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NEW CHIRAL AMINE LIGANDS FOR ENANTIOSELECTIVE SYNTHESIS OF CERTAIN (S)- AND (R)-MONOBACTAMS

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مركبان جديدان من نوع الأمينات ثلاثية المخالب أمكن الاستفاده منهما فى تكاثف مركبى ملح الليثيوم لإينول الاستر مع بنزالدهيد-بارا أنيسيدين إمين ، أمكن التحكم إختياريا فى الناتج الفراغى (S) ، (R) للمونوباكتام الناتج من التكاثف. لوحظ أيضا فى هذه الدراسة أن الأمينات ثلاثية المخالب تزيد معدلات التفاعلات كما تزيد من التوجه الفراغى للناتج.

*Two new tridentate chiral amine ligands **7a** and **7b** mediated the condensation reaction of lithium ester enolate **2** with benzaldehyde p-anisidineimine **3** providing selectively the required (S)- or (R)-monobactam **4**. It is also noticed that the coexistence of **2** and chiral lithium amides that formed -in situ- from **7a,b** is an important factor for the enhancement of the reactivity and enantioselectivity of **2**.*

INTRODUCTION

The importance of the stereodivergent synthesis of both enantiomers of ß-lactams is ever-increasing in connection with the structure-activity relationship studies and the development of new derivatives of this antibiotic.[1,2] In 1995, (S)-1-(4-methoxyphenyl)-3,3-dimethyl-4-phenylazetidin-2-one; (S)-**4** was prepared through condensation of the optically pure ester derived from (+)-camphor derivative with benzaldehyde *p*-anisidineimine; **3**.[3]

Lithium ester enolate was found to be among the powerful carbonucleophiles applied for the formation of carbon-carbon bonds.[4] Application of this reagent into asymmetric reactions relies on a chiral external ligand, which opens the way for a catalytic methodology of the asymmetric reactions.[4,5] The stoichiometric and catalytic asymmetric reactions of **2** with benzaldehyde p-anisidineimine **3** which is based on the formation of a ternary complex have been previously described.[5] The system in this complex comprises three components; a chiral ether ligand **1**, an achiral lithium amide such as lithium diisopropyl amide (LDA), and a lithium ester enolate **2** giving rise to the (S)-monobactam; (S)-**4** in high enantiomeric excess (ee). Another remarkable feature of the ternary complex was the reactivity enhancement of **2**. The reactivity differences indicated that the coexistence of the lithium amide and chiral ether ligand **1** was essential to increase the reactivity of the lithium ester enolate **2**. The structure of the ternary complex could be shown in the assumed structure **5** (Chart 1).

The lithium atom (introduced by arrow) in **5** (Chart 1) is available for the coordination with the benzaldehyde *p*-anisidineimine **3**, providing the origin for high reactivity. The (S)-monobactam **4** could be produced through the postulated complex structure **6**. This hypothesis explains the enhancement of reactivity as well as the sense of enantiofacial selection. It is thus possible to assume that chiral lithium amides that -in situ- formed from the new chiral amine ligands **7a,b**, bearing coordinating moieties are capable for complexation with lithium ester enolate.

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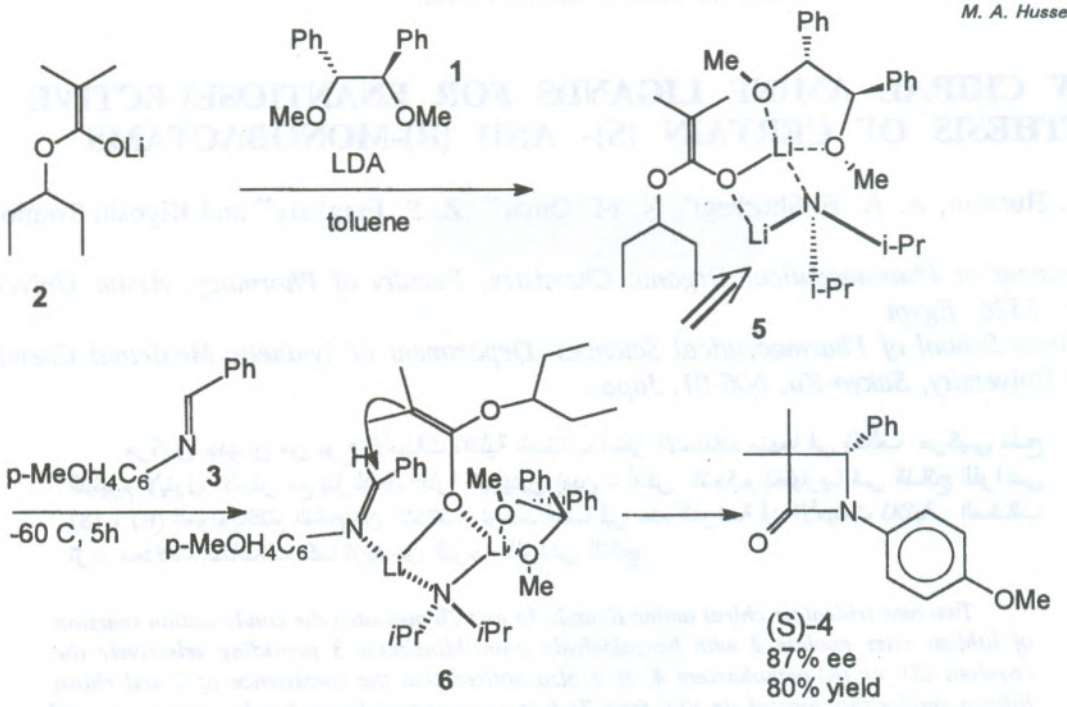


Chart 1: Condensation of **2** with **3** through a ternary complex reagent **5**.

