Asymmetric Michael addition reaction using a chiral catalyst containing amino diol

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Dedicated to Prof. S. V. Kessar on the occasion of his 70th birthday

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Abstract

A C_2–symmetric amino diol, (*R*,*R*)-2-(benzyl–(2-hydroxy-2-phenylethyl)-amino)-1-phenylethanol **1** was predominantly utilized to synthesise Li-Al heterobimetallic chiral catalyst. This catalyst is effective for carrying various Michael addition reactions. (*R*,*R*)-2-(*p*-vinyl benzyl–(2-hydroxy-2-phenylethyl)-amino)-1-phenylethanol **2** (Scheme 4), carrying a polymerisable vinyl tether, was also synthesised and used for preparing polymer anchored Li-Al heterobimetallic chiral catalyst. These catalysts are quite effective for enhancing various Michael addition reactions. The optimized reaction conditions produced Michael adducts in good yield with high enantiomeric excesses.

Keywords: Asymmetric Michael addition, C_2-symmetric chiral ligand, heterobimetallic complexes, polymer anchored catalysts, enantiomeric excess

Introduction

Asymmetric Michael addition, an important carbon-carbon and carbon–hetero atom bond forming reaction[1], essential for synthesis, is gaining more importance and study by chiral auxiliary, chiral monometallic, chiral heterobimetallic and chiral crown complexes techniques.[2a-d] Considerable new work concerning reactions mediated by synthetic enzymes (chemzymes)[3] like heterobimetallic complex[4] has been reported. Use of chiral heterobimetallic complex is common in asymmetric Michael addition,[5] nitroaldol, hydrophosphorylation, epoxide ring opening, epoxidation of α,β-unsaturated ketones, Diels-Alder, and nitro-Mannich type reactions.[6a-f] The metal centers in these complexes probably "communicate" with one another within the catalyst, showing some cooperative effects[6g] to position the reactants and to enhance the reactivities of both the reactants.

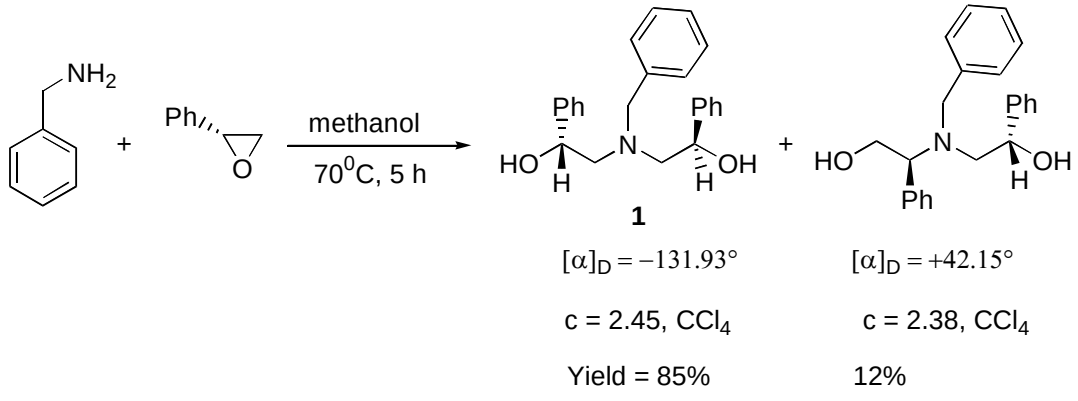
There is a reasonable suggestion that with C_2-symmetric ligands in a chiral catalyst the number of diastereomeric transition states are minimum and this might increase the enantiomeric excess of the product.[7] The C_2-symmetric amino diol (*R*, *R*)-2-[benzyl-(2-hydroxy-2-phenylethyl)-amino]-1-phenylethanol[8] **1** has been used for synthesizing lithium-aluminum and lanthanum-sodium heterobimetallic complex. This has effectively catalyzed asymmetric Michael addition reactions with high enantioselectivity[9] and this is discussed in this paper.

A practical difficulty in performing conventional homogeneous catalytic reactions lies in separating the product from the catalyst. Also, the possibility of oligomerization of the catalyst that may be unavoidable in some cases could lower activity and a decrease in the enantiomeric excess (ee). Such aggregations can however be restricted by supporting the catalyst onto a polymer backbone.[10]

Chiral polymers have been used in the chromatographic separation of enantiomers, as chiral auxiliaries in phase transfer catalysis or as chiral polymer catalysts in hydrogenation, hydroformylation, alkylation, hydrosilation, epoxidation, dihydroxylation, Diels-Alder[11a-i] and Michael addition reactions.[12] The advantages of this method being the ease of purification of the reaction mixture, reusability of the catalyst and as these polymers have bulkier groups they may provide a respective small space for the reactions to enhance stereoselectivity. These show some general resemblance to the reactive sites like those found in enzymes.[13] Preparation of polymer chiral catalyst using (*R*,*R*)-2-[*p*-vinylbenzyl-(2-hydroxy-2-phenylethyl)-amino]-1-phenylethanol, **2** and asymmetric Michael addition reaction using polymer anchored chiral catalyst will be also discussed in this paper.

Results and Discussion

Trost reported[14] the synthesis of amino diol **1** under neat conditions; we modified the reaction procedure and synthesized chiral amino diol **1** in good yield (Scheme 1) by refluxing for 5 hours in methanol and obtained the single crystal XRD of the chiral amino diol **1.** The unsymmetrical diol formed in lower yield was also isolated, characterized and optical rotation measured.



Scheme 1. Preparation of amino diol, **1**.

Studies using LiAl-1

In order to evaluate the efficiency of amino diol, **1** in catalytic reactions we adopted the procedure by Shibasaki to synthesize Li-Al heterobimetallic catalyst using BINOL. Typically the heterobimetallic catalyst was synthesized by *in situ* reaction of amino diol with $LiAlH_4$. The amount of hydrogen gas evolved was measured and found to be in agreement with the value calculated for a complete reaction of the hydride. The inductively coupled plasma analysis showed the presence of Li and Al in the catalyst with expected amounts for complete incorporation of the metals. The ^{27}Al-NMR spectrum showed a new broad singlet at 60.04 ppm (δ) while ^{7}Li- NMR showed a signal at higher field at -0.25ppm (δ) indicating the different environments around Al and Li metals.[15]

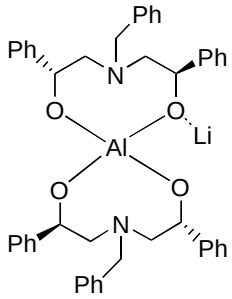
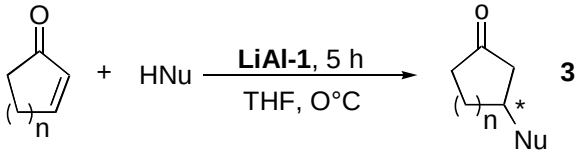


Figure 1. Structure of LiAl-1.

