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1,1′-Methylene-bis(1,1′,2,2′,3,3′,4,4′-octahydroisoquinoline): synthesis, reaction, resolution, and application in catalytic enantioselective transformations

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ABSTRACT

The preparation of new chiral 1,3-diamine ligand systems based on the 1,1′-methylene-bis(1,1′,2,2′,3,3′,4,4′-octahydroisoquinoline) framework is described. Synthesis of various mono-, di-, and bridged *N*-alkyl derivatives are presented. Resolution of one compound, its Cu(I)Br X-ray crystallographic structure and the preliminary results on its application in the enantioselective Henry and Aldol reactions are disclosed.

1. Introduction

Application of chiral nitrogen ligands in the form of metal complexes, auxiliaries and organocatalysts in various catalytic asymmetric transformations is well documented.[1] For example, the privileged catalyst, salen has been extensively used in many enantioselective reactions.[2] We[3] and others[4] have been interested in constructing chiral bidentate 1,1′-bisisoquinolines, such as **1** and **2** (Fig. 1) and employing them as catalysts for various enantioselective reactions. Moderate to very good selectivities have been obtained suggesting great potential for further improvements.[3b,4] Based upon our solution and solid state studies[3a,c,d] as well as DFT calculations,[5] we found that 1,1′-bisisoquinolines assume different structural conformations depending upon the degree of saturation of the heterocyclic ring (i.e., **1** vis **2**, Fig. 1) as well as the type (alkyl, acyl, sulfonyl) and steric bulkiness of the substituents on the nitrogens. Additionally, the structural conformations were found to have direct impact on the reactivity and selectivity in the enantioselective addition of Et_2Zn to aldehydes.[3b] Such a discovery, combined with limited structural varieties of chiral 1,1′-bisisoquinolines, prompted us to search for more efficient 1,1′-bisisoquinoline ligands.

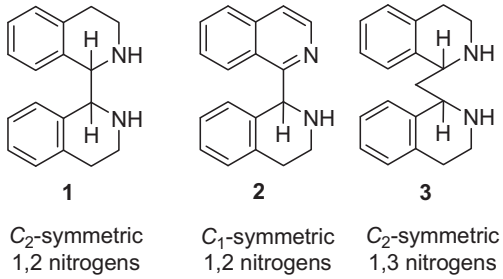

Fig. 1. Structures of 1,1′-bisisoquinolines.

Without exceptions, to our knowledge, all the reported[3,4a,b] reduced and partially reduced chiral 1,1′-bisisoquinolines have their two nitrogens in a 1,2-disposition (e.g., **1** and **2**, Fig. 1) and would form five-membered chelated rings after coordination with metal ions. Considering the vital influence of the bite angle and the conformational flexibility of the ligands on the reactivity and selectivity, we envisaged that a new arrangement in which the two nitrogens are 1,3-disposed (i.e., 1,3-diamine) to form six-membered chelating rings (e.g., **3**, Fig. 1), would bring a new conformation different to those obtained with five-membered chelated ring as in the case of **1** and **2**. In anticipation of doing so, this would be the first time that the framework **3** has been applied in asymmetric catalysis.

Herein, we report on the chemistry of 1,1′-methylene-bis(1,1′,2,2′,3,3′,4,4′-octahydroisoquinoline) **3** including its

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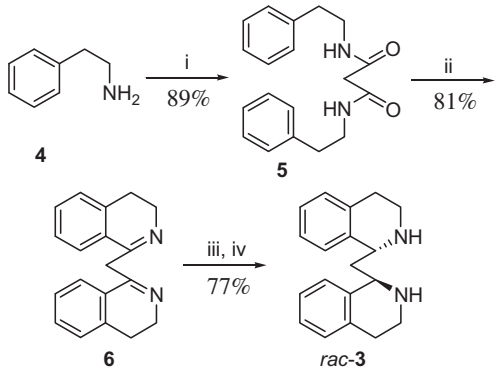
synthesis, reactivity, resolution, and its complexation with CuBr. Preliminary results on the application of **3** in the enantioselective Henry and Aldol reactions will also be presented.

2. Results and discussion

2.1. Preparation of *rac*-1,1′-methylene-1,1′,2,2′,3,3′,4,4′-octahydrobisisoquinoline

We and others have exploited Bischler–Napieralski reaction successfully for the synthesis of a wide range of 1,1′-bis(3,3′,4,4′-tetrahydroisoquinoline) compounds using various dehydrating agents.[3a–e,4a,6a–e] Building on our experience in this area, we chose to synthesize **3** as shown in Scheme 1. Reaction between phenethylamine **4** and diethyl malonate gave bisamide **5**, which upon cyclization using $POCl_3/P_2O_5$ as dehydrating agents gave compound **6**.[6d,e] Earlier studies on the reduction of similar 1,1′-bis(3,3′,4,4′-tetrahydroisoquinoline) compounds, where C1 and C1′ are directly connected, using $NaBH_4$ gave mixtures of *racemic* and *meso* 1,1′-bis(1,1′,2,2′,3,3′,4,4′-octahydroisoquinoline) compounds while reduction of the same using $NaCNBH_3$ gave only *racemic* isomers.[3c,6a,c] Therefore, we chose to reduce **6** using $NaCNBH_3$ in anticipation of obtaining the desired *rac*-**3** (Scheme 1).[6a]



