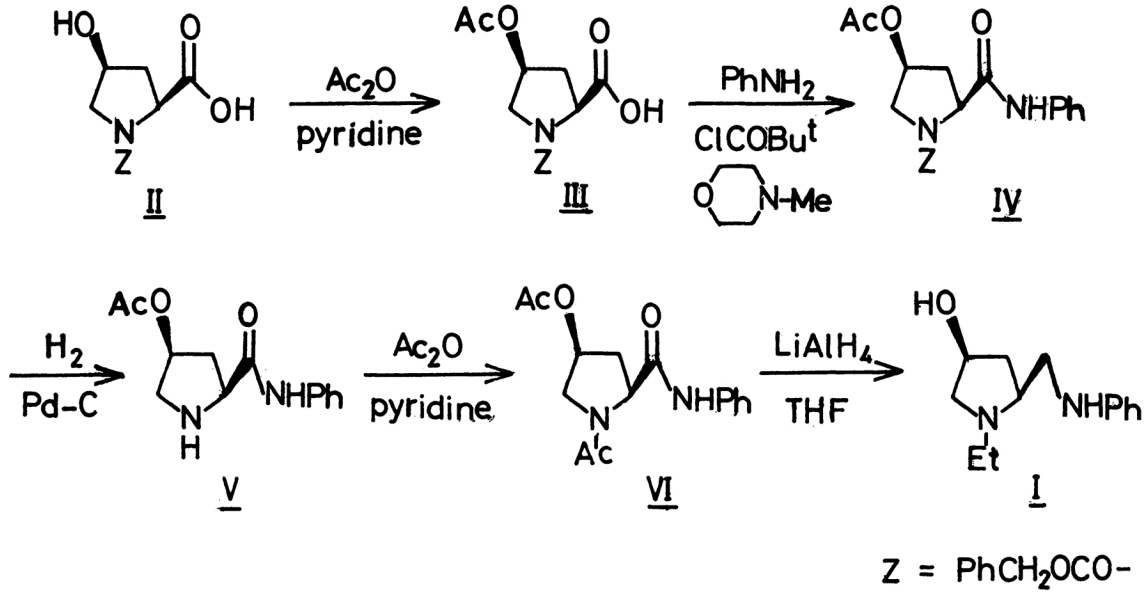
Optically active 3-arylthiocyclohexanones are produced in good optical yields by treating 2-cyclohexenone with aryl thiols in the presence of (2S,4S)-2-(anilinomethyl)-1-ethyl-4-hydroxypyrrolidine as a chiral catalyst.

Asymmetric synthesis promoted by chiral catalysts has been of great interest in recent years.[1] Especially, the asymmetric hydrogenation of prochiral olefins has been most extensively studied with success. However, such reactions have been much less successful in other cases, such as C-C bond forming reactions and so on. Among various approaches to such catalytic process, there have been reported some synthetically useful reactions catalyzed by chiral bases such as cinchona alkaloids. For example, Wynberg et al. reported the asymmetric Michael addition of thiols to 2-cyclohexenone using quinine as a chiral catalyst.[2a)]

In this communication, we wish to report a new type of chiral base, (2S,4S)-2-(anilinomethyl)-1-ethyl-4-hydroxypyrrolidine(I), which acts as an efficient catalyst in the asymmetric Michael addition of thiols to 2-cyclohexenone.

The amino alcohol I was prepared according to the following procedure: (2S,4S)-N-Benzyloxycarbonyl-4-hydroxyproline[3] (II) was treated with Ac_2O-pyridine/CH_2Cl_2 to afford the corresponding acetate III (75%, m.p. 107-108°C, $[\alpha]_D^{27}$-58.7° (c 1.03, $CHCl_3$)), which in turn was condensed with aniline by utilizing pivaloyl chloride as a condensing agent to give the amide IV (75%, m.p. 87.0-93.5°C, $[\alpha]_D^{27}$-65.4°(c 1.0, $CHCl_3$)). Hydrogenation of IV on 10% Pd-C in MeOH gave the amine V (100%, m.p. 64-72°C, $[\alpha]_D^{22}$-13.4°(c 1.06, EtOH)), which was acetylated with Ac_2O-pyridine to give the amide VI (95%, $[\alpha]_D^{25}$-115°(c 1.01, CH_2Cl_2)). Finally, reduction of VI with $LiAlH_4$ in THF afforded the chiral amino alcohol I (80%, b.p. 150-170°C / 2 mmHg (bath temp.), $[\alpha]_D^{23}$-58.1°(c 1.03, EtOH)).[4]