Complexes of lithium ester enolate with lithium amides derived from 7a,b

Two types of complexes are assumed to be formed from the reaction of lithium ester enolate **2** with lithium amides derived from **7a** or **7b**, analogous to the ternary complex **5** (Chart 2).

Type **1** is characterized by the presence of the terminal Li-N bond, available from amine **7a**, while in type **2** which is derived from **7b**, the secondary amino group separates the two atoms responsible for chelation. The absolute configuration (1*R*,2*R*) in ligand **1** was changed to the (1*S*,2*S*) type in ligand **7b**. This idea is motivated by the observation that all the reported cases for the enantioselective syntheHxs of **4** involve the use of the (1*R*,2*R*)-1,2-diphenylethane derivatives, whereas, no relevant information is available for the use of a ligand having the (1*S*,2*S*)-configuration in this synthesis.. Thus, upon reacting **7a,b** with lithium, their derived lithium amides can be considered not only as chiral ligands, but also as versions of lithium diisopropylamide (LDA), that is widely used in organic syntheses as a strong base. Formation of such tentative types of complexes can provide certain spatial arrangements, in which, the introduced lithium atoms can lead to enantiofacial selectivity.

Synthesis of the chiral amine ligands 7a,b

2-Methoxyethanol **8**, was esterified to give its *p*-toluenesulfonate ester **9**,[6] which was then allowed to react with (-)-(2R)-2-(isopropylamino)-2-phenylethanol, **10** to give the chiral amine ligand **7a** (Chart 3).

Ligand **7b** (Chart 4) on the other hand was prepared starting from the synthesized enantiomerically pure (*1R,2R*)-diol **11**.[7,8] The diol **11** was converted to the di-*p*-toluenesulfonate **12**, which was allowed to react with sodium azide affording the diazide **13**. Compound **13** was then reduced to the optically pure (-)-(*1S,2S*)-1,2-diphenylethane-1,2-diamine **14**.[9-12] The diamine **14** was monoacylated in the presence of dicyclohexycarbodiimide (DDC) to afford **15** which was dimethylated to **16**. Reduction of the amide carbonyl function of **16** was then effected by lithium aluminum hydride to give **7b**.

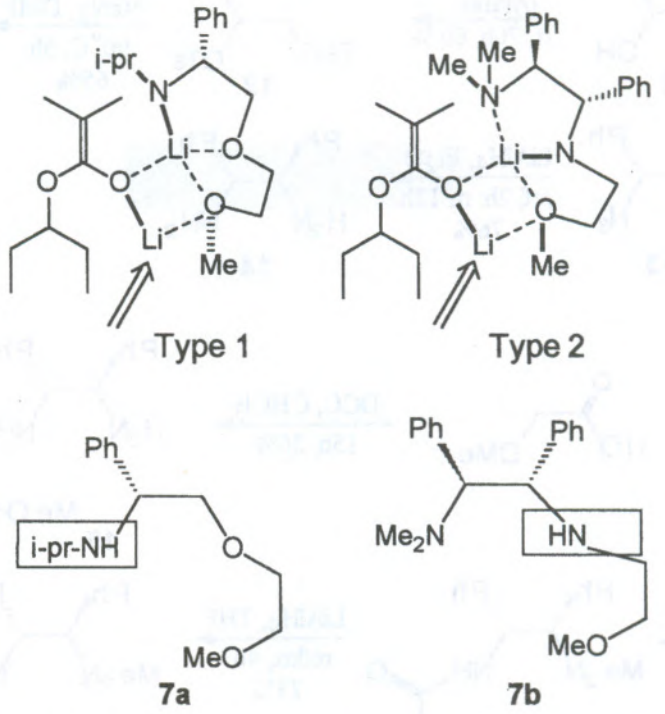


Chart 2: Chiral amine ligands **7a,b** and their complexes with **2**.

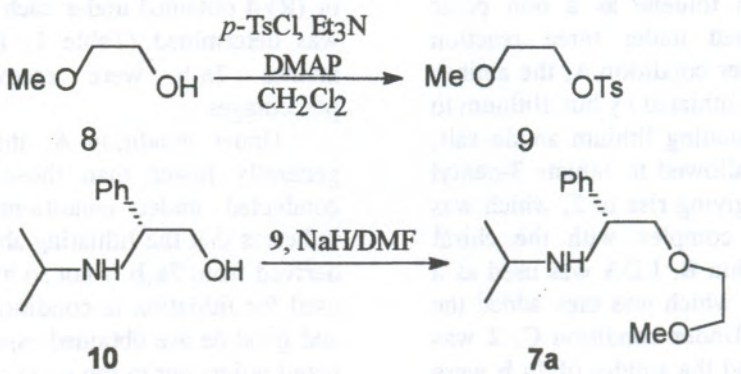


Chart 3: Synthesis of **7a**.

