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Desymmetrization of *meso*-bicyclic hydrazines by Rhodium catalyzed enantioselective hydroformylation

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An asymmetric hydroformylation of three *meso*-bicyclic hydrazines followed by the reduction of the formyl product into the corresponding alcohols allowed producing the corresponding desymmetrized optically enriched hydroxymethyl hydrazines (up to 77.5 % *ee*).

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Introduction

The enantioselective transition metal-catalyzed hydroformylation of olefins constitutes one of the most attractive atom economic, clean, and environmentally friendly process for introduction of a formyl residue with a concomitant creation of chirality in an organic compound.^[1,2] In this context, lot of efforts have been devoted to the design of phosphorous based chiral ligands in order to modify platinum and rhodium hydroformylation catalysts.^[1-4] From a substrate standpoint, styrene and other vinyl arenes, vinyl acetate, and allyl cyanide, for example,^[3,4] have been used in order to evaluate the newly designed catalytic systems. Conversely, norbornene and its related derivatives have been hydroformylated selectively into the *exo*-formyl products in the presence of platinum and rhodium catalysts modified by chiral diphosphorous auxiliaries.^[5,6]

We have an ongoing interest both in asymmetric transformations involving bicyclic hydrazines to synthesize polyfunctional aminocyclopentanes^[7-9] and hydroformylation.^[10] As such, we have reported recently on the rearrangement,^[11,12] hydroboration,^[8,13,14] and asymmetric nucleophilic ring opening^[15,16] of bicyclohydrazine derivatives. We extended our study on such substrates and explored their behaviour under enantioselective hydroformylation conditions. Here, we report on

the desymmetrization though asymmetric hydroformylation of three bicyclic hydrazine substrates.

Results and Discussion

As mentioned above, we have investigated the desymmetrization of polycyclic hydrazines by hydroformylation with the aim of having access to new valuable intermediates for further elaboration into polyfunctional cyclopentanes. Initial experiments have been carried out on substrate **S1** (Figure 1). The structural analogy between this compound and norbornene prompted us to first evaluate reactions conditions described by Stille for the norbornene hydroformylation.^[5c] However, no hydroformylated product could be obtained in the presence of a platinum catalyst generated from Pt(cod)Cl₂ (1 mol-%), SnCl₂ (2 mol-%), and (*S,S*)-BPPM (2 mol-%) (Figure 2) under the following conditions: syngas (CO/H₂ 1:1) 60 bar, 60 °C, 18 h. The lower initial pressure applied compared to that utilized by Stille for the hydroformylation of norbornene (165 bar) can account for this result. As we planned to apply rather mild reaction conditions (< 100 bar), we favoured the use of rhodium based catalytic systems.^[11] The next attempt of hydroformylation of **S1** has been performed in the presence of the catalytic system obtained from Rh(acac)(CO)₂ and (*S,S*)-BPPM (1/4) in toluene at 80 °C under 40 bar of syngas (Scheme 1).

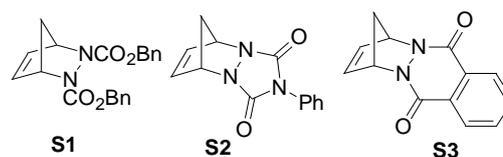


Figure 1. Substrates for hydroformylation studies.

The conversion was quantitative as determined by ^1H NMR and the hydroformylated product **2** was isolated in 84% yield after workup as a single *exo* diastereomer. No hydrogenated derivative could be detected in the crude reaction mixture. As the optical purity determination could not be carried out on the aldehyde **2** because of its partial chemical and configurational instability, the crude was first reduced into the corresponding alcohol **3** (NaBH_4 , MeOH , $0\text{ }^\circ\text{C}$, 80 %) prior to the enantiomeric purity determination by chiral HPLC. An encouraging *ee* of 44 % was obtained.