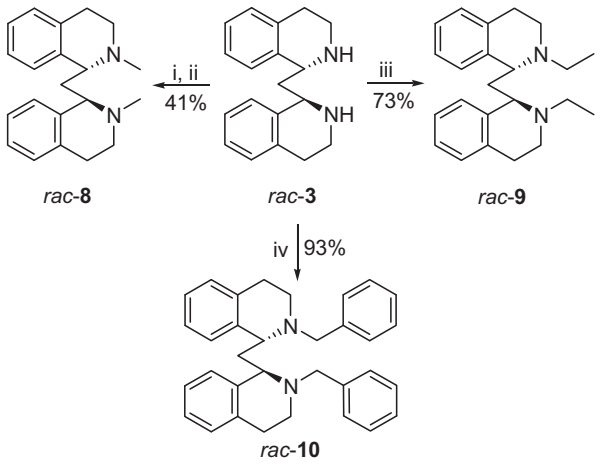
Reagents and conditions: i) $(EtOCO)_2CH_2$, 80 °C, 2 days; ii) $POCl_3$, P_2O_5, toluene, reflux, 24 h; iii) $NaCNBH_3$, MeOH, HCl, 0.5 h; iv) NaOH, H_2O, CH_2Cl_2

Scheme 1. Synthesis of *rac*-**3**.

Reduction of **6** with $NaCNBH_3$ gave single isomer **3** whose stereochemistry needed to be established since one of the main objectives of this work was to obtain **3** in enantiopure form for application in asymmetric catalysis. Therefore, we synthesized (see later) formaldehyde adduct **7** and examined its ^1H NMR spectrum focusing on the N–CH2–N′ protons. If **3** is *racemic*, the N–CH2–N′ protons should appear as a singlet since they are in a similar environment with respect to the lone pair electrons on the adjacent nitrogens.[6c] Indeed, we were delighted to see a singlet at δ 3.84 ppm corresponding to the N–CH2–N′ protons confirming the *racemic* nature of **3**. In a *meso*-**3** isomer, the N–CH2–N′ proton signals would be split and appear as an AB quartet with two different chemical shifts.[6c] More evidence to the *racemic* nature of **3** comes from single X-ray crystallography discussed later.

2.2. Alkylation of *rac*-1,1′-methylene-bis(1,1′,2,2′,3,3′,4,4′-octahydroisoquinoline) *rac*-3

Having established the *racemic* nature of **3**, we set to prepare both its symmetric and unsymmetric derivatives through alkylation of the nitrogens. Once used as ligands in enantioselective reactions, these derivatives would be expected to exhibit differing selectivities and reactivities since they possess contrasting effects: the symmetric ligands will maintain the C_2-symmetry and possess similar sp^3 nitrogens having the same basicity while the unsymmetric ligands will possess C_2-symmetry and two electronically different sp^3 nitrogens (alkylated and none alkylated nitrogens) having diverse basicities. Such contrasting effects are important to add variety to the framework of *rac*-**3** and distinguish between the two nitrogens especially in the chelated state since the Lewis acidity/basicity directly impact ligands selectivities and reactivities.[7] Thus, *rac*-**3** was subjected to standard alkylation conditions using suitable alkyl halides to produce the doubly *N*-alkyl ligands *rac*-**8**–**10**.[8] Reaction between *rac*-**3** and neat iodomethane followed by treatment with aqueous NaOH gave the desired product *rac*-**8** (Scheme 2). Reaction between *rac*-**3** and both ethyl bromide and benzyl bromide in the presence of K_2CO_3 gave *rac*-**9** and **10**, respectively, in excellent yields (Scheme 2).



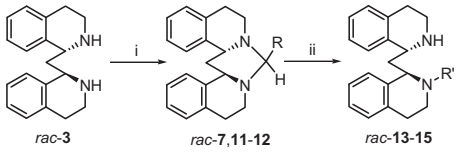
Reagent and conditions: i) neat CH_3I, 12 h; ii) NaOH, H_2O, CH_2Cl_2; iii) 2.2 equiv ethyl bromide, K_2CO_3, THF, 60 °C, overnight; iv) 2.2 equiv benzyl bromide, K_2CO_3, THF, 60 °C, overnight

Scheme 2. Synthesis of doubly *N*-alkyls *rac*-**8**–**10**.

Attempts to directly prepare mono *N*-alkyl derivatives by treatment of *rac*-**3** with 1 mol of ethyl or benzyl bromides, failed to produce the desired mono *N*-alkylated products. Instead, mixtures of mono *N*-alkylated, doubly *N*-alkylated products were obtained along with the starting material *rac*-**3** thus indicating that the second alkylation step (to form the doubly *N*-alkylated products) is faster than the first one (which forms the mono *N*-alkylated products). To overcome this problem, we adapted the sequence of aminal formation followed by reduction.[8b] Therefore, condensation of *rac*-**3** with formaldehyde, acetaldehyde, and benzaldehyde gave aminals *rac*-**7**, *rac*-**11**, and *rac*-**12**, respectively, which upon reduction using $NaCNBH_3$ gave the required corresponding mono *N*-alkylated derivatives *rac*-**13**, *rac*-**14**, and *rac*-**15**, respectively, in very good overall yields (Scheme 3).

2.3. Resolution of *rac*-1,1′-methylene-bis(1,1′,2,2′,3,3′,4,4′-octahydroisoquinoline) *rac*-3

We required access to enantiopure **3** for further enantioselective catalysis studies. After a survey of different chiral acids, we found that the salt of *rac*-**3** and L-(+)-citramalic acid (2 equiv) crystallizes in a mixture of H_2O and EtOH (1:1.5, v:v) to give enantiopure and highly enriched batches of crystals upon standing at rt. The enantiopure batches were treated separately with 10% NaOH and



	R	% yield
rac-**7**	H	85
rac-**11**	CH_3	80
rac-**12**	Ph	90

	R'	% yield
rac-**13**	CH_3	72
rac-**14**	CH_2CH_3	70
rac-**15**	CH_2Ph	78

Reagents and conditions: i) RCHO, EtOH, 4A molecular sieve; ii) $NaCNBH_3$, HCl, MeOH.