Asymmetric Michael addition reaction of dialkylmalonates with cycloalkenones were carried out using **LiAl-1** chiral catalyst (Figure 1). The reaction conditions were optimized and observed that the Michael adduct gave rise to good yield and high enantiomeric excess. We also noted a slight variation in the enantiomeric excesses upon changing the ester substituents of the nucleophiles. (Table 1)

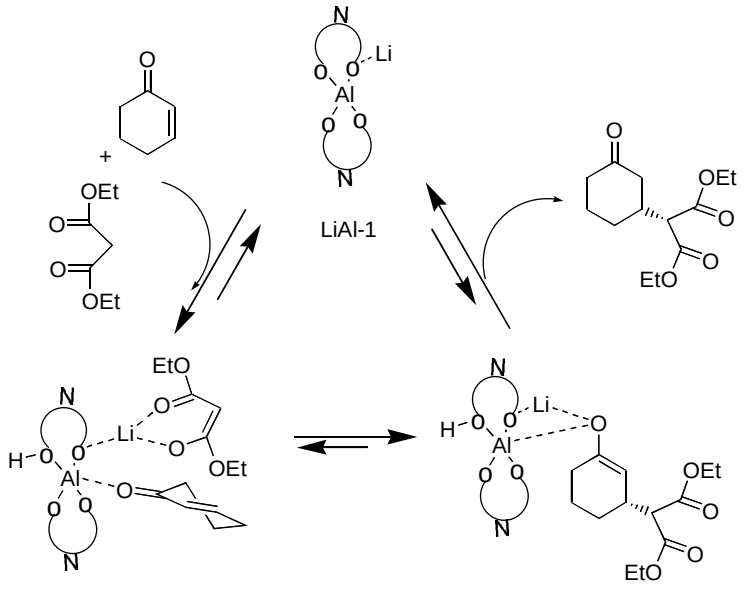


Nu: -CH(CO_2Et)$_2$, -CH(CO_2Bn)$_2$, -CH(CO_2^{t}Bu)$_2$

Table 1. Asymmetric Michael addition reaction of dialkyl malonates to cycloalkenones

Product	Nu	n	Time (h)	Yield (%)	ee (%)
3a	$CH_2(CO_2Et)_2$	1	20	82	86
3b	$CH_2(CO_2Et)_2$	2	20	85	80
3c	$CH_2(CO_2Bn)_2$	1	20	84	83
3d	$CH_2(CO_2Bn)_2$	2	20	86	92
3e	$CH_2(CO_2{}^tBu)_2$	1	20	86	90
3f	$CH_2(CO_2{}^tBu)_2$	2	20	80	94

A mechanism was proposed for the formation of Michael adduct using **LiAl-1** catalyst where the carbonyl group gets coordinated to the central aluminum metal and the enolate to the lithium metal. The enolate subsequently attacks the cyclohexenone to yield the Michael adduct.



Scheme 2. Proposed mechanism for the Michael addition.

Reactions of thiols with cycloalkenones also progressed leading to high yield and moderate enantiomeric excesses. These reactions get completed in less time of 60 seconds. The time required for the conversion to product was less compared to other similar addition reactions of thiols to α,β-unsaturated ketones.[16] (Table 2)

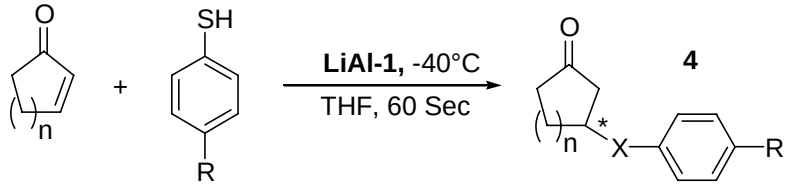


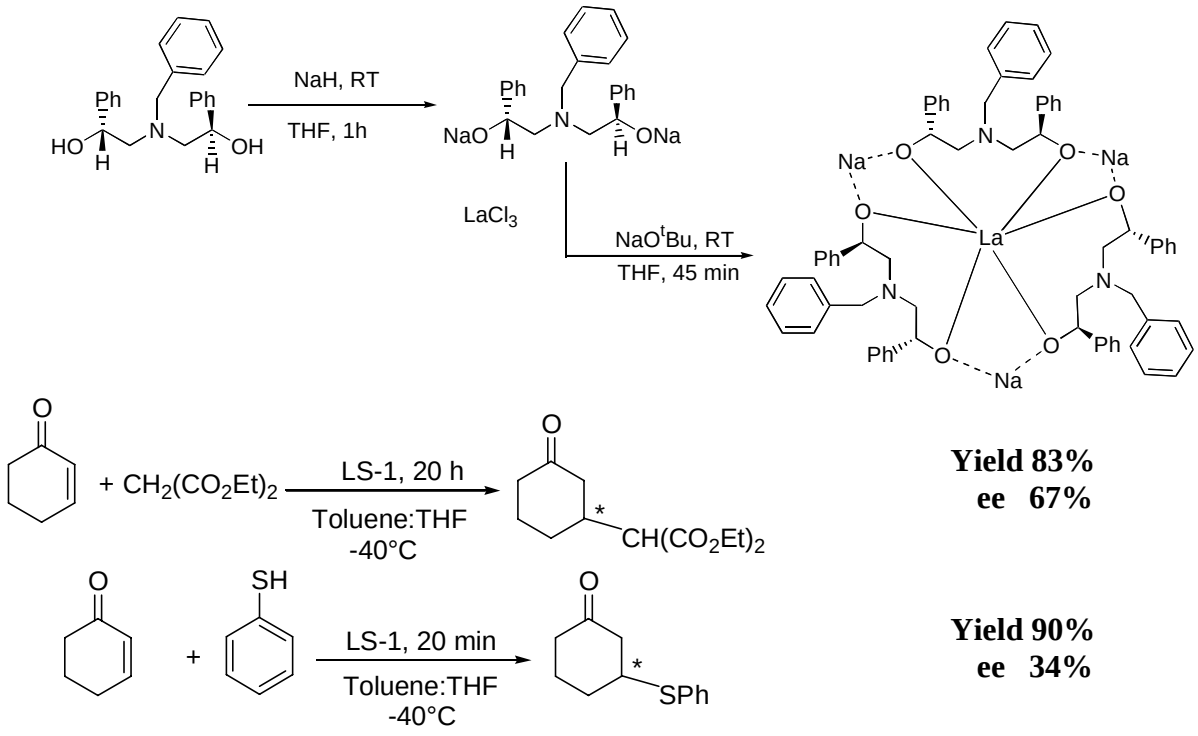
Table 2. Michael addition of thiols to cycloalkenones

