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Novel chiral C_1-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinolines: synthesis, resolution, and applications in catalytic enantioselective reactions

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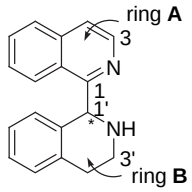
ABSTRACT

A straightforward synthesis of a structurally constrained C_1-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline **1** is described. Resolution of this compound has been achieved successfully. The preparation of chiral *N*-alkyl, urea, and thiourea derivatives as potential new chiral ligands, based on the parent compound **1**, is reported. Chiral compound **1** induced very good selectivity and yield in the addition of either Et_2Zn (85% ee, 96% yield) or nitromethane (85% ee, 60% yield) to benzaldehyde.

1. Introduction

Chiral diamines[1] have been used successfully as ligands in various enantioselective reactions such as hydrogenation,[2] hydrosilylation,[3] conjugate addition,[4] and allylic substitution.[5] The most commonly used chiral diamines are based upon C_2-symmetric cyclohexane-1,2-diamine, 1,2-diphenylethan-1,2-diamine, and 2,2′-diaminobinaphthyl derivatives.[6] We have been involved in developing the chemistry of 1,1′-bisisoquinolines for the past few years[7] and are interested in their use as specialized 1,2-diamino chiral ligands since they provide a geometrically constrained chiral environment due to the presence of stereogenic centers at C1 and/or C1′.[7] Interestingly, the use of 1,1′-bisisoquinolines as chiral ligands has been scarcely reported although they present structurally robust motifs amenable for further stereoelectronic tuning and optimization. Poor to modest enantioselectivities have been reported.[8] For example, chiral 1,1′-bisisoquinolines and their derivatives (i.e., *N*,*N*′-dioxide or carbenes) were used as ligands for: (i) asymmetric conjugate addition of diethylzinc to cyclohexanone (10% ee);[8a] (ii) oxidative coupling of β-naphthol-2-carboxylate (48% ee);[8b] (iii) allylation of benzaldehyde with allyl(trichloro)silane (34–83% ee);[8c] (iv) allylic alkylation of naphthyls with EtMgBr (67–77% ee);[8d] (v) hydrogenation of methyl 2-acetamidoacrylate (67% ee);[8e] and (vi) transfer hydrogenation (28% ee) and hydrosilylation (24% ee) of acetophenone.[8f]

It is our aim to develop novel chiral 1,1′-bisisoquinolines and explore their utility as ligands in various asymmetric reactions. To achieve this aim, chiral C_1-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline framework **1** (Fig. 1) where heterocyclic ring **A** is fully aromatic while ring **B** is fully saturated was sought. The chirality in this framework resides on C1′. This design is anticipated to present different electronic and structural constrains compared to those observed in the previously reported C_2-symmetric 1,1′-bisisoquinoline ligands,[8] and allows for easy functionalization of the NH to provide further electronic and structural tuning, e.g., a 'handle'.



1

Figure 1. C_1-1,1′-bisisoquinoline framework.

Herein, we present a detailed investigation of the chemistry of C_1-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline **1**, including a straightforward synthesis and its highly efficient resolution. We also present our studies on the use of **1** as ligand for enantioselective addition of Et_2Zn and CH_3NO_2 to benzaldehyde to demonstrate the efficacy of these ligands.

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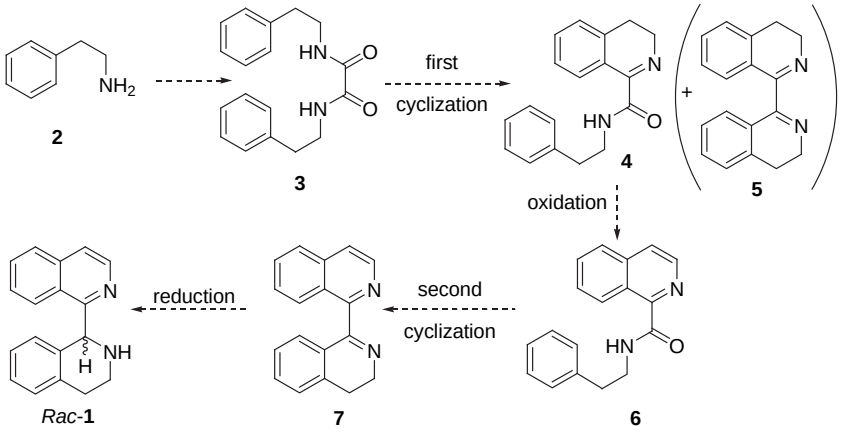
2. Results and discussion

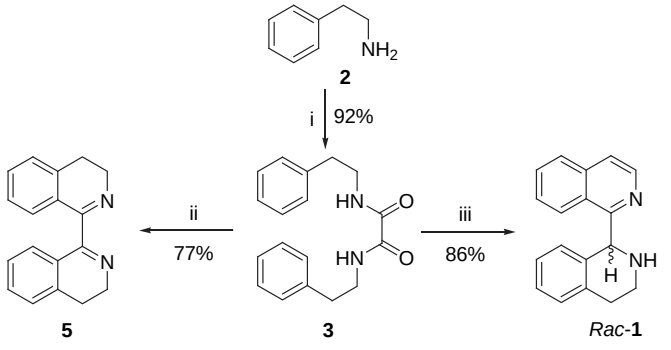
2.1. Preparation of *rac*-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline *rac*-1

Double Bischler–Napieralski reaction is a common method used to prepare 1,1′-bisisoquinolines through cyclization of bisoxamides using dehydrating agents such as $POCl_3$, P_2O_5, and polyphosphoric acid (PPA).[9] We planned to prepare the proposed C_1-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline *rac*-**1** framework (Fig. 1) through condensation, stepwise cyclization, oxidation, and reduction as shown in Scheme 1.



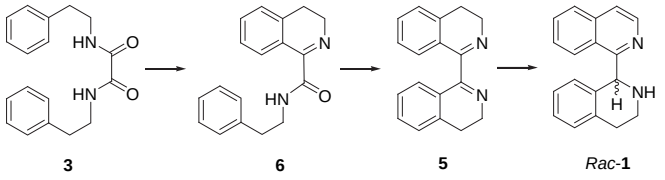
Scheme 1. Anticipated route to *rac*-C_1-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline *rac*-**1** framework.

Thus, condensation of phenethylamine **2** with diethyloxalate in ethanol gave bisoxamide **3** as fluffy needles in 92% yield (Scheme 2). Unfortunately, when bisoxamide **3** was treated with varying amounts of $POCl_3$ or P_2O_5 under different conditions, Bischler–Napieralski reaction failed to give the expected product **4** (Scheme 1), but afforded bisimine **5** as the only product (Scheme 2). However, when **3** was treated with PPA at 190 °C for 12 h, unexpectedly, the desired target product *rac*-**1** was obtained in 86% yield (Scheme 2). This approach represent a rapid and convenient method for obtaining the desired *rac*-C_1-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline *rac*-**1** framework.



Scheme 2. Synthesis of *rac*-C_1-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline *rac*-**1**. Reagents and conditions: (i) $(EtOCO)_2$, EtOH, 25 °C, 2 h; (ii) $POCl_3$, P_2O_5, toluene reflux, 24 h; (iii) neat PPA, 190 °C, 12 h.

The mechanism of formation of *rac*-**1**, was explored at a lower temperature of 140 °C. Representative crude samples were taken at various time intervals over a period of 26 days and examined by ^{1}H NMR spectroscopy. These samples were then subjected to purification using column chromatography on silica gel (EtOAc/CH_2Cl_2, 1:9) and the structure of each component separated was fully analyzed using various spectroscopic techniques; the analysis was confirmed by comparing the spectroscopic data with those of authentic samples.[7] After carefully analyzing all spectroscopic data of the crude and pure fractions, it emerged that bisoxamide **3** underwent through a two stage stepwise cyclization (i.e., from **3**→**6**→**5**) to form **5** (Scheme 3). After complete consumption of **3** and **6**, compound **5** underwent a slow disproportionation reaction to form the final product *rac*-**1**.

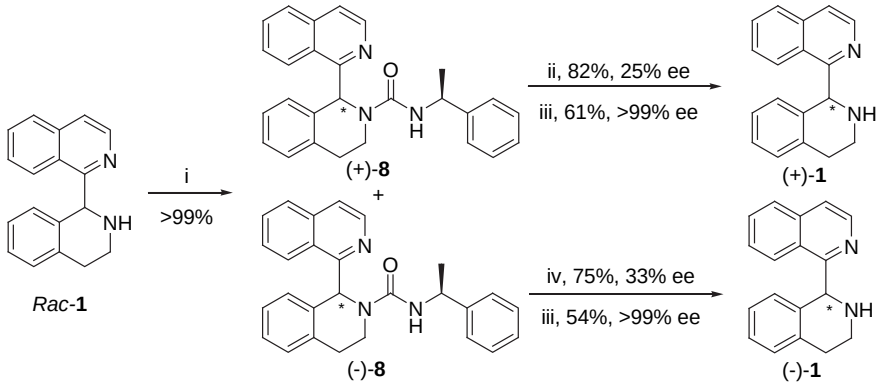


Scheme 3. Stepwise formation of *rac*-C_1-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline *rac*-**1**. Reagents and conditions: neat PPA, 140 °C, 26 days.

2.2. Resolution of *rac*-C_1-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline *rac*-1

Numerous attempts to facilitate complete resolution of *rac*-**1** through diastereomeric salt formation using various chiral acids such as (L)-lactic acid, α-bromocamphor-π-sulfonic acid, (D)-camphor sulfonic acid were unsuccessful. Fortunately, treatment of *rac*-**1** with a stoichiometric quantity of enantiopure (*S*)-(−)-α-methylbenzyl isocyanate[10] (Scheme 4) gave the diastereomeric ureas (+)-**8** and (−)-**8** in quantitative yield.

Preferential recrystallization of diastereomeric ureas (+)-**8** and (−)-**8** in various solvents resulted in crystalline products that were found to be equal mixture of diastereomers. Complete separation of diasteromers (+)-**8** and (−)-**8** was achieved successfully after repetitive column chromatography using a gradient mixture of EA/CH_2Cl_2. Despite that pure diastereomers (+)-**8** and (−)-**8** were accessible by column chromatography, other routes of separation were sought to avoid the complexity of this procedure. Interestingly, when a mixture enriched with either (+)-**8** (fraction 1, Fig. 2) or (−)-**8** (fraction 3, Fig. 2) was recrystallized from EtOAc/hexane, the crystals formed were found (by ^{1}H NMR) to be a 1:1 mixture of (+)-**8** and (−)-**8** while the mother liquor gave, after solvent evaporation, a highly enriched diasteromeric mixture of



Scheme 4. Resolution of *rac*-**1**. Reagents and conditions: (i) (*S*)-(−) -¦Á-methylbenzyl isocyanate, CH_2Cl_2, 25 °C, 1 h; (ii) 1 N HCl, EtOH, reflux, 12 h; (iii) 0.5 equiv NaOBu, *n*-BuOH, 120 °C, 2 h, recrystallization from EtOH; (iv) 1 N HCl, EtOH, reflux, 24 h.