Scheme 3. Synthesis of aminals *rac*-**7**, *rac*-**11**, and *rac*-**12** and mono *N*-alkyls *rac*-**13**–**15**.

extracted with CH_2Cl_2 to give the (−)-**3** and (+)-**3** enantiomeric products. The enantiomeric purities of (−)-**3** and (+)-**3** were confirmed by chiral HPLC and were found to be >99%. Crystallization of a mixture of (+)-**3** and (L)-(+)-citramalic acid from EtOH produced colorless cubic crystals suitable for single X-ray crystallographic analysis.[9] The crystal structure of the salt of (+)-**3** (Fig. 2) proved that (i) (+)-**3** has the (*R*,*R*) absolute configuration and consequently (−)-**3** should have the (*S*,*S*) absolute configuration; and (ii) reduction of **6** using $NaBH_3CN$ produced *rac*-**3** (Scheme 1).

We were delighted to obtain single crystals suitable for X-ray crystallographic analysis when a methanolic solution of *rac*-**3** and CuBr was allowed to crystallize at rt. The X-ray structure of the *rac*-**3**/CuBr complex **16** demonstrated a mononuclear six-membered chelated ring (Fig. 2).[10]

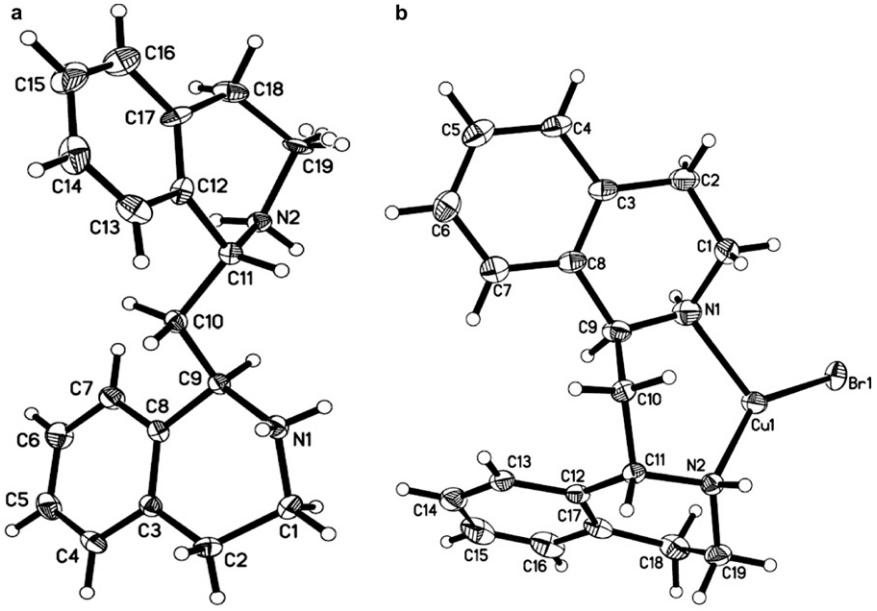


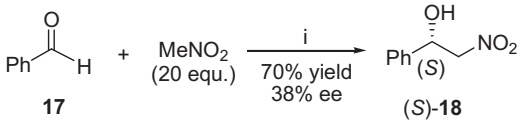
Fig. 2. ORTEP diagrams of (a) (*R*,*R*)-**3** and (b) *rac*-**3**/**CuBr** complex **16**.

2.4. Application of (*R*,*R*)-3 in catalytic enantioselective Henry and Aldol reactions

With the chiral diamine (*R*,*R*)-**3** in hand, we then examined its ability to catalyze the enantioselective Henry (Scheme 4) and Aldol (Scheme 5) reactions.

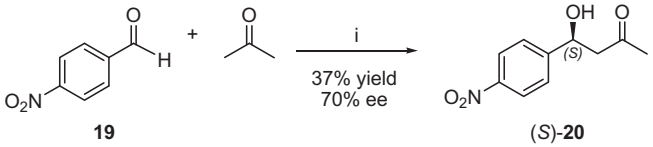
Henry reaction is a very powerful C–C bond-forming tool in organic synthesis. The resultant nitroalcohol adducts can be transformed using well documented protocols into many important building blocks, such as nitroalkenes, amino alcohols, and amino acids etc.[11] Chiral diamine/copper complexes have been reported as catalysts for this reaction with variable success.[12] Therefore, it was logical to use this reaction as a test-bed to examine the effectiveness of (*R*,*R*)-**3**. Our preliminary results indicated that the addition of nitromethane (20 equiv) to benzaldehyde **17** in the presence of 10 mol % (*R*,*R*)-**3** and 10 mol % CuBr gave the desired product (*S*)-**18** in 70% yield and 38% ee (Scheme 4).

The stereochemical observation of the product in Scheme 4 can be explained based on the reaction mechanism shown in Fig. 3. The nitro group is known to strongly coordinate to soft metals.[13] Thus, nitomethane is activated and deprotonated to generate the active nitronate nucleophile on the (*R*,*R*)-**3**/Cu(I) complex.[7,13] The nitronate group assumes an axial position in Fig. 3 with the help of the hydrogen bonding between the nitro group and the sp^3-N–H. Subsequent coordination of the benzaldehyde in such a way that it occupies the outside position by appropriately orienting itself in such a way to avoid steric hindrance with the isoquinoline ring results in formation of a tetracoordinated Cu(I) transition state which favors the *Re* face nucleophilic attack of the nitronate on the benzaldehyde carbonyl to give the corresponding (*S*)-**18** (Fig. 3).



Reagents and conditions: i) 10 mol% (*R*,*R*)-**3**, 10 mol% CuBr, dioxane, r.t., 40 h.