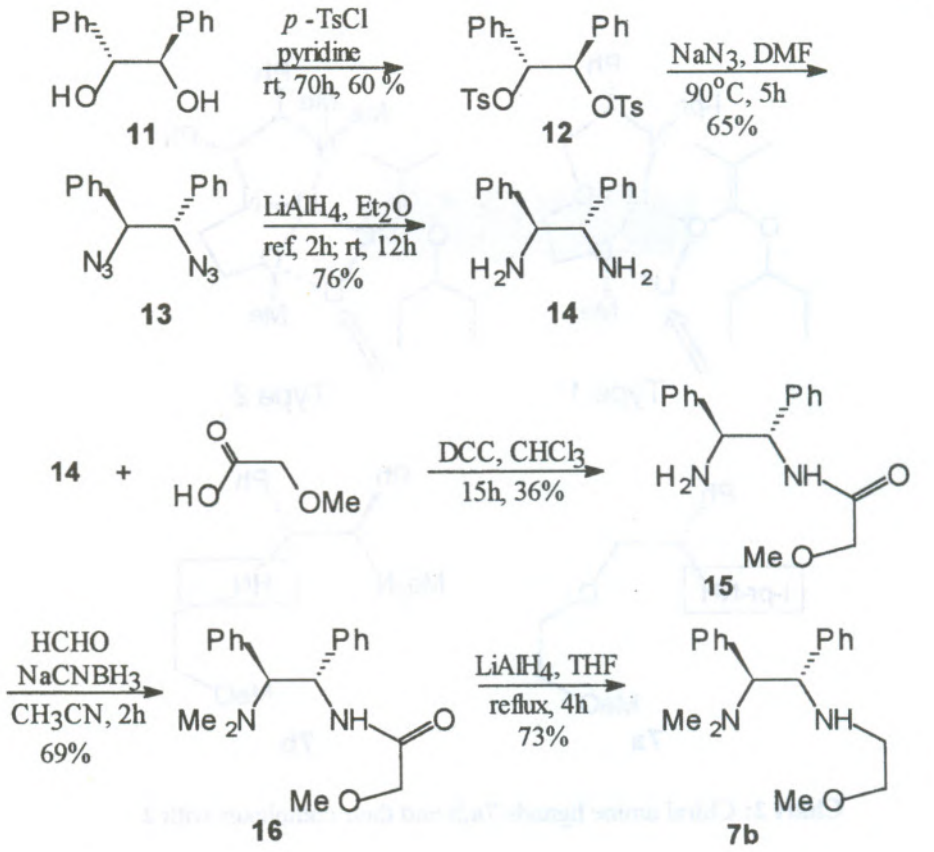


Chart 4: Synthesis of **7b**

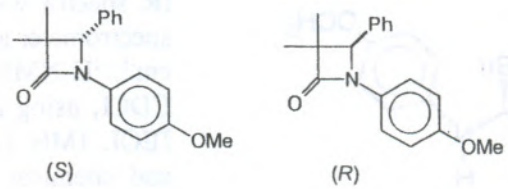
Stoichiometric evaluations of 7a,b as chiral ligands

The asymmetric reactions of lithium ester enolate **2** with **3** in toluene as a non polar solvent was examined under three reaction conditions **A-C**. Under condition **A**, the amines **7a,b** were separately lithiated by butyllithium to generate the corresponding lithium amide salt. The latter was then allowed to lithiate 3-pentyl 2-methylpropanoate giving rise to **2**, which was capable to make a complex with the chiral amine. Under condition **B**, LDA was used as a base to generate **2** to which was then added the proper amine **7a,b**. Under condition **C**, **2** was generated by LDA and the amides of **7a,b** were generated by butyllithium prior mixing together to form the required complex. The complexes formed under the aforementioned reaction conditions were allowed to condense with **3** and the reactions were monitored by tlc until the disappearance of **3**. The ee of the resulting (S)-**4** or (R)-**4** obtained under each reaction condition was determined (Table 1, Fig.1). The chiral amines **7a,b** were recovered in varied percentages.

Under condition **A**, the yields of **4** are generally lower than those of the reactions conducted under conditions **B** or **C**. This indicates that the lithiating ability of the amides derived from **7a,b** is not so high. When LDA is used for lithiation in condition **B**, higher yields and good ee are obtained especially by **7b**. The result points out to the good coordinating ability of ligand **7b** in the presence of LDA. Further improvement in reactivity and selectivity was obtained by using condition **C**.

Table 1: Asymmetric synthesis of 4 under different experimental conditions

Reaction	7a	7b
Condition A:		
reaction time (h)	12	20
yield (%)	80	14
ee (%)	15, (S)-form	30, (R)-form
Condition B:		
reaction time (h)	7	3
yield (%)	81	92
ee (%)	12, (S)-form	73, (R)-form
Condition C:		
reaction time (h)	3	2
yield (%)	93	96
ee (%)	42, (S)-form	74, (R)-form
Catalytic:		
reaction time (h)	-	20
yield (%)	-	86
ee (%)	-	52, (R)-form



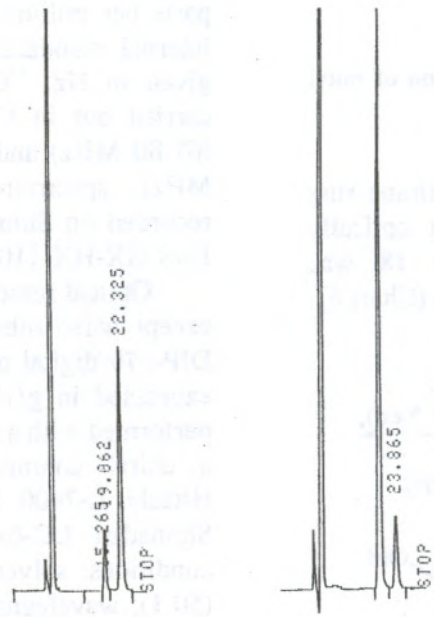


Fig. 1: The HPLC profile of (S)-4 and (R)-4 enantiomers.

Catalytic evaluations of 7b as a promising chiral ligand

Upon using catalytic amounts of **7b**, the monobactam (R)-**4** could be obtained in a good ee result (Table 1).

The reaction of benzaldehyde *p*-anisidineimine **3** with butyl lithium in toluene, as previously published, affording the racemic N-(1-phenyl-1-pentyl)-*p*-anisidine **17**.[4] The results of using a catalytic amount of **7b** in this reaction (Chart 5) succeeded to provide an enantiomeric excess of (R)-**17**.