(+)-**8** (in case of fraction 1) or (−)-**8** (in case of fraction 3) (Fig. 2). Therefore, multiple recrystallizations of the enriched fractions obtained after chromatographic separation gave pure single diastereomers, and the remaining diasteromeric mixtures with an equal ratios of (+)-**8** and (−)-**8** were recycled for further chromatographic separation. The complete process is depicted in Figure 2. The above crystallization behavior may be attributed to the fact that once diastereomers (+)-**8** and (−)-**8** crystallize, they do so in a 1:1 ratio in the unit cell.

origin of the racemization was not investigated, it may have occurred through opening and closing of the saturated heterocyclic ring **B** or through an enolisation-type process involving migration of H from the chiral centre (C1′) to the nitrogen of the ring **B**. Thus, hydrolysis under acidic conditions was abandoned. Gratifyingly, when an alcoholic solution of ureas (+)-**8** or (−)-**8** was treated with sodium *n*-butoxide (NaOBu) in hot *n*-BuOH (Scheme 4), both reactions gave cleaved products (+)-**1** and (−)-**1**, respectively, in 85% ee. Fortunately, only one re-

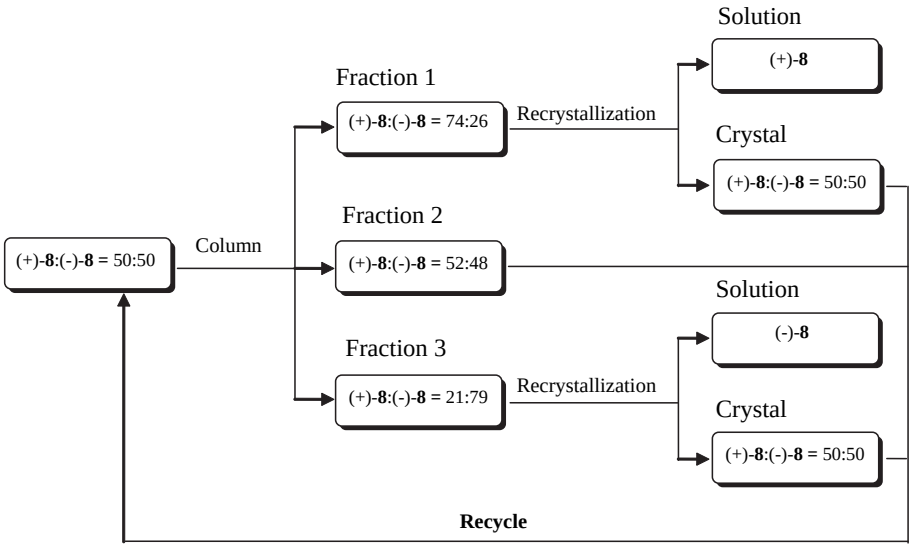


Figure 2. Separation of (+)-**8** and (−)-**8**.

The ^{1}H NMR spectra of (+)-**8** and (−)-**8** before and after separation are shown in Figure 3.

We next attempted acid- and base- catalysed hydrolysis of the urea bonds to obtain the desired enantiomerically pure (+)-**1** and (−)-**1** (Scheme 4). Interestingly, the hydrolysis rates of (+)-**8** and (−)-**8** using 1 N HCl under reflux conditions in EtOH were quite different. For complete hydrolysis, (+)-**8** took 12 h while (−)-**8** needed 24 h. Such finding provides the possibility of preferential hydrolysis of the 1:1 mixture of (+)-**8** and (−)-**8**. However, when (+)-**8** and (−)-**8** were subjected to hydrolysis, and the products were analysed by HPLC, (+)-**1** was obtained in 25% ee while (−)-**1** was obtained in 33% ee indicating that racemization occurred during acidic hydrolysis. Although the crystallization of the product from ethanol was needed to give an ee of >99%.

2.3. Preparation of chiral derivatives based on (+)-1

Enantiopure (+)-**1** was subjected to alkylation and cyanation reactions to assess its reactivity for further developments into more versatile and specialized ligands for application in various asymmetric reactions. Various alkyl groups were introduced by standard treatment of (+)-**1** with alkyl halides in presence of K_2CO_3 under refluxing conditions in CH_3CN. Thus, treatment of (+)-**1** with ethyl bromide, benzylbromide, and 2-hydroxy-5-nitro-benzyl bromide afforded, after workup and column chromatography on silica gel

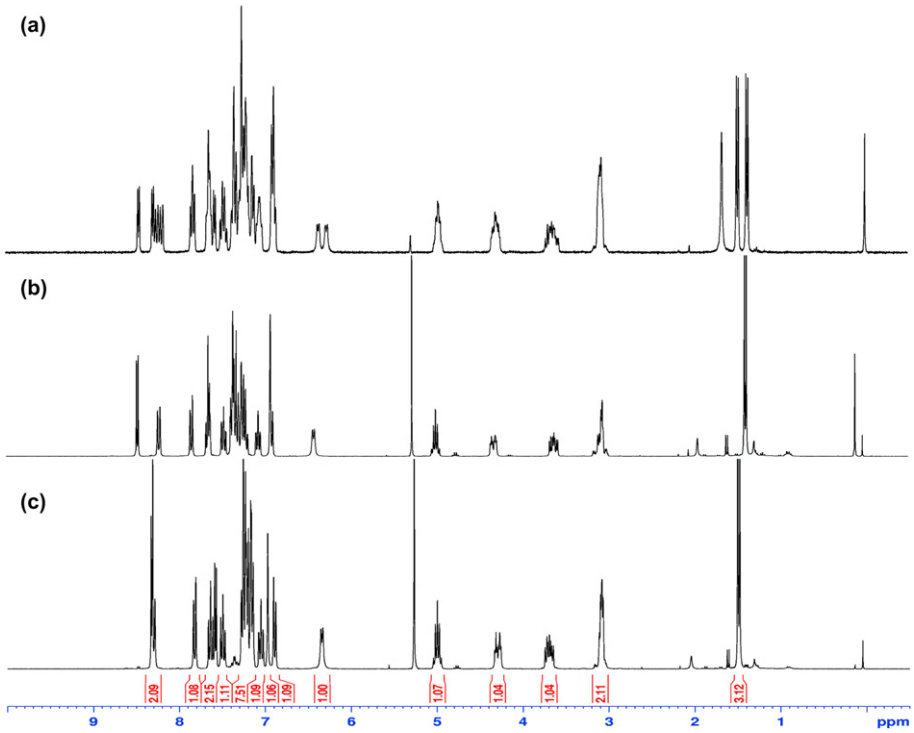
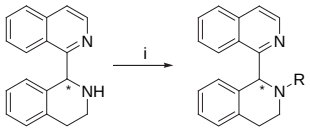


Figure 3. ^{1}H NMR (300 MHz) spectra of (a) 1:1 mixture of (+)-**8** and (−)-**8** before separation; (b) pure (+)-**8** after separation; (c) pure (−)-**8** after separation.

purification, the expected compounds (+)-**9**–**11**, respectively (Scheme 5). However, under the same alkylation conditions, isopropyl bromide could not be made to react with (+)-**1** even after extended reaction time. In this case, steric congestions were believed to prevent the formation of the product.



(+)-**1** (+)-**9**-**11**

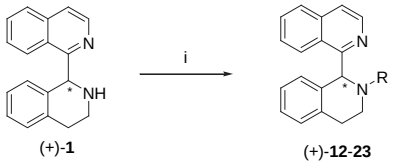
	R	%Yield
(+)-**9**	Et	92
(+)-**10**	CH_2Ph	95
(+)-**11**	CH_2-C_6H_4-2-OH,5-NO_2	91

Scheme 5. Synthesis of *N*-alkyl derivatives of (+)-**1**. Reagents and conditions: (i) 1.1 equiv alkyl bromide, K_2CO_3, CH_3CN, 50 °C, overnight.

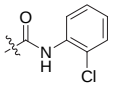
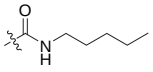
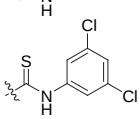
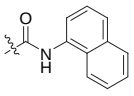
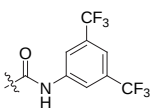
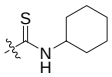
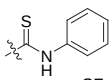
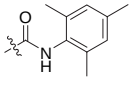
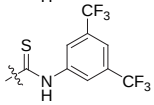
Likewise, (+)-**1** reacted smoothly with stoichiometric amounts of isocyanates and thioisocyanates in CH_2Cl_2 at room temperature to give the expected products (+)-**12**–**23** as white solids in excellent yields (Scheme 6).

Based on the above reactivity profile, enantiopure (+)-**1** can undergo various reactions under standard conditions to give structurally robust and interesting motifs in excellent yields. These characteristics coupled with simple synthesis advocate an excellent chiral framework, that is, amenable for further developments and exploitation.

Attempts to grow single crystals of compounds (+)-**12**–**23** for X-ray diffraction analysis were not successful. Fortunately, single crystals were obtained by recrystallization of thiourea *rac*-**17**[11] from ethanol. The X-ray structure (Fig. 4) revealed that: (i) the isoquinoline rings **A** and **B** are joined by an axial C1–C1′ bridging bond; (ii) the two isoquinoline ring systems are splayed apart and oriented in different planes with the dihedral angle C30–C31–C32–C33 measuring 101°. The aromatic isoquinoline ring system shows an almost complete offset with respect to the mean plane of the reduced isoquinoline ring system and (iii) heterocyclic ring **B** adopted a twist-boat conformation. The thiourea substituent is oriented far away from both rings **A** and **B** for steric reasons.



(+)-**1** (+)-**12**-**23**

Urea	R	%Yield	Thiourea	R	%Yield
(+)-**12**		99	(+)-**17**		96
(+)-**13**		96	(+)-**18**		85
(+)-**14**		94	(+)-**19**		90
			(+)-**20**		80
(+)-**15**		90	(+)-**21**		92
			(+)-**22**		89
(+)-**16**		92	(+)-**23**		87

Scheme 6. Synthesis of chiral ureas and thioureas based on (+)-**1**. Reagents and conditions: (i) 1.0 equiv R–NCO or R–NCS, CH_2Cl_2, 25 °C, overnight.

