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New 2-azanorbornyl derivatives: chiral (N,N)-donating ligands for asymmetric catalysis

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ABSTRACT

New chiral 2-azanorbornane derivatives were prepared and used as (N,N)-donating ligands in a copper-catalyzed Henry reaction yielding up to 62% ee.

1. Introduction

Modern asymmetric synthesis makes special use of so-called privileged catalysts/ligands, chiral inducers that are effective in numerous, diverse, and industrially useful enantioselective transformations.[1] Among them, (N,N)-donor ligands play an important role due to their relative robustness and ability to be associated with different metals, which allows performing a wide range of catalytic reactions to be carried out with excellent enantiocontrol and with high yield.[2] A number of such compounds have been prepared using a 1,2-diphenylethylene-1,2-diamine, 1,2-diaminocyclohexane, 2,2′-bipiridine, or bis(oxazoline) skeletons. There is also a wide interest in ligands and catalysts bearing a bicyclic chiral framework, such as the derivatives of camphor[3] or *Cinchona* alkaloids.[4] A configurationally stable, rigid backbone ensures a proper localization of donor centers, leading to significant stereodifferentiation in catalytic reactions.

A bicyclic system containing a 2-azanorbornene (2-azabicyclo[2.2.1]heptene) skeleton has been proven to be an attractive precursor of chiral ligands useful in asymmetric synthesis. Compound **1** can be prepared on a multigram scale in a stereoselective aza-Diels–Alder reaction.[5] Various possibilities for the modification of the basic structure and the application of 2-azanorbornyl-derived ligands in asymmetric catalysis have been extensively explored by Andersson et al.[6] and others.[7] Over the course of our studies on the preparation and utilization of chiral organochalcogen compounds, we obtained a series of 2-azabicyclo[2.2.1]heptane derivatives with (N,S), (N,Se), and (N,N) donor atoms and used them as ligands in a palladium-catalyzed asymmetric allylic alkylation (Trost–Tsuji reaction), yielding up to 95% ee.[8] The family of these bicyclic ligands containing two nitrogen donors is relatively small and their use in catalytic reactions was rather limited.[9] This contribution concerns the synthesis of novel enantiopure 2-azanorbornyl derivatives bearing two nitrogen donors and their application in stereoselective Henry reactions.

2. Results and discussion

The *exo*-ester (1*S*,3*R*,4*R*)-**1** was obtained as the main product of the reaction of cyclopentadiene and an iminium ion derived from ethyl glyoxylate and (*S*)-1-phenylethylamine.[5] A two-step reduction of compound *exo*-**1** leading to alcohol *exo*-**2** was performed as described previously.[8,10] This derivative served as a starting material for the synthesis of a series of enantiomerically pure ligands with (N,S), (N,Se) donor atoms, and an (N,N)-donating Schiff base.[8] To enlarge the pool of 2-azanorbornyl-derived ligands containing two nitrogen donors, a conversion of alcohol *exo*-**2** to an azide *exo*-**3** was undertaken. A reaction of compound *exo*-**2** with diphenylphosphoryl azide led to a desired product, but the yield was unsatisfactory. Significantly better result was achieved with HN_3/DEAD combination and (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-3-azidemethyl-2-azabicyclo[2,2,1]heptane *exo*-**3** was obtained in 88% yield. A subsequent reduction with triphenylphosphine resulted in amine *exo*-**4** (92%, Scheme 1). Both compounds *exo*-**3** and *exo*-**4** opened up the route to the synthesis of (N,N)-donating ligands containing four stereogenic centers.

The *endo*-isomer of compound **1**, (1*S*,3*S*,4*R*)-**1** could be also isolated as the minor product of the Diels–Alder reaction, formed in 10–15% yield. This compound was subsequently converted into alcohol *endo*-**2**, azide *endo*-**3**, and amine *endo*-**4** (Scheme 1). Thus, the influence of the configuration of carbon-3 on the coordination and catalytic properties of the respective ligands could also be tested.

A series of imines **5a**–**5e** were obtained via the reaction of amine *exo*-**4** with aryl aldehydes (Scheme 2). However, compounds **5** were found to be too unstable to be isolated. All attempts at chromatographic purification led to their decomposition. Thus, they were reduced in situ to the corresponding secondary amines *exo*-**6a**–**6e** bearing different aryl substituents. The *endo*-isomer of