Scheme 4. Enantioselective addition of nitromethane to benzaldehyde **17** using (*R*,*R*)-**3**.



Reagents and conditions: 20 mol% (*R*,*R*)-**3**, 20 mol% PTSA, acetone, r.t., 4 d.

Scheme 5. Enantioselective addition of acetone to 4-nitrobenzaldehyde **19** catalyzed by (*R*,*R*)-**3**.

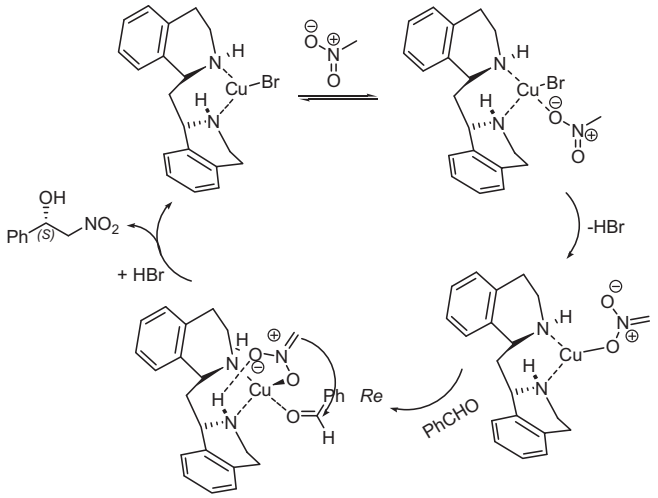


Fig. 3. Proposed mechanism for the asymmetric Henry reaction catalyzed by (*R*,*R*)-**3**/CuBr complex.

Additionally, the enantioselective Aldol[14] reaction between 4-nitrobenzaldehyde **19** and acetone in the presence of (*R*,*R*)-**3** and *p*-toluenesulfonic acid (PTSA) was also examined briefly. The desired aldol product (*S*)-**20** was obtained smoothly in 37% yield and 70% ee (Scheme 5).

While a wide range of conditions have not been evaluated in both the Henry and Aldol reactions, the fact that 38% ee and 70% ee, respectively, were obtained using ligand (*R*,*R*)-**3** is very promising and suggests great potential for development and optimization.

3. Conclusion

We have successfully achieved the synthesis of a new ligand framework, the 1,1′-methylene-bis(1,1′,2,2′,3,3′,4,4′-octahydroisoquinoline) **3** and prepared its symmetric and unsymmetric ligands through the synthesis of various mono-, di-, and bridged *N*-alkyls. The absolute stereochemistry of the new framework was established through X-ray crystallography for the first time. Metal complexation with Cu(I)Br revealed the formation of mononuclear complex. Preliminary results on application of (*R*,*R*)-**3** in the enantioselective Henry and Aldol reaction were very promising and warrant further investigations. Optimization of the reaction conditions and further applications in other asymmetric reactions of the new ligands are still in progress in our laboratory and will be reported in due course.

4. Experimental section

4.1. General remarks

All chemicals were reagent grade unless otherwise specified. Analytical thin layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plates (0.2 mm thickness). Products separation was achieved on Merck Silica Gel 60 (230–400 mesh) using column chromatography. Melting points were determined on Bamstead Electrothermal 9100 melting point tester. FTIR spectra were recorded on Perkin–Elmer FTIR system Spectrum BX. ^{1}H (300 MHz) and ^{13}C (75.47 MHz) NMR spectra were recorded on a Bruker Advanced DPX 300 spectrometer with TMS as internal reference. High resolution mass spectra were recorded on Finigan MAT 95*P spectrometer. X-single crystal diffraction data were obtained on Bruker-AXS Smart Apex CCD single-crystal diffractometer. HPLC separation was performed on Agilent 1100 using Diacel Chiralcel OD-H and AS-H chiral columns. LC–Mass spectra were recorded on Agilent LC system with Agilent Mass selective detector. Optical rotation values were measured using JASCO P-1020 polarimeter.

4.2. Preparation of *N*,*N*′-bisphenethylmalonamide 5

Diethyl malonate (3.2 mL, 0.021 mol) was added dropwise over a period of 10 min to phenethylamine (5.2 mL, 0.042 mol) and the mixture was vigorously stirred at 80 °C for 2 days whereby thick yellow solid was obtained. After reaction completion (TLC analysis), the yellow solid was transferred to a Buckner funnel, washed with hexane (3×10 mL), and dried in a dissector. *N*,*N*′-Bisphenethylmalonamide **5** was obtained as a fluffy white solid (5.8 g, 89%), mp 102–104 °C. FTIR (KBr) ν_{max}: 3298, 1659, 1633, 1548, 1229, 747, 698, 575 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.82 (4H, t, J=7.2 Hz), 3.04 (2H, s), 4.16 (4H, t, J=7.2 Hz), 6.93 (2H, br s), 7.17–7.56 (10H, m). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 35.5, 40.9, 43.2, 126.6, 128.6, 128.7, 138.6, 167.2. *m*/*z* (ESI): calcd for $C_{19}H_{22}N_2O_2$: 310, found 311 (M+1).