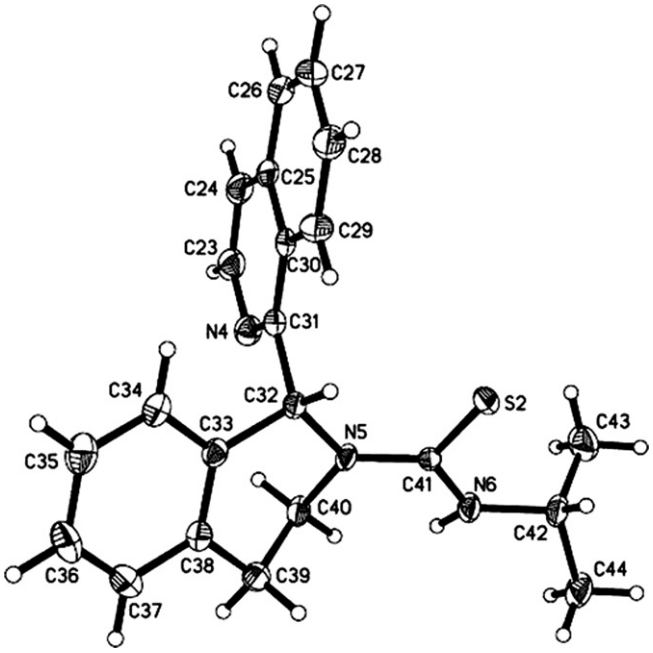
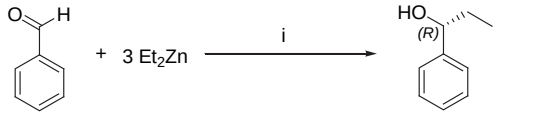


Figure 4. ORTEP diagram of thiourea *rac*-**17** with crystallographic numbering.[†]

2.4. Applications in catalytic asymmetric reactions

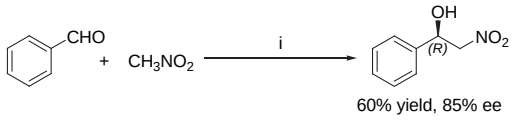
The next goal was to examine the catalytic and enantioselective properties of ligand (+)-**1** in C–C bond forming reactions through the addition of Et_2Zn and nitromethane to benzaldehyde **24**. Various chiral catalysts based on amino alcohols, diols, thiols, disulfides, diselenides, diamines, oxazaborolidines, bisoxazolidines, sulfinamides, and BINOLs have been used successfully for the asymmetric addition of dialkylzinc to aldehydes.[12] Interestingly, the present ligand is an amine–imine type ligand, which has been rarely used in enantioselective addition of Et_2Zn to aldehydes. In preliminary results, the addition of Et_2Zn to benzaldehyde **24** using 15 mol % of (+)-**1** proceeded with excellent selectivity and conversion to give the corresponding alcohol (*R*)-**25** in 96% yield and 85% ee (Scheme 7).[13]



Scheme 7. Enantioselective addition of Et_2Zn to benzaldehyde **24** using (+)-**1**. Reagents and conditions: (i) 15 mol % (+)-**1**, THF/hexane (1:3), 0 °C, 30 h.

Ligand (+)-**1** was also examined in the enantioselective Henry reaction through addition of CH_3NO_2 to benzaldehyde **24** (Scheme 8).[14] The addition using 10 mol % (+)-**1** in the presence of CuCl gave the desired adduct (*R*)-**26** in 60% yield and 85% ee.

These above initial results represent an encouraging prospect for further investigation and optimization.



Scheme 8. Asymmetric addition of CH_3NO_2 to benzaldehyde **24** using (+)-**1**. Reagents and conditions: (i) 10 mol % (+)-**1**, 5 mol % CuCl, $ClCH_2CH_2Cl$, 0 °C, 72 h.

3. Conclusion

A straightforward synthesis of new geometrically-constrained C_1-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline *rac*-**1** has been achieved efficiently. Resolution of *rac*-**1** was accomplished using (*S*)-(−)-α-methylbenzyl isocyanate. The preparation of potential new ligand systems based on (+)-**1** has been achieved successfully where a range of enantiopure *N*-alkyl, urea, and thiourea derivatives have been synthesized. Preliminary results indicated that (+)-**1** is an efficient ligand for the enantioselective addition of both Et_2Zn (85% ee, 96% yield) and CH_3NO_2 (85% ee, 60% yield) to benzaldehyde indicating great potential for further development and optimization. These results coupled with a simple synthesis of (+)-**1** advocate an excellent chiral ligand candidate amenable to further developments. Application of (+)-**1** and (+)-**9**–**23** as chiral motifs in various asymmetric reactions is under investigation, and our findings will be reported in due course.

4. Experimental

4.1. General

All commercial materials were used as received. Analytical thin layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plate (0.2 mm thickness) and visualized using UV radiation (254 nm). Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). Anhydrous THF was freshly taken from PURE SOLV PS-400-5-MD system. ^{1}H NMR spectrum was recorded at 300 MHz and ^{13}C NMR spectrum was recorded at 75.47 MHz on a Bruker Advanced DPX 300. Unless stated, data refer to solutions in $CDCl_3$ with the TMS as internal reference. Routine mass spectrum was recorded on ABI QSTAR Elite mass spectrometer. High resolution mass spectrum was recorded on Qstar XL MS/MS system. X-ray single crystal diffraction data was obtained on Bruker-AXS Smart Apex CCD single-crystal diffractometer. HPLC was performed on Agilent 1100 using Diacel chiralcel OD-H chiral column. GC was conducted on Agilent 6890 using Agilent HP-5 or Astec Chiraldex G-TA column. GC-Mass spectrum was recorded on Agilent 6890 GC system with Agilent 5973 Mass selective detector. Optical rotation value was measured on JASCO P-1020 polarimeter.

4.2. Preparation of *N*,*N*′-bisphenethyloxamide 3

A solution of diethyloxalate (11.2 mL, 0.083 mol) in absolute ethanol (25 mL) was added dropwise over a period of 10 min to a stirred solution of phenethylamine (20.0 g, 0.165 mol) in absolute ethanol (80 mL). The mixture was vigorously stirred at room temperature for 4 h. The solvent was evaporated under vacuum and the solid obtained was washed with hexane (3×50 mL) and then dried under vacuum pressure for 12 h to give *N*,*N*′-bisphenethyloxamide **3** as white powder (22.63 g, 92%). Mp 186–188 °C. FTIR (KBr) ν_{max}: 3307, 1654, 1522, 1280, 1226, 1190, 742, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.79 (4H, t, J=7.2 Hz, H2 and H2′), 3.50 (4H, q, J=6.9 Hz, H1 and H1′),

[†] CCDC 746423 contains the Supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

7.12–7.27 (10H, m, H2″, H3″, H4″, H5″, H6″ and H2‴, H3‴, H4‴, H5‴, H6‴), 7.53 (2H, br s, N*H*). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 35.5 (C2 and C2′), 40.9 (C1 and C1′), 126.7 (C4″ and C4‴), 128.7 (C2″, C6″ and C2‴, C6‴), 128.8 (C3″, C5″ and C3‴, C5‴), 138.1 (C1″ and C1‴), 159.7 (2×*C*O). HRMS (ESI) calcd for $C_{18}H_{20}N_2O_2$: 296.1525, found 319.1078 ($M+Na^+$).

4.3. Preparation of 3,3′,4,4′-tetrahydro-1,1′-bisisoquinoline 5

$POCl_3$ (110 mL, 1.2 mol) was added dropwise over 30 min to a stirred suspension of bisoxamide **3** (35.5 g, 0.12 mol) and P_2O_5 (171 g, 1.2 mol) in toluene (200 mL) in an ice bath. After complete addition, the mixture was heated under reflux overnight. The reaction mixture was cooled to room temperature, hexane (200 mL) was added and the mixture was left undisturbed for 2 h. The solvent was then decanted and the remaining black solid was dissolved in water. Solid Na_2CO_3 was added until no bubbling was observed followed by addition of 1.0 M NaOH solution to adjust pH to 10. The alkaline solution was extracted with CH_2Cl_2 (4×150 mL) and the combined extracts were washed with brine and then dried over $MgSO_4$, and filtered. The solvent was removed under vacuum, and the obtained dark purple solid was dissolved in EtOH (250 mL) and heated at reflux with charcoal (60 g) for 3 h to remove coloring material. Charcoal was filtered and the solution was concentrated to a tenth of the original volume and left to stand overnight where 3,3′,4,4′-tetrahydro-1,1′-bisisoquinoline **5** was obtained as dark yellow powder (18.5 g, 59%). Mp 104–106 °C. FTIR (KBr) ν_{max}: 1607, 1231, 1215, 1010, 913, 740 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.86 (4H, t, *J*=7.7 Hz, H4 and H4′), 3.94 (4H, t, *J*=7.5 Hz, H3 and H3′), 7.15–7.36 (8H, m, H5, H6, H7, H8 and H5′, H6′, H7′, H8′). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 25.8 (C4 and C4′), 47.4 (C3 and C3′), 126.9 (C8 and C8′), 127.0 (C5 and C5′), 127.6 (C7 and C7′), 128.2 (C8a and C8′a), 131.2 (C6 and C6′), 137.5 (C4a and C4′a), 165.4 (C1 and C1′). Mass (ESI) calcd for $C_{18}H_{16}N_2$: 260.13, found 261.27 (M+1). ^{1}H NMR and ^{13}C NMR assignments were confirmed through H–H COSY, HMQC, HMBC, and DEPT experiments at 300 MHz.

4.4. Preparation of *rac*-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline 1

Bisoxamide **3** (5.0 g, 16.9 mmol) was mixed with polyphosphoric acid (70.0 g), under N_2 atmosphere and stirred at 190 °C for 12 h. The mixture was then cooled, diluted with water (30 mL) and NaOH (10% in water, w/w) was added to obtain pH 11. The alkaline solution was extracted with CH_2Cl_2 (4×50 mL). The combined extracts were washed with brine (3×15 mL) and dried over $MgSO_4$, and filtered. The solvent was removed under vacuum and the residue was recrystallized from EtOH to give *rac*-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline **1** as light-yellow needles (3.76 g, 86%). Mp 125–129 °C. FTIR (KBr) ν_{max}: 3301, 2805, 1494, 1452, 1345, 1121, 826, 751, 735 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.44 (1H, br s, N*H*), 2.86–2.96 (1H, m, 1×H4′), 3.20–3.34 (2H, m, 1×H4′ and 1×H3′), 3.47–3.57 (1H, m, 1×H3′), 6.01 (1H, s, H1′), 6.60 (1H, d, *J*=7.8 Hz, H5′), 6.94 (1H, t, *J*=7.5 Hz, H7′), 7.14 (1H, t, *J*=7.2 Hz, H6′), 7.22 (1H, d, *J*=7.8 Hz, H8′), 7.54 (1H, t, *J*=7.8 Hz, H6), 7.62 (1H, d, *J*=5.7 Hz, H4), 7.67 (1H, t, *J*=7.7 Hz, H7), 7.86 (1H, d, *J*=8.4 Hz, H5), 8.34 (1H, d, *J*=8.7 Hz, H8), 8.50 (1H, d, *J*=5.7 Hz, H3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 29.6 (C4′), 43.4 (C3′), 61.1 (C1′), 120.7 (C4), 126.0 (C8), 126.1 (C7′), 126.5 (C7), 126.8 (C6′), 127.0 (C5), 127.3 (C8a), 127.4 (C5′), 129.4 (C8′), 129.9 (C6), 134.9 (C4′a), 137.0 (C4a), 137.8 (C8′a), 141.8 (C3), 161.8 (C1). HRMS (ESI) calcd for $C_{18}H_{16}N_2$: 260.1313, found 261.1157 (M+1). ^{1}H NMR and ^{13}C NMR assignments were confirmed through H–H COSY, HMQC, HMBC, and DEPT experiments at 300 MHz.