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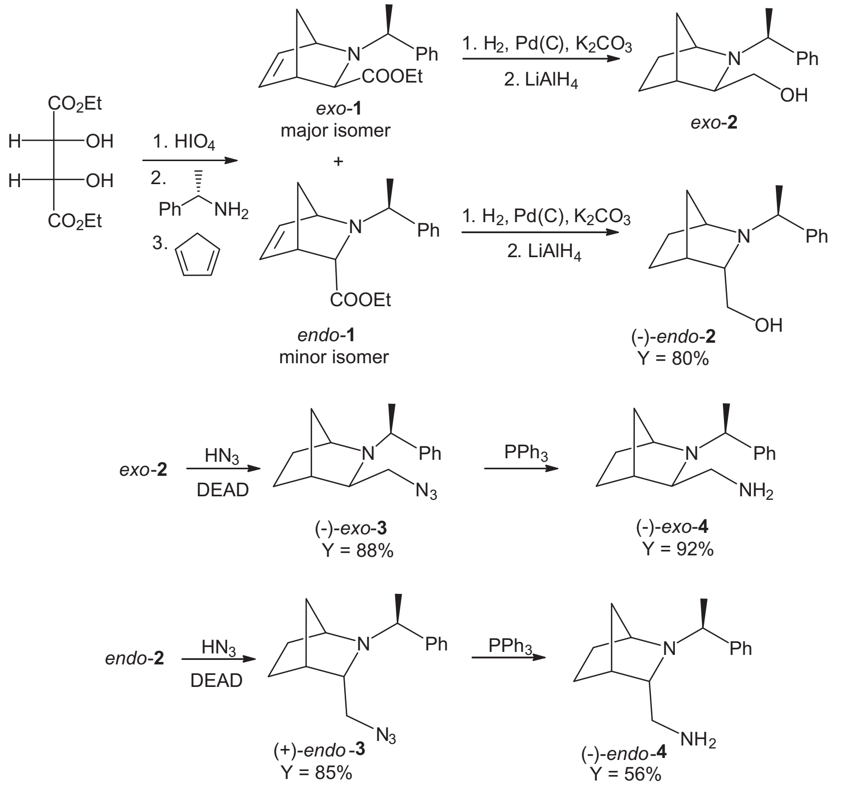
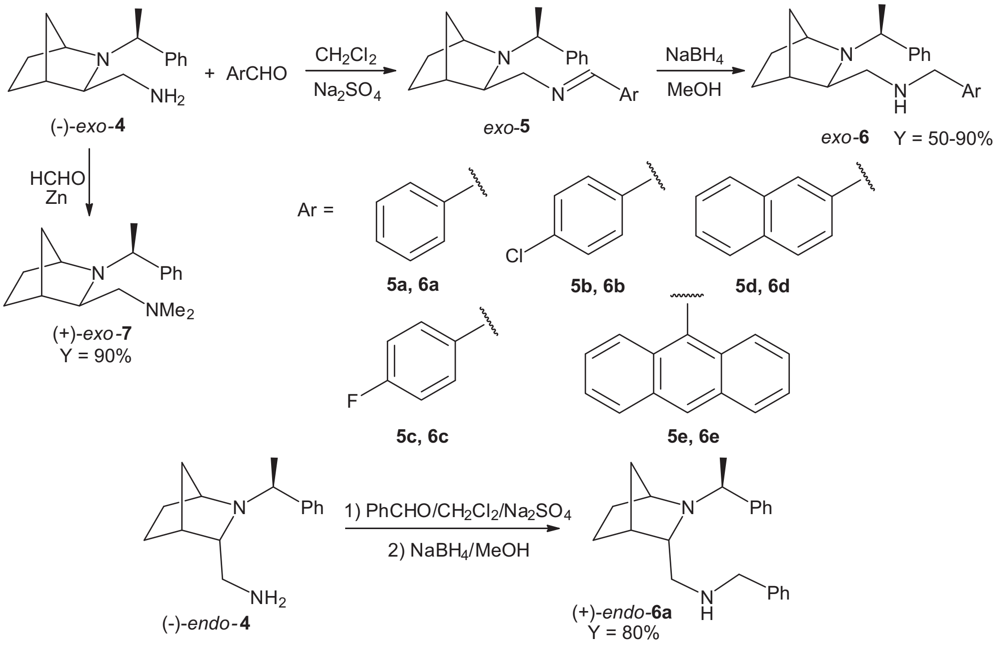


Scheme 1.



Scheme 2.

ligand **6a** was also prepared starting from *endo*-**4**. A set of (N,N)-donating ligands was completed with tertiary amine *exo*-**7**, which was synthesized by methylation of *exo*-**4** in 90% yield. For this purpose, a reaction of amine *exo*-**4** with formaldehyde in the presence of zinc was performed.[11] All new compounds were characterized by HRMS, IR, proton, and carbon NMR spectroscopy, and their structures were further confirmed by 2D NMR spectra (COSY, NOESY, ^{1}H–^{13}C HMQC, and ^{1}H–^{13}C HMBC). In particular, the NOESY spectra revealed specific contacts of protons that readily distinguished between the *exo* and *endo* diastereomers.