4.3. Preparation of 1,1′-methylene-bis(3,3′,4,4′-tetrahydroisoquinoline) 6

$POCl_3$ (3.66 mL, 0.04 mol) was added dropwise to a stirred cooled (ice bath) suspension of *N*,*N*′-bisphenethylmalonamide **5** (1.34 g, 0.004 mol) and P_2O_5 (5.7 g, 0.04 mol) in toluene (15 mL). After complete addition, the ice bath was removed and the mixture was heated under reflux overnight. The reaction mixture was then cooled to rt, the solvent was decanted and saturated $NaHCO_3$ solution (20 mL) was added to the remaining yellow solid until gas evolution was no longer observed. Saturated NaOH (25 mL) was then added to adjust the pH of the mixture to pH 11. The alkaline solution was extracted with CH_2Cl_2 (4×30 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting dark brown gum was purified by column chromatography to give 1,1′-methylene-3,3′,4,4′-tetrahydrobisisoquinoline **6** as a brown gum (0.89 g, 81%). FTIR (KBr) ν_{max}: 1618, 1311, 1272, 1232, 1029, 746 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.80 (4H, t, J=6.6 Hz), 3.60 (4H, t, J=6.9 Hz), 5.93 (1H, s), 7.17–7.19 (2H, m), 7.25–7.35 (4H, m), 7.72–7.77 (2H, m). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 28.5, 42.4, 84.9, 124.6, 126.7, 127.8, 129.2, 131.5, 137.2, 157.8. HRMS (ESI): found (M+1) 275.1553. $C_{19}H_{18}N_2$+H requires 275.1548.

4.4. Preparation of *rac*-1,1′-methylene-bis(1,1′,2,2′,3,3′,4,4′-octahydroisoquinoline) *rac*-3

1,1′-Methylene-bis(3,3′,4,4′-tetrahydroisoquinoline) **6** (0.89 g, 3.25 mmol) was dissolved into 0.5 M HCl/MeOH solution (10 mL) and the resulting brown solution was evaporated to give a gummy brown residue. The residue was redissolved in MeOH (6 mL) and the resultant dark brown solution was added over 5 min to a stirred suspension of $NaCNBH_3$ (0.35 g, 5.52 mmol) in a mixture of MeOH (8 mL) and 3% HCL-MeOH (2 mL) at rt. After complete addition, the mixture was kept stirring for another 0.5 h. The solvent was then removed under reduced pressure until almost dry. NaOH solution (20 mL, 10%) was added to bring the solution to pH 11. The alkaline solution was then extracted with CH_2Cl_2 (how much 3×15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and the filtrates were evaporated under reduced pressure to give brown solid that was recrystallized from EtOH to give *rac*-1,1′-methylene-bis(1,1′,2,2′,3,3′,4,4′-octahydroisoquinoline) *rac*-**3** (0.70 g, 77%), mp 98–102 °C. FTIR (KBr) ν_{max}: 3325, 3249, 2923, 2853, 1497, 1453, 1127, 866, 767, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.19 (2H, t, J=6.6 Hz), 2.46 (2H, br s), 2.63–2.72 (2H, m), 2.76–2.85 (2H, m), 2.91–2.99 (2H, m), 3.18–3.26 (2H, m), 4.17 (2H, t, J=6.6 Hz), 6.99–7.10 (8H, m). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 30.0,

40.9, 42.0, 52.9, 125.8, 125.9, 126.0, 129.4, 135.5, 139.7. HRMS (ESI): found 279.1855 (M+1). $C_{19}H_{22}N_2$+H requires 279.1861.

4.5. Resolution of *rac*-3 with (L)-(+)-citramalic acid

(L)-(+)-Citramalic acid (1.04 g, 7.0 mmol) was added to a solution of *rac*-**3** (1.0 g, 3.5 mmol) in EtOH/H_2O (1.5:1, 15 mL) and stirred for 15 min at 40 °C. The resulting solution was left undisturbed at rt for several days where six crystalline batches were harvested. The first two batches of crystals were combined and suspended in CH_2Cl_2 (6 mL). NaOH solution (10 mL, 10%) was added to make the pH 11. The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (3×6 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the filtrate evaporated under reduced pressure to give (*S*,*S*)-**3** as a light yellow solid (150 mg, 15%, >99% ee). The next three batches of crystals were treated in a similar manner to the first two batches to give **3** (240 mg, 24%, (*S*,*S*)-**3** was obtained as enriched product in 70–80% ee). The sixth batch of crystals was processed similarly to give (*R*,*R*)-**3** as a white solid (30 mg, 3%, >99% ee). The mother liquor was evaporated to give white solid that was also processed similarly as described for the above batches to give (*R*,*R*)-**3** (540 mg, 54%, 40% *ee*). The ees of enantiomers were determined by HPLC (Daicel Chiralcel OD-H column), hexane/*i*-PrOH/Et_3N=90/9.9/0.1, 1.0 mL/min, 256 nm, t_1=12.12 min for (*R*,*R*)-**3**, t_2=17.72 min for (*S*,*S*)-**3**. For (*R*,*R*)-**3**, $[\alpha]_D^{25}$ +20.53 (*c* 1.00, $CHCl_3$). For (*S*,*S*)-**3**, $[\alpha]_D^{25}$ −22.94 (*c* 1.01, $CHCl_3$).

4.6. Preparation of double *N*-substituted *rac*-3 derivatives

General procedure: Alkyl bromide or alkyl iodide (4.4 mmol) was added to a mixture of *rac*-**3** (2 mmol) and K_2CO_3 (4.4 mmol) in THF (8 mL). The mixture was stirred and heated at reflux for overnight. The reaction mixture was then cooled to rt, filtered and the solid was washed with CH_2Cl_2. The combined organic filtrates were evaporated to dryness. The residue was recrystallized from EtOH or subjected to column chromatography on silica gel to give the double *N*-substituted derivatives.