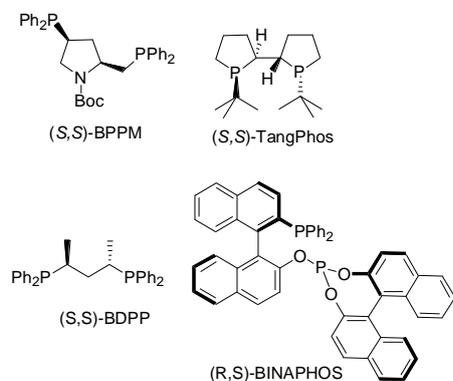
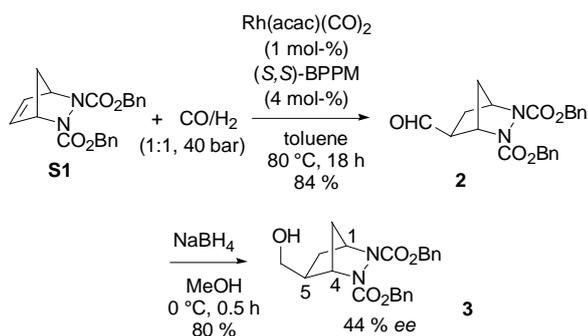
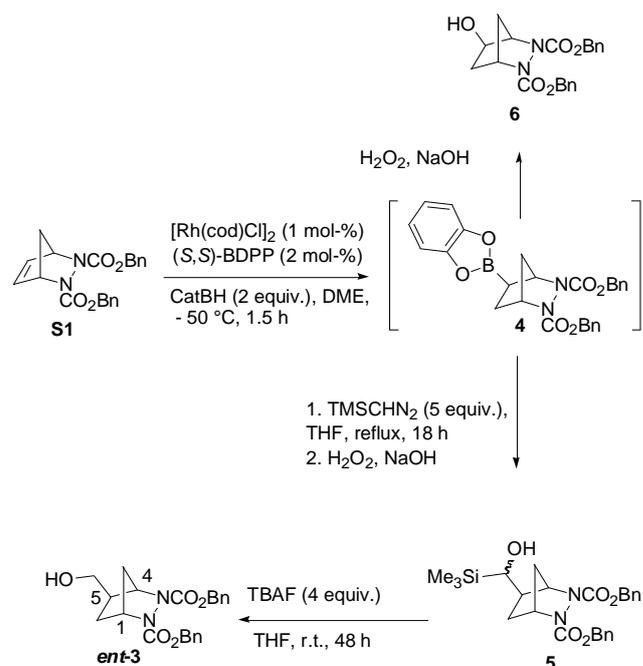


Figure 2. Chiral ligands used in this study.



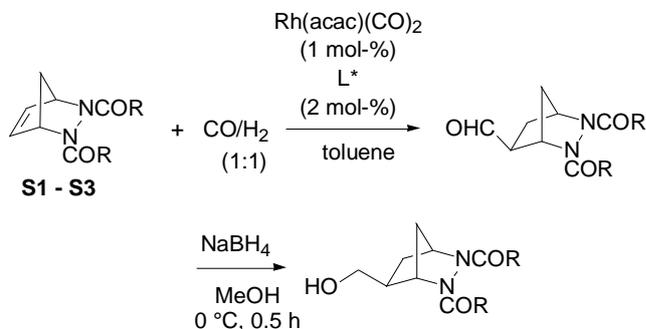
Scheme 1. Hydroformylation of **S1**.

The absolute configuration of the major enantiomer was assessed by a chemical correlation. Thus, we first performed an enantioselective hydroboration of substrate **S1** followed by the trapping of the hydroborated intermediate **4** by trimethylsilyldiazomethane. The homologated boronate was then subjected to an oxydative cleavage, leading to the hydroxy silyl derivative **5** in 95 % overall yield (Scheme 4).^[17] Then, a desilylation provided the primary alcohol **3** in 87 % isolated yield and with 80 % *ee* determined by HPLC. Since the absolute configuration of the hydroboration product **6** resulting from the transformation of **S1** under the same catalytic conditions followed by an oxydative cleavage had previously been established to be (1*S*, 4*R*, 5*R*), a (1*S*, 4*S*, 5*S*) configuration could be assigned to alcohol **3**. As the retention times for the major isomers obtained following both synthetic routes depicted in schemes 1 and 2 were identical, we deduced that both alcohols possess the same absolute configuration (1*S*, 4*S*, 5*S*).



Scheme 2. Chemical correlation for the assignment of the absolute configuration of **3**.