No.	N	R	Yield (%)	ee %
4a	1	H	95	32
4b	2	H	90	45
4c	1	CH_3	90	26
4d	2	CH_3	90	40

Studies using LS-1

Lanthanum-sodium heterobimetallic catalyst, **LS-1** also can be used for catalysing asymmetric Michael addition reaction. **LS-1** complex were prepared using lanthanum isopropoxide and sodium amino diol. On using this catalyst for Michael addition reaction of diethyl malonate to cyclohexenone we observed 67% ee for the Michael adduct. Reaction of thiophenol with cyclohexenone was also carried out using **LS-1** leading to Michael adduct of 34 % ee. (Scheme 3)

Lanthanum sodium aminodiol complex is a good chiral catalyst for Michael addition reactions of dialkyl malonates and thiols giving moderate enantiomeric excesses.



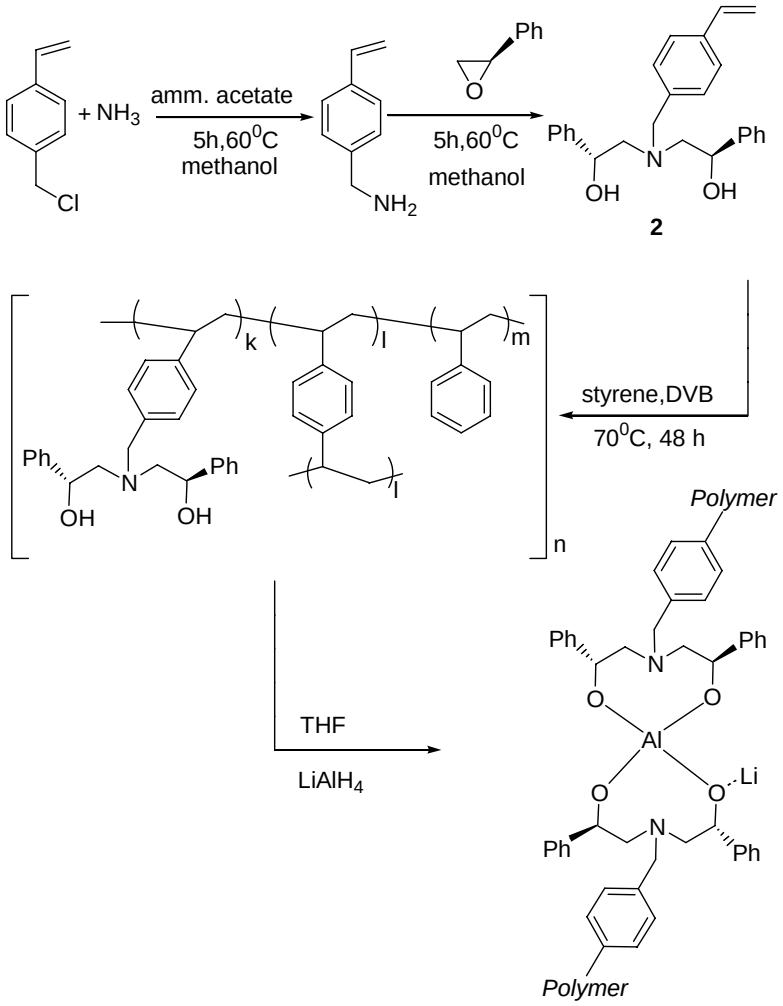
Scheme 3. Michael addition reaction using LS-1.

Studies using LiAl-poly2

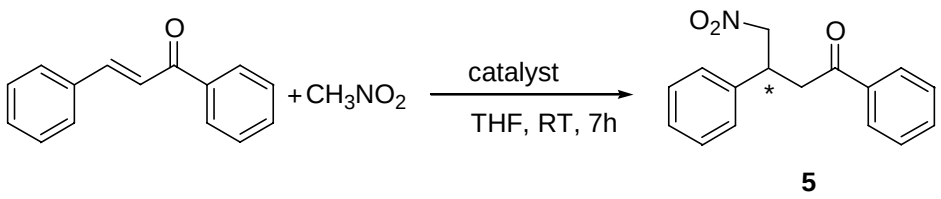
In view of the above-mentioned positive aspects of polymer anchored chiral catalysts, we decided to synthesize and evaluate the efficiency of the polymer chiral ligand incorporating the crucial C_2-symmetric aminodiol **1** onto a macromolecular backbone. Accordingly, vinyl amino diol **2** carrying a polymerisable vinyl tether, was synthesised by refluxing *p*-vinylbenzylamine with two equivalents of *R* (+) styrene oxide in 30 % yield with a high co-production of dimer and other oligomers.[17] The chiral polymer (**poly2a**) was synthesized by free radical copolymerization of the corresponding chiral monomer with *p*-divinylbenzene and styrene as cross-linking reagent and co-monomer in ratio of 1:1:4 (Scheme 4).[18]

The polymeric chiral catalyst **LiAl-poly2A** was prepared by the reaction of excess polymer chiral ligand **poly2A** with $LiAlH_4$ in THF under an inert atmosphere. The amount of hydrogen gas evolved was measured and found to be in agreement with the value calculated for a complete reaction of the hydride. The inductively coupled plasma (icp) analysis of the product showed the presence of lithium and aluminum in the polymer chiral catalyst with expected amounts for a complete incorporation of the metals.

Scanning electron microscopy (SEM) was used to observe qualitatively and pictorially the changes in the specific morphologies of **poly2A** as such and on the **LiAl-poly2A**.[12] **LiAl-Poly2A** was used for promoting asymmetric Michael addition reaction of nitromethane to the chalcone (Table 3). The very reaction catalyzed by chiral alkaloids was done earlier under high pressure and for a longer time.[19] But, here the reaction could be completed at atmospheric pressure and for lesser reaction time of 6 hours.



