Enantioselective Desymmetrization of Meso Bicyclic Hydrazines: A Novel Approach to the Asymmetric Synthesis of Polysubstituted Amino Cyclopentanic Cores

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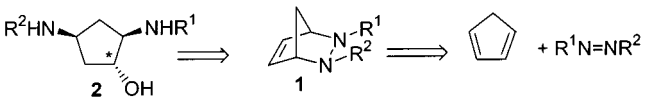
Abstract: Catalytic asymmetric hydroboration can be successfully applied to meso bicyclic hydrazines. The resulting alcohols are of great synthetic interest and can lead in a straightforward manner to cyclopentanic diamino alcohols with good enantiomeric purity.

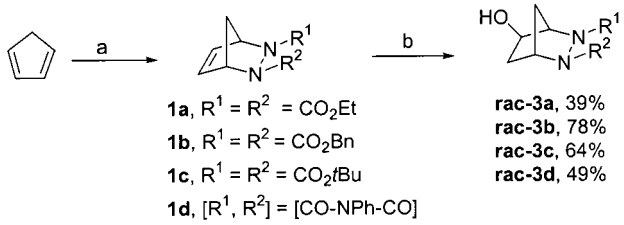
Desymmetrization of meso compounds provides an efficient route to asymmetric synthons of high value in a limited number of steps.[1] This approach is particularly powerful when performed by a catalytic enantioselective transformation, since a small amount of chiral nonracemic material allows the simultaneous creation of several asymmetric centers from an easily available precursor.[2] In the course of our studies on cyclic hydrazines as enantiopure α−ω polyfunctional diamine precursors,[3] our attention was drawn to an elegant racemic approach of diaminocyclopentitols **2** based on hydroboration of meso bicyclic hydrazines **1** followed by the reductive cleavage of the N−N bond (Scheme 1).[4]

If one considers the obvious structural analogy between compounds **1** and norbornene, it is possible to speculate that the numerous desymmetrization operations performed with norbornene could be used on bicyclic hydrazines **1** and lead to compounds of significant synthetic and biological interest.[5]We report here our first studies on desymmetrization of **1** using asymmetric catalytic hydroboration.[6]

Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) $R_1N{=}NR^2$, CH_2Cl_2, 0 °C, quantitative, (b) (i) BH_3·THF, THF, 0 °C, 3 h, (ii) aq NaOH, H_2O_2, rt, 2 h.

Hydrazines **1a**−**c** were prepared on a multigram scale in quantitative yields from the corresponding commercial dialkylazodicarboxylates and cyclopentadiene. Urazole **1d** was prepared according to a reported procedure.[7] The corresponding racemic alcohols **3a**−**d** were obtained by standard hydroboration with BH_3·THF followed by oxidative workup (Scheme 2). As previously noted, this procedure led to the exclusive formation of exo alcohols.[4]

Our first trials of asymmetric hydroboration were made on hydrazine **1b** at low temperature, with $[Rh(COD)Cl]_2$ as rhodium source and (*S*,*S*)-BDPP as chiral diphosphine in various solvents (Table 1). The best results were obtained with DME as a solvent. Under these experimental conditions, (*S*,*S*)-BDPP proved to be the ligand of choice, leading to the best chemical yield and enantiomeric excess (Table 2). The stereochemical outcome of the reaction[8] was the same as previously reported for the hydroboration of norbornene with this ligand.[6r] Interestingly, the use of (*S*,*S*)-DIOP afforded alcohol **3b** of opposite configuration, as already observed in the case

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(8) *Exo* selectivity of the hydroboration was determined by ^1H NMR analysis. The absolute configuration of **3b** was confirmed by X-ray analysis of the final diamino alcohol protected as *p*-bromo dibenzamide (Chiaroni, A.; Cesario, M., unpublished results).