4.5. Preparation of *N*-phenethyl-3,4-dihydroisoquinoline-1-carboxamide 4

Bisoxamide **3** (1.0 g, 3.4 mmol) was mixed with polyphosphoric acid (14.0 g) and stirred at 140 °C for 3 h. The mixture was cooled, diluted with water (10 mL) and NaOH (10% in water, w/w) was added till pH 11. The alkaline solution was extracted with CH_2Cl_2 (3×15 mL), the combined organic extracts were washed with brine (3×10 mL) and then dried over $MgSO_4$, and filtered. The solvent was removed under vacuum and the residue was purified by column chromatography (pure EtOAc) to give *N*-phenethyl-3,4-dihydroisoquinoline-1-carboxamide **4** as yellow gum (0.36 g, 38%). FTIR (KBr) ν_{max}: 3368, 3027, 2940, 1670, 1610, 1522, 1236, 751, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.65 (2H, t, *J*=7.4 Hz, H4), 2.87 (2H, t, *J*=7.2 Hz, H2′), 3.60 (2H, apparent q, *J*=6.9 Hz, H1′), 3.68 (2H, t, *J*=7.5 Hz, H3), 7.13 (1H, d, *J*=7.2 Hz, H5), 7.19–7.35 (7H, m, H6, H7, H2″, H3″, H4″, H5″, and H6″), 7.47 (1H, br s, N*H*), 8.10 (1H, d, *J*=7.5 Hz, H8). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 25.8 (C4), 35.8 (C2′), 40.7 (C1′), 47.2 (C3), 126.3 (C8a), 126.5 (C5), 127.0 (C4″), 127.1 (C6), 128.4 (C8), 128.6 (C3″ and C5″), 128.8 (C2″ and C6″), 131.3 (C7), 137.9 (C4a), 138.9 (C1″), 159.9 (C1), 164.4 (*C*O). Mass (ESI) calcd for $C_{18}H_{18}N_2O$: 278.14, found 279.79 (M+1). ^{1}H NMR and ^{13}C NMR assignments were confirmed through H–H COSY, HMQC, HMBC, and DEPT experiments at 300 MHz.

4.6. Resolution of *rac*-1 with (*S*)-(−)-α-methylbenzyl isocyanate

*4.6.1. Preparation and separation of (+)-2′-((S)-1′-phenylethylcarbamoyl)-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline (+)-8 and (−)-2′-((S)-1′-phenylethylcarbamoyl)-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline (−)-**8**.* A solution of (*S*)-(−)-α-methylbenzyl isocyanate (7.4 g, 50 mmol) in CH_2Cl_2 (80 mL) was added to an ice-cold stirred solution of *rac*-**1** (13.0 g, 50 mmol) in CH_2Cl_2 (100 mL). After complete addition, the reaction mixture was stirred at room temperature for 1 h, washed with brine (3×30 mL) and then dried over $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure to give the diastereomeric urea mixture (+)-2′-((*S*)-1′-phenylethylcarbamoyl)-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline (+)-**8** and (−)-2′-((*S*)-1′-phenylethylcarbamoyl)-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline (−)-**8** as white powder (20.4 g, >99%). All attempts to separate ureas (+)-**8** and (−)-**8** by recrystallizing the mixture from various solvents (MeOH, EtOH, IPA, CH_3CN, THF, EtOAc, $CHCl_3$ or combination of these solvents) were not successful. Therefore, the mixture was subjected to column chromatography on silica gel (EtOAc/CH_2Cl_2 gradient from 1:4 to 1:1). Mixture ((+)-**8**:(−)-**8**=50:50, 10.0 g) was passed through a chromatography column containing 800 g silica gel and eluted with the solvent mixture to give three fractions with the ratio of (+)-**8**:(−)-**8** as 74:26 (first fraction, 2.93 g), 52:48 (second fraction, 4.34 g), and 21:79 (third fraction, 2.73 g). The first fraction (2.93 g) was dissolved into minimum amount of EtOAc at 60 °C. Hexane was added to the hot solution dropwise till it just turned cloudy. The solution was then kept at room temperature undisturbed overnight. It produced white crystals (1.21 g, 41%) in which the ratio of (+)-**8**:(−)-**8** was exactly 50:50. After filtering off the crystals, the filtrate was evaporated to dryness to give a white powder (1.72 g, 59%) with the ratio of (+)-**8**:(−)-**8** as 91:9. The procedure was repeated again to give urea (+)-**8** as white powder (1.40 g, 28% of the total amount of urea (+)-**8** in starting mixture). Mp 83–88 °C. FTIR (KBr) ν_{max}: 3337, 1624, 1527, 1376, 1235, 747 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36 (3H, d, *J*=6.9 Hz, CH_3), 2.98–3.13 (2H, m, 1×H4′ and 1×H3′), 3.59 (1H, ddd, *J*=13.2 Hz, 10.4 Hz, 4.8 Hz, 1×H4′), 4.29 (1H, m, 4.1 Hz, 1×H3′), 4.97 (1H, m, PhC*H*CH_3), 6.39 (1H, br d, *J*=6.6 Hz, CON*H*), 6.88 (1H,

d, J=8.7 Hz, aromatic H), 6.89 (1H, s, H1′), 7.03 (1H, t, J=7.4 Hz, aromatic H), 7.15–7.36 (7H, m, 7×aromatic H), 7.43 (1H, ddd, J=8.7 Hz, 6.9 Hz, 1.2 Hz, aromatic H), 7.59–7.64 (2H, m, 2×aromatic H), 7.81 (1H, d, J=8.1 Hz, aromatic H), 8.19 (1H, d, J=8.7 Hz, aromatic H), 8.44 (1H, d, J=5.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 22.9 (*C*H$_3$), 29.1 (C4′), 38.7 (C3′) 50.3 (PhCHCH$_3$), 59.4 (C1′), 121.3, 126.1, 126.2, 126.4, 126.6, 126.9, 127.0, 127.47, 127.51, 127.52, 128.5, 129.3, 130.1, 134.7, 135.3, 137.5, 140.9, 144.9, 157.2 (21×aromatic C), 161.4 (NCON). HRMS (ESI) calcd for $C_{27}H_{25}N_3O$: 407.1998, found 408.1524 (M+1), 430.1329 (M+Na). The de was determined by HPLC (Chiralcel OD-H column): hexane/IPA=90/10, 0.8 mL/min, 25 °C, 280 nm, t=18.31 min for (+)-**8**. $[\alpha]_D^{25}$ +235.7 (c 0.71, CH_2Cl_2).

The third fraction (2.73 g) was treated in a similar manner to the first fraction to give urea (−)-**8** as white powder (1.56 g, 31% of the total amount of urea (−)-**8** in starting mixture). Mp 85–88 °C. FTIR (KBr) ν_{max}: 3337, 1623, 1528, 1377, 1235, 828, 747, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.45 (3H, d, J=6.9 Hz, C*H*$_3$), 3.02–3.07 (2H, m, 1×H4′ and 1×H3′), 3.60–3.70 (1H, m, 1×H4′), 4.25 (1H, m, 1×H3′), 4.95 (1H, m, PhC*H*CH$_3$), 6.30 (1H, br d, J=6.6 Hz, CON*H*), 6.85 (1H, d, J=7.8 Hz, aromatic H), 6.93 (1H, s, H1′), 7.01 (1H, t, J=7.5 Hz, aromatic H), 7.09–7.21 (7H, m, 7×aromatic H), 7.45 (1H, ddd, J=8.4 Hz, 6.9 Hz, 1.2 Hz, aromatic H), 7.54 (1H, d, J=5.7 Hz, aromatic H), 7.59 (1H, ddd, J=8.1 Hz, 7.1 Hz, 1.2 Hz, aromatic H), 7.78 (1H, d, J=8.1 Hz, aromatic H), 8.25 (1H, d, J=7.5 Hz, aromatic H), 8.28 (1H, d, J=5.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 23.2 (*C*H$_3$), 29.2 (C4′), 38.9 (C3′) 50.5 (PhCHCH$_3$), 59.0 (C1′), 121.0, 126.0, 126.1, 126.4, 126.6, 126.8, 126.9, 127.44, 127.49, 127.53, 128.4, 129.2, 130.1, 134.8, 135.4, 137.4, 141.1, 144.7, 157.1 (21×aromatic C), 161.5 (NCON). HRMS (ESI) calcd for $C_{27}H_{25}N_3O$: 407.1998, found 408.1614 (M+1), 430.1395 (M+Na). The de was determined by HPLC (Chiralcel OD-H column): hexane/IPA=90/10, 0.8 mL/min, 25 °C, 280 nm, t=15.69 min for (−)-**8**. $[\alpha]_D^{25}$ −297.5 (c 1.15, CH_2Cl_2).

*4.6.2. Alcoholysis of urea (+)-8 and (−)-8: preparation of (+)-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline (+)-1 and (−)-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline (−)-**1**.* Sodium butoxide (3.07 mmol, 1.8 mL of 1.71 M solution in *n*-BuOH) was added to a stirred solution of urea (+)-**8** (2.5 g, 6.14 mmol) in *n*-BuOH (50 mL) under a nitrogen atmosphere. The mixture was heated to 120 °C for 2 h. The mixture was then cooled to room temperature and 1.0 M HCl solution (10 mL) was added to quench the reaction. The solvent was evaporated under vacuum and the resulting yellow solid was dissolved in a mixture of Et_2O (30 mL) and H_2O (50 mL). The organic layer was separated and further extracted with H_2O (3×25 mL). NaOH solution (1.0 M) was added to the combined extracts to bring the pH to 11. The alkaline solution was extracted with CH_2Cl_2 (3×50 mL) and the combined organic extracts were washed with brine (3×30 mL) and dried over $MgSO_4$, and filtered. The solvent was removed under vacuum, and the residue was recrystallized from EtOH to give (+)-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline (+)-**1** as off-white needles (0.97 g, 61%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR, and ESI-Mass of (+)-**1** were identical to those of *rac*-**1**. The ee of >99% was determined by HPLC (Chiralcel OD-H column): hexane/IPA/TEA=90/10/0.1, 0.5 mL/min, 25 °C, 254 nm, t=19.88 min for (+)-**1**. $[\alpha]_D^{25}$ +202.0 (c 0.9, CH_2Cl_2).