We tested the newly obtained chiral azanorbornane derivatives as ligands in the copper-catalyzed Henry reaction. The Henry (or nitroaldol) reaction between a nitroalkane and a carbonyl compound serves as a useful tool for the creation of a new carbon–carbon bond, and the resulting 2-nitroalcohols are versatile building blocks and intermediates in organic synthesis, as they can be easily converted into 1,2-aminoalcolhols or amino acids.[12] Recently, several efficient methods have been developed for the enantioselective version of this process.[13] Despite significant advances in this field, there are certain shortcomings, such as complex ligand syntheses, high catalyst loadings, substrate specificity limitations, or the need for special reaction conditions, which require further research.

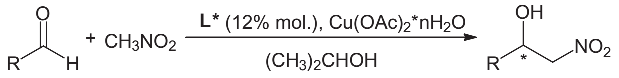
A model reaction between benzaldehyde and nitromethane was chosen for the preliminary ligand testing. Amine *exo*-**6a**, which appeared to be the most promising ligand, was then used for the conversion of various aldehydes. The results are collected in Table 1.

Among the nine ligands tested in the model catalytic reaction, the highest enantiomeric excess of 61% was noted for amine *exo*-**6a** (Table 1, entry 3), while its *endo*-isomer and *exo*-**6d** led to the optimal yield of nitroalcohol (95%). Ee values were rather moderate, but not lower than 31%. The effect of the size of the amine substituent could be illustrated by the *exo*-**4**/*exo*-**6a**/*exo*-**6d** series (entries 1, 3 and 7), for which an increase in yield was accompanied by the generally maintained ee level. However, a significant drop in the reaction outcome was observed for *exo*-**6e** bearing a 9-anthryl substituent (entry 8); apparently such an attachment brought about steric hindrance which decreased the effectiveness of the catalyst.

For all *exo* ligands, (*S*)-nitroalcohol was formed as the main enantiomer, independent of the substituent at the 3-position. Changing from the *exo*- to *endo*-isomer (as observed for compounds **4** and **6a**, entries 1–2 and 3–4) resulted in a reversal of the stereochemical preference together with the lowering of the ee value and an increase of the chemical yield.

The influence of the reaction conditions on the outcome of the catalytic reaction was investigated for *exo*-**6a** ligand. Changing the solvent from isopropanol to ethanol led to a decrease in the ee value (55%) and an increase of yield to 95% (entry 10). The use of 6 mol % instead of 12 mol % of catalyst resulted in a pronounced decrease of enantiomeric excess (49%, entry 11). When benzaldehyde was replaced with other aldehydes (entries 12–16), comparable stereoselectivities (ee = 46–62%) and high yields (up to 95%) were observed. Chiral ligand *exo*-**6a** was also tested in a copper-catalyzed diastereoselective reaction of benzaldehyde and nitroethane. A slight preference for the *anti*-diastereomer was noted (de = 26%), which was formed with 49% ee; for the *syn*-isomer, the ee was significantly higher (76%) and the overall yield was 70%.

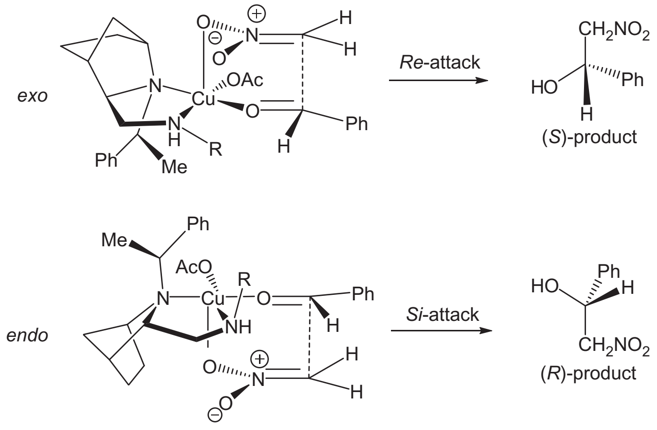
Table 1
Results of the copper-catalyzed Henry reaction



Entry	Ligand **L***	R	Yield of product (%)	ee
1	*exo*-**4**	Ph	48	54% (*S*)
2	*endo*-**4**	Ph	58	34% (*R*)
3	*exo*-**6a**	Ph	71	**61% (*S*)**
4	*endo*-**6a**	Ph	**95**	33% (*R*)
5	*exo*-**6b**	Ph	72	54% (*S*)
6	*exo*-**6c**	Ph	65	43% (*S*)
7	*exo*-**6d**	Ph	**95**	52% (*S*)
8	*exo*-**6e**	Ph	24	31% (*S*)
9	*exo*-**7**	Ph	84	50% (*S*)
10	*exo*-**6a**[a]	Ph	95	55% (*S*)
11	*exo*-**6a**[b]	Ph	76	49% (*S*)
12	*exo*-**6a**	Cyclohexyl	67	59% (*S*)
13	*exo*-**6a**	4-F-C_6H_4–	95	59% (*S*)
14	*exo*-**6a**	4-Cl-C_6H_4–	95	46% (*S*)
15	*exo*-**6a**	4-Br-C_6H_4–	90	52% (*S*)
16	*exo*-**6a**	1-Naphthyl	95	62% (*S*)

[a] Reaction conducted in ethanol.
[b] 6 mol % of *exo*-**6a** used.