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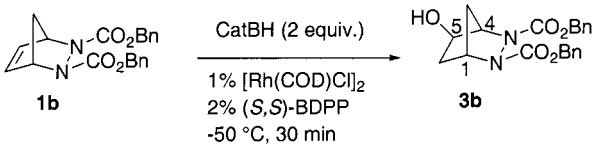
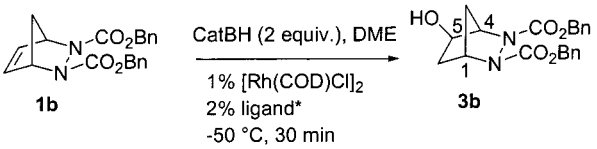
Table 1



solvent	yield (%)	ee[a] (%)	config
toluene	40	66	(1*R*,4*R*,5*R*)
THF	47	64	(1*R*,4*R*,5*R*)
Et_2O	56	60	(1*R*,4*R*,5*R*)
DME	90	84	(1*R*,4*R*,5*R*)
CH_2Cl_2	3	nd[b]	

[a] Determined by chiral HPLC. [b] ee not determined.

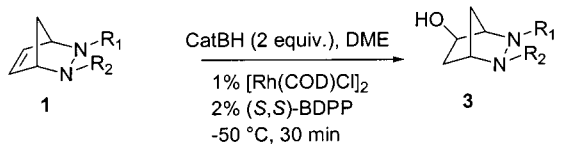
Table 2



ligand	yield (%)	ee[a] (%)	config
(*S*,*S*)-BDPP	90	84	(1*R*,4*R*,5*R*)
(*R*)-BINAP	20	0	
(*R*)-QUINAP	11	24	(1*R*,4*R*,5*R*)
(*S*,*S*)-DIOP	46	44	(1*S*,4*S*,5*S*)

[a] Determined by chiral HPLC.

Table 3



R^1	R^2	yield (%)	ee[a] (%)
CO_2Et	CO_2Et	49	83[c]
CO_2Bn	CO_2Bn	90	84
CO_2tBu	CO_2tBu	58	80[c]
CONPhCO		78	60[c]
norbornene		<10	nd[b]

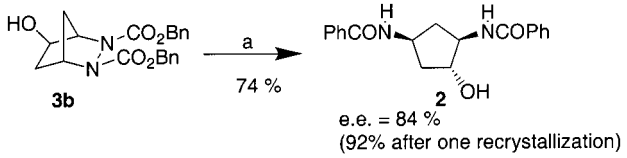
[a] Determined by chiral HPLC. [b] ee not determined. [c] Absolute configuration not determined.

of the norbornene series. Surprisingly, a complete lack of enantioselectivity and a low conversion was observed when BINAP was used, although this chiral phosphine has been reported to give good results in the hydroboration of norbornene.[6r]

The influence of the nitrogen protective groups was studied (Table 3). In all cases, bicyclic hydrazines were more reactive under these conditions than norbornene. This enhanced reactivity is probably due to some neighboring participation of the protected nitrogens, as previously observed in some regioselectivity studies on substituted norbornene, although the mechanistic features of this phenomenon remain to be clarified.[9]

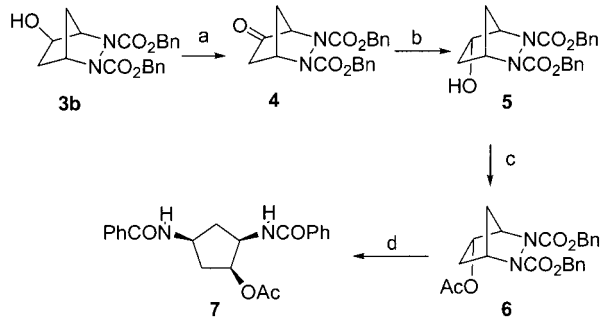
Finally, the best results were obtained with compound **1b**, which could be hydroborated in very good yield and good ee in less than 30 min at − 50 °C. The experimental procedure had to be intensively optimized to get reproducible results with standard commercially available reagents (see the Experimental Section for more details).