The variation of the hydroformylation parameters (ligand/Rh ratio, source of Rh, temperature, pressure, ligand) on the reaction course were then investigated (Table 1). A rhodium/ligand ratio from 1/1.2 to 1/4 delivered close catalytic results, especially in terms of enantioselectivity (entries 1-4). Two rhodium sources ($\text{Rh}(\text{acac})(\text{CO})_2$ and $\text{Rh}(\text{H})(\text{CO})(\text{PPh}_3)_3$) generated catalysts of similar efficiencies whereas $[\text{Rh}(\text{cod})\text{Cl}]_2$ proved to be less efficient for this transformation (entries 5-7). The temperature had a significant impact on the selectivity, the highest *ee* being reached at $20\text{ }^\circ\text{C}$ (59 % *ee* at $20\text{ }^\circ\text{C}$ vs. 45 % *ee* at $80\text{ }^\circ\text{C}$, entries 8-11). Among the four chiral ligands evaluated, (*S,S*)-BPPM proved to be the most efficient, with a 59 % *ee* obtained at $20\text{ }^\circ\text{C}$. In our hands, the use of (*S,S,R,R*)-TangPhos ligand at $60\text{ }^\circ\text{C}$ led to the hydroformylated compound with a 53 % enantiomeric excess, whereas a 60 % *ee* has been reported for this reaction conducted at room temperature by Huang *et al* during our investigations.^[6] The use of (*S,S*)-BDPP and (*R,S*)-BINAPHOS provided selectivities of 13% and 32 % *ee*, respectively (entries 11-14).



Scheme 3. Hydroformylation of substrates **S1 – S3**.

From the analysis of the results obtained with substrate **S1** while varying the catalytic parameters, we selected (*S,S*)-BPPM and

(*S,S,R,R*)-TangPhos ligands to examine the hydroformylation of two other bicyclic hydrazine substrates, **S2** and **S3** into **P2** and **P3** after reduction of the intermediate formyl derivatives (Figure 1 and scheme 3). The results are summarized in table 2. Despite their apparent structural similarities, the three substrates proved to behave differently in the hydroformylation reaction. Thus, lowering the reaction temperature led to an improvement of the enantioselectivity when working on substrate **S1** (entries 3, 5, 11, and 15) and **S3** (entries 23, 24) with BPPM ligand, while it proved to be detrimental for both catalyst rate and selectivity for substrate **S2** (entries 18-20). A similar behaviour could be observed with the (*S,S,R,R*)-TangPhos ligand for substrates **S1** and **S2** (entries 16, 17

and 21, 22). Substrate **S3** was not very soluble in the reaction medium. Thus, the yield into the aldehyde was lower than for the two other substrates **S1** and **S2**. Nevertheless, this substrate led to the best result in terms of selectivity as, after reduction, the corresponding alcohol could be isolated with 77.5 % ee. It appears thus that the desymmetrization of *meso* hydrazines using catalytic asymmetric hydroformylation reactions is far from being straightforward, and highly substrate-dependent.

Table 1. Asymmetric hydroformylation of **S1**.^[a]

Entry	Rh source	Chiral auxiliary	Rh/ligand	P _{H₂CO} (bar),	Temp. (°C)	3 Yield (%) ^[b]	ee (%) ^[c] alcohol
1	Rh(acac)(CO) ₂	(<i>S,S</i>)-BPPM	1/4	40,	80	88	44
2	Rh(acac)(CO) ₂	(<i>S,S</i>)-BPPM	1/3	40	80	87	46
3	Rh(acac)(CO) ₂	(<i>S,S</i>)-BPPM	1/2	40	80	84	45
4	Rh(acac)(CO) ₂	(<i>S,S</i>)-BPPM	1/1.2	40	80	85	37
5	Rh(acac)(CO) ₂	(<i>S,S</i>)-BPPM	1/2	20	45	85	53
6	[Rh(cod)Cl] ₂	(<i>S,S</i>)-BPPM	1/2	20	45	18	50
7	Rh(H)CO(PPh ₃) ₃	(<i>S,S</i>)-BPPM	1/2	20	45	88	53
8	Rh(acac)(CO) ₂	(<i>S,S</i>)-BPPM	1/2	45	80	84	45
9	Rh(acac)(CO) ₂	(<i>S,S</i>)-BPPM	1/2	45	60	84	49
10	Rh(acac)(CO) ₂	(<i>S,S</i>)-BPPM	1/2	45	45	85	53
11	Rh(acac)(CO) ₂	(<i>S,S</i>)-BPPM	1/2	20	20	80	59
12	Rh(acac)(CO) ₂	(<i>R,R</i>)-BDPP	1/4	45	80	72	13
13	Rh(acac)(CO) ₂	(<i>S,S,R,R</i>)-TangPhos	1/2	30	60	84	53
14 ^[d]	Rh(acac)(CO) ₂	(<i>R,S</i>)-BINAPHOS	1/4	30	50	86	32

[a] General conditions of hydroformylation: Rh precursor 1 mol-%, toluene 5 mL, non optimized reaction times of 15 or 18 h. [b] The conversion of **S1** is total in all cases. Yield of the isolated product **3** obtained by reduction of **2**. [c] ee determination was carried out on the alcohol by chiral HPLC, configuration of the major enantiomer (1*S*,4*S*,5*S*), see text. [d] Reaction time of 4 h.