*4.6.1. N,N′-Dimethyl-1,1′-methylene-bis(1,1′,2,2′,3,3′,4,4′-octahydroisoquinoline) rac-**8**.* Compound *rac*-**3** (560 mg, 2 mmol) was stirred in neat iodomethane (5 mL) at 50 °C for 5 h. The volatiles were removed under reduced pressure to give a yellow gum. A mixture of 5 M NaOH (15 mL) and CH_2Cl_2 (15 mL) was added to the gum and the mixture formed was then stirred for 2 h at rt. The organic phase was separated, dried over NaOH (pellets), filtered, and evaporated to dryness. The resulting yellow solid was recrystallized from EtOH to give *N*,*N*′-dimethyl-1,1′-methylene-1,1′,2,2′,3,3′,4,4′-octahydrobisisoquinoline *rac*-**8** as light yellow crystals (245 mg, 41%), mp 106–109 °C. FTIR (KBr) ν_{max}: 2924, 1448, 1378, 1284, 1116, 1031, 775, 743, 609 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.84 (2H, apparent t, *J*=7.2 Hz), 2.41 (1H, d, *J*=6 Hz), 2.46 (1H, d, *J*=5.7 Hz), 2.51 (6H, s), 2.88–3.05 (4H, m), 3.27–3.36 (2H, m), 3.91 (2H, t, *J*=6.6 Hz), 7.00–7.06 (8H, m). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 22.5, 42.2, 44.5, 45.9, 59.9, 125.5, 125.8, 128.3, 128.7, 134.0, 139.1. HRMS (ESI): found (M+1) 307.2166. $C_{21}H_{26}N_2$+H requires 307.2174.

*4.6.2. N,N′-Diethyl-1,1′-methylene- bis(1,1′,2,2′,3,3′,4,4′-octahydroisoquinoline) rac-**9**.* Compound *rac*-**3** (560 mg, 2 mmol) was treated with bromoethane (360 μl, 4.4 mmol, 2.2 equiv) as described in general procedure. Purification of the product using silica gel column chromatography (EtOAc/Hex, 1:5) gave *N*,*N*′-diethyl-1,1′-methylene-1,1′,2,2′,3,3′,4,4′-octahydrobisisoquinoline *rac*-**9** as light yellow solid (490 mg, 73%), mp 118–121 °C. FTIR (KBr) ν_{max}: 2957, 1447, 1379, 1117, 1095, 1035, 768, 743, 616 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (6H, t, *J*=7.2 Hz), 1.97 (2H, apparent t, *J*=6.6 Hz), 2.43 (1H, d, *J*=4.5 Hz), 2.49 (1H, d, *J*=4.2 Hz), 2.66–2.73 (2H, m), 2.79–2.85 (2H, m), 3.02–3.20 (4H, m), 3.36–3.42 (2H, m), 4.13 (2H, t, *J*=6.6 Hz), 7.08–7.16 (8H, m). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 13.8, 22.3, 41.5, 46.0, 46.9, 57.8, 125.4, 125.7, 128.4, 128.8, 134.4, 139.8. HRMS (ESI): found (M+1) 335.2477. $C_{23}H_{30}N_2$+H requires 335.2487.

*4.6.3. N,N′-Dibenzyl-1,1′-methylene-bis(1,1′,2,2′,3,3′,4,4′-octahydroisoquinoline) rac-**10**.* Compound *rac*-**3** (560 mg, 2 mmol) was treated with benzyl bromide (523 μl, 4.4 mmol, 2.2 equiv) as described in the general procedure. Purification of the product using silica gel column chromatography (EtOAc/Hex, 1:10) gave *N*,*N*′-dibenzyl-1,1′-methylene-1,1′,2,2′,3,3′,4,4′-octahydrobisisoquinoline *rac*-**10** as a light yellow solid (852 mg, 93%), mp 159–161 °C. FTIR (KBr) ν_{max}: 2951, 2818, 1493, 1450, 1346, 1097, 1023, 744, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.87 (2H, apparent t, *J*=6.6 Hz), 2.27 (1H, d, *J*=4.0 Hz), 2.33 (1H, d, *J*=4.5 Hz), 2.82 (2H, dd, *J*=12.0, 6.0 Hz), 2.91–2.98 (2H, m), 3.13–3.19 (2H, m), 3.40 (2H, d, *J*=13.2 Hz), 3.66 (2H, d, *J*=12.9 Hz), 4.02 (2H, t, *J*=6.9 Hz), 6.96–7.23 (9H, m). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 22.2, 40.7, 46.9, 57.5, 59.2, 125.6, 126.0, 126.9, 128.2, 128.3, 129.0, 129.1, 134.3, 139.7, 140.1. HRMS (ESI): found 459.2808 (M+1). $C_{33}H_{34}N_2$+H requires 459.2800.

4.7. Preparation of mono *N*-substituted *rac*-3 derivatives

*4.7.1. Condensation of rac-**3** with aldehydes. General procedure*: The aldehyde (2.7 mmol) was added dropwise or portionwise (for solids) to a stirred solution of *rac*-**3** (560 mg, 2 mmol) in EtOH or Et_2O (10 mL) at rt. Stirring of the resultant reaction mixture was continued at rt or heated to reflux for a specific time (TLC). After the reaction completion, the mixture was filtered through Celite and the filtrates evaporated to dryness. The residue was then purified by column chromatography on silica gel to afford the piperimidine products.

4.7.2. Reaction with formaldehyde. Reaction between *rac*-**3** (560 mg, 2 mmol) and 37% formaldehyde (205 μl, 2.7 mmol, methanol solution) in EtOH at reflux for 2 days, according to the general procedure, afforded a yellow solid. Purification by chromatography on silica gel (EtOAc/Hex, 1:1) gave piperimidine *rac*-**7** as a light yellow solid (490 mg, 85%), mp 116–119 °C. FTIR (KBr) ν_{max}: 1492, 1454, 1361, 1287, 1156, 1093, 1026, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.57 (2H, t, *J*=5.7 Hz), 2.68–2.75 (2H, m), 2.91–3.15 (4H, m), 3.24–3.31 (2H, m), 3.73 (2H, s), 3.90–4.05 (2H, m), 6.99–7.15 (8H, m). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 26.6, 32.0, 47.7, 55.6, 69.7, 125.6, 126.3, 126.3, 129.3, 134.9, 136.8. HRMS (ESI): found (M+1) 291.1860. $C_{20}H_{22}N_2$+H requires 291.1861.