Urea (−)-**8** (2.5 g, 6.14 mmol) was treated with sodium butoxide (3.07 mmol, 1.8 mL of 1.71 M solution in *n*-BuOH) in *n*-BuOH (50 mL) in a similar fashion used for urea (+)-**8** to give a yellow gum, which was recrysatllized from EtOH to give (−)-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline (−)-**1** as an off-white needles (0.86 g, 54%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR, and ESI-Mass of (−)-**1** were identical to those of *rac*-**1**. The ee of >99% was determined by HPLC (Chiralcel OD-H column): hexane/IPA/TEA=90/10/0.1, 0.5 mL/min, 25 °C, 254 nm, t=27.40 min for (−)-**1**. $[\alpha]_D^{25}$ −195.8 (c 1.2, CH_2Cl_2).

4.7. Synthesis of chiral derivatives based on (+)-1

*4.7.1. N-Alkyl derivatives (+)-**9**–**11**. General procedure*: Alkyl bromides were added to a stirred mixture of (+)-**1** and K_2CO_3 in dry CH_3CN under nitrogen atmosphere. The mixture was heated to 50 °C overnight. The reaction mixture was cooled to room temperature, filtered, and the solid was washed with CH_2Cl_2. The combined organic phases were evaporated under vacuum to dryness. The residue was subjected to column chromatography to give pure *N*-alkyl derivative.

*4.7.1.1. Preparation of (+)-N′-ethyl-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline (+)-**9**.* Compound (+)-**1** (130 mg, 0.5 mmol) was reacted with bromoethane (45 μl, 0.55 mmol) in presence of K_2CO_3 (138 mg, 1.0 mmol) in CH_3CN (4 mL) to give an off-white solid that was purified by column chromatography (EtOAc) to give (+)-*N*′-ethyl-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline (+)-**9** as an off-white foam (132.5 mg, 92%). Mp 59–63 °C. FTIR (KBr) ν_{max}: 3400, 2968, 2797, 1586, 1459, 1376, 1342, 1298, 1139, 826, 736 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz, C*H*$_3$), 2.32 (1H, hex, J=6.7 Hz, C*H*HCH$_3$), 2.55 (1H, hex, J=6.8 Hz, CH*H*CH$_3$), 2.62–2.71 (1H, m, 1×H4′), 2.90–2.98 (1H, m, 1×H4′), 3.36–3.48 (2H, m, H3′), 5.27 (1H, s, H1′), 6.55 (1H, d, J=7.8 Hz, aromatic H), 6.84 (1H, t, J=7.7 Hz, aromatic H), 7.06 (1H, t, J=7.5 Hz, aromatic H), 7.18 (1H, d, J=7.5 Hz, aromatic H), 7.32 (1H, t, J=7.1 Hz, aromatic H), 7.53 (1H, t, J=7.5 Hz, aromatic H), 7.59 (1H, d, J=5.7 Hz, aromatic H), 7.75 (1H, d, J=8.1 Hz, aromatic H), 8.51 (1H, d, J=5.7 Hz, aromatic H), 8.59 (1H, d, J=8.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 11.3 (*C*H$_3$), 29.7 (C4′), 48.2 (NCH$_2$CH$_3$), 49.0 (C3′), 72.5 (C1′), 120.9, 125.8, 126.1, 126.2, 126.7, 126.9, 127.1, 127.6, 128.6, 129.7, 134.0, 137.3, 138.0, 141.0, 162.5 (15×aromatic C). Mass (ESI) calcd for $C_{20}H_{20}N_2$: 288.16, found 289.13 (M+1). HPLC (Chiralcel OD-H column): hexane/IPA=95/5, 1.0 mL/min, 25 °C, 254 nm, t_1=9.92 min for (−) and t_2=10.34 min for (+). $[\alpha]_D^{25}$ +158.2 (c 1.0, CH_2Cl_2).

*4.7.1.2. Preparation of (+)-N′-benzyl-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline (+)-**10**.* Compound (+)-**1** (130 mg, 0.5 mmol) was reacted with benzylbromide (65 μl, 0.55 mmol) in presence of K_2CO_3 (138 mg, 1.0 mmol) in CH_3CN (4 mL) to give an off-white solid that was purified by column chromatography (EtOAc) to give (+)-*N*′-benzyl-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline (+)-**10** as light yellow foam (166.5 mg, 95%). Mp 92–95 °C. FTIR (KBr) ν_{max}: 3048, 3022, 2927, 2788, 1585, 1493, 1451, 1344, 1138, 1125, 823, 746, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.55 (1H, m, 1×H4′), 2.86 (1H, apparent d, J=16.5 Hz, 1×H4′), 3.21–3.40 (3H, m, 1×H3′ and PhC*H*$_2$), 3.69 (1H, d, J=9.6 Hz, 1×H3′), 5.31 (1H, s, H1′), 6.62 (1H, d, J=7.8 Hz, aromatic H), 6.88 (1H, t, J=7.5 Hz, aromatic H), 7.06–7.20 (7H, m, 7×aromatic H), 7.39 (1H, t, J=7.8 Hz, aromatic H), 7.56 (1H, t, J=7.5 Hz, aromatic H), 7.60 (1H, d, J=5.7 Hz, aromatic H), 7.76 (1H, d, J=8.1 Hz, aromatic H), 8.52 (1H, d, J=5.7 Hz, aromatic H), 8.67 (1H, d, J=8.4 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 29.6 (C4′), 48.8 (C3′), 58.4 (NCH$_2$Ph), 73.7 (C1′), 121.1, 125.9, 126.2, 126.3, 126.5, 126.7, 127.0, 127.2, 127.8, 128.1, 128.7, 128.8, 129.8, 134.0, 137.5, 137.6, 139.1, 141.0, 162.3 (21×aromatic C). Mass (ESI) calcd for $C_{25}H_{22}N_2$: 350.18, found 351.13 (M+1). HPLC (Chiralcel OD-H column): hexane/IPA=95/5, 1.0 mL/min, 25 °C, 254 nm, t_1=12.66 min for (+) and t_2=13.50 min for (−). $[\alpha]_D^{25}$ +147.5 (c 0.83, CH_2Cl_2).

*4.7.1.3. Preparation of (+)-N′-(2-hydro-5-nitro-benzyl)-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline (+)-**11**.* Compound (+)-**1** (65 mg, 0.25 mmol) was reacted with 2-hydro-5-nitro-benzylbromide (58 mg, 0.28 mmol) in presence of K_2CO_3 (69 mg, 0.5 mmol) in CH_3CN (3 mL) to give an off-white solid that was purified by column chromatography (EtOAc) to give (+)-*N*′-(2-hydro-5-nitro-benzyl)-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline (+)-**11** as an off-white foam (93.5 mg, 91%). Mp 98–101 °C. FTIR (KBr) ν_{max}: 3058, 2832, 1588, 1491, 1337, 1288, 1091, 829, 750 cm^{-1}. ^{1}H NMR (300 MHz,

$CDCl_3$) δ: 2.73–2.82 (1H, m, 1×H4′), 2.92 (1H, d, J=Hz, 1×H4′), 3.32–3.43 (2H, m, H3′), 3.52 (1H, d, J=14.4 Hz, NC*H*H), 3.91 (1H, d, J=14.1 Hz, NCH*H*), 5.60 (1H, s, H1′), 6.61 (1H, d, J=7.8 Hz, aromatic H), 6.72 (1H, d, J=9.0 Hz, aromatic H), 6.91 (1H, t, J=7.5 Hz, aromatic H), 7.11 (1H, t, J=7.4 Hz, aromatic H), 7.19 (1H, d, J=6.9 Hz, aromatic H), 7.56–7.69 (3H, m, 3×aromatic H), 7.83–7.86 (2H, m, 2×aromatic H), 7.97 (1H, dd, J=9.0 Hz, 2.7 Hz, aromatic H), 8.16 (1H, d, J=8.4 Hz, aromatic H), 8.54 (1H, d, J=5.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 29.0 (C4′), 48.9 (C3′), 58.0 (NCH_2Ph), 69.0 (C1′), 116.5, 121.5, 122.1, 125.1, 125.2, 125.3, 126.5, 126.9, 127.2, 127.3, 127.91, 127.94, 129.0, 130.4, 133.5, 136.1, 137.3, 140.0, 142.0, 160.2, 163.7 (21×aromatic C). Mass (ESI) calcd for $C_{25}H_{21}N_3O_3$: 411.16, found 412.07 (M+1). HPLC (Chiralcel OD-H column): hexane/IPA=95/5, 1.0 mL/min, 25 °C, 254 nm, t_1=26.17 min for (−) and t_2=29.72 min for (+). $[\alpha]_D^{25}$ +62.5 (c 0.77, CH_2Cl_2).

*4.7.2. Urea derivatives (+)-**12**–**16**. General procedure*: Isocyanates were added to a solution of (+)-**1** in dry CH_2Cl_2 under nitrogen atmosphere and the mixture was stirred overnight. The reaction mixture was washed with brine, the organic phase was separated, dried over $MgSO_4$, and filtered and the solvent was removed under vacuum. The residue was subjected to column chromatography to give the pure urea derivative.