Scheme 3[a]



[a] Reagents and conditions: (a) (i) H_2, CH_3COOH, Pt, (ii) PhCOCl, Py.

Scheme 4[a]



[a] Reagents and conditions: (a) oxalyl chloride, DMSO, Et_3N, 84%; (b) BH_3·THF, 76%; (c) Ac_2O, Py, DMAP, 82%; (d) (i) H_2, CH_3COOH, Pt, (ii) PhCOCl, Py, 78%.

Changing to the cationic rhodium source $Rh(COD)_2BF_4$ had little effect on the reaction, since compound **3b** could be obtained in 88% yield and 76% ee. Using optimal conditions, no differences were observed between a 200 mg and a 5 g scale run, showing the high potential of this synthetic pathway.

Access to diaminocyclopentitol **2** was achieved in a straightforward manner from **3b** (Scheme 3). Optical purity of the final compound was checked by chiral HPLC. Enantiomeric excess could be increased to 92% by a single recrystallization from methanol.

Alcohol **3b** is of great synthetic interest. As an example, it can be oxidized to the ketone **4** in a nearly quantitative way, leading to the endo alcohol **5** after selective reduction. The final all-cis diamino alcohol **7** was obtained after O-protection, subsequent reductive cleavage, and benzoylation in a good overall yield (Scheme 4).

In conclusion, we have shown that desymmetrization reactions with catalytic asymmetric hydroboration are not restricted to norbornene or nonfunctionnalized substrates and can be successfully applied to meso bicyclic hydrazines. The resulting alcohols are of great synthetic interest and can lead in a straightforward manner to cyclopentanic diamino alcohols with good enantiomeric purity. Scopes and limitations of this new synthetic strategy are under investigation in our laboratory.

Experimental Section

General Comments. NMR spectra were obtained at 200, 300, or 400 MHz (^1H field value). IR spectra were recorded as thin film unless otherwise stated. Elemental analyses were obtained from the Service de microanalyze of the Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France. Enantiomeric excesses were determined by chiral HPLC (Chiralpak AD column). Compounds **1a**−**d** were prepared according to literature procedures.[4,7,10]

General Procedure for Asymmetric Hydroboration. Asymmetric hydroboration of **1b** is representative: [Rh(COD)-

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$Cl]_2$ (2.5 mg, 0.005 mmol), (*S*,*S*)-BDPP (4.2 mg, 0.01 mmol), and **1b** (0.5 mmol) were placed in a Schlenk tube, dried under vacuum (0.1 mmHg) for 1 h, and then placed under argon. DME (2 mL) was degassed at −50 °C and added to the mixture at this temperature. The yellow-green slurry was stirred at −50 °C for 30 min. Catecholborane (0.11 mL, 1 mmol) was added, and the mixture became orange but remained heterogeneous. The reaction was kept at −50 °C for an additional 30 min. Ethanol (0.5 mL) was then added, and the cooling bath was removed. When the orange mixture became clear, hydrogen peroxide (30% in water, 0.5 mL) and aqueous sodium hydroxide (3 M, 0.85 mL) were added, turning the solution to black. After 15 h of stirring, aqueous sodium hydroxide (1 M, 5 mL) was added, and the mixture was extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with sodium hydroxide (1 M, 2 × 10 mL), water (10 mL), andbrine (10 mL) and concentrated. Purification by flash chromatography (cyclohexane/ethyl acetate = 50:50) afforded **3b** as a colorless oil (182 mg, 90%).