Scheme 4. Synthesis of polymer chiral catalyst **LiAl-poly2A**.



catalyst : Li, Al, and ligand*

Table 3. Michael addition of nitromethane with chalcone

Ligand*	% of Amino diol in catalyst#	Yield(%)	ee(%)
1	100	92	5.3
Poly**2a**	41	90	51

In all cases the ratio, [Al] / [Michael acceptor] was kept at 0.5

In addition, the purification process is simple being just a quick filtration of the reaction mixture to separate the catalyst from the organics. On using the amino diol **1** as ligand we could obtain just 5.3% ee of the Michael adduct, whereas on using **poly2A** as the ligand, the ee of the product rose to 51% (Table 3) for the nitromethane adduct.

In our earlier report we had noted that the Michael addition of thiols to enones gets completed in seconds and that the stereo specificity is optimum. We attempted the same reaction with **LiAl-poly2A** catalyst and found that the reactions were comparatively slow, 30 min. but the ee's were slightly higher(Table 4).

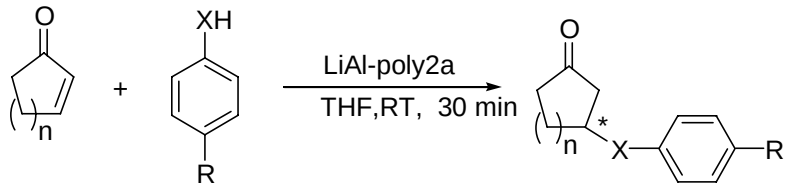


Table 4. Michael addition of thiols to cycloalkenones

No.	n	R	X	Yield (%)	ee %
4a	1	H	S	95	41
4b	2	H	S	90	57
4c	1	CH_3	S	90	52
4d	2	CH_3	S	90	33
6	1	H	CH_2S	85	52
7	2	H	CH_2S	90	76

Cyclopentenone and cyclohexenone were also used as Michael acceptors and the Michael donors were thiophenol, *p*-methyl thiophenol and benzyl mercaptan. The yields and the ee's are in

general high when compared with other methods. Asymmetric Michael addition of benzylamine to α,β-unsaturated ester group has also been studied recently.[20] The asymmetric Michael addition of benzylamine with ethyl cinnamate using **LiAl-poly2A** catalyst we could obtain higher ee of the product (Table 5). On using the aminodiol **1** as the chiral ligand we obtained 60% ee for this reaction. With **LiAl-poly2A** as the chiral ligand, the ee was found to be higher at 80%.

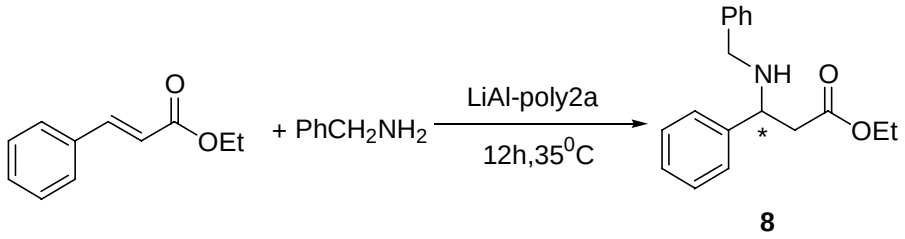


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Table 5. Michael addition of benzylamine to ethyl cinnamate

Complex	Yield (%)	ee %
LiAl-poly2a	60	80.9

To conclude, we have developed a new C_2-symmetric heterobimetallic chiral catalyst **LiAl-1** and **LS-1** as a promoter for asymmetric Michael addition reaction of dialkyl malonates and thiophenols to cyclic enones leading to good yield and high enantioselectivity. We have also synthesised a novel polymer chiral ligand **poly2** and polymer anchored chiral catalyst **LiAl-poly2A** and used it as an activator for Michael addition reaction of nitromethane to chalcone with good yield and high enantioselectivity. Addition of thiophenols to unsaturated cycloalkenones also shows acceleration in the presence of this catalyst resulting in a greater yield and moderate enantioselectivity.

Experimental Section

General Procedures. All reactions were performed under an inert atmosphere of dry nitrogen. (*R*)- (+)-styrene oxide, 2-cyclopentenone, 2-cyclohexenone, $LiAlH_4$, $LaCl_3$, thiophenol, *p*-methyl thiophenol and benzyl mercaptan were purchased from E-Merck and used as such. Anhydrous THF was obtained by distillation over sodium-benzophenone ketyl. All other reagents were purified by literature procedures.

The ^1H and ^{13}C NMR were recorded in $CDCl_3$ with JEOL 400 *MHz* (model GSX 400). ^1H-NMR and ^{13}C-NMR data are reported in parts per million (δ) downfield from tetramethylsilane. The following abbreviations are used for the resonance patterns: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. The ^1H-^1H COSY spectrum was recorded in $CDCl_3$ with Bruker Avance 400 instrument. IR spectra were recorded with Shimadzu (model 470) IR spectrophotometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter

(with 50 mm and 10 mm cell) and the ee's were determined by comparing with literature values. Wherever chiral separation was possible by HPLC, the Waters HPLC with Waters 486 Tunable absorbance detector (λ) containing chiralcel OD column was used for confirming the ee's obtained from optical rotation method.
Mass spectra (high and low resolution mass spectra) were obtained from Finnigan MAT (model 8230) High Resolution Mass Spectrometer. ICP–AES analysis was done by ARC 3410 ICP-AES with mini torch.