4.7.2.1. Preparation of (+)-N′-(2-chlorophenyl)-1,1′-bisisoquinoline-2′-carboxamide (+)-12. Compound (+)-**1** (130 mg, 0.5 mmol) was reacted with 2-chlorophenyl isocyanate (76.8 mg, 0.5 mmol) in CH_2Cl_2 (4 mL) to give an off-white solid that was purified by column chromatography (EtOAc/hexane=1/9) to give (+)-*N*′-(2-chlorophenyl)-1,1′-bisisoquinoline-2-carboxamide (+)-**12** as light gray foam (205.0 mg, 99%). Mp 170–173 °C. FTIR (KBr) ν_{max}: 3231, 1656, 1591, 1502, 1438, 1383, 1288, 1220, 821, 746 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.21–3.25 (2H, m, H4′), 3.90–3.99 (1H, m, 1×H3′), 4.15–4.22 (1H, m, 1×H3′), 6.93 (1H, m, aromatic H), 7.02 (1H, d, J=7.5 Hz, aromatic H), 7.10 (1H, m, aromatic H), 7.18–7.33 (5H, m, H1′ and 4×aromatic H), 7.57 (1H, m, aromatic H), 7.60 (1H, d, J=5.4 Hz, aromatic H), 7.67 (1H, m, aromatic H), 7.84 (1H, d, J=8.1 Hz, aromatic H), 8.09 (1H, dd, J=8.4 Hz, 1.5 Hz, aromatic H), 8.15 (1H, br s, CON*H*), 8.43 (1H, d, J=8.7 Hz, aromatic H), 8.47 (1H, d, J=5.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 28.8 (C4′), 39.9 (C3′), 57.8 (C1′), 121.0, 122.0, 123.0, 123.3, 125.8, 126.5, 126.7, 127.1, 127.46, 127.53, 127.6, 127.7, 128.9, 129.3, 130.1, 134.6, 135.3, 136.3, 137.3, 141.5, 154.8 (21×aromatic C), 160.9 (N*C*ON). Mass (ESI) calcd for $C_{25}H_{20}ClN_3O$: 413.13, found 414.13 (M+1). HPLC (Chiralcel OD-H column): hexane/IPA=95/5, 1.0 mL/min, 25 °C, 254 nm, t_1=14.16 min for (+) and t_2=15.64 min for (−). $[\alpha]_D^{25}$ +310.4 (c 0.91, CH_2Cl_2).

*4.7.2.2. Preparation of (+)-N′-pentyl-1,1′-bisisoquinoline-2′-carboxamide (+)-**13***. Compound (+)-**1** (65 mg, 0.25 mmol) was reacted with pentyl isocyanate (32.5 μl, 0.25 mmol) in CH_2Cl_2 (3 mL) to give an off-white solid that was purified by column chromatography (EtOAc/hexane=1/9) to give (+)-*N*′-pentyl-1,1′-bisisoquinoline-2′-carboxamide (+)-**13** as white foam (88.9 mg, 96%). Mp 139–142 °C. FTIR (KBr) ν_{max}: 3282, 3057, 2953, 2926, 2859, 1610, 1543, 1250, 826, 740 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.86 (3H, t, J=6.9 Hz, H5″), 1.16–1.35 (4H, m, H4″ and H3″), 1.45 (2H, p, J=7.1 Hz, H2″), 3.05–3.08 (2H, m, H4′), 3.11–3.30 (2H, m, H1″), 3.66–3.75 (1H, m, 1×H3′), 4.14 (1H, m, 1×H3′), 5.72 (1H, br s, CON*H*), 6.88 (1H, d, J=7.8 Hz, aromatic H), 6.99 (1H, s, H1′), 7.04 (1H, t, J=7.5 Hz, aromatic H), 7.17 (1H, t, J=7.4 Hz, aromatic H), 7.23 (1H, d, J=7.5 Hz, aromatic H), 7.52 (1H, apparent t, J=7.2 Hz, aromatic H), 7.57 (1H, d, J=5.4 Hz, aromatic H), 7.63 (1H, t, J=7.5 Hz, aromatic H), 7.81 (1H, d, J=8.1 Hz, aromatic H), 8.39 (1H, d, J=7.5 Hz, aromatic H), 8.41 (1H, d, J=5.4 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 14.0 (C5″), 22.4 (C4″), 28.9 (C3″), 29.1 (C2″), 29.8 (C4′), 38.9 (C1″), 41.0 (C3′), 58.4 (C1′), 120.9, 126.1, 126.3, 126.7, 126.8, 127.4, 127.50, 127.55, 129.1, 130.0, 134.8, 135.6, 137.2, 141.2, 157.9 (15×aromatic C), 161.6 (N*C*ON). Mass (ESI) calcd for $C_{24}H_{27}N_3O$: 373.22, found 374.13 (M+1). HPLC (Chiralcel OD-H column): hexane/IPA=95/5, 1.0 mL/min, 25 °C, 254 nm, t_1=17.51 min for (+) and t_2=26.26 min for (−). $[\alpha]_D^{25}$ +298.7 (c 0.91, CH_2Cl_2).

*4.7.2.3. Preparation of (+)-N′-naphthyl-1,1′-bisisoquinoline-2′-carboxamide (+)-**14***. Compound (+)-**1** (65 mg, 0.25 mmol) was reacted with 1-naphthyl isocyanate (36 μl, 0.25 mmol) in CH_2Cl_2 (3 mL) to give a white solid that was purified by column chromatography (EtOAc/hexane=1/9) to give (+)-*N*′-naphthyl-1,1′-bisisoquinoline-2′-carboxamide (+)-**14** as white powder (100.9 mg, 94%). Mp 153–157 °C. FTIR (KBr) ν_{max}: 3276, 3053, 1619, 1525, 1502, 1389, 1248, 1224, 824, 790, 773, 745 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.13 (1H, apparent d, J=16.2 Hz, 1×H4′), 3.29 (1H, ddd, J=16.5 Hz, 16.2 Hz, 5.4 Hz, 1×H4′), 3.67 (1H, td, J=12.6 Hz, 3.3 Hz, 1×H3′), 4.62 (1H, apparent dd, J=10.5 Hz, 3.0 Hz, 1×H3′), 6.98 (1H, d, J=7.8 Hz, aromatic H), 7.10 (1H, s, H1′), 7.11 (1H, t, J=7.2 Hz, aromatic H), 7.27 (1H, t, J=7.5 Hz, aromatic H), 7.36 (1H, d, J=7.8 Hz, aromatic H), 7.40–7.54 (4H, m, 4×aromatic H), 7.61 (1H, d, J=8.1 Hz, aromatic H), 7.65 (1H, t, J=7.2 Hz, aromatic H), 7.71 (1H, d, J=5.7 Hz, aromatic H), 7.81–7.89 (3H, m, 3×aromatic H), 8.07(1H, d, J=8.7 Hz, aromatic H), 8.12 (1H, d, J=8.1 Hz, aromatic H), 8.55 (1H, d, J=5.7 Hz, aromatic H), 9.03 (1H, br s, CON*H*). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 29.2 (C4′), 38.8 (C3′), 60.8 (C1′), 119.9, 121.7, 121.8, 124.2, 125.6, 125.7, 125.9, 126.3, 126.62, 126.63, 127.2, 127.5, 127.56, 127.64, 127.7, 128.5, 129.5, 130.2, 134.3, 134.6, 134.8, 134.9, 137.9, 141.0, 156.4 (25×aromatic C), 161.0 (N*C*ON). Mass (ESI) calcd for $C_{29}H_{23}N_3O$: 429.18, found 430.27 (M+1). $[\alpha]_D^{25}$ +342.4 (c 1.04, CH_2Cl_2).

*4.7.2.4. Preparation of (+)-N′-(3,5-di-trifluoromethylphenyl)-1,1′-bisisoquinoline-2′-carboxamide (+)-**15***. Compound (+)-**1** (65 mg, 0.25 mmol) was reacted with 3,5-di-trifluoromethylphenyl isocyanate (43.5 μl, 0.25 mmol) in CH_2Cl_2 (3 mL) to give a white solid that was purified by column chromatography (EtOAc/hexane=0.5/9.5) to give (+)-*N*′-(3,5-di-trifluoromethylphenyl)-1,1′-bisisoquinoline-2′-carboxamide (+)-**15** as white foam (115.5 mg, 90%). Mp 103–107 °C. FTIR (KBr) ν_{max}: 3328, 3058, 1654, 1560, 1474, 1444, 1376, 1278, 1179, 1131, 934, 883, 829, 747 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.98–3.17 (2H, m, H4′), 3.55 (1H, apparent t, J=14.0 Hz, 1×H3′), 4.51 (1H, apparent d, J=12.3 Hz, 1×H3′), 6.90 (1H, d, J=7.8 Hz, aromatic H), 6.92 (1H, d, J=4.5 Hz, aromatic H), 7.04 (1H, t, J=7.4 Hz, aromatic H), 7.18–7.27 (2H, m, 2×aromatic H), 7.37 (1H, t, J=7.8 Hz, aromatic H), 7.45 (1H, s, H1′), 7.57 (1H, t, J=6.9 Hz, aromatic H), 7.63 (1H, d, J=5.7 Hz, aromatic H), 7.78 (1H, d, J=8.1 Hz, aromatic H), 7.98 (3H, s, 3×aromatic H), 8.49 (1H, d, J=5.7 Hz, aromatic H), 9.78 (1H, br s, CON*H*). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 29.0 (C4′), 38.6 (C3′), 60.5 (C1′), 115.6 (1×*C*F$_3$), 119.2 (1×*C*F$_3$), 121.6, 122.1, 125.2, 126.0, 126.5, 126.8, 127.3, 127.4, 127.8, 129.5, 130.4, 131.7, 132.1, 134.16, 134.20, 137.9, 140.6, 141.6, 155.2 (21×aromatic C), 160.5 (N*C*ON). Mass (ESI) calcd for $C_{27}H_{19}F_6N_3O$: 515.14, found 516.07 (M+1). HPLC (Chiralcel OD-H column): hexane/IPA=95/5, 1.0 mL/min, 25 °C, 254 nm, t_1=9.18 min for (−) and t_2=9.79 min for (+). $[\alpha]_D^{25}$ +375.7 (c 1.05, CH_2Cl_2).

*4.7.2.5. Preparation of (+)-N′-(2,4,6-trimethylphenyl)-1,1′-bisisoquinoline-2′-carboxamide (+)-**16***. Compound (+)-**1** (65 mg, 0.25 mmol) was reacted with 2,4,6-trimethylphenyl isocyanate (40.3 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) to give a white solid that was purified by column chromatography (EtOAc/hexane=1/9) to give (+)-*N*′-(2,4,6-trimethylphenyl)-1,1′-bisisoquinoline-2′-carboxamide (+)-**16** as white powder (97.1 mg, 92%). Mp 223–227 °C. FTIR (KBr) ν_{max}: 3260, 3024, 2942, 1625, 1509, 1396, 1292, 1238, 842, 831, 740 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.01 (6H, s, 2″-C*H*$_3$ and 6″-C*H*$_3$), 2.23 (3H, s, 4″-C*H*$_3$), 3.03 (1H, m, 1×H4′), 3.17 (1H, ddd, J=16.2 Hz, 13.8 Hz, 5.1 Hz, 1×H4′), 3.66 (1H, m, 1×H3′), 4.36 (1H, dd, J=13.2 Hz, 2.7 Hz, 1×H3′), 6.82 (2H, s, H3″ and H5″),

6.91 (1H, d, J=7.8 Hz, aromatic H), 7.07 (1H, s, H1′), 7.07 (1H, t, J=6.9 Hz, aromatic H), 7.22 (1H, t, J=7.4 Hz, aromatic H), 7.29 (1H, d, J=7.2 Hz, aromatic H), 7.38 (1H, br s, CONH), 7.45 (1H, t, J=7.8 Hz, aromatic H), 7.61–7.66 (2H, m, 2×aromatic H), 7.83 (1H, d, J=8.4 Hz, aromatic H), 8.26 (1H, d, J=8.4 Hz, aromatic H), 8.43 (1H, d, J=5.4 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 18.3 (2″-CH_3 and 6″-CH_3), 20.9 (4"-CH_3), 29.3 (C4′), 39.0 (C3′), 59.7 (C1′), 121.2, 126.2, 126.4, 126.7, 127.0, 127.48, 127.54, 127.7, 128.8, 129.4, 130.1, 133.1, 134.8, 135.2, 135.3, 135.7, 137.5, 141.2, 156.1 (21×aromatic C), 161.5 (NCON). Mass (ESI) calcd for $C_{28}H_{27}N_3O$: 421.22, found 422.53 (M+1). $[\alpha]_D^{25}$ +213.8 (c 0.95, CH_2Cl_2).