The results presented clearly indicate that the direction of the asymmetric induction is dependent primarily on the configuration of the carbon-3 atom of the chiral ligand. While (3*R*) (*exo*) amines led mainly to (*S*)-product, their (3*S*) (*endo*) counterparts exhibited the reverse preference. Molecular models of the postulated transition state reveal the distinct structures of copper(II) complexes formed by the two diastereomeric ligands (Scheme 3). The N(2) atom also becomes chiral upon coordination to the metal ion, and the configuration of this newly formed stereogenic center is different for the *exo*- and *endo*-isomers. As a consequence, the (*S*)-1-phenylethyl substituent on N(2) has a different orientation. According to the generally accepted considerations,[13,14] benzaldehyde approaches the copper(II) ion in the equatorial plane, and the coordination *trans* to N(2) should be preferred due to the presence of a bulky substituent on N(2). A favorable orientation of the aldehyde should also minimize the steric repulsion exerted by the phenylethyl group. Deprotonated nitromethane binds to the Cu^{2+} ion at the axial position. However, the accessibility of the metal center from one side is restricted by the N(2) substituent. In the case of the *exo*-isomer, this results in preferential *Re* attack of the nitronate (Scheme 3) and the formation of a nitroalcohol with an (*S*)-configuration. The opposite enantiomer is expected as the main product from the reaction catalyzed by the *endo*-amine as a result of *Si* attack.



Scheme 3.

The analysis reveals the key importance of the 2-phenylethyl group for the observed asymmetric induction. The minor influence of the substituent of the secondary amine (R in Scheme 3) is connected to its more remote localization with respect to the metal ion.

3. Conclusions

The use of the new bicyclic (N,N)-donating ligands in a copper-catalyzed Henry reaction resulted in good to excellent yields and enantioselectivities of up to 62%. An interesting reversal of the stereochemical outcome was observed for diastereomeric derivatives, as shown by the *exo*-**4**, *endo*-**4** and *exo*-**6a**, *endo*-**6a** pairs. The precursors of both forms, esters *exo*-**1** and *endo*-**1**, are available from one Diels–Alder reaction.

The catalytic performance of these ligands may be improved upon by further structural modification. The conversion of the 3-substituent containing an amine function could change its donating properties and allow the introduction of a more pronounced steric hindrance. Such transformations leading to 2-azanorbornyl derivatives bearing two diverse nitrogen donors are currently underway in our laboratory.

4. Experimental

4.1. General

IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance DRX (^{1}H, 300 MHz) or a Bruker Avance 600 (^{1}H, 600 MHz) spectrometer using TMS as an internal standard or solvent residual peak as a reference. Optical rotations were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. High resolution mass spectra were recorded using a microTOF-Q and WATERS LCT Premier XE instruments utilizing electrospray ionization mode. Separations of products by chromatography were performed on Silica Gel 60 (230–400 mesh) purchased from Merck. Thin layer chromatography was carried out using Silica Gel 60 precoated plates (Merck). HPLC analyses were performed on Chiracel OD-H or Chiralpak AD-H chiral columns (flow rate of 1.0 mL/min).

4.2. Synthesis of (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2,2,1]hept-5-ene-3-carboxylic acid ethyl ester *exo*-1 and (1*S*,3*S*,4*R*)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2,2,1]hept-5-ene-3-carboxylic acid ethyl ester *endo*-1

These compounds were prepared according to the literature procedure via an aza-Diels–Alder reaction of cyclopentadiene, an iminium ion derived from ethyl glyoxylate and (*S*)-1-phenylethylamine.[5c] The isomers were separated on a silica gel column using *n*-hexane–ethyl acetate mixture (9:1 v/v) as eluent (R_f (*endo*-**1**) = 0.21, R_f (*exo*-**1**) = 0.08).