Table 2. Asymmetric hydroformylation of **S1** – **S3**.^[a]

Entry	Substrate	L*	P _{H₂CO} (bar)	T (°C)	Time (h)	Conv. (%) ^[b]	Yield (%) ^[c]	ee (%) ^[d]
3	S1	(<i>S,S</i>)-BPPM	40	80	18	100	84	45
5	S1	(<i>S,S</i>)-BPPM	20	45	15	100	85	53
11	S1	(<i>S,S</i>)-BPPM	20	20	24	100	80	59
15	S1	(<i>S,S</i>)-BPPM	100	- 4	16	100	74	59
16	S1	(<i>S,S,R,R</i>)-TangPhos	30	60	15	100	84	53
17	S1	(<i>S,S,R,R</i>)-TangPhos	100	- 4	20	100	90	34
18	S2	(<i>S,S</i>)-BPPM	45	80	15	100	84	52 ^[e]
19	S2	(<i>S,S</i>)-BPPM	20	45	15	100	90	49 ^[e]
20	S2	(<i>S,S</i>)-BPPM	100	- 4	20	40	22	23 ^[e]
21	S2	(<i>S,S,R,R</i>)-TangPhos	30	60	15	100	80	29 ^[e]
22	S2	(<i>S,S,R,R</i>)-TangPhos	95	- 6	20	nd	33	7 ^[e]
23	S3	(<i>S,S</i>)-BPPM	45	20	15	nd	42	42 ^[e]
24	S3	(<i>S,S</i>)-BPPM	100	- 4	20	30	21	77.5 ^[e]

[a] General conditions of hydroformylation: Rh(acac)(CO)₂ 1 mol-%, chiral auxiliary 2 mol-%, toluene 5 mL. [b] Conversion of **S1** – **S3** determined by ¹H NMR. [c] Yield of the isolated reduction products. [d] ee determination was carried out on the alcohol by chiral HPLC, configuration of the major enantiomer (1*S*,4*S*,5*S*), see text [e] Absolute configuration not determined.

Conclusion

In summary, we have shown that a desymmetrization of *meso*-bicyclic hydrazines is possible through asymmetric hydroformylation. The reaction proceeds efficiently with a high diastereoselectivity as the *exo*-products are obtained exclusively. The alcohols prepared by the reduction of the hydroformylated products could be obtained with an *ee* up to 77.5 % under the catalytic conditions examined in this study. This reaction seems to be much more substrate-dependent than the hydroboration, and its optimisation is still a challenging task.

Experimental Section

¹H NMR, ¹³C NMR spectra were recorded on a BRUKER Avance 400 or 300 spectrometer at 25 °C. Chemical shifts are reported in ppm downfield of internal tetramethylsilane. All melting points are uncorrected. All reagents are commercially available and were used without further purification. The organic syntheses were carried out under classical conditions unless otherwise stated. The reactions are performed under nitrogen. THF was dried over CaCl₂, filtrated through basic alumina and distilled over Na under nitrogen. Toluene was distilled over Na under nitrogen. Substrates **S1-S3** were prepared following reported procedures.^[15]

General procedure for hydroformylation.

Under nitrogen, a Schlenk flask was charged with a magnetic stir bar, Rh(acac)(CO)₂ (2.6 mg, 0.01 mmol), the chiral auxiliary (0.02 mmol), and toluene (5 mL). The solution was stirred at room temperature for one hour. The substrate (1 mmol) was placed in a double walled stainless steel autoclave equipped with a stir bar under nitrogen. The solution containing the rhodium precatalyst was transferred into the autoclave via cannula under nitrogen. The autoclave was then pressurized with syngas (CO/H₂ 1:1) at the selected pressure and placed at the desired temperature. At the end of the reaction, the autoclave is cooled to room temperature and depressurized. Toluene is evaporated under reduced pressure. The crude residue is dissolved in methanol and the mixture is cooled to 0 °C. NaBH₄ (113 mg, 3 mmol) was added in small portions over 30 min. Then, ethyl acetate (30 mL) and saturated ammonium chloride (10 mL) were added. The aqueous phase was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried over magnesium sulfate. After filtration and evaporation of the solvent, the crude residue was purified through silica gel flash chromatography.