*4.7.3. Thiourea derivatives (+)-**17–23**. General procedure*: Isothiocyanates were added to a solution of (+)-**1** in dry CH_2Cl_2 under nitrogen atmosphere and the reaction mixture was stirred overnight at room temperature. The mixture was washed with brine, the organic phase was separated, dried over $MgSO_4$, and filtered and the solvent was removed under vacuum. The residue was subjected to column chromatography to give the pure thiourea derivative.

*4.7.3.1. Preparation of (+)-N′-isopropyl-1,1′-bisisoquinoline-2′-carbothioamide (+)-**17***. Compound (+)-**1** (65 mg, 0.25 mmol) was reacted with isopropyl isothiocyanate (26.7 μl, 0.25 mmol) in CH_2Cl_2 (3 mL) to give a white solid that was purified by column chromatography (EtOAc/hexane=1/9) to give (+)-N′-isopropyl-1,1′-bisisoquinoline-2′-carbothioamide (+)-**17** as white foam (86.8 mg, 96%). Mp 102–105 °C. FTIR (KBr) ν_{max}: 3331, 2970, 1522, 1491, 1346, 1306, 1234, 1192, 1166, 830, 735 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (3H, d, J=6.6 Hz, CH_3CHCH$_3$), 1.33 (3H, d, J=6.3 Hz, CH$_3$CHCH_3), 3.12–3.30 (2H, m, H4′), 3.78 (1H, ddd, J=10.5 Hz, 13.2 Hz, 4.5 Hz, 1×H3′), 4.62 (1H, m, J=6.6 Hz, CH$_3$CHCH$_3$), 5.36 (1H, m, J=13.2 Hz, 4.2 Hz, 1×H3′), 6.96 (1H, d, J=7.8 Hz, aromatic H), 7.07 (1H, s, H1′), 7.08 (1H, t, J=7.4 Hz, aromatic H), 7.23 (1H, t, J=7.1 Hz, aromatic H), 7.31 (1H, d, J=7.2 Hz, aromatic H), 7.41 (1H, apparent t, J=7.8 Hz, aromatic H), 7.62 (1H, apparent t, J=7.2 Hz, aromatic H), 7.65 (1H, d, J=6.0 Hz, aromatic H), 7.82 (1H, d, J=8.1 Hz, aromatic H), 7.99 (1H, d, J=8.4 Hz, aromatic H), 8.16 (1H, br d, J=6.0 Hz, CSNH), 8.44 (1H, d, J=5.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 22.4 (CH_3CHCH$_3$), 23.1 (CH$_3$CHCH$_3$), 28.7 (C4′), 43.6 (C3′), 47.8 (CH$_3$CHCH$_3$), 64.3 (C1′), 121.8, 126.1, 126.5, 126.7, 127.0, 127.4, 127.5, 127.7, 129.4, 130.2, 134.6, 134.7, 137.9, 140.4, 159.7 (15×aromatic C), 181.6 (NCSN). Mass (ESI) calcd for $C_{22}H_{23}N_3S$: 361.16, found 362.00 (M+1). $[\alpha]_D^{25}$ +268.0 (c 0.88, CH_2Cl_2).

*4.7.3.2. Preparation of (+)-N′-(3,5-dichlorophenyl)-1,1′-bisisoquinoline-2′-carbothioamide (+)-**18***. Compound (+)-**1** (65 mg, 0.25 mmol) was reacted with 3,5-dichlorophenyl isothiocyanate (51 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) to give an off-white solid that was purified by column chromatography (EtOAc/hexane=1/9) to give (+)-N′-(3,5-dichlorophenyl)-1,1′-bisisoquinoline-2′-carbothioamide (+)-**18** as light yellow foam (98.8 mg, 85%). Mp 108–110 °C. FTIR (KBr) ν_{max}: 3449, 2962, 2884, 1588, 1543, 1444, 1421, 1371, 1318, 1192, 1048, 834, 804, 756 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.11 (1H, apparent d, J=16.8 Hz, 1×H4′), 3.36 (1H, td, J=14.4 Hz, 5.1 Hz, 1×H4′), 3.65 (1H, td, J=12.0 Hz, 3.3 Hz, 1×H3′), 5.47 (1H, apparent d, J=11.7 Hz, 1×H3′), 6.98 (1H, d, J=7.5 Hz, aromatic H), 7.10–7.15 (2H, m, 2×aromatic H), 7.22 (1H, s, H1′), 7.27–7.39 (3H, m, 3×aromatic H), 7.45 (1H, s, aromatic H), 7.46 (1H, s, aromatic H), 7.65 (1H, apparent t, J=7.5 Hz, aromatic H), 7.74 (1H, d, J=8.4 Hz, aromatic H), 7.77 (1H, d, J=5.7 Hz, aromatic H), 7.88 (1H, d, J=8.1 Hz, aromatic H), 8.58 (1H, d, J=5.7 Hz, aromatic H), 11.00 (1H, br s, CSNH). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 28.5 (C4′), 44.1 (C3′), 64.7 (C1′), 122.3, 122.4, 124.4, 126.0, 126.8, 127.0, 127.2, 127.8, 127.89, 127.91, 129.7, 130.5, 133.9, 134.3, 134.5, 138.1, 140.5, 142.6, 159.3 (21×aromatic C), 182.2 (NCSN). Mass (ESI) calcd for $C_{25}H_{19}Cl_2N_3S$: 463.07, found 463.93 (M+1). HPLC (Chiralcel OD-H column): hexane/IPA=95/5, 1.0 mL/min, 25 °C, 254 nm, t_1=24.56 min for (−) and t_2=42.08 min for (+). $[\alpha]_D^{25}$ +381.6 (c 0.94, CH_2Cl_2).

*4.7.3.3. Preparation of (+)-N′-ethyl-1,1′-bisisoquinoline-2′-carbothioamide (+)-**19***. Compound (+)-**1** (65 mg, 0.25 mmol) was reacted with ethyl isothiocyanate (22 μl, 0.25 mmol) in CH_2Cl_2 (3 mL) to give an off-white solid that was purified by column chromatography (EtOAc/hexane=1/9) to give (+)-N′-ethyl-1,1′-bisisoquinoline-2′-carbothioamide (+)-**19** as yellow foam (78.6 mg, 90%). Mp 93–96 °C. FTIR (KBr) ν_{max}: 3310, 2971, 2930, 1685, 1523, 1450, 1388, 1307, 1230, 829, 748 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (3H, t, J=7.4 Hz, CH_3), 3.15–3.28 (2H, m, H4′), 3.60–3.74 (2H, m, CH_2CH$_3$), 3.75–3.83 (1H, m, 1×H3′), 5.25 (1H, m, J=12.9 Hz, 4.1 Hz, 1×H3′), 6.97 (1H, d, J=7.5 Hz, aromatic H), 7.07 (1H, t, J=7.5 Hz, aromatic H), 7.17 (1H, s, H1′), 7.21 (1H, t, J=7.5 Hz, aromatic H), 7.29 (1H, d, J=7.5 Hz, aromatic H), 7.42 (1H, t, J=7.8 Hz, aromatic H), 7.59–7.64 (2H, m, 2×aromatic H), 7.81 (1H, d, J=8.1 Hz, aromatic H), 8.03 (1H, br s, CSNH), 8.05 (1H, d, J=8.4 Hz, aromatic H), 8.43 (1H, d, J=5.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 14.4 (CH_2CH_3), 28.6 (C4′), 41.3 (CH_2CH_3), 43.5 (C3′), 63.7 (C1′), 121.6, 126.1, 126.5, 126.6, 127.1, 127.3, 127.5, 127.7, 129.2, 130.2, 134.7, 134.8, 137.6, 140.6, 159.9 (15×aromatic C), 182.4 (NCSN). Mass (ESI) calcd for $C_{21}H_{21}N_3S$: 347.15, found 348.07 (M+1). $[\alpha]_D^{25}$ +43.7 (c 0.83, CH_2Cl_2).

*4.7.3.4. Preparation of (+)-N′-(tert-butyl)-1,1′-bisisoquinoline-2′-carbothioamide (+)-**20***. Compound (+)-**1** (65 mg, 0.25 mmol) was reacted with *tert*-butyl isothiocyanate (31.7 μl, 0.25 mmol) in CH_2Cl_2 (3 mL) to give an off-white solid that was purified by column chromatography (EtOAc/hexane=0.5/9.5) to give (+)-N′-(*tert*-butyl)-1,1′-bisisoquinoline-2′-carbothioamide (+)-**20** as white foam (74.6 mg, 80%). Mp 97–101 °C. FTIR (KBr) ν_{max}: 3407, 3052, 2961, 1527, 1394, 1350, 1196, 1162, 829, 747 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.58 (9H, s, 3×CH_3), 3.09–3.29 (2H, m, H4′), 3.72 (1H, ddd, J=14.4 Hz, 10.7 Hz, 4.2 Hz, 1×H3′), 5.25 (1H, m, 1×H3′), 6.97 (1H, d, J=7.5 Hz, aromatic H), 7.04 (1H, t, J=7.4 Hz, aromatic H), 7.12 (1H, s, H1′), 7.19 (1H, t, J=7.4 Hz, aromatic H), 7.27 (1H, d, J=7.5 Hz, aromatic H), 7.37 (1H, t, J=7.5 Hz, aromatic H), 7.57 (1H, t, J=7.7 Hz, aromatic H), 7.61 (1H, d, J=5.4 Hz, aromatic H), 7.78 (1H, d, J=8.1 Hz, aromatic H), 7.98 (1H, d, J=8.4 Hz, aromatic H), 8.24 (1H, br s, CSNH), 8.42 (1H, d, J=5.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 29.3 (3×CH_3), 30.7 (C4′), 43.1 (C3′), 54.4 (C(CH$_3$)$_3$), 64.3 (C1′), 121.7, 126.1, 126.5, 126.6, 127.0, 127.3, 127.5, 127.7, 129.4, 130.1, 134.9, 135.0, 137.8, 140.5, 159.9 (15×aromatic C), 181.6 (NCSN). Mass (ESI) calcd for $C_{23}H_{25}N_3S$: 375.18, found 376.00 (M+1). HPLC (Chiralcel OD-H column): hexane/IPA=95/5, 1.0 mL/min, 25 °C, 254 nm, t_1=7.55 min for (−) and t_2=8.13 min for (+). $[\alpha]_D^{25}$ +228.2 (c 0.83, CH_2Cl_2).