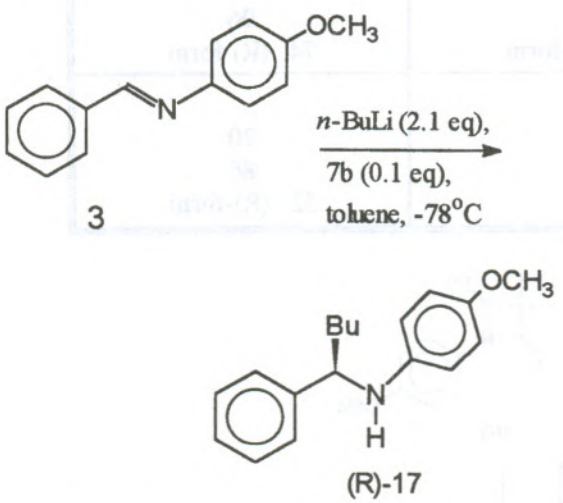


Chart 5: Catalytic asymmetric addition of butyl lithium on imine **3**.

Furthermore, the asymmetric oxirane ring opening by phenyl lithium to form optically active (*1R,2S*)-2-phenylcyclohexanol **18** was achieved by catalytic application of **7b** (Chart 6).

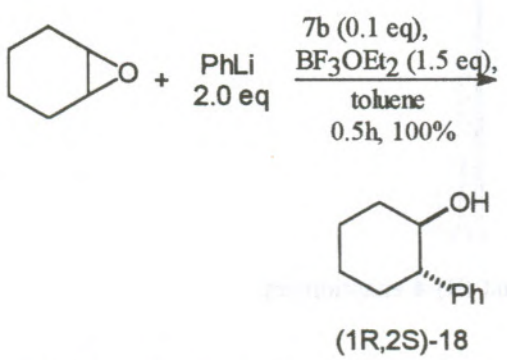


Chart 6: Catalytic asymmetric oxirane ring opening.

From the previously mentioned examples it can be concluded that, although **7b** was used in 0.1 eq, the results indicate that, it is able to induce enatioeselectivity giving rise to the required optically active products.

EXPERIMENTAL

All melting points were determined on a hot stage melting point apparatus and are uncorrected. Precoated silica gel plates (Kieselgel 60 GF, Merck, Germany) were used for monitoringof the reactions; visualization was effected by UV, iodine and/or heating with phosphomolybdic acid. Elemental microanalyses were performed by the microanalytical center, Graduate School of Pharmaceutical Sciences, Kyoto University, Japan. BW-200 silica gel (Fuji Silysia) was employed for separations and purifications using column chromatography. The IR spectra were taken on a Shimadzu IR-435 spectrometer and wave numbers are expressed as cm^{-1}. ^{1}H-NMR (PMR) spectra were recorded in $CDCl_3$ using a JEOL EX-270 (270 MHz), and JEOL JMN LA-500 (500 MHz) spectrometers and chemical shifts are reported in δ-scale in parts per million using tetramethylsilane as an internal standard. Coupling constants (J) are given in Hz. ^{13}C-NMR (CMR) spectra were carried out in $CDCl_3$ using a JEOL EX-270 (67.80 MHz) and JEOL JMN LA-500 (125.65 MHz) spectrometers. Mass spectra were recorded on Shimadzu GCMS-QP5000, JEOL-JMS-HX-HX-110A mass spectrometers.

Optical rotations were measured in $CHCl_3$, except when otherwise stated, with a JASCO DIP-370 digital polarimeter (concentrations are expressed in g/100 ml). HPLC analyses were performed with a Hitachi 655 A apparatus, using a chiral column (Daicel Chiralcel OD-H); Hitachi L-7400 UV source and recorded on Shimadzu LC-6A unit under the following conditions: solvent system, hexane/isopropanol (50:1); wavelegnth, 250 nm; and flow rate, 0.5 ml/min. The required intermediates were prepared according to conventional procedures, such as:

3-Pentyl 2-methylpropanoate, **2**, (52%) as a colorless oil, as reported (ref. 6, 13).

N-Benzylidene-4-methoxyaniline, **3**, (83%) as colorless leaflets, m.p 70-71°; as reported (ref. 14, 15).

(±)-1-(4-Methoxyphenyl)-3,3-dimethyl-4-phenylazetidin-2-one, (±)-4, (98%) as colorless needles, m.p 147-8°, as reported (ref. 4).

(+)-(*S*)-1-(4-Methoxyphenyl)-3,3-dimethyl-4-phenylazetidin-2-one, (S)-4, (81 %), pale yellow crystals, m.p 99-100°, $[\alpha]_D^{25}$ +116.6° (c 0.96, $CHCl_3$), as reported (ref. 4).

2-(Methoxyethyl) tosylate, **9** (82%) as a colorless oil; as reported (ref. 6).

(+)-(*1R,2R*)-1,2-Diphenylethane-1,2-diol, **11** (94% and 100% ee) as colorless prisms, m.p 147.5-148.5° and $[\alpha]_D^{25}$ + 92.1° (c 1.0); as reported (ref. 7,8).

(-)-(*1R,2R*)-1,2-Diphenyl-1,2-ditosyloxyethane, **12**, (60%) as white crystals; m.p 131-133° (dec.), $[\alpha]_D^{25}$-40.2° (c 0.885); as reported (ref. 9-11).

(+)-(*1S,2S*)- 1,2-Diazido-1,2-diphenylethane, **13**, (65%); $[\alpha]_D^{25}$ +161.4° (c 1.475); as reported (ref. 9-11)

(-)-(*1S,2S*)-1,2-Diamino-1,2-diphenylethane, **14**, (78%); mp 85-6°, $[\alpha]_D^{25}$ -106.3° (c 1.03, MeOH); as reported (ref. 9-11).

(±)-N-(1-Phenyl-1-pentyl)-*p*-anisidine, **17**, (100%) as a pale yellow oil, bp 210°/1.5 mmHg, as reported (ref. 16).

(±)-2-Phenyl cyclohexanol, **18**, (97%), a colorless crystalline product, R_f 0.37 (phH/EtOAc, 9/1), as reported (ref. 17).