4.3. Reduction of Diels–Alder products 1

Alcohols (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-3-hydroxymethyl-2-azabicyclo[2,2,1]heptane *exo*-**2** and (1*S*,3*S*,4*R*)-2-[(*S*)-1-phenylethyl]-3-hydroxymethyl-2-azabicyclo[2,2,1]heptane *endo*-**2** were obtained by reduction of *exo*-**1** and *endo*-**1**, respectively, with H_2 (1 atm) and 5% of Pd–C in the presence of potassium carbonate[10] followed by the reduction of formed esters with $LiAlH_4$ according to a literature procedure.[7a,8,15] The characteristics of *exo*-**2** was in agreement with the literature data.[7a] *endo*-**2**: Yield 80%, mp = 45.5–46.5 °C, $[\alpha]_D^{20} = -4.5$ (*c* 1.12, CH_2Cl_2), ^{1}H NMR ($CDCl_3$): δ = 1.05–1.09 (m, 1H), 1.21–1.30 (m, 3H), 1.33 (d, 3H, *J* = 6.3 Hz), 1.50–1.63 (m, 1H), 1.62–1.82 (m, 1H), 1.85–2.00 (m, 1H), 2.25–2.30 (m, 1H), 2.35–2.41 (m, 1H), 2.98 (br s, 1H), 3.49–3.57 (m, 2H), 3.67 (q, 1H, *J* = 6.6 Hz), 7.23–7.32 (m, 5H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.8, 24.5, 29.1, 35.7, 43.8, 58.9, 59.8, 65.4, 66.7, 126.9, 127.2, 128.5, 145.2 ppm. IR (film): 701, 766, 1026, 1163, 1306, 1453, 1492, 1747, 2873, 2969, 3244 cm^{-1}. HRMS (ESI): 232.1690 ([M+H]$^+$); for $(C_{15}H_{22}NO)^+$ *m*/*z* = 232.1701.

4.4. Preparation of azides

Alcohol **2** (0.46 g, 2 mmol) and triphenylphosphine (0.68 g, 2.6 mmol, 1.3 equiv) were dissolved in 15 mL of dry toluene and cooled in an ice bath. A 1 M solution of HN_3 in benzene (2.6 mL, 2.6 mmol, 1.3 equiv) was then added in one portion under an inert atmosphere, followed by a 40% solution of DEAD in toluene (1.37 mL, 3 mmol, 1.5 equiv), which was added dropwise. The reaction mixture was stirred overnight under argon. After evaporation of the solvent, the residue was chromatographed on a silica column using *n*-hexane–ethyl acetate (6:1 v/v), yielding a fraction containing azide **3**.

4.4.1. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-azidemethyl-2-azabicyclo[2,2,1]heptane *exo*-3

Yield 88%, $[\alpha]_D^{20} = -71.3$ (*c* 0.60, CH_2Cl_2), ^{1}H NMR ($CDCl_3$): δ = 1.28–1.48 (m, 3H), 1.33 (d, 3H, *J* = 6.6 Hz), 1.68–1.82 (m, 2H), 2.12 (d, 1H, *J* = 11.7 Hz), 2.24 (AB_qX, 1H, J_1 = 13.2 Hz, J_2 = 3.6 Hz), 2.30–2.38 (m, 1H), 2.56 (AB_q, 1H, *J* = 13.2 Hz), 3.23–3.29 (m, 1H), 3.36 (q, 1H, *J* = 6.6 Hz), 3.58–3.63 (m, 1H), 7.20–7.38 (m, 5H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.5, 21.9, 27.2, 34.2, 38.9, 47.8, 56.0, 60.7, 62.5, 127.0, 127.5, 128.4, 145.2 ppm. IR (film): 701, 770, 1264, 1453, 1749, 2097 (N_3), 2953, 3026 cm^{-1}. HRMS (ESI): 257.1678 ([M+H]$^+$); for $(C_{15}H_{21}N_4)^+$ M = 257.1766.

4.4.2. (1*S*,3*S*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-azidemethyl-2-azabicyclo[2,2,1]heptane *endo*-3

Yield 85%, $[\alpha]_D^{20} = +34.5$ (*c* 0.58, CH_2Cl_2), ^{1}H NMR ($CDCl_3$): δ = 1.15–1.50 (m, 3H), 1.23 (d, 3H, *J* = 6.6 Hz), 1.52–2.10 (m, 4H), 2.36 (s, 1H), 2.40–2.52 (m, 1H), 2.98–3.12 (m, 2H), 3.40 (br s, 1H), 7.17–7.45 (m, 5H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.9, 22.0, 27.0, 33.6, 38.8, 47.1, 570, 60.6, 62.0, 126.9, 127.6, 128.3, 145.2 ppm. IR (film): 548, 702, 767, 955, 1029, 1046, 1160, 1263, 1453, 1492, 1748, 2096 (N_3), 2810, 2871, 2972, 3026 cm^{-1}. HRMS (ESI): 257.1757 ([M+H]$^+$); for $(C_{15}H_{21}N_4)^+$ *m*/*z* = 257.1766.

4.5. Reduction of azides[16]

Azide **3** (0.42 g, 1.6 mmol) was dissolved in 20 mL of methanol. Triphenylphosphine (0.63 g, 2.4 mmol, 1.5 equiv) was added and the reaction mixture was heated overnight at reflux. The solvent was evaporated, and the residue was chromatographed on a silica column. Elution with chloroform yielded the unreacted phosphine and phosphine oxide, while a chloroform–methanol mixture (90:10 v/v) eluted the desired product **4**.