Preparation of aminodiol, (1). To a cooled solution of benzylamine (1.07 g, 9.985 mmol) in 2 mL of methanol, (R) –styrene oxide (2.40 g, 19.975mmol) in 4 mL of methanol was added at 0 ^{o}C and stirred for 1 h. It was then refluxed for 4 h. After the completion of reaction, the solvent was removed under reduced pressure to give isomeric diols as syrupy mass which on flash column chromatography using ethylacetate: hexane (20:80) as eluent yielded the major isomer as a colorless crystal (yield 85%).
(*R, R*)-2-[Benzyl-(2-hydroxy-2-phenylethyl)-amino]-1-phenylethanol (1). mp 68-69 °C. IR (neat): 3376, 3024, 2832, 1946, 1875, 1805, 1491, 1446, 1242, 1056, 758, 701. ^{1}H NMR (400 *MHz*, $CDCl_3$) δ 2.83 (dd_{ABX}, 2H, 2.9 and 13.2 *Hz*), 2.94 (dd_{ABX}, 2H, 9.7 and 13.2 *Hz*), 3.80 (d, 1H, 13.6 *Hz*), 4.03 (d, 1H, 13.6 *Hz*), 4.30 (2H, broad s, OH), 4.84(dd_{ABX}, 2H, 2.9 and 9.7 *Hz*), 7.28. - 7.51 (m, 15H). ^{13}C NMR (400 *MHz*, $CDCl_3$) δ 62.50, 70.17, 71.23, 125.86, 127, 50, 127.74, 128.35, 128.46, 129.23, 137.73, 142. 03. (The assignments are verified by running the ^{1}H-^{1}H *COSY* spectra shown below). MS (*m/z)* 240 (-Ph-CH-OH), 132 (2 Ph-CH-OH), 105, 91 (base peak, $PhCH_2$), 77. $[\alpha]^{25}_{D}$: -131.7 (*c* = 2.45, CCl_4).
Preparation of heterobimetallic complex LiAl-1. Enantiomerically pure amino diol 1 (183 mg, 0.53 mmol)in dry THF (2 mL) was added to a cooled solution of $LiAlH_4$ (10 mg, 0.268 mmol) in dry THF (1 mL). The mixture was then stirred for 30 min. at 0 ^{o}C. For ^{27}Al, ^{7}Li, ^{1}H and ^{13}C-NMR spectral data, the complex was generated in a NMR tube and the NMR spectra were recorded at room temperature using aluminum nitrate, lithium chloride and TMS as references respectively. For a blank, 10 mg of $LiAlH_4$ was taken in 1.5 mL THF to record ^{27}Al and ^{7}Li NMR. ^{1}H NMR ($CDCl_3$, 400 *MHz*) δ 2.53-2.66 (m, 4H), 3.42(d_{AB}, 1H, *j* =13.7 *Hz*), 3.75 (d_{AB}, 1H, *j* =13.7 *Hz*), 4.54(d, 2H, *j* =8.5 *Hz*), 7.25-7.61(m, 15H); ^{13}C NMR ($CDCl_3$, 100 *MHz*) δ: 59.68 (t), 62.44 (t), 70.73 (d), 72.33(d), 125.94(d), 127.32(d), 127.44(d),128.30(d), 128.44(d), 129.17(d), 138.19(s), 142.36(s); ^{27}Al-NMR (104 *MHz*, THF): for $LiAlH_4$ = 98.43 ppm (quintet, due to coupling of aluminum with 4H) for heterobimetallic complex δ 60.04 (bs); ^{7}Li-NMR (155 *MHz*, THF): for $LiAlH_4$ δ = -0.255 ppm (s), for heterobimetallic complex δ +1.12 ppm(s).

Gasimetric and ICP analysis of LiAl-1. Enantiomerically pure amino diol **1** (183 mg, 0.53 mmol)in dry THF (4 mL) was added to a cooled solution of $LiAlH_4$ (10 mg, 0.26 mmol) in dry THF. The evolved hydrogen gas was measured by the usual displacement technique. The volume of gas evolved was 23.60 mL (calculated gas volume = 23.74 mL). The mixture was stirred for 30 minutes at 0 ^{o}C and the reaction mixture was filtered through Celite using Schlenck

apparatus. After removal of the solvent, the complex was obtained as a semi-solid. From this 44 mg of the complex was weighed and made upto 10 mL using 1:1 mixture of water and concentrated nitric acid. The aqueous solution was filtered through Whatman 40 filter paper and this solution was used for ICP analysis. The observed values are Al = 165.24 ppm, Li = 44.02 (calculated values Al = 164.01, Li = 43.00).

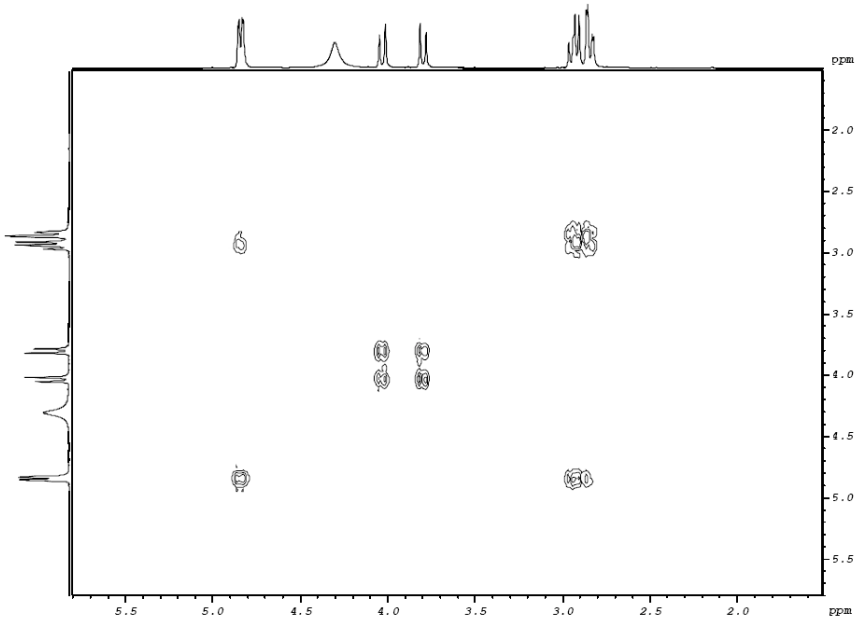

Figure 1. ^{1}H-^{1}H-*COSY* for the (*R*, *R*)-2-[Benzyl-(2-hydroxy-2-phenylethyl)-amino]-1-phenylethanol, **1** (showing only the regions of correlation).

General procedure for Michael addition reaction of malonates to cycloalkenones using LiAl-1

Enantiomerically pure amino diol **1** (201 mg, 0.58 mmol) in dry THF (4 mL) was added to a cooled solution of $LiAlH_4$ (11 mg, 0.29 mmol) in dry THF. The mixture was stirred for 30 minutes at 0 ^{o}C, then the cycloalkenones (1.45 mmol) in dry THF (2 mL) and malonates (1.45 mmol) in dry THF (2mL) were added. The mixture was warmed to room temperature and stirred for 3 to 7 h. After completion of the reaction, the mixture was quenched with 1N HCl, and the product was extracted with ethylacetate. The organic layer was washed successively with saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a syrupy mass, which on flash column chromatography using acetone: hexane (4:96) as eluent gave the products.