4.7.3. Reaction with acetaldehyde. Reaction between *rac*-**3** (560 mg, 2 mmol) and acetaldehyde (151 μl, 2.7 mmol) in Et_2O at rt overnight, according to the general procedure, gave a yellow gum. Purification of the gum using silica gel column chromatographic (EtOAc) gave piperimidine *rac*-**11** as a light yellow gum (483 mg, 80%). FTIR (KBr) ν_{max}: 1490, 1452, 1376, 1161, 1074, 1032, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.31 (3H, d, *J*=6.0 Hz), 2.24–2.29 (1H, m), 2.41–2.46 (2H, m), 2.74–2.97 (5H, m), 3.12–3.20 (1H, m), 3.27–3.29 (1H, m), 3.78–3.82 (1H, m), 3.90 (1H, q, *J*=6 Hz), 4.30 (1H, br s), 6.90–7.17 (7H, m), 7.28 (1H, d, *J*=7.2 Hz). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 18.3, 23.8, 29.9, 31.8, 37.1, 47.2, 55.4, 57.1, 68.9, 125.6, 126.1, 126.3, 126.5, 126.7, 128.9, 129.4, 134.6, 135.9, 136.7, 139.2. HRMS (ESI) calcd for $C_{21}H_{24}N_2$: 304.2018, found 305.2019 (M+1).

4.7.4. Reaction with benzaldehyde. Reaction between *rac*-**3** (560 mg, 2 mmol) and benzaldehyde (270 μl, 2.7 mmol) in Et_2O at rt overnight, according to the general procedure, gave yellow solid. Purification of the solid by silica gel column chromatography (EtOAc/Hex=1:1) gave piperimidine **12** as a yellow fluffy solid (483 mg, 90%), mp 73–76 °C. FTIR (KBr) ν_{max}: 1603, 1494, 1453, 1308, 1149, 1124, 1032, 842, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ:

2.14 (1H, td, J=11.4, 3.6 Hz), 2.46–2.53 (3H, m), 2.62–2.74 (1H, m), 2.86–2.94 (3H, m), 3.08–3.17 (2H, m), 3.64 (1H, d, J=11.1 Hz), 4.30 (1H, s), 4.64–4.72 (1H, m), 7.07 (1H, d, J=7.5 Hz), 7.17–7.49 (10H, m), 7.62–7.65 (2H, m). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 24.2, 29.8, 34.5, 46.5, 47.1, 56.1, 57.1, 80.8, 124.9, 125.6, 125.8, 126.0, 126.3, 126.7, 128.39, 128.42, 128.8, 129.1, 129.2, 129.6, 129.8, 135.3, 135.7, 136.8, 138.5, 140.9. HRMS (ESI): found (M+1) 367.2158. $C_{26}H_{26}N_2$+H requires 367.2174.

*4.7.5. Reductive cleavage of piperimidines rac-**7**, rac-**11**, and rac-**12**. General procedure*: A solution of the piperimidine (0.49 mmol) in MeOH (1.8 mL) was added to a mixture of $NaCNBH_3$ (47 mg, 0.75 mmol, 1.5 equiv) and TFA (154 μl, 2 mmol, 4 equiv) in MeOH (3.5 mL) at 0 °C. The mixture was stirred at rt for another 1 h. The reaction was then quenched with 30% NaOH solution (10 mL) and extracted with EtOAc (3×8 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the filtrates evaporated to dryness. The crude product was purified by column chromatography over silica gel (EtOAc) to give mono *N*-substituted derivatives *rac*-**13**–**15**.

*4.7.5.1. Reductive cleavage of piperimidine rac-**7**.* Piperimidine **7** (142 mg, 0.49 mmol) was treated as described in the general procedure to give *N*-methyl-1,1′-methylene-bis(1,1′,2,2′,3,3′,4,4′-octahydroisoquinoline) *rac*-**13** as a light yellow gum (103 mg, 72%). FTIR (KBr) ν_{max}: 3300, 2930, 1675, 1452, 1373, 1200, 1125, 1068, 1026, 745 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.31–2.33 (2H, m), 2.46–2.47 (3H, m), 2.78–2.89 (6H, m), 3.01–3.32 (2H, m), 3.73–3.80 (1H, m), 4.08–4.19 (2H, m), 7.13–7.20 (8H, m). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 24.7, 29.9, 40.5, 40.8, 42.2, 47.0, 53.8, 61.3, 125.8, 125.96, 125.99, 126.1, 126.2, 127.4, 128.9, 129.3, 134.7, 135.5, 137.7, 139.1. HRMS (ESI): found (M+1) 293.2021. $C_{20}H_{24}N_2$+H requires 293.2018.

*4.7.5.2. Reductive cleavage of piperimidine rac-**11**.* Piperimidine *rac*-**11** (150 mg, 0.49 mmol) was treated as described in the general procedure to give *N*-ethyl-1,1′-methylene-bis(1,1′,2,2′,3,3′,4,4′-octahydroisoquinoline) *rac*-**14** as a light yellow gum (105 mg, 70%). FTIR (KBr) ν_{max}: 3251, 2930, 1676, 1490, 1452, 1378, 1270, 1200, 1118, 1034, 768, 744 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.92 (3H, t, J=7.2 Hz), 2.05–2.09 (1H, m), 2.16–2.21 (1H, m), 2.40–2.48 (3H, m), 2.65–2.85 (5H, m), 3.14–3.29 (2H, m), 3.70–3.73 (2H, m), 4.11 (1H, d, J=7.8 Hz), 6.91–7.04 (8H, m). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 13.4, 23.4, 30.1, 41.2, 41.4, 42.9, 47.0, 54.0, 58.0, 125.8, 125.9, 126.0, 126.0, 126.1, 127.8, 129.0, 129.3, 134.7, 135.7, 138.4, 139.4. HRMS (ESI): found (M+1) 307.2168. $C_{21}H_{26}N_2$+H requires 307.2174.