5-Hydroxy-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylic Acid Diethyl Ester 3a. Spectral data are consistent with those reported in the literature.[4a]

5-Hydroxy-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylic Acid Dibenzyl Ester 3b: ^{1}H NMR (300 MHz, DMSO-d_6, 70 °C) δ 1.46 (dt, J = 13.7, 2.5 Hz, 1H), 1.54 (d, J = 10.5 Hz, 1H), 1.98 (d, J = 10.5 Hz, 1H), 1.98−2.04 (m, 1H), 4.28 (s, 1H), 4.52 (s, 1H), 4.68 (s, 1H), 5.16 (m, 4H), 7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.0, 38.0 (br), 59.6, 64.3, 68.1, 68.2, 70.4, 128.0, 128.3, 135.8, 135.9, 155.0 (br); IR (neat) 3453, 3063, 3032, 2952, 1760, 1633, 1496; MS 400 (M + 18), 383 (MH^+), 339, 249. Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33. Found: C, 65.79; H, 5.96; N, 7.33.

5-Hydroxy-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylic Acid Di-*tert*-butyl Ester 3c. The title compound was prepared from **1c** according to the general procedure. Purification by flash chromatography (cyclohexane/ethyl acetate = 60:40) afforded **3c** as a white solid (91 mg, 58%): mp = 58−59 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 18H), 2.6 (m, 4H), 4.15−4.60 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 33.8, 39.0 (br), 59.3 (br) 63.5, 64.2, 69.3, 70.7, 81.6, 157.0 (br); IR (neat) 3691, 3606, 3413, 1772, 1735, 1688; MS 332 (M + 18), 315 (MH^+), 215. Anal. Calcd for $C_{15}H_{26}N_2O_5$: C, 57.31; H, 8.34; N, 8.91. Found: C, 57.42; H, 8.42; N, 8.72.

8-Hydroxy-4-phenyl-2,4,6-triazatricyclo[5.2.1.0]decane-3,5-dione 3d. The title compound was prepared from **1d** according to the general procedure. Purification by flash chromatography (cyclohexane/ethyl acetate = 50:50) afforded **3d** as a white solid (103 mg, 78%): mp = 163−173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (br d, J = 14.1 Hz, 1H), 1.93 (br d, J = 10.8 Hz, 1H), 2.21 (d, J = 10.8 Hz, 1H), 2.30 (ddd, J = 14.0, 6.8, 2.3 Hz, 1H), 4.26 (s, 1H), 4.48 (s, 1H), 4.65 (s, 1H), 7.35−7.49 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.2, 39.4, 59.0, 64.2, 69.9, 125.5, 128.6, 129.3, 131.5, 156.7 (br); IR ($CHCl_3$) 3692, 3606, 3470, 3040, 1771, 1713; MS 277 (M + 18), 260 (MH^+). Anal. Calcd for $C_{13}H_{13}N_3O_5 \cdot 0.5H_2O$: C, 58.20; H, 5.26; N, 15.66. Found: C, 58.21; H, 5.27; N, 15.51.

Preparation of *N*-(4-Benzoylamino-2-hydroxycyclopentyl)benzamide 2. A solution of **3b** (580 mg, 1.52 mmol) in AcOH (3 mL) was stirred over Pt black at room temperature under hydrogen atmosphere for 48 h. After filtration, the solvent was evaporated, the residue was dissolved in a 1:1 aq $NaHCO_3$/*t*-BuOH mixture (8 mL), and benzoyl chloride (0.528 mL, 4.55 mmol, 3 equiv) was added to the mixture. The reaction mixture was stirred 16 h at 25 °C, and the excess *t*-BuOH was removed under reduced pressure. Brine (30 mL) was added to the residue, and the product was extracted with ethyl acetate (4 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give a residue that was purified by flash column chromatography (AcOEt/MeOH = 86:14) to give **2** as a white solid (370 mg, 76%): mp = 235−237 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.88 (dt, J = 13.5, 7.1 Hz, 1H), 2.10−2.26 (m, 2H), 2.79 (dt, J = 13.5, 6.3 Hz, 1H),4.28 (m, 1H), 4.40 (m, 1H), 4.62 (quint, J = 7.6 Hz, 1H), 4.92 (s, 3H), 7.52−7.69 (m, 6H) 7.90−8.00 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ 36.8, 39.5, 49.2, 59.2, 76.9, 128.3, 128.4, 129.6, 132.7, 169.1, 171.0; IR (KBr) 3296, 1628, 1530, 1490; MS 325 (MH^+). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.31; H, 6.33; N, 8.49.