4.5.1. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-aminemethyl-2-azabicyclo[2,2,1]heptane *exo*-4

Yield 92%, $[\alpha]_D^{20} = -17.5$ (*c* 0.40, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 1.25–1.37 (m, 3H), 1.31 (d, 3H, *J* = 6.6 Hz), 1.60–1.70 (m, 2H), 1.87 (br s, 2H), 2.03 (d, 1H, *J* = 10.2 Hz), 2.10–2.20 (m, 1H), 2.24 (d, 2H, *J* = 2.7 Hz), 2.54–2.62 (m, 1H), 3.34 (q, 1H, *J* = 6.6 Hz), 3.56 (t, 1H, *J* = 2.4 Hz), 7.20–7.30 (m, 5H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.3, 21.4, 28.0, 33.4, 41.5, 50.9, 52.2, 56.4, 62.6, 126.8, 127.4, 128.3, 145.6 ppm. IR (film): 549, 701, 771, 952, 1134, 1453, 1491, 1599, 2812, 2864, 2947, 3025, 3365 cm^{-1}. HRMS (ESI): 231.1846 ([M+H]$^+$); for $(C_{15}H_{23}N_2)^+$ *m*/*z* = 231.1861.

4.5.2. (1*S*,3*S*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-aminemethyl-2-azabicyclo[2,2,1]heptane *endo*-4

Yield 56%, $[\alpha]_D^{20} = -19.8$ (*c* 0.61, CH_2Cl_2), ^{1}H NMR ($CDCl_3$): δ = 1.10–1.40 (m, 4H), 1.23 (d, 3H, *J* = 6.6 Hz), 1.70–1.80 (m, 1H), 1.85–1.95 (m, 1H), 2.10–2.20 (m, 1H), 2.29 (br s, 2H), 2.38–2.49 (m, 2H), 2.71–2.80 (m, 1H), 2.92–3.10 (m, 1H), 3.35 (q, 1H, *J* = 6.6 Hz), 7.21–7.35 (m, 5H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.0, 22.1, 27.9, 33.0, 41.6, 50.6, 51.1, 57.6, 61.9, 126.7, 127.5, 128.3, 146.0 ppm. IR (film): 543, 703, 772, 967, 1050, 1180, 1305, 1370, 1453, 1492, 1602, 1741, 2790, 2820, 2873, 2971, 3468 cm^{-1}. HRMS (ESI): 231.1882 ([M+H]$^+$); for $(C_{15}H_{23}N_2)^+$ *m*/*z* = 231.1861.

4.6. Preparation of imines 5 and their reduction to secondary amines 6

In a typical procedure, amine **4** (0.5 mmol) and the respective aldehyde (0.5 mmol) dissolved in 8 mL of dichloromethene were mixed overnight at room temperature over anhydrous Na_2SO_4. The filtrate was evaporated and the solid residue was dissolved in 8 mL of methanol. Sodium borohydride (28.5 mg, 0.75 mmol, 1.5 equiv) was added in one portion and the solution was stirred for 2 h and evaporated. Chromatography on silica using chloroform removed the alcohol (a side-product coming from the reduction of the unreacted aldehyde), and a chloroform–methanol mixture (90:10 v/v) eluted amines **6**.

4.6.1. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-(benzylamine)methyl-2-azabicyclo[2,2,1]heptane *exo*-6a

Yield 80%, $[\alpha]_{\mathrm{D}}^{20} = +15.7$ (*c* 0.60, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 1.25–1.37 (m, 3H), 1.31 (d, 3H, *J* = 6.6 Hz), 1.70–1.73 (m, 2H), 1.85 (br s, 1H), 1.97 (d, 1H, *J* = 11.7 Hz), 2.11 (AB$_q$X, 1H, J_1 = 12.3 Hz, J_2 = 2.1 Hz), 2.33–2.35 (m, 2H), 2.52 (AB$_q$, 1H, *J* = 12.3 Hz), 3.36 (q, 1H, *J* = 6.3 Hz), 3.55 (t, 1H, *J* = 5.7 Hz), 3.61 (s, 2H), 7.22–7.36 (m, 10H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.5, 21.6, 28.0, 33.9, 38.8, 47.9, 51.4, 56.0, 56.3, 62.8, 126.8, 126.8, 127.5, 128.3, 128.4, 128.4, 140.7, 145.8 ppm. IR (film): 700, 735, 770, 1136, 1371, 1453, 1492, 1602, 1668, 2813, 2863, 2946, 3060 cm^{-1}. HRMS (ESI): 321.2340 ($[M+H]^+$); for $(C_{22}H_{29}N_2)^+$ *m*/*z* = 321.2331.