Next, the asymmetric Michael addition of thiols to 2-cyclohexenone was examined by using a catalytic amount (2 mol % to thiols) of I. Typical experimental procedure is as follows: Under an argon atomosphere, a solution of benzenethiol (440 mg, 4 mmol) in 25 ml of toluene and a toluene (25 ml) solution of 2-cyclohexenone (480 mg, 5 mmol) containing freshly distilled I (20 mg, 0.08 mmol) were mixed at -5°C and the reaction mixture was magnetically stirred for 5 days at the same temperature. The mixture was washed successively



with 1N HCl (5 ml x 3), brine (5 ml x 1), 1N NaOH (5 ml x 3), brine (5 ml x 1) and dried over anhydrous sodium sulfate. Toluene was evaporated under reduced pressure and the residue was chromatographed on silica gel TLC (hexane—AcOEt). 3-Phenylthiocyclohexanone thus obtained was further purified by short path distillation (b.p. 150-170°C / 1 mmHg (bath temp.)) to give a colorless oil (685 mg, 83%) which has 77% optical purity ($[\alpha]_{577}^{21}$ + 55.6°, $[\alpha]_{365}^{21}$ +497°(c 2.00, benzene)).

The results of the addition reaction of some other thiols are listed in the Table.

As shown in the Table, the chiral amino alcohol I is shown to be a very effective catalyst in the present reaction and high optical yields are realized compared with the previous methods.

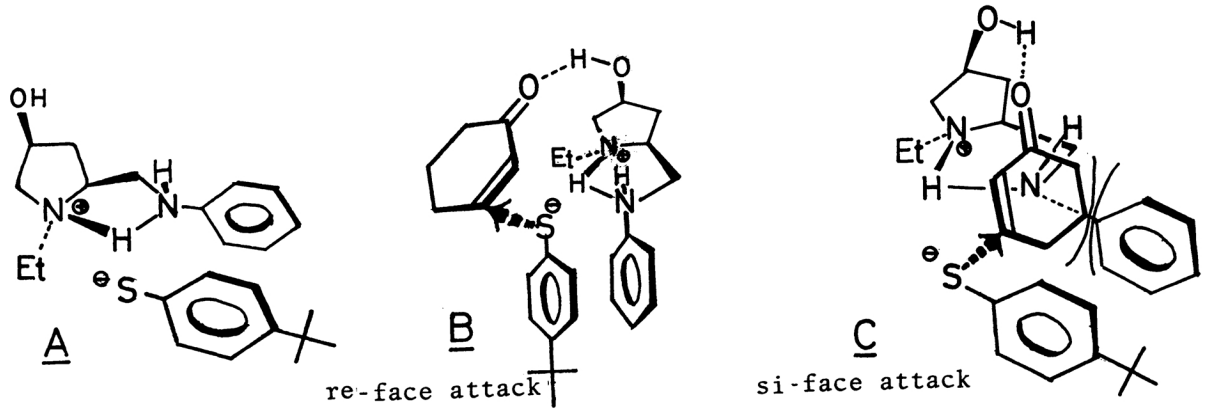
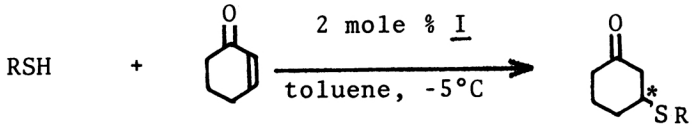
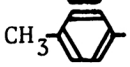
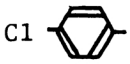
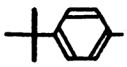
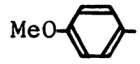


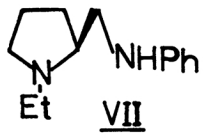
Table Enantioselective Addition of Thiols to 2-Cyclohexenone Using I



Entry	R	Yield(%)[c]	$[\alpha]_{577}^{21}$(c 2.00, benzene)	Optical Purity(%)
1		83	+55.6°	77[a]
2		75	+51.0°	73[a]
3		84	+36.5°	47[a]
4		74	+44.6°	88[a)b)]
5		75	+49.0°	83[b]

a) Calculations are based on the values reported in ref. 2a).
b) Enantiomer excess was confirmed by the ^{13}C NMR method[5] developed by Wynberg et al. and estimated to be 85±5% (entry 4) and 83±5%, (entry 5), respectively.
c) All the products gave satisfactory NMR and IR spectra.