Dibenzyl 5-Formyl-2,3-diaza-bicyclo[2.2.1]heptane-2,3-dicarboxylate (2)

Yellow oil (330 mg, 84 %). ¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.46 (d, *J* = 10.5 Hz, 1H), 1.69 (d, *J* = 10.5 Hz, 1H), 1.81-2.20 (m, 2H), 2.99 (br. s, 1H), 4.51-5.15 (m, 2H), 5.10-5.27 (m, 4H), 7.26-7.34 (m, 10H), 9.46 (br. s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ [ppm] 29.3, 36.2, 52.3, 60.5, 68.3, 128.1, 128.4, 128.7, 135.9, 157.2, 199.1.

Dibenzyl 5-(Hydroxymethyl)-2,3-diaza-bicyclo[2.2.1]heptane-2,3-dicarboxylate (3, P1)

Yellow oil (364 mg, 80 %). ¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.00-1.30 (m, 1H), 1.50-1.70 (m, 2H), 1.80-2.00 (m, 1H), 2.10-2.40 (m, 2H), 3.20-3.40 (m, 1H), 3.40-3.60 (br. s, 1H), 4.40-4.80 (m, 2H), 5.10-5.30 (m, 4H), 7.26-7.32 (m, 10H). ¹³C NMR (100 MHz, CDCl₃): δ [ppm] 32.5, 35.3, 42.7, 60.5, 62.1, 64.2, 68.1, 128.1, 128.3, 128.6, 136.1, 157.7. HRMS calcd for C₂₂H₂₅N₂O₅: 397.1763, found 397.1765. Conditions for chiral HPLC analysis: Samples were injected in elution solvent at a 0.1 gL⁻¹ concentration in a 20 mL injection loop. Analysis conditions: Chiralpack AD column (0.46 cm I.D. x 25 cm) equipped with a precolumn (0.46 cm I. D. x 5 cm),

detection at λ = 220 nm, Flow = 0.8 mL.Min⁻¹, eluent : hexane/iPrOH 70/30, retention time: t_{r1} = 11.87 min, t_{r2} = 13.81 min.

3,5-Dioxo-4-phenyl-2,4,6-triazatricyclo[5.2.1.0^{2,6}]decane-8-carbaldehyde

White amorphous solid (270 mg, 99 %). ¹H NMR (300 MHz, CDCl₃): δ [ppm] 1.70 (d, *J* = 11.0 Hz, 1H), 1.91 (d, *J* = 11.0 Hz, 1H), 2.15 (dd, *J* = 11.5, 9.0 Hz, 1H), 2.29 (m, 1H), 3.26 (m, 1H), 4.99 (s, 1H), 5.31 (s, 1H), 7.40 (m, 1H), 7.47 (m, 4H), 9.78 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ [ppm] 28.7, 36.9, 52.4, 60.1, 125.5, 128.6, 129.4, 131.4, 157.0, 198.2.

8-(Hydroxymethyl)-4-phenyl-2,4,6-triazatricyclo[5.2.1.0^{2,6}]decane-3,5-dione (P2)

White solid (245 mg, 90 %). M.p. = 180-182 °C. ¹H NMR (300 MHz, CDCl₃): δ [ppm] 1.47 (ddd, *J* = 13.0, 5.0, 3.0 Hz, 1H), 1.94 (m, 2H), 2.11 (m, 2H), 2.41 (m, 1H), 3.44 (m, 1H), 3.64 (m, 1H), 4.68 (br.s, 1H), 4.88 (br.s, 1H), 7.40 (m, 1H), 7.47 (m, 2H), 7.49 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ [ppm] 31.5, 36.2, 43.0, 60.3, 61.9, 63.7, 125.6, 128.5, 129.3, 131.6, 157.0. MS (ES) 296 (MNa⁺) Conditions for chiral HPLC analysis: Samples were injected in elution solvent at a 0.1 gL⁻¹ concentration in a 20 mL injection loop. Analysis conditions: Chiralpack AD column (0.46 cm I.D. x 25 cm) equipped with a precolumn (0.46 cm I. D. x 5 cm), detection at λ = 220 nm, Flow = 0.8 mL.Min⁻¹, eluent : hexane/iPrOH 70/30, retention time: t_{r1} = 11.9 min, t_{r2} = 13.8 min.