5-Oxo-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylic Acid Dibenzyl Ester 4. Oxalyl chloride (0.2 mL, 2.3 mmol) was dissolved in anhydrous CH_2Cl_2 (4 mL) under argon and cooled to −30 °C, and DMSO (0.3 mL, 4.2 mmol) was added dropwise. Compound **3b** (382 mg, 1 mmol) in CH_2Cl_2 (3 mL) was added, and the resulting mixture was stirred for 3 h at −50 °C. Triethylamine (0.9 mL) was added, and the solution was stirred for 20 min at −50 °C and allowed to reach 0 °C. The reaction was quenched with water. The organic phase was separated and washed with brine, aq HCl (1 M), aq $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and concentrated to give a residue that was purified by flash column chromatography (AcOEt/cyclohexane = 1:1) to give **4** as a white solid recrystallized from AcOEt/hexane = 9:1 (320 mg, 84%): mp = 77−78 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.50 (s, 2H), 2.25−2.30 (m, 2H), 4.40 (s, 1H), 4.95 (s, 1H), 5.07−5.19 (m, 4H), 7.10−7.36 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.3, 40.4, 58.1, 65.2, 68.4, 68.5, 127.9, 127.9, 128.2, 128.5, 135.3, 156.4, 157.8, 201.6; IR (neat) 1713, 1497; MS 381 (MH^+), 132. Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.20; H, 5.50; N, 7.15.

Reduction of Ketone 4. Borane·THF complex (6.13 mL, 1 M in THF) was added dropwise to a solution of ketone **4** (3.50 g, 9.20 mmol) in THF (34 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2.5 h. A second portion of borane solution (3.13 mL) was added, and the mixture was stirred for 30 min at 0 °C. The reaction was quenched with water (5 mL) and stirred for 2 h at room temperature. Brine (30 mL) was added, and the resultant mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (hexanes/AcOEt = 6:4) to afford **5** (2.69 g, 76%).

Acetic Acid 2,4-Bis(benzoylamino)cyclopentyl Ester 7. To a solution of the endo alcohol **5** (300 mg, 0.78 mmol) in CH_2Cl_2 (2 mL) at 0 °C were added freshly distilled pyridine (0.64 mL, 7.84 mmol) and DMAP (1 mg). To this mixture was added acetic anhydride (0.8 mL, 7.84 mmol) over a 10 min period. After being stirred at room temperature for 30 h, the reaction mixture was quenched with H_2O (20 mL). The mixture was stirred for 1 h and extracted with ethyl acetate twice. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give **6** as a white oil (270 mg, 82%).

The nitrogen−nitrogen bond reductive cleavage of **6** (200 mg, 0.47 mmol) with Pt black and benzoylation was performed according to the same procedure as for **3b**. **7** was obtained as a white oil (134 mg, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (m, 1H), 2.04−2.17 (m, 1H), 2.05 (s, 3H), 2.47 (m, 1H), 2.65 (dt, J = 14.3, 8.0 Hz, 1H), 4.36 (m, 1H), 4.62 (dt, J = 12.6, 7.5 Hz, 1H), 5.22 (dt, J = 10.7, 5.4 Hz, 1H), 7.39−7.54 (m, 8H), 7.60 (d, J = 7.1 Hz, 1H) 7.88 (d, J = 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 36.1, 36.2, 47.2, 51.3, 74.5, 126.8, 127.1, 128.6, 131.5, 134.3, 167.1, 167.2, 170.3; IR (neat) 3027, 1736, 1658; MS 367 (MH^+).

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