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

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, a lot of effort has been devoted to the design of phosphorus-based chiral ligands in order to modify platinum and rhodium hydroformylation catalysts.[1–4] From a substrate standpoint, styrene and other vinyl arenes, vinyl acetates and allyl cyanides, 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 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.

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Results and Discussion

As mentioned above, we 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 were carried out on substrate **S1** (Figure 1). The structural analogy between this compound and norbornene prompted us to first evaluate reaction conditions described by Stille for norbornene hydroformylation.[5c] However, no hydroformylated product could be obtained in the presence of a platinum catalyst generated from Pt(cod)-Cl_2 (1 mol-%), $SnCl_2$ (2 mol-%) and (*S*,*S*)-bppm (2 mol-%) (Figure 2) under the following conditions: syngas (CO/H_2, 1:1) 60 bar, 60 °C, 18 h. The lower initial pressure applied relative 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.[1] The next attempt at hydroformylation of **S1** was 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).

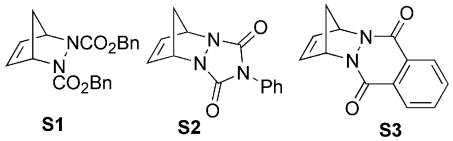


Figure 1. Substrates for hydroformylation studies.

The conversion was quantitative as determined by ^1H NMR spectroscopy, and 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 determination of optical purity could not be carried out on aldehyde **2**, because of

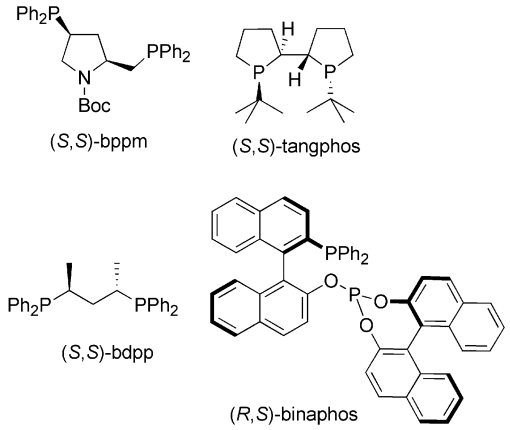
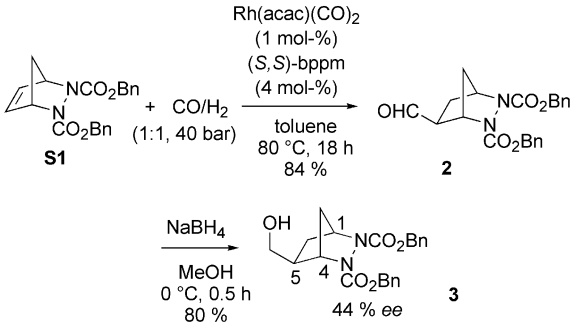


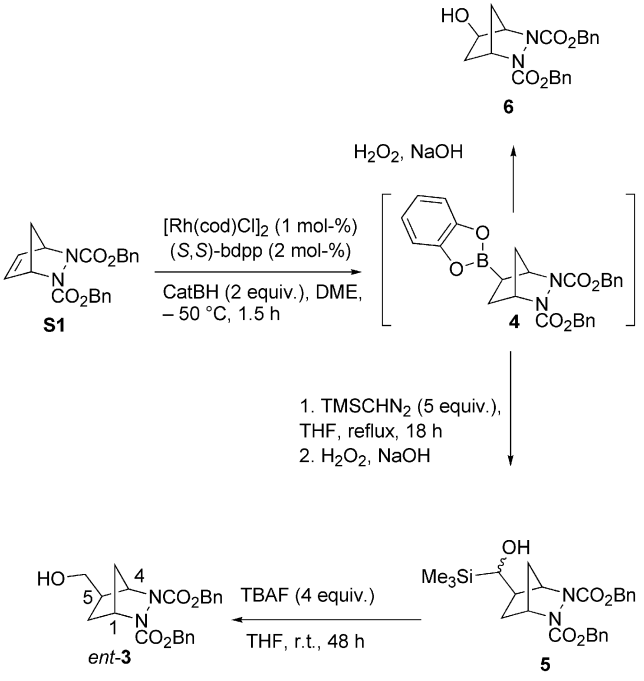
Figure 2. Chiral ligands used in this study.