2-(Hydroxymethyl)-1,4-methano-1,2,3,4-tetrahydropyridazino[1,2-b]phtalazine-6,11-dione (P3)

Yellow oil (125 mg, 42 %). ¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.66 (m, 1H), 2.08 (sl, 2H), 2.15 (m, 1H), 2.45 (m, 1H), 3.53 (m, 1H), 3.69 (br.s, 1H), 3.75 (m, 1H), 5.37 (br.s, 1H), 5.43 (br.s, 1H), 7.76 (m, 2H), 8.26 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ [ppm] 31.8, 35.4, 43.7, 58.6, 60.4, 63.9, 127.3, 129.9, 133.1, 153.4, 153.7. MS (ES) 281 (MNa⁺) Conditions for chiral HPLC analysis: Samples were injected in elution solvent at a 0.1 gL⁻¹ concentration in a 20 mL injection loop. Analysis conditions: Chiralpack AD column (0.46 cm I.D. x 25 cm) equipped with a precolumn (0.46 cm I. D. x 5 cm), detection at λ = 220 nm, Flow = 0.8 mL.Min⁻¹, eluent : hexane/iPrOH 80/20, retention time: t_{r1} = 14.18 min, t_{r2} = 15.56 min.

Chemical correlation

[Rh(cod)Cl]₂ (5 mg, 0.01 mmol), (*S,S*)-BDPP (8.8 mg, 0.02 mmol) and **S1** (365 mg, 1 mmol) were placed in a Schlenk tube, dried under vacuum (0.1 mmHg) for 1 h, and then placed under argon. DME (4 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 (210 μL, 2 mmol) was then added dropwise, and the mixture became orange but remained heterogeneous. The reaction was kept at -50 °C for an additional 30 min. Solvent and excess reagent were then carefully removed under vacuum (0.1 mm Hg, 3 h) to give the intermediate borane **4** as a dark yellow foam. A solution of **4** in THF (6 mL) under argon was then added over a 2 M solution of trimethylsilyldiazomethane in Et₂O (2.5 mL, 5 mmol). After refluxing overnight, 10 mL of a freshly prepared 1:1 mixture of 2N aqueous sodium hydroxide and 30 % hydrogen peroxide were then added dropwise at 0 °C, turning the solution to black, and the mixture was stirred for an additional 4 h at room temperature. After extraction with EtOAc (3x20 mL), the combined organic layers were washed with 1M HCl (20 mL), dried over MgSO₄, filtered and concentrated. The crude reaction mixture was then purified by silica gel flash chromatography (cyclohexane / ethylacetate 2:1) to give **5** as a mixture of diastereomers (446 mg, 95 %). Tetrabutylammonium fluoride (250 mg, 0.8 mmol) was added to a solution of **5** (188 mg, 0.4 mmol) in THF (2 mL) and stirred at room temperature for 24 h. More reagent was then added (250 mg, 0.8 mmol), and the mixture was kept at room temperature until complete consumption of the starting material. After concentration under vacuum, the crude reaction mixture was

purified by silica gel flash chromatography to give **3** (138 mg, 87 %). The absolute configuration of compound **3** was established from the known configuration of compound **6**, obtained by an oxidative treatment of boronate **5** (see ref 7).

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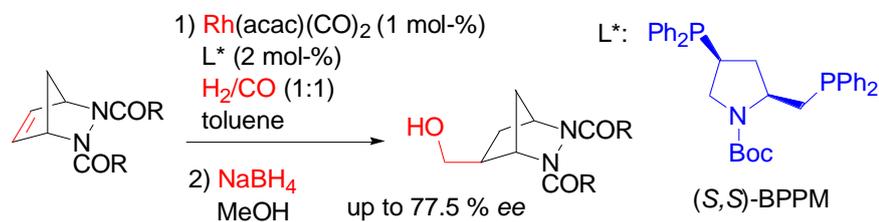
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Entry for the Table of Contents (Please choose one layout)

Layout 2:

((Asymmetric Hydroformylation))



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Laurent Micouin,^{[a],*} Catherine
Méliet,^[b] Francine Agbossou-
Niedercorn^{[b],*} Page No. – Page
No.

Desymmetrization of *meso*-bicyclic
hydrazines by Rhodium catalyzed
enantioselective hydroformylation

Keywords: asymmetric
hydroformylation, rhodium, hydrazine

Asymmetric hydroformylation of three
meso-bicyclic hydrazines followed by the
reduction of the formyl product yielded

the corresponding desymmetrized optically
enriched hydroxymethyl hydrazines (up to
77.5 % ee).