*4.7.3.5. Preparation of (+)-N′-cyclohexyl-1,1′-bisisoquinoline-2′-carbothioamide (+)-**21***. Compound (+)-**1** (52 mg, 0.2 mmol) was reacted with cyclohexyl isothiocyanate (27.3 μl, 0.2 mmol) in CH_2Cl_2 (3 mL) to give an off-white solid that was purified by column chromatography (EtOAc/hexane=0.5/9.5) to give (+)-N′-cyclohexyl-1,1′-bisisoquinoline-2′-carbothioamide (+)-**21** as white foam (73.4 mg, 92%). Mp 176–179 °C. FTIR (KBr) ν_{max}: 3233, 3015, 2929, 2847, 1585, 1450, 1399, 1362, 1174, 1143, 754 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.20–2.13 (10H, m, 5×CH_2), 3.12 (1H, m, 1×H4′), 3.26 (1H, ddd, J=16.5 Hz, 11.1 Hz, 5.1 Hz, 1×H4′), 3.74 (1H, ddd, J=12.9 Hz, 11.3 Hz, 3.9 Hz, 1×H3′), 4.31–4.40 (1H, m, CH$_2$CHCH$_2$), 5.41 (1H, m, 1×H3′), 6.94 (1H, d, J=7.5 Hz, aromatic H), 7.01 (1H, s, H1′), 7.06 (1H, t, J=7.2 Hz, aromatic H), 7.22 (1H, t, J=7.4 Hz, aromatic H), 7.30 (1H, d, J=7.5 Hz, aromatic H), 7.38 (1H, t, J=7.2 Hz, aromatic H), 7.60 (1H, t, J=7.7 Hz, aromatic H), 7.65 (1H, d,

J=5.4 Hz, aromatic H), 7.82 (1H, d, J=8.1 Hz, aromatic H), 7.93 (1H, d, J=8.7 Hz, aromatic H), 8.34 (1H, br d, J=6.3 Hz, CSN*H*), 8.44 (1H, d, J=5.4 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 24.6, 24.7, 25.8 (3×CH_2), 28.7 (C4′), 32.4, 33.1 (2×CH_2), 43.6 (C3′), 54.4 (CH_2CHCH_2), 64.6 (C1′), 121.9, 126.2, 126.6, 126.7, 127.0, 127.4, 127.5, 127.7, 129.4, 130.2, 134.6, 134.7, 137.9, 140.4, 159.6 (15×aromatic C), 181.6 (NCSN). Mass (ESI) calcd for $C_{25}H_{27}N_3S$: 401.19, found 402.13 (M+1). HPLC (Chiralcel OD-H column): hexane/IPA=95/5, 1.0 mL/min, 25 °C, 254 nm, t_1=13.31 min for (+) and t_2=14.45 min for (−). $[\alpha]_D^{25}$ +195.6 (*c* 1.2, CH_2Cl_2).

*4.7.3.6. Preparation of (+)-N′-phenyl-1,1′-bisisoquinoline-2′-carbothioamide (+)-**22**.* Compound (+)-**1** (52 mg, 0.2 mmol) was reacted with phenyl isothiocyanate (38.1 μl, 0.2 mmol) in CH_2Cl_2 (3 mL) to give a white solid, which was purified by column chromatography (EtOAc/hexane=0.5/9.5) to give (+)-*N*′-phenyl-1,1′-bisisoquinoline-2′-carbothioamide (+)-**22** as white foam (70.2 mg, 89%). Mp 102–104 °C. FTIR (KBr) ν_{max}: 3246, 3026, 2928, 1498, 1329, 1228, 934, 827, 748, 694 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.08 (1H, m, 1×H4′), 3.28 (1H, ddd, J=15.9 Hz, 12.2 Hz, 5.1 Hz, 1×H4′), 3.72 (1H, m, 1×H3′), 5.28 (1H, apparent d, J=12.3 Hz, 1×H3′), 6.95 (1H, d, J=7.5 Hz, aromatic H), 7.06–7.11 (2H, m, 2×aromatic H), 7.19–7.40 (8H, m, H1′ and 7×aromatic H), 7.57 (1H, t, J=7.7 Hz, aromatic H), 7.65 (1H, d, J=5.4 Hz, aromatic H), 7.79 (1H, d, J=8.1 Hz, aromatic H), 7.94 (1H, d, J=8.4 Hz, aromatic H), 8.48 (1H, d, J=5.7 Hz, aromatic H), 10.43 (1H, br s, CSN*H*). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 28.6 (C4′), 43.9 (C3′), 64.5 (C1′), 122.1, 124.8, 125.1, 126.1, 126.8, 126.9, 127.2, 127.6, 127.7, 127.8, 128.6, 129.6, 130.4, 134.4, 134.6, 138.0, 140.57, 140.62, 159.6 (21×aromatic C), 182.8 (NCSN). Mass (ESI) calcd for $C_{25}H_{21}N_3S$: 395.15, found 396.07 (M+1). $[\alpha]_D^{25}$ +159.9 (*c* 1.0, CH_2Cl_2).

*4.7.3.7. Preparation of (+)-N′-(3,5-di-trifluromethylphenyl)-1,1′-bisisoquinoline-2′-carbothioamide (+)-**23**.* Compound (+)-**1** (52 mg, 0.2 mmol) was reacted with 3,5-di-trifluromethylphenyl isothiocyanate (36.5 μl, 0.2 mmol) in CH_2Cl_2 (3 mL) to give an off-white solid that was purified by column chromatography (EtOAc/hexane=0.5/9.5) to give (+)-*N*′-(3,5-di-trifluromethylphenyl)-1,1′-bisisoquinoline-2′-carbothioamide (+)-**23** as an off-white foam (92.1 mg, 87%). Mp 102–105 °C. FTIR (KBr) ν_{max}: 2935, 1474, 1380, 1278, 1180, 1133, 884, 745 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.13 (1H, apparent d, J=16.5 Hz, 1×H4′), 3.36 (1H, ddd, J=16.2 Hz, 12.5 Hz, 5.1 Hz, 1×H4′), 3.66 (1H, t, J=11.6 Hz, 1×H3′), 5.50 (1H, apparent d, J=9.3 Hz, 1×H3′), 6.98 (1H, d, J=7.5 Hz, aromatic H), 7.12 (1H, t, J=7.5 Hz, aromatic H), 7.23–7.38 (4H, m, 3×aromatic H and H1′), 7.60–7.74 (3H, m, 3×aromatic H), 7.77 (1H, d, J=5.7 Hz, aromatic H), 7.86 (1H, d, J=8.4 Hz, aromatic H), 8.06 (2H, s, 2×aromatic H), 8.56 (1H, d, J=5.7 Hz, aromatic H), 11.55 (1H, br s, CSN*H*). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 28.4 (C4′), 43.9 (C3′), 65.1 (C1′), 117.7 (1×CF_3), 122.8 (aromatic C), 123.8 (1×CF_3), 125.1, 125.9, 126.8, 127.1, 127.9, 128.0, 128.7, 129.8, 130.6, 131.4, 131.8, 132.3, 133.5, 134.2, 138.3, 140.2, 142.2, 159.0 (20×aromatic C), 182.4 (NCSN). Mass (ESI) calcd for $C_{27}H_{19}F_6N_3S$: 531.12, found 531.93 (M+1). HPLC (Chiralcel OD-H column): hexane/IPA=95/5, 1.0 mL/min, 25 °C, 254 nm, t_1=10.44 min for (−) and t_2=15.88 min for (+). $[\alpha]_D^{25}$ +199.2 (*c* 1.89, CH_2Cl_2).

4.8. Catalytic enantioselective addition of Et_2Zn to benzaldehyde using ligand (+)-1

Ligand (+)-**1** (39 mg, 0.15 mmol) was dissolved in dry THF (1 mL) and Et_2Zn (3 mL of 1.0 M in hexane, 3 mmol) was added dropwise at room temperature. After complete addition, the color of solution turned orange-red. The mixture was cooled down to 0 °C and stirred for 10 min whereby the benzaldehyde **24** (106 mg, 0.1 mL, 1.0 mmol) was injected dropwise via a syringe needle. The mixture was stirred for 30 h at 0 °C under N_2 atmosphere. The reaction was then quenched with saturated NH_4Cl solution (5 mL). The organic phase was separated and washed with diluted HCl solution (3×5 mL), saturated Na_2CO_3 solution (3×5 mL) and dried over $MgSO_4$, and filtered. The resulting organic solution was diluted with diethyl ether (5 mL) and subjected to GC directly to give (1*R*)-1-phenyl-1-propanol (*R*)-**25** (96%, GC yield). The ee of 85% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate=2.0 mL/min, oven=110 °C, t_1=8.98 min for (*R*) and t_2=9.23 min for (*S*). $[\alpha]_D^{25}$ +43.8 (*c* 1.30, $CHCl_3$) {lit.[15] $[\alpha]_D^{26}$ +40.3 (*c* 1.21, $CHCl_3$) for 96% ee (*R*)}.

4.9. Enantioselective addition of CH_3NO_2 to benzaldehyde using (+)-1

Ligand (+)-**1** (0.02 mmol) and CuCl (0.01 mmol) were dissolved in $ClCH_2CH_2Cl$ (1.5 mL) and allowed to stir at room temperature for 2 h whereby a dark green solution was obtained. To the above stirred solution, benzaldehyde **24** (0.2 mmol) was added and the mixture was stirred for another 5 min before addition of CH_3NO_2 (4 mmol). The reaction mixture was further stirred at 0 °C for 30 h. The crude β-nitroalcohol product was purified on silica gel by flash column chromatography (EtOAc/hexane=1/5) to give (*R*)-1-Phenyl-2-nitroethanol (*R*)-**26** as a colorless oil (60% yield). The ee of 85% was determined by HPLC. HPLC (Chiralcel OD-H column): hexane/IPA=90/10, 0.8 mL/min, 25 °C, 215 nm, t_1=18.1 min for (*R*) and t_2=22.2 min for (*S*).

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.03.106. These data include MOL files and InChIKeys of the most important compounds described in this article.

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