Preparation of the heterobimetallic complex LS-1. To 41 mg of sodium hydride (1.71 mmol) in THF, 290 mg of amino diol, I (0.836 mmol) was added and allowed to react for one hour to obtain sodiated amino diol. To 68 mg of $LaCl_3$, 327 mg of sodiated amino diol (0.836 mmol) kept at 0 °C was added 4 mmol of sodium *t*-butoxide and the mixture was allowed to stir for

45 min and the solution was filtered and half of the solution as such or the dried complex, was used as catalyst for Michael addition reactions.

ICP analysis of LS-1. To 68 mg (0.278 mmol) of $LaCl_3$ in dry THF a solution of sodiated amino diol (327 mg, 0.836 mmol) in dry THF was added and stirred for 45 minutes at 0 ^oC after removal of the solvent 26 mg of the complex was weighed and made up to 10 ml using 1:1 mixture of water and conc. nitric acid. The aqueous solution was filtered and this solution was used for ICP analysis. The metal contents were found to be La: 286.57 mg/L (calculated 290.58 mg/L) and Na: 140.21 mg/L (calcd 144.28 mg/L).

Michael addition reaction of donors to cycloalkenones using LS-1

To 10 mol% of **LS-1** complex, 1 eq. of cycloalkenones and 1 eq. of Michael donors were added sequentially using solvent. After 30 min the reaction mixture was quenched with 1N HCl, and the product was extracted with ethylacetate. The organic layer was washed successively with saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a syrupy mass, which on flash chromatography using acetone: hexane (4:96) as eluent gave the products.

Synthesis of monomer

To a cooled solution of vinyl benzylamine (5 mmol) in 2 mL of methanol (*R*)-(+)-styrene oxide (10 mmol) in 4 mL methanol were added slowly drop by drop at 0 ^oC for 15 min, stirred for 1h and refluxed for 5 h. After completion of the reaction, the solvent was removed under reduced pressure to give a syrupy mass which on column chromatography (alumina) using ethylacetate : hexane (10:90) as eluent gave the product.

(*R, R*)-2-[*p*-Vinylbenzyl-(2-hydroxy-2-phenylethyl)-amino]-1-phenylethanol (2). Yield 30%. IR (cm^{-1}, neat) 3376, 3024, 2832, 1946, 1875, 1805, 1491, 1446, 1292, 1056, 758, 701. ^1H NMR ($CDCl_3$, 400 *MHz*) δ: 2.72 (dd_{ABX}, 2H, 2.8 and 13.1 *Hz*), 2.83 (dd_{ABX}, 2H, 9.7 and 13.1 *Hz*), 3.81 (broad s, 2H, OH), 3.83 (d, 2H, 13.4 *Hz*), 4.04 (d, 2H, 13.4 *Hz*), 4.75 (dd_{ABX}, 2H, 2.8 and 9.7 *Hz*), 5.25 (dd_{AMX}, 1H, 1 and 11.2 *Hz*), 5.75 (dd_{AMX}, 1H, 1 and 17.5 *Hz*), 6.68 (dd_{AMX}, 1H,17.5 & 11.2 *Hz*), 7.20-7.39 (m, 14H). ^{13}C NMR ($CDCl_3$, 100 *MHz*) δ: 59.74, 62.53, 70.77, 114.07, 125.86, 127.41, 127.53, 128.50, 129.14, 138.03, 137.70, 142.10. MS (EI, *m/z*) 373 (M^+), 339, 270, 240, 208, 135, 107. HRMS (*m/z*) calculated 373.2041 and observed mass 373.2022. $[\alpha]^{25}_D$ = -118.01, (*c* = 2.1, $CHCl_3$).

Preparation of catalyst (poly2a). To one mole of (*R,R*)-3-aza-3-(*p*-vinylbenzyl)-1,5-diphenyl-1,5-dihydroxy pentane one mole of divinylbenzene and respective mole of styrene were added in the presence of 10 mg of benzoylperoxide and sealed at nitrogen atmosphere. Then the reaction mixture was heated at 70 °C for 48 h. The resulting polymer was washed with methanol and used as such. To 250 mg of **poly2a**, 10 mg of $LiAlH_4$ (0.268 mmol) in dry THF was added slowly at 0 ^oC and stirred for 30 min.

Gasimetric and ICP analysis of the catalyst poly2a. To **poly2a** (500 mg) in THF a solution of $LiAlH_4$ (10 mg, 0.268 mmol) in dry THF was added drop by drop at 0 ^oC. The hydrogen gas evolved, measured by usual displacement technique was 23.58 mL (calcd 23.74 mL).

To) **poly2a** (580 mg) in dry THF a solution of $LiAlH_4$ (12 mg, 0.32 mmol) in dry THF was added and stirred for 30 min at 0 ^oC, after removal of the solvent 44 mg of the complex was weighed and made up to 10 mL using 1:1 mixture of water and conc. nitric acid. The aquous solution was filtered and this solution was used for ICP analysis. The metal contents were found to be Al : 63.20 mg/L (calculated 63.27 mg/L) and Li : 16.12 mg/L (calculated 16.27 mg/L).

General procedure for the Michael addition reaction using (poly2a)

To the polymer chiral ligand (250 mg) in THF a solution of $LiAlH_4$ (10 mg, 0.268 mmol) in dry THF was added slowly, drop by drop at 0 ^oC. The mixture was stirred for 30 min, and then the mixture was warmed to room temperature the Michael acceptor and donor were added subsequently. After the reaction was over it was quenched with 1N HCl and mixture extracted with ethylacetate. The organic layer was washed successively with saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a syrupy mass, which on flash column chromatography gave the product.