(-)-(*1R*)-1-(Isopropylamino)-2-(2-methoxyethoxy)-1-phenylethane (7a)

A mixture of (-)-(2*R*)-(isopropylamino)-2-phenylethanol, **10** (1.79 g, 10 mmol) and NaH (480 mg, 12 mmol) in DMF (10 ml) was stirred under argon at ambient temperature for 30 min, then cooled to 0°. A solution of 2-methoxyethyl tosylate, **9** (2.76 g, 12 mmol) in DMF (4 ml) was added dropwise. The reaction mixture was stirred at ambient temperature for 3 h, cooled to 0°, quenched with ice-water and extracted with ether. The combined organic extract was washed with brine and dried (K_2CO_3). Concentration and column chromatography ($CHCl_3$/MeOH = 3%) followed by distillation at 150°/1.0 mmHg gave compound **7a**, 2.2 g (93%) as a colorless oil; $[\alpha]_D^{25}$ -65.0 (c 1.0) and R_f 0.51 ($CHCl_3/CH_3OH$ = 4/1). PMR: 0.98 (3H, d, CH_3, J= 6.41, one Me of $CHMe_2$), 1.04 (3H, d, CH_3, J= 6.10, one Me of $CHMe_2$), 1.73 (1H, brs, NH), 2.61-2.68 (1H, m, C<u>H</u>Me_2), 3.38 (3H, s, OMe), 3.34-3.65 (6H, m, <u>$CH_2CH_2OCH_2$</u>) 4.04-4.06 (1H, m, NCH), and 7.23-7.47 (5H, m, C_6H_5). CMR δ: 22.07, 24.41, 45.87, 58.99 59.86, 70.29, 71.73, 76.56, 121.18, 127.61, 128.22, 141.49. IR (neat): 3300, 3050, 2900, 1600, 1450, 1360, 1100, 760, 700. MS *m/z*: 238 (M^+ +1), 236, 162, 148. $C_{14}H_{23}NO_2$: Calcd: C, 70.85; H, 9.77; N, 5.90. Found: C, 71.08; H, 9.95; N, 5.67.

(-)-(1S,2S)-1-Amino-1,2-diphenyl-2-(methoxymethylenecarboxamido) ethane (15)

To a solution of (-)- (1S,2S)-1,2-Diphenylethane-1,2-diamine, **14** (5.0 g, 23.5 mmol) and 2-methoxyacetic acid (2.1 g, 23.5 mmol, 1.0 eq) in $CHCl_3$ (100 ml) was added a solution of dicyclohexylcarbodiimide (4.8 g, 23.5 mmol, 1.0 eq) in $CHCl_3$ (20 ml) with stirring at -5°. The reaction mixture was stirred at -5° for 0.5h and then at rt for 15 h. The precipitated N,N-dicyclohexyl urea was removed by filtration and the organic solution was washed with 1 M $NaHCO_3$ solution (40 ml X 3), brine (40 ml X 3), dried (Na_2CO_3), filtered, and evaporated. Column chromatography (SiO2, 300 g, $CHCl_3$/ CH_3OH, 5-20%) gave the product (2.4 g, 36%), as colorless powder of mp 82-83°. PMR δ: 3.34 (s, 3H, OMe), 3.76 (d, 1H, C<u>H</u>NH_2, J= 15.25 Hz), 3.89 (d, 1H, C<u>H</u>NH, J= 15.25), 4.43 (d, 1H, CH_2, J= 3.66), 5.15-5.18 (m, 3H, 1H of CH_2, and NH_2), 7.10-7.72 (m, 10H, Ar), and 7.73 (s, 1H, NH). CMR δ: 57.95 (OMe), 59.38 ($CHNH_2$), 59.66 (CHNH), 72.10 (CH_2), 126.45-141.93 (Ar), and 169.29 (C=0). IR (nujol): 3300, 3050, 2900, 1660, 1520, 1450, 1200, 1150, 770, 700. MS m/z: [M+1] 285. Anal: Cald for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.62; H, 7.17; N, 9.57.

(-)-(1S,2S)-1-Dimethylamino-1,2-diphenyl-2-(methoxymethylenecarbox-amido) ethane (16)

To a solution of (-)-(1S,2S)-1-Amino-1,2-diphenyl-2-(methoxymethylene-carboxamido) ethane, **15** (3.6 g, 12.67 mmol) and formalin, 37% (1.54 g 38 mmol, 3 eq), in acetonitrle (12 ml) at 0° was added sodium cyanoborohydride (2.4 g, 38 mmol, 3 eq). The reaction mixture was stirred for 15 min at rt, then glacial acetic acid was added till the solution tested neutral (pH paper). The mixture was stirred for 2h at rt with addition of glacial acetic acid at intervals to maintain the solution nearly neutral. The solvent was removed by evaporation under vacuum. 2 N KOH solution (15 ml) was added and the mixture was extracted with ether (30 ml X 3). The combined ethereal extract was washed with 0.5 N KOH solution (20 ml X 3), dried (K_2CO_3), filtered and evaporated to afford colorless oil (5.1 g). Column chromatography (SiO_2, 150 g, $CHCl_3$/ CH_3OH, 1-10%) gave the product (2.7 g, 69%), as white powder of mp 108°. PMR δ: 2.17 (s, 6H, $2CH_3$), 3.48 (s, 3H, OMe), 3.73 (d, 1H, CHN, J= 10.3 Hz), 3.93 (s, 2H, CH_2), 5.21-5.25 (dd, 1H, CHNH, J= 5.18, J= 5.18), 7.04-7.25 (m, 10H, Ar), and 7.83 (s, 1H, NH). CMR δ: 40.92 (Me_2), 53.73 (OMe), 59.30 (CH_2), 72.45 (CHN), 73.51, 126.83-140.76 (Ar), and 169.45 (C=0). IR (nujol): 3300, 3050, 2900, 1670, 1500, 1450, 1110, 770, 700. MS m/z: [M+1] 313. Anal: Cald for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C; 73.23, H, 7.70; N, 8.95.