*4.7.5.3. Reductive cleavage of piperimidine rac-**12**.* Piperimidine **12** (180 mg, 0.49 mmol) was treated as described in general procedure to give *N*-benzyl-1,1′-methylene-bis(1,1′,2,2′,3,3′,4,4′-octahydroisoquinoline) *rac*-**15** as a light yellow gum (144 mg, 80%). FTIR (KBr) ν_{max}: 3340, 2930, 1651, 1490, 1453, 1360, 1201, 1118, 1023, 972, 743, 699 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.97–2.05 (1H, m), 2.39 (1H, apparent t, J=12 Hz), 2.62–2.70 (1H, m), 2.73–2.89 (4H, m), 3.05–3.12 (3H, m), 3.43–3.60 (1H, m), 3.69–3.81 (2H, m), 3.87 (1H, dd, J=11.1, 3.0 Hz), 4.30 (1H, d, J=8.7 Hz), 7.08–7.21 (8H, m), 7.31–7.38 (5H, m). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 23.0, 30.1, 41.4, 42.9, 43.3, 53.1, 56.8, 57.6, 125.8, 125.9, 126.0, 126.2, 126.3, 127.4, 128.2, 128.6, 129.3, 129.3, 129.4, 134.3, 135.5, 138.3, 139.5, 139.6. HRMS (ESI): found (M+1) 369.2328. $C_{26}H_{28}N_2$+H requires 369.2331.

4.8. Procedure for the asymmetric Henry reaction

(*R*,*R*)-**3** (0.02 mmol, 10 mol %) and CuBr (0.02 mmol, 10 mol %) were dissolved in dioxane (1.5 mL) and allowed to stir at rt for 1 h, whereby a green solution was obtained. To the above stirred solution, nitromethane (4 mmol, 20 equiv) and benzaldehyde (0.2 mmol, 1 equiv) were added sequentially. The reaction mixture was further stirred at rt 40 h (TLC) and then subjected to column chromatography on silica gel to give (*S*)-1-phenyl-2-nitroethanol **18** in 70% yield. HPLC analysis: (Chiralcel OD-H column) hexane/IPA=90/10, 0.8 mL/min, 215 nm, minor enantiomer t_1=18.10 min, major enantiomer t_2=22.20 min, 38% ee.[15] ^{1}H NMR ($CDCl_3$, δ ppm): 2.08–2.81 (1H, br s), 4.39–4.56 (2H, m), 5.37 (1H, dd, J=12.6, 3.3 Hz), 7.34–7.40 (5H, m); ^{13}C NMR: 71.0, 81.3, 126.0, 129.0, 129.1, and 138.2.

4.9. Procedure for the asymmetric Aldol reaction

To a stirred mixture of (*R*,*R*)-**3** (0.04 mmol, 20 mol %) and PTSA (0.04 mmol, 20 mol %) in acetone (2.5 mL), 4-nitrobenzaldehyde **19** was added (0.2 mmol) dropwise at rt. The reaction mixture was continuously stirred for 4 days and then subjected to silica gel column chromatography purification to give (*S*)-4-hydroxy-4-(4′-nitrophenyl)-butan-2-one **20** in 37% yield. HPLC analysis: (Chiralpak AS-H column) hexane/IPA=70/30, 1.0 mL/min, 254 nm, major enantiomer t_1=10.76 min, major enantiomer t_2=13.24 min, 70% ee.[16] ^{1}H NMR ($CDCl_3$, δ ppm): 2.19 (3H, s), 2.83–2.86 (2H, m), 3.91 (1H, br s), 5.24–5.26 (1H, m), 7.51 (2H, d, J=5.7 Hz), 8.13 (2H, d, J=5.7 Hz); ^{13}C NMR: 30.7, 51.6, 68.8, 123.7, 126.5, 147.2, 150.3, and 208.5.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.04.004.

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9. X-ray crystallographic data for (*R*,*R*)-**3**·(L)-citramalic acid salt: Formula $C_{26.5}H_{36}N_2O_{8.5}$, M=518, tetragonal, space group $P4(3)2(1)2$, a=11.7780 (3) Å, b=11.7789 (3) Å, c=37.4305 (10) Å, β=90°, V=5192.4(2) Å^3, D_{calcd}=1.327 Mg/m^3, Z=8.2.45°<θ<31.07°. The number of reflections was 4798 considered to be observed of 4139 unique data. Final R indices ($I>2\sigma(I)$) R_1=0.0395, wR_2=0.0938.

CCDC 800288 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/.

10. X-ray crystallographic data for *rac*-**3**/Cu(I)Br complex: Formula $C_{19}H_{22}BrCuN_2$, M=422, triclinic, space group $P\bar{1}$, a=8.9034 (2) Å, b=8.9512(2) Å, c=11.4646(2) Å, β=103.6100(10)°, V=854.84(3) Å^3, D_{calcd}=1.639 Mg/m^3, Z=2.1. 85°<θ<31.18°. The number of reflections was 5542 considered to be observed of 4626 unique data. Final R indices ($I>2\sigma(I)$) R_1=0.0396, wR_2=0.0953. CCDC 800289 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/.
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