3-[Bis(ethoxy carbonyl) methyl]cyclopentanone (3a). Yield 82%. IR (CCl_4, cm^{-1}): 2976, 2928, 1744, 1734, 1148. ^1H NMR ($CDCl_3$, 400 *MHz*) δ: 1.20 (t,3H, 7.3 *Hz*), 1.21 (t, 3H, 7.3 *Hz*), 1.58 – 1.66 (m, 1H), 1.93 – 2.0 (m,1H), 2.1 – 2.31 (m, 1H), 2.45– 2.86 (m, 4H), 3.27 (d, 1H, 9.3 *Hz*), 4.12 – 4.19 (m,4H). ^{13}C NMR ($CDCl_3$, 100 *MHz*) δ: 13.93, 13.96, 27.34, 36.18, 38.06, 42.77, 56.38, 61.47, 61.57, 167.95, 168.04, 217.11. MS (EI, *m/z*): 242 (M^+), 197, 160, 83. $[\alpha]_D^{25}$ = 29.9, ee 86%, *c* = 1.71, $CHCl_3$ (Lit:[21a] $[\alpha]_D^{25}$ = 28.35, ee 82%, *c* = 1.89, $CHCl_3$).

3-[Bis(ethoxy carbonyl) methyl]cyclohexanone (3b). Yield 85%. IR (CCl_4, cm^{-1}) : 2968, 2930, 1754, 1724, 1443, 1359, 1134. ^1H NMR ($CDCl_3$, 400 *MHz*) δ: 1.27 (t,3H, 7.3 *Hz*), 1.28 (t, 3H, 7.3 *Hz*), 1.52 - 1.69 (m, 2H), 1.96 – 2.11 (m, 2H), 2.22 – 2.31 (m, 1H), 2.38 – 2.47 (m, 2H), 2.49 – 2.57 (m, 2H), 3.35 (d, 1H, 7.8Hz), 4.20 (q, 2H, 7.3 *Hz*), 4.21 (q, 2H, 7.3 *Hz*). ^{13}C NMR ($CDCl_3$, 100 *MHz*) δ: 14.07, 14.10, 27.50, 29.35, 36.32, 38.20, 42.91, 56.52, 61.62, 61.45, 168.09, 168.18, 217.27. MS (EI, *m/z*): 256 (M^+), 211, 182, 160, 97. $[\alpha]_D^{25}$ =2.8, ee 80%, *c* = 2.5, $CHCl_3$ (Lit:[21a] $[\alpha]_D^{25}$ = 2.9, ee 81%, *c* = 2.56, $CHCl_3$).

3-[Bis(benzyloxy carbonyl) methyl]cyclopentanone (3c). Yield: 84%. IR (CCl_4, cm^{-1}) : 2978, 2928, 1747, 1733, 1452, 1398. ^1H NMR ($CDCl_3$, 400 *MHz*) δ: 1.58 – 1.77 (m, 2H), 1.97 — 2.98 (m, 5H), 3.33 (d, 1H, 7.81 *Hz*), 5.11 (s, 2H), 5.12 (s, 2H), 7.20 – 7.41 (m, 10 H). ^{13}C NMR ($CDCl_3$, 100 *MHz*) δ: 24.41, 38.32, 40.53, 41.06, 55.72, 66.28, 66.30, 128.13, 128.24, 128.53, 135.13, 135.24, 170.83, 170.92, 217.30. MS (EI, *m/z*): 366 (M^+), 289, 107, 91. $[\alpha]_D^{25}$ = 28.3, ee 83%, *c* = 1.73, $CHCl_3$ (Lit:[21a] $[\alpha]_D^{25}$ = 28.35, ee 85%, *c* = 1.89, $CHCl_3$).

3-[Bis(benzyloxy carbonyl) methyl]cyclohexanone (3d). Yield : 86%. IR (CCl_4, cm^{-1}) : 3040, 2944, 1753, 1721. ^1H NMR ($CDCl_3$, 400 *MHz*) δ: 1.40 - 1.60 (m, 2H) 1.81 – 1.96 (m, 2H), 2.11 – 2.19 (m, 1H), 2.27 – 2.38 (m, 2H), 2.43 – 2.51 (m, 2H), 3.33 (d, 1H, 7.81 *Hz*), 5.06 (s, 2H), 5.07 (s, 2H), 7.17 – 7.25 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 *MHz*) δ: 24.46, 28.59, 38.06, 40.90, 45.00, 56.63, 66.76, 67.21, 128.30, 128.47, 128.51, 135.07, 135.17, 167.48, 167.58, 209.34. MS (EI, *m/z*): 380 (M^+), 289, 91. $[\alpha]_D^{25}$ = 1.15, ee 92%, *c* = 1.18, $CHCl_3$ (Lit:[21a] $[\alpha]_D^{25}$ = 1.1, ee 88%, *c* = 2.21, $CHCl_3$).

3-[Bis(t-butoxy carbonyl)methyl]cyclopentanone (3e). Yield : 86%. IR (KBr, cm^{-1}): 2976, 1741, 1718, 1401, 1129. ^{1}H NMR ($CDCl_3$, 400 *MHz*) δ: 1.38 (s, 9H), 1.4 (s, 9H), 1.54 – 1.94 (m, 2H), 2.10 – 2.29 (m, 3H), 2.43 - 2.75 (m, 2H), 3.09 (d, 1H, 9.8 *Hz*). ^{13}C NMR ($CDCl_3$, 100 *MHz*) δ: 27.41, 27.83, 36.22, 38.17, 42.86, 58.51, 81.84, 81.87, 167.4, 167.48, 217. 69. MS (EI, *m/z*): 298 (M^+), 186, 82, 57. $[\alpha]^{25}_D$ = 12.4, ee 90%, *c* = 1.88, $CHCl_3$ (Lit:[21b] $[\alpha]^{25}_D$ = 13.2, ee 96%, *c* = 2.0, $CHCl_3$).

3-[Bis(t-butoxy carbonyl)methyl]cyclohexanone (3f). Yield : 80%. IR (CCl_4, cm^{-1}) :2976, 2928, 1740, 1724, 1366, 1158. ^{1}H NMR ($CDCl_3$, 400 *MHz*) δ: 1.39 (s, 9H), 1.40 (s, 9H), 1.41 – 1.65 (m, 2H), 1.89 - 2.02 (m, 2H), 2.14 – 2.21 (m, 1H), 2.30 – 2.40 (m, 4H), 3.01 (d, 1H, 7.81 *Hz*). ^{13}C NMR ($CDCl_3$, 100 *MHz*) δ: 27.56, 27.94, 28.79, 37.88, 41.1, 45.2, 58.75, 81.85, 81.83, 167.18, 167.28, 210.09. MS (EI, *m/z*): 312 (M^+), 256, 200, 96, 57. $[\alpha]^{25}_D$ = 6.4, ee 94%, *c* = 1.73, $CHCl_3$ (Lit:[21b] $[\alpha]^{25}_D$ = 4.2, ee 65%, *c* = 1.02, $CHCl_3$).