(-)-(1S,2S)-1-N,N-Dimethylamino-2-(2-methoxy-xethylamino)-1,2-diphenyl-ethane (7b)

Under Ar, to a stirred suspension of $LiAlH_4$ (356 mg,9.6 mmol, 1 eq) in dry THF (35 ml) at 0° was added a solution of (-)- (1S,2S)-1-Dimethylamino-1,2-diphenyl-2-(methoxymethylenecarboxamido) ethane **16** (3.0 g, 9.6 mmol) in dry THF (15 ml) dropwise. The reaction mixture was refluxed for 4 h. The resultig mixture was treated with ice-cold water (0.4 ml, mmol) dropwise, 15% NaOH solution (0.4 ml) and then water (1.2 ml). The solid was filtered off and the organic layer was dried (Na_2SO_4), filtered and evaporated to afford a pale yellow oil (3.2 g). Column chromatography (SiO_2, 100 g, $CHCl_3/CH_3OH$, 1-10%) afforded the product which by distillation (165°, 0.7 mmHg) gave **7b** (2.1 g, 73%), as colorless oil of $[\alpha]_D^{25}$ -55° (c 0.835, $CHCl_3$). PMR δ: 1.68 (br.s., 1H, CHNH), 2.18 (s, 6H, $2CH_3$), 2.56-2.64 (m, 1H, one of CH_2N), 2.69-2.74 (m, 1H, one of CH_2N), 3.36 (s, 3H, OMe), 3.40-3.50 (m, 2H, CH_2O), 3.72 (d, 1H, CHN, J= 10.3 Hz), 4.09 (d, 1H, CHNH, J= 10.37 Hz), and 6.99-7.25 (m, 10H, Ar). CMR δ: 40.60 (Me_2N), 45.89 (OMe), 58.62 (CH_2N), 62.82 (CH_2O), 72.04 (CHN), 74.08 (CHNH), and 126.74-141.48 (Ar). IR (nujol): 3300, 3050, 2800, 1450, 1150, 750, 700. MS m/z: [M+1] 299.

Asymmetric syntheses of 1-(4-methoxyphenyl)-3,3-dimethyl-4-phenyl-azetidin-one (4)

1- Using ligands 7a,b as bases (Condition A)

To the chiral amines; **7a,b** (1.1 mmol, 2.2 eq) in toluene (5 ml), at -78° under argon, was added butyl lithium (70.4 mg, 1.1 mmol, 2.2 eq). After stirring for 0.5 h, 3-pentyl 2-methylpropanoate; **2** (158 mg, 1.0 mmol, 2.0 eq) in toluene (2.5 ml) was added dropwise. The mixture was stirred for 1 h at -20°, then a solution of *p*-anisidineimine; **3** (105 mg, 0.5 mmol, 1.0 eq) in toluene (2.0 ml) was added dropwise. The reaction mixture was stirred at -20° for the specified time, quenched with 10% HCl (10 ml) while stirring at ambient temperature for 10 min. The reaction mixture was extracted with ethyl acetate and the combined organic extract was washed with water, saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). Concentration followed by column chromatography (hexane/ether 5:1) gave **4**. The ligands were recovered for reuse from the aqueous phase by treatment with 10% sodium hydroxide solution till alkaline and extraction with chloroform. PMR ($CDCl_3$): 0.84 and 1.51 (each 3H, s, Me) 3.76 (3H, s, OMe), 4.77 (1H, s, CH), 6.79-6.83 (2H, m, C_6H_4) 7.1-7.4 (7H, m, 5H of C_6H_5 and 2H of C_6H_4). CMR δ: 17.9, 22.8, 55.2, 55.4, 66.5, 114.2, 118.4, 126.6, 128.6, 127.9, 131.4, 135.6, 155.8, 170.8. IR (nujol): 1730, 1510, 1460, 1240, 830, 730, 690.

entry 1: Compd. 4; 112 mg (80%), colorless needles, m.p 136-7°, $[\alpha]_D^{25}$ +20.9° (c 0.925, $CHCl_3$). The ee was determined by HPLC analysis to be 15% under the following conditions: Daicel Chiralcel OD-H, hexane-iPrOH 50:1, 0.5 ml/min, 250 nm, 22.1 min (42.5 %, *R*): 26.1 min (57.4 %, *S*). Ligand **7a** was recovered in 95%.

entry 2: Compd. 4; 20 mg (14%), colorless needles, mp 130-3°, $[\alpha]_D^{25}$ -36.8° (c 0.5, $CHCl_3$). The ee was determined by HPLC analysis to be 30% under the following conditions: Daicel Chiralcel OD-H, hexane-iPrOH 50:1, 0.5 ml/min, 250 nm, 18.1 min (30.3 %, *R*): 21.1 min (16.5 %, *S*). Ligand **7b** was recovered in 93%.

2-Using diisopropylamine as the base (Condition B)

To diisopropylamine (0.154 ml, 1.1 mmol, 2.2 eq) in toluene (5 ml) at -78° under argon was added butyl lithium (70.4 mg, 1.1 mmol, 2.2 eq). After stirring for 0.5 h, a solution of 3-pentyl isobutyrate; **2** (158 mg, 1.0 mmol, 2.0 eq) in toluene (1.5 ml) was added dropwise. The mixture was stirred for 0.5 h at -20°, cooled to -78°, the chiral amine derivative; compds **7a,b** (1.1 mmol, 2.2 eq), in toluene (1.5 ml), was added dropwise and the mixture was stirred at -20° for 1 h. The reaction mixture was stirred at -78° for 20 min, and a solution of *p*-anisidine imine; **3** (105 mg, 0.5 mmol) in toluene (1.5 ml) was added dropwise. Stirring of the mixture was continued at -20° for the specified time, quenched with 10% HCl (10 ml). Further workup of the reaction mixture was effected to give **4**.