4.6.2. (1*S*,3*S*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-(benzylamine)methyl-2-azabicyclo[2,2,1]heptane *endo*-6a

Yield 80%, $[\alpha]_{\mathrm{D}}^{20} = +24.0$ (*c* 1.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 1.07–1.33 (m, 3H), 1.27 (d, 3H, *J* = 6.6 Hz), 1.62–1.90 (m, 3H), 2.28–2.42 (m, 3H), 2.53 (br s, 1H), 2.95–3.05 (m, 2H), 3.40 (q, 1H, *J* = 6.3 Hz), 3.83 (AB$_q$, 2H, *J* = 13.2 Hz), 7.19–7.43 (m, 10H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.6, 21.9, 27.8, 33.3, 38.1, 47.4, 51.2, 56.3, 57.5, 62.2, 126.8, 126.9, 127.6, 128.3, 128.4, 128.5, 140.8, 145.8 ppm. IR (film): 549, 700, 768, 953, 1028, 1134, 1260, 1452, 1492, 2809, 2863, 2948, 3025, 3060 cm^{-1}. HRMS (ESI): 321.2325 ($[M+H]^+$); for $(C_{22}H_{29}N_2)^+$ *m*/*z* = 321.2331.

4.6.3. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-[(4-chlorophenyl)methylamine]methyl-2-azabicyclo[2,2,1]heptane *exo*-6b

Yield 50%, $[\alpha]_{\mathrm{D}}^{20} = -8.5$ (*c* 1.36, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 1.25–1.37 (m, 3H), 1.31 (d, 3H, *J* = 6.6 Hz), 1.67–1.75 (m, 2H), 1.89 (br s, 1H), 1.95 (d, 1H, *J* = 11.6 Hz), 2.08 (d, 1H, *J* = 12.4 Hz), 2.29–2.32 (m, 2H), 2.47 (d, 1H, *J* = 12.4 Hz), 3.32–3.38 (m, 1H), 3.52–3.55 (m, 1H), 3.56 (s, 2H), 7.17–7.33 (m, 9H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.5, 21.5, 27.9, 33.8, 38.7, 47.9, 50.6, 55.9, 56.2, 62.5, 127.3, 128.2, 128.3, 128.4, 128.7, 129.5, 139.4, 145.5 ppm. IR (film): 541, 696, 722, 749, 1119, 1183, 1437, 1668, 2951, 3055, 3391 cm^{-1}. HRMS (ESI): 355.1947 ($[M+H]^+$); for $(C_{22}H_{28}N_2Cl)^+$ *m*/*z* = 355.1941.

4.6.4. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-[(4-fluorophenyl)methylamine]methyl-2-azabicyclo[2,2,1]heptane *exo*-6c

Yield 91%, $[\alpha]_{\mathrm{D}}^{20} = -16.0$ (*c* 0.75, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 1.18–1.45 (m, 3H), 1.31 (d, 3H, *J* = 6.6 Hz), 1.60–1.92 (m, 4H), 1.91–2.10 (m, 1H), 2.10–2.15 (m, 1H), 2.28–2.40 (m, 2H), 2.48 (d, 1H, *J* = 12.6 Hz), 3.36 (q, 1H, *J* = 7.2 Hz), 3.57 (s, 2H), 6.94–7.00 (m, 2H, ArH), 7.19–7.34 (m, 7H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.5, 21.5, 27.9, 33.8, 38.8, 48.0, 50.6, 56.0, 56.2, 62.6, 115.1 (d, *J* = 20.8 Hz), 126.8, 127.4, 128.4, 129.7 (d, *J* = 7.6 Hz), 136.4, 146.1, 161.8 (d, *J* = 238.9 Hz) ppm. IR (film): 542, 699, 722, 828, 1120, 1197, 1220, 1438, 1509, 1602, 2948, 3059, 3332 cm^{-1}. HRMS (ESI): 339.2267 ($[M+H]^+$); for $(C_{22}H_{28}N_2F)^+$ *m*/*z* = 339.2237.

4.6.5. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-[(2-naphthyl)methylamine]methyl-2-azabicyclo[2,2,1]heptane *exo*-6d

Yield 54%, $[\alpha]_{\mathrm{D}}^{20} = -8.3$ (*c* 0.36, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 1.27–1.43 (m, 3H), 1.33 (d, 3H, *J* = 6.7 Hz), 1.69–1.77 (m, 3H), 2.10–2.17 (m, 2H), 2.39–2.42 (m, 2H), 2.57–2.61 (m, 1H), 3.43–3.46 (m, 1H), 3.60 (br s, 1H), 3.79 (AB$_q$, 2H, *J* = 13.2 Hz), 7.26 (t, 1H, *J* = 7.0 Hz, ArH), 7.33 (t, 2H, *J* = 7.4 Hz, ArH), 7.36–7.39 (m, 2H, ArH), 7.41–7.48 (m, 3H, ArH), 7.69 (s, 1H, ArH), 7.77–7.82 (m, 3H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.3, 21.8, 27.8, 33.7, 38.7, 48.0, 51.4, 56.1, 56.3, 62.8, 125.4, 125.9, 126.5, 126.8, 126.9, 127.5, 127.6, 127.7, 127.9, 128.4, 132.6, 133.4, 138.0, 146.1 ppm. IR (film): 542, 698, 723, 748, 1015, 1091, 1120, 1182, 1455, 1490, 1598, 1660, 2869, 2949, 3057, 3283 cm^{-1}. HRMS (ESI): 371.2499 ($[M+H]^+$); for $(C_{26}H_{31}N_2)^+$ *m*/*z* = 371.2487.