Further, it was observed that (S)-2-(anilinomethyl)-1-ethylpyrrolidine (VII)[6] has little efficacy as the chiral catalyst in the present reaction. Thus, it it noted that the hydroxyl group of the catalyst I plays an important role in the enantioselection. In the cases of cinchona alkaloid catalyzed asymmetric syntheses, such as cyanohydrin reactions[7a] or the Michael additions,[7b] several authors also pointed out the role of the hydroxyl group of the catalyst in these types of asymmetric inductions.



VII

Since absolute configuration of the predominantly formed enantiomer has proved to be R,[8] we tentatively present a possible transition state model for the present reaction from CPK model inspection. Initially, a chiral ammonium thiolate complex A with a rigid fused 5-5 membered bicyclic structure[9] is formed by hydrogen bonding. And the approach of the cyclohexenone to the complex A takes place in a limited way with a hydrogen bond interaction between the carbonyl oxygen and the hydroxyl group of the pyrrolidine ring. Finally, the thiolate shift to the enone system occurs with enantioface differentiation (re-face attack), owing to the difference of the stabilities of the two transition states B and C (steric approach control).

Although the detailed mechanism of this reaction is not yet clear, intensive studies concerning the relationship between enantioselectivity and structure of the catalyst are now in progress in our laboratory.

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References and Notes

1) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice Hall Inc., 1971.

2) a) R. Helder, R. Arends, W. Bolt, H. Hiemstra and H. Wynberg, Tetrahedron Lett., 1977, 2181.
b) Other examples of asymmetric addition of thiols to prochiral olefins: H. Pracejus, F. W. Wilke and K. Hanemann, J. Prakt. Chem. 319, 219 (1977); Y. Ueyanagi and S. Inoue, Makromol. Chem., 178, 235 (1977); N. Kobayashi and K. Iwai, J. Am. Chem. Soc., 100, 7071 (1978); H. Wynberg and B. Greijdanus, J. Chem. Soc. Chem. Commun., 1978, 427; N. Kobayashi and K. Iwai, Tetrahedron Lett., 21, 2167 (1980).

3) A. A. Patchett and W. Witkop, J. Am. Chem. Soc., 79, 185 (1957).

4) ^{1}H-NMR (δ, $CDCl_3$): 1.1 (t, J=8 Hz, 3H), 1.5-1.9 (m, 1H), 2.1-2.5 (m, 3H), 2.5-3.0 (m, 2H), 3.0-3.3 (m, 4H), 4.1-4.5 (m, 2H), 6.5-7.3 (m, 5H). IR (neat, cm^{-1}): 3375, 1600, 1500, 750, 695.

5) H. Hiemstra and H. Wynberg, Tetrahedron Lett., 1977, 2183.

6) ^{1}H-NMR (δ, $CDCl_3$): 1.1 (t, J=8 Hz, 3H), 1.6-3.4 (m, 11H), 3.9-4.4 (broad, 1H) 6.5-7.3 (m, 5H). IR (neat, cm^{-1}): 3375, 1610, 1510, 755, 700. $[\alpha]_D^{25}$-53°(c 1.0, CH_2Cl_2).

7) a) V. Prelog and M. Wilhelm, Helv. Chim. Acta, 37, 1634 (1954).
b) K. Hermann and H. Wynberg, J. Org. Chem., 44, 2238 (1979).

8) Personal communication from Professor Hans Wynberg, University of Groningen, the Netherlands.

9) This structure in combination with electronic effects provides an effective environment for asymmetric induction; M. Asami, H. Ohno, S. Kobayashi and T. Mukaiyama, Bull. Chem. Soc. Jpn., 51, 1869 (1978); T. Mukaiyama, K. Soai, T. Sato, H. Shimizu and K. Suzuki, J. Am. Chem. Soc., 101, 1455 (1979); T. Mukaiyama, Y. Sakito and M. Asami, Chem. Lett., 1978, 1253.

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