entry 1: Compd. 4; 113 mg (81%) colorless needles, mp 139-40°, $[\alpha]_D^{25}$ +13.7° (c 0.9, $CHCl_3$). The ee was determined by HPLC analysis to be 12% under the following conditions: Daicel Chiralcel OD-H, hexane-iPrOH 50:1, 0.5 ml/min, 250 nm, 21.5 min (32.2 %, *R*): 25.2 min (40.7 %, *S*). Ligand **7a** was recovered in 93.5%.

entry 2: Compd. 4; 128 mg (91.4%) colorless needles, mp 92-3°, $[\alpha]_D^{25}$ -101.6° (c 0.81, $CHCl_3$). The ee was determined by HPLC analysis to be 73% under the following conditions: Daicel Chiralcel OD-H, hexane-iPrOH 50:1, 0.5 ml/min, 250 nm, 19.4 min (58.0 %, *R*): 22.9 min (9.2 %, *S*). Ligand **7b** was recovered in 100%.

3- Using chiral lithium amides (Codition C)
Method 1

To the chiral ligand; compounds **7a,b** (1.3 mmol, 2.6 eq) in toluene (6 ml), at -78° under argon was added butyl lithium (70.4 mg, 1.1 mmol, 2.2 eq), with stirring for 0.5 h. A solution of 3-pentyl 2-methylpropanoate; **2** (158 mg, 1.0 mmol, 2.0 eq) in toluene (2.5 ml) was added dropwise. The mixture was stirred for 1 h at -78°, butyl lithium (70.4 mg, 1.1 mmol, 2.2 eq) was then added dropwise and stirring was continued for further 0.5 h. A solution of *p*-anisidineimine; **3** (105 mg, 0.5 mmol, 1.0 eq) in toluene (2.0 ml) was added dropwise and the reaction mixture was stirred at -20° for the specified time, quenched with 10% HCl (10 ml). Further work up of the reaction mixture was effected to provide **4**, 35 mg (25%), colorless needles, mp 110-12°, $[\alpha]_D^{25}$ -46.0° (c 0.55, $CHCl_3$). The ee was determined by HPLC analysis to be 40% under the following conditions: Daicel Chiralcel OD-H, hexane-iPrOH 50:1, 0.5 ml/min, 250 nm, 17.9 min (61.2 %, *R*): 21.1 min (26.1 %, *S*). Ligand **7b** was recovered in 92%.

Method 2

To diisopropylamine (0.308 ml, 2.2 mmol, 4.4 eq) in toluene (5 ml) at -78° under argon was added butyl lithium (140.8 mg, 2.2 mmol, 4.4 eq). After stirring for 0.5 h, a mixture of 3-pentyl 2-methylpropanoate; **2** (158 mg, 1.0 mmol, 2.0 eq) and the chiral amine derivative **7a** (1.1 mmol, 2.2 eq) in toluene (3.0 ml) was added dropwise. The mixture was stirred for 1.5 h at -20° followed by 20 min at -78°. A solution of *p*-anisidineimine; **3** (105 mg, 0.5 mmol) in toluene (1.5 ml) was added dropwise and the mixture was stirred at -20° for 3 h, quenched with 10% HCl (10 ml) and stirred for 10 min at

ambient temperature. Further work up of the reaction mixture was effected to afford **4**, 137 mg (97.5%), as colorless needles, mp 137-8°, $[\alpha]_D^{25}$ +15.4° (c 0.5, $CHCl_3$). The ee was determined by HPLC analysis to be 13% under the following conditions: Daicel Chiralcel OD-H, hexane-iPrOH 50:1, 0.5 ml/min, 250 nm, 19.8 min (14.4 %, *R*): 23.0 min (18.8 %, *S*). Ligand **7a** was recovered in 62.5%.

Method 3

Mixture a: To diisopropylamine (0.154 ml, 1.1 mmol, 2.2 eq) in toluene (5 ml) at -78° under argon, was added butyl lithium (70.4 mg, 1.1 mmol, 2.2 eq) with stirring for 0.5 h. A solution of 3-pentyl 2-methylpropanoate; **2** (158 mg, 1.0 mmol, 2.0 eq) in toluene (1.5 ml) was added dropwise and the mixture was stirred for 1 h at -20°, then cooled to -78°.

Mixture b: To the appropriate chiral ligand; compds **7a,b** (1.3 mmol, 2.6 eq) in toluene (5 ml) at -78° under argon was added butyl lithium (70.4 mg, 1.1 mmol, 2.2 eq), dropwise and stirring was continued for 1h at -78°. The resulting **mixture b** was added dropwise to **mixture a** while the temperature was kept at -78° during the addition. After stirring at -20° for 1h, and at -78° for 20 min, a solution of *p*-anisidineimine; **3** (105 mg, 0.5 mmol) in toluene (1.5 ml) was added dropwise. The reaction mixture was stirred at -20° for the specified time, quenched with 10% HCl (10 ml) and stirring was continued for 10 min at ambient temperature. Further work up of the reaction mixture was effected to provide **4**.

entry 1: Compd. 4; 130 mg (93%) colorless needles, m.p 111-3°, $[\alpha]_D^{25}$ +56.3° (c 0.75, $CHCl_3$). The ee was determined by HPLC analysis to be 42% under the following conditions: Daicel Chiralcel OD-H, hexane-iPrOH 50:1, 0.5 ml/min, 250 nm, 21.8 min (28.8 %, *R*): 25.7 min (71.1 %, *S*). Ligand **7a** was recovered in 100%.

entry 2: Compd. 4; 134 mg (96%) colorless needles, mp 96-7°, $[\alpha]_D^{25}$ -100.9° (c 0.95, $CHCl_3$). The ee was determined by HPLC analysis to be 74%
under the following conditions: Daicel Chiralcel OD-H, hexane-iPrOH 50:1, 0.5 ml/min, 250 nm, 20.2 min (75.0 %, *R*): 23.6 min (11.3 %, *S*). Ligand **7b** was recovered in 90%.