3-(Phenylthio)cyclopentanone (4a). Yield : 95%. IR (CCl_4, cm^{-1}) : 3024, 2945, 1748 (C=O), 1150. ^{1}H NMR ($CDCl_3$, 400 *MHz*) δ: 1.96 -2.23 (m, 2H), 2.26 - 2.37 (m, 2H) 2.45 (dd, 1H, 6.8 & 18.0 *Hz*), 2.59 (dd, 1H, 6.8 & 18.0 *Hz*), 3.85-3.92 (m, 1H), 7.24-7.41 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 *MHz*) δ: 29.18, 36.62, 43.22, 45.09, 127.27, 128.98, 131.81, 134.08, 216.6. MS (EI, *m/z*): 192 (M^+) 110, 83, 55. $[\alpha]^{25}_D$ = 3.17, ee 39%, *c* = 1.0, CCl_4 (Lit:[21c] $[\alpha]^{25}_D$ = 1.8, ee 22.5%, *c* = 1.54, CCl_4).

3-(Phenylthio)cyclohexanone (4b). Yield : 91%. IR (CCl_4,cm^{-1}): 3072, 2928, 1715 (C=O), 1433, 1302, 1213. ^{1}H NMR ($CDCl_3$, 400 *MHz*) δ: 1.67-1.78 (m, 2H), 2.10-2.15 (m, 2H), 2.28-2.66 (m, 4H), 3.39-3.45 (m, 1H), 7.25-7.32 (m, 3H), 7.4 -7.43 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 *MHz*) δ: 23.9, 31.09, 40.75, 45.98, 47.62, 127.66, 128.95, 132.92, 133.08, 208.61. MS (EI, *m/z*): 206 (M^+), 110, 97, 77, 55. $[\alpha]^{25}_D$ = 38.45, ee 54% *c* = 1.6, benzene (Lit:[16] $[\alpha]^{25}_D$ = 16.4, ee 22.5% *c* = 1.0, benzene).

3-(*p*-Methyl-phenylthio) cyclopentanone (4c). Yield : 90%. IR (CCl_4, cm^{-1}) : 3024, 2944, 1747, 1149. ^{1}H NMR ($CDCl_3$, 400 *MHz*) δ: 1.94-2.24 (m, 2H), 2.25-2.30 (m, 2H), 2.34 (s, 3H), 2.46 (dd, 1H, 6.8 & 18.3 *Hz*), 2.55 (dd, 1H, 6.8 & 18.3 *Hz*) 3.77-3.89 (m, 1H), 7.12 (d, 2H, 8.5Hz), 7.3 (d, 2H, 8.5Hz). ^{13}C NMR ($CDCl_3$, 100 *MHz*) δ: 21.08, 29.26, 36.73, 43.80, 45.14, 129.85, 130.26, 132.77, 137.71, 216.43. MS (EI, *m/z*): 206 (M^+), 124, 91, 55, $[\alpha]^{25}_D$ = 3.5, ee 43 % *c* = 1.20, CCl_4 (Lit:[21c] $[\alpha]^{25}_D$ = 1.8, ee 22.8 % *c* = 2.00, CCl_4).

3-(*p*-Methyl-phenylthio)cyclohexanone (4d). Yield : 90%. IR (CCl_4, cm^{-1}) : 2928, 1718, 1485, 1443, 1305, 1273. ^{1}H NMR ($CDCl_3$, 400 *MHz*) δ: 1.65-1.72 (m, 2H), 2.09-2.15 (m, 2H), 2.32 (s, 3H), 2.27 - 2.67 (m, 4H), 3.31-3.37 (m, 1H), 7.11 (d, 2H, 8.3 *Hz*), 7.32 (d, 2H, 8.3 *Hz*). ^{13}C NMR ($CDCl_3$, 100 *MHz*) δ: 21.00, 23.91, 31.12, 40.72, 46.33, 47.65, 129.70, 133.81, 137.98, 208.75. MS (EI, *m/z*) 220 (M^+), 124, 97, 79, 55. $[\alpha]^{25}_D$ = 32.10, ee 45% *c* = 1.2, benzene (Lit:[16] $[\alpha]^{25}_D$ = +70, ee 100% *c* = 2.0, benzene).

4-Nitro-1,3-diphenylbutane-1-one (5). Yield 90%. IR (CCl_4, cm^{-1}) 3056, 2944, 2864, 1692, 1596, 1558, 1491, 1449, 1372, 1225, 1200, 1177, 1097, 1027. ^{1}H NMR ($CDCl_3$, 400 *MHz*) δ: 3.38-3.5 (m, 2H), 4.18-4.24 (m, 1H), 4.63-4.83 (m, 2H), 7.20-7.9 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 *MHz*) δ: 39.42, 41.59, 79.61, 127.53, 127.92, 128.20, 128.74, 128.80, 129.12, 133.69,

136.44, 139.23. MS (EI, *m/z*) 223 (M-46, NO_2). $[\alpha]^{25}_D$ = 21, ee 51% *c* = 1.6, CH_2Cl_2 (Lit:[21d] $[\alpha]^{25}_D$ = 11, ee 27% *c* = 4.0, CH_2Cl_2)

Ethyl 3-(benzylamino)-3-phenylpropanoate (8). Yield 60%. IR (CCl_4, cm^{-1}) 3680, 3568, 3376, 2272, 1654, 1609, 1254, 1024, 732, 704, 646, 617. ^{1}H NMR (Acetone –D_6, 400 *MHz*) δ: 1.33 (t, 3H, 7.3 *Hz*), 2.8 (m, 2H), 3.1 (bs, 1H), 3.64 (t, 1H), 3.94 (s, 2H), 4.26 (q, 2H, 7.3 *Hz*), 7.34 (m, 10H). ^{13}C NMR (Acetone-D_6, 100 *MHz*) δ: 18.41, 33.81, 58, 59.2, 64.39, 126.8, 127.5, 127.9, 128.64, 128.84, 129.67, 130.22, 130.78, 171.8. MS (EI, *m/z*) 283, 239, 148, 106, 91. $[\alpha]^{25}_D$ = 11.5, ee 81 % *c* = 1.14, acetone (Lit:[20] $[\alpha]^{25}_D$ = 5.7, ee 40 %, *c* = 0.5, acetone).

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