Asymmetric induction in Michael addition reactions mediated by C2-symmetric aluminate

G Manickam & G Sundararajan
Department of Chemistry, Indian Institute of Technology
Madras 600 036, India
Received 22 April 1997

The C2-symmetric chiral amino-diol, (1R, 5R)-3-aza-3-benzyl-1,5-diphenylpentan-1,5-diol (1) is available readily from the reaction of benzylamine with a twofold excess of enantiopure R(+) -styrene epoxide. We have recently shown that the titanate complexes formed from these promote Diels-Alder and ene reactions. The adducts are obtained in high enantiomeric excess under extremely mild reaction conditions. However, this Lewis acid complex was incapable of promoting Michael addition reactions. But the corresponding aluminate of the amino diol 1 was found to act as efficient catalyst for Michael addition reactions and the homochiral aluminate was capable of inducing high enantiomeric excess in the corresponding Michael addition products. In this paper the synthesis of 1, the complexation with LiAlH₄ and its ability to promote a chiral variant in the Michael addition of various donors and acceptors (Eq.1) are discussed.

In recent years there has been sustained interest in development and use of optically pure C2-symmetric diols and derivatives as chiral auxiliaries leading to the optically active products with higher level of enantioselection. The control of relative and absolute configuration in carbon-carbon bond formation through the conjugate addition reactions has been intensively investigated. A large number of efficient metal alkoxides as catalysts for asymmetric Michael addition reactions have also been developed. Although numerous C2-symmetric metal alkoxides are known for asymmetric Michael addition reactions, only rare earth heterobimetallic complexes of BINOLS are found to be efficient catalysts with >90% enantioselectivity.

Recently, we reported the synthesis of a new C2-symmetric titanium alkoxide catalyst derived from amino diol, (1R, 5R)-3-aza-3-benzyl-1,5-diphenylpentan-1,5-diol (1), which successfully promotes Diels-Alder and ene reactions. Though this titanium alkoxide failed to promote Michael addition reactions, the aluminate of amino diol 1 synthesised by its reaction with LiAlH₄, was able to effect asymmetric induction in this reaction.

Here we present the synthesis of optically pure amino diol 1, its complexation with LiAlH₄ and its ability to promote asymmetric Michael addition reaction with cyclic as well as acyclic enones as acceptors and malonates as donors.

Results and Discussion

The amino diol 1 was readily accessed by the reaction of benzylamine with a twofold excess of enantiopure styrene epoxide in methanol (Eq.1).
It has recently been reported that the multifunctional heterobimetallics of rare earth transition element or aluminium and lithium BINOL complexes are excellent catalysts for asymmetric Michael addition reactions. We followed the same procedure and obtained a heterobimetallate with 1 and this was found to successfully promote Michael addition reactions.

The multifunctional heterobimetallic aluminate was generated in situ by the reaction of 2 equivalents of racemic amino diol 1 with 1 equivalent of LiAlH4 in THF, followed by the addition of donors and acceptors which yielded Michael adducts in good yield. To find the catalytic efficiency of the aluminate, we used both acyclic and cyclic enones as acceptors with malonates as donors. After completion of the reaction, the reaction mixture was quenched with 1N HCl at 0°C and the amino diol and the products were separated by flash column chromatography with an acetone:hexane mixture (10:90) as the eluent. The recovered amino diol was recycled. The results obtained from Michael addition reactions are shown in Table 1.

Encouraged by these observations, we investigated the chiral variant of the aluminate synthesised from homochiral amino diol [R, R-(1)]. This chiral aluminate was used as a promoter for Michael addition of malonates to cyclic enones, resulting in >80% enantiomeric excess (Eq.2).

The yield and time required for conversion of products and enantiomeric excess are shown in Table 2 and are compared with recent literature reports. The enantiomeric excess was calculated by comparison of the observed optical rotation with literature values. For reference we have also prepared the aluminate from TADDOL and this also promotes Michael addition reaction with comparable enantioselectivity, but the yields are lower for the same period of reaction time. The experimental results reveal that the time period required for the formation of product is less compared to that reported in the literature.

In conclusion, we have succeeded in developing a new C2-symmetric amino diol and its aluminate as a promoter for asymmetric Michael addition reaction under milder reaction conditions, resulting in good yields and enantioselectivity. The amino diol was readily obtained and can be recycled. The isolation and structural characterization of the aluminate and elucidation of the mechanism for achieving such high enantioselectivity are in progress.

### Materials and Methods

All reactions were done under an atmosphere of dry nitrogen, unless otherwise mentioned. Anhydrous solvents were transferred using oven-dried syringe or cannula. Tetrahydrofuran was distilled from
sodium-benzophenone ketyl and stored over sodium wire. Cyclic and acyclic alkenones, and malonic esters were synthesized according to the reported literature procedures. R(+)-Styrene epoxide, LiAlH₄ and benzylamine were purchased from E-Merck and used as such without further purification. All the compounds studied were purified by flash column chromatography using 230-400 mesh silica gel. The IR measurements were obtained as neat using Shimadzu (Model-470) IR spectrophotometer. IH NMR spectra were recorded with Hitachi (Model R600) 60 MHz NMR instrument while high resolution IH and ¹³C spectra were recorded on a JEOL 400 MHz (Model GSX 400) high resolution NMR spectrometer. CDCl₃ was used as the solvent for the NMR spectral measurements and the spectra were recorded in parts per million with TMS as the internal standard. Optical rotations were measured using a JASCO DIP-370 digital polarimeter.

\((1R, 5R)-3\text{-AzA-3-benzyl-1,5-dihydroxy-1,5 diphenylpentane (I)\text{}}\)

A solution of R(+)-styrene epoxide (2.1 equivalents) in dry methanol was added to a stirred, cooled solution of benzylamine (1 equivalent) in dry methanol over a period of ca. 30 minutes. The reaction mixture was stirred at 0°C for 1 h then refluxed for 4h. The solvent was removed under reduced pressure and the syrupy mass was loaded onto a column of 60-120 mesh silica gel, using 20% EtOAc-hexane as eluent to get the optically pure symmetrical diol (I) as a colourless resin.

**General procedure for Michael addition reaction**

To a cooled solution of LiAlH₄ (1 equivalent) in THF, optically pure amino diol (I) (2 equivalents) in THF was added slowly and the reaction mixture was stirred for 30 min at 0°C. To this stirred solution cyclohexenone and malonate were added and slowly warmed to room temperature and stirred for 6h. The reaction mixture was quenched with 1N HCl at 0°C and extracted with ethylacetate. The organic layer was washed successfully with saturated sodium bicarbonate solution, brine and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a syrupy mass, which on flash column chromatography gave the product as a colourless oil.

**Acknowledgement**

We acknowledge financial assistance from CSIR (Project No: 01/1279/93/EMR-II). We also thank RSIC, IIT, Madras for spectral measurements.

**References**