Catalytic asymmetric synthesis of 4

To diisopropylamine (0.154 ml, 1.1 mmol, 2.2 eq) in toluene (5 ml) at -78° under argon, was added butyl lithium (70.4 mg, 1.1 mmol, 2.2 eq) with stirring for 0.5 h. A solution of 3-pentyl 2-methylpropanoate; **2** (158 mg, 1.0 mmol, 2.0 eq) in toluene (1.5 ml) was added. The mixture was stirred for 0.5 h at -20°, cooled to -78°, the amine derivative; compds **7b** (0.05 mmol, 0.1 eq), in toluene (1.5 ml), was added dropwise and the reaction mixture was stirred at -20° for 1 h. After stirring at -78° for 20 min, a solution of benzaldehyde *p*-anisidineimine; **3** (105 mg, 0.5 mmol) in toluene (1.5 ml) was added dropwise. The reaction mixture was stirred at -20° for 20 h, then quenched with 10% HCl (10 ml) and stirring was continued for 10 min at ambient temperature. Further workup of the reaction mixture was effected to give **4**, 120 mg (86%) pale yellow solid, mp 112-5°, $[\alpha]_D^{25}$ -69.5° (c 1.065, $CHCl_3$). The ee was determined HPLC analysis to be 52% under the following conditions: Daicel Chiralcel OD-H, hexane-iPrOH 50:1, 0.5 ml/min, 250 nm, 20.6 min (76.1 %, *R*): 24.2 min (23.8 %, *S*). Ligand **7b** was recovered in 100%.

Catalytic asymmetric synthesis of (R)-N-(1-phenyl-1-pentyl)-*p*-anisidine (17)

To a mixture of *p*-anisidine imine; **3** (105 mg, 0.5 mmol) and the chiral ligand; **7b** (0.05 mmol, 0.1 eq) in toluene (10 ml) at -78° under argon was added butyl lithium (67.3 mg, 1.05 mmol). The reaction mixture was stirred at -78° for 1 h. Further work up of the reaction mixture was effected to give compd. (*R*)-**17**, 135 mg (100%), a pale yellow oil, bp 210°/1.5 mmHg. The ee was determined by HPLC analysis to be 22% under the following conditions: Chirpak AD, hexane-iPrOH 40:1, 0.25 ml/min, 250 nm,

47.8 min (29.6 %, *R*): 51.8 min (46.3 %, *S*). Ligand **7b** was recovered in 100%. PMR ($CDCl_3$): 0.88 (3H, t, J= 7.32, 7.02, CH_3), 1.26-1.39 (4H, m, CH_2CH_2), 1.72-1.80 (2H, m, CH_2), 3.68 (3H, s, OMe), 3.81 (1H, brs, NH), 4.21 (1H, t, J= 6.7, CH), 6.44-6.47 (2H, m, C_6H_4), 6.66-6.69 (2H, m, C_6H_4), 7.18-7.33 (5H, m, C_6H_5). CMR δ: 13.97, 22.60, 28.49, 38.74, 55.74, 59.06, 114.39, 114.74, 126.41, 126.76, 128.47, 141.80, 144.58, 151.77. IR (neat): 3400, 3050, 2900, 1510, 1240, 1040, 820, 730, 700.

Catalytic asymmetric synthesis of (*1R,2S*)-2-phenyl cyclohexanol (18)

To a solution of the chiral ligand; **7b** (0.05 mmol, 0.1 eq) in toluene (5 ml) at -78° under argon was added phenyl lithium (84 mg, 1.0 mmol) with stirring at -78° for 20 min. A solution of cyclohexene oxide (49 mg, 0.5 mmol) in toluene (1.5 ml) was added, followed by a solution of boron trifluoride diethyletherate (106 mg, 0.75 mmol) in toluene (1.5 ml) dropwise over 5 min. The reaction mixture was stirred at -78° for 0.5 h. Further work up of the reaction mixture was effected to afford compd. (*1R,2S*)-18, 88 mg (100%) a colorless crystalline product. $[\alpha]_D^{31}$-2.8° (c 1.0, benzene). The ee was determined by HPLC analysis to be 5% under the following conditions: Daicel Chiralcel AD, hexane-iPrOH 100:1, 1.0 ml/min, 250 nm, 28.5 min (47.4 %,): 30.8 min (52.5 %). Ligand **7b** was recovered in 100%. PMR ($CDCl_3$): 1.25-1.57 (5H, m, CH_2CH_2CH), 1.75-1.87 (3H, m, CH_2CH), 2.11-2.17 (1H, m, CHPh), 2.40-2.45 (1H, m, CHOH), 3.65-3.68 (1H, m, OH) and 7.23-7.40 (5H, m, C_6H_5). CMR δ: 25.03, 26.02, 33.28, 34.40, 53.19, 74.37, 126.79, 127.87, 128.72, 143.24. IR (nujol): 3400, 1600, 1450, 1300, 1050, 740, 700.

Conclusion

The most striking result encountered in this work involves the behavior of the new chiral ligand **7b**. Under all reaction conditions the monobactam formed was preferentially of the (R)-configuration; (R)-**4**. This observation constitutes the first case in which (R)-**4** can be obtained in a high enantiomeric excess and reflects the remarkable enantioselectivity of the (1S,2S) configuration of diphenylethane derivative for the production of monobactam **4** in the (R)-configuration. In addition, **7b** can be considered as a promising prototype ligand for catalytic reactions.

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* To whome all correspondence

** Dedicated for the memory of late Prof. Dr. Nabil M. Omar and Dr. Zeinab S. Farghaly.