4.6.6. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-[(9-anthryl)methylamine]methyl-2-azabicyclo[2,2,1]heptane *exo*-6e

Yield 75%, $[\alpha]_{\mathrm{D}}^{20} = -22.0$ (*c* 1.10, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 1.25–1.40 (m, 6H), 1.73–1.80 (m, 3H), 2.02 (br s, 1H), 2.22 (d, 1H, *J* = 11.2 Hz), 2.43 (br s, 1H), 2.69 (br s, 1H), 2.78 (d, 1H, *J* = 11.9 Hz), 3.43 (br s, 1H), 3.56 (br s, 1H), 4.50 (AB$_q$, 2H, *J* = 11.5 Hz), 7.21–7.25 (m, 1H, ArH), 7.34 (t, 2H, *J* = 7.4 Hz, ArH), 7.39–7.42 (m, 2H, ArH), 7.43–7.48 (m, 2H, ArH), 7.51–7.56 (m, 2H, ArH), 8.00 (d, 2H, *J* = 8.3 Hz, ArH), 8.28 (d, 2H, *J* = 8.8 Hz, ArH), 8.38 (s, 1H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.2, 21.5, 28.1, 34.1, 39.7, 44.1, 48.0, 56.1, 58.7, 62.8, 124.5, 124.8, 125.9, 126.8, 126.9, 127.5, 128.4, 129.1, 130.3, 131.6, 132.2, 146.0 ppm. IR (KBr): 695, 732, 1284, 1452, 1678, 2939, 3057, 3404 cm^{-1}. HRMS (ESI): 421.2546 ($[M+H]^+$); for $(C_{30}H_{33}N_2)^+$ *m*/*z* = 421.2644.

4.7. Dimethylation of *exo*-4

The reaction was performed according to a literature procedure.[11] Amine *exo*-**4** (0.2 g, 0.87 mmol), acetic acid (8 equiv), zinc dust (2 equiv), aqueous 37% formaldehyde (1.5 equiv) and 1 mL of dioxane were stirred for 30 min at room temperature. Aqueous ammonia was added to the filtered reaction mixture and the resulting solution was extracted with chloroform. The solvent was evaporated, and the residue was chromatographed on silica using a chloroform–methanol mixture (90:10 v/v) yielding *exo*-**7**.

4.7.1. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-3-(*N*,*N*-dimethylamine)methyl-2-azabicyclo[2,2,1]heptane *exo*-7

Yield 85%, $[\alpha]_{\mathrm{D}}^{20} = +25.0$ (*c* 0.24, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 1.18–1.40 (m, 4H), 1.29 (d, 3H, *J* = 6.6 Hz), 1.50–1.59 (m, 1H), 1.68–1.80 (m, 2H), 1.82–1.92 (m, 1H), 2.12 (s, 6H), 2.38–2.48 (m, 1H), 2.55 (d, 1H, *J* = 13.2 Hz), 3.18–3.35 (m, 1H), 3.60 (t, 1H, *J* = 4.5 Hz), 7.10–7.40 (m, 5H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.8, 21.8, 28.3, 33.4, 36.8, 44.2, 46.2, 54.7, 56.6, 62.7, 126.7, 127.4, 128.3, 145.6 ppm. IR (film): 702, 770, 1134, 1278, 1453, 1660, 2766, 2814, 2953, 3060, 3437 cm^{-1}. HRMS (ESI): 259.2171 ($[M+H]^+$); for $(C_{17}H_{27}N_2)^+$ *m*/*z* = 259.2174.

4.8. A general procedure for the nitroaldol reaction

The ligand (0.06 mmol, 12 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (10.0 mg, 0.05 mmol, 10 mol %) were dissolved in 1 mL of isopropanol and stirred for 1 h at room temperature. The appropriate aldehyde (0.5 mmol, 1 equiv) and nitroalkane (5.0 mmol, 10 equiv) were added with an additional 1 mL of *i*-PrOH. The reaction mixture was cooled to 0 °C. After 3 days, the crude product was isolated by column chromatography (*n*-hexane/AcOEt 6:1) to yield β-nitroalcohol or the desired β-nitroalcohols as a mixture of diastereomers. Products were analyzed by ^{1}H NMR, and the enantiomeric excess was determined using chiral HPLC.

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