Scheme 1. Hydroformylation of **S1**.

its partial chemical and configurational instability, the crude was first reduced into corresponding alcohol **3** ($NaBH_4$, MeOH, 0 °C, 80%) prior to the determination of enantiomeric purity by chiral HPLC. An encouraging 44%*ee* was obtained.

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



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

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

Entry	Rh source	Chiral auxiliary	Rh/ligand	$P_{H_2/CO}$ [bar]	*T* [°C]	Yield of **3** [%][b]	*ee* of alcohol [%][c]
1	$Rh(acac)(CO)_2$	(*S*,*S*)-bppm	1:4	40	80	88	44
2	$Rh(acac)(CO)_2$	(*S*,*S*)-bppm	1:3	40	80	87	46
3	$Rh(acac)(CO)_2$	(*S*,*S*)-bppm	1:2	40	80	84	45
4	$Rh(acac)(CO)_2$	(*S*,*S*)-bppm	1:1.2	40	80	85	37
5	$Rh(acac)(CO)_2$	(*S*,*S*)-bppm	1:2	20	45	85	53
6	$[Rh(cod)Cl]_2$	(*S*,*S*)-bppm	1:2	20	45	18	50
7	$Rh(H)CO(PPh_3)_3$	(*S*,*S*)-bppm	1:2	20	45	88	53
8	$Rh(acac)(CO)_2$	(*S*,*S*)-bppm	1:2	45	80	84	45
9	$Rh(acac)(CO)_2$	(*S*,*S*)-bppm	1:2	45	60	84	49
10	$Rh(acac)(CO)_2$	(*S*,*S*)-bppm	1:2	45	45	85	53
11	$Rh(acac)(CO)_2$	(*S*,*S*)-bppm	1:2	20	20	80	59
12	$Rh(acac)(CO)_2$	(*R*,*R*)-bdpp	1:4	45	80	72	13
13	$Rh(acac)(CO)_2$	(*S*,*S*,*R*,*R*)-tangphos	1:2	30	60	84	53
14[d]	$Rh(acac)(CO)_2$	(*R*,*S*)-binaphos	1:4	30	50	86	32

[a] General conditions for hydroformylation: Rh precursor (1 mol-%), toluene (5 mL), unoptimized reaction times of 15 or 18 h. [b] The conversion of **S1** is total in all cases. Yield of isolated product **3** obtained by reduction of **2**. [c] Determination of *ee* 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.

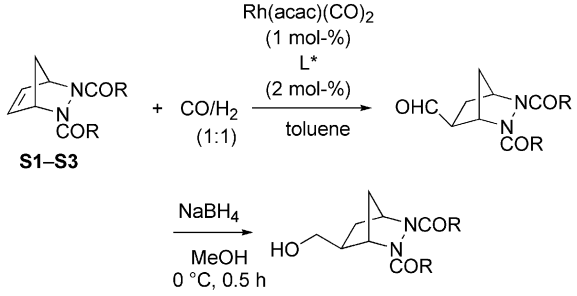
Table 2. Asymmetric hydroformylation of **S1**–**S3**.[a]

Entry	Substrate	L*	$P_{H_2/CO}$ [bar]	T [°C]	Time [h]	Conv. [%][b]	Yield [%][c]	*ee* [%][d]
1	**S1**	(*S*,*S*)-bppm	40	80	18	100	84	45
2	**S1**	(*S*,*S*)-bppm	20	45	15	100	85	53
3	**S1**	(*S*,*S*)-bppm	20	20	24	100	80	59
4	**S1**	(*S*,*S*)-bppm	100	–4	16	100	74	59
5	**S1**	(*S*,*S*,*R*,*R*)-tangphos	30	60	15	100	84	53
6	**S1**	(*S*,*S*,*R*,*R*)-tangphos	100	–4	20	100	90	34
7	**S2**	(*S*,*S*)-bppm	45	80	15	100	84	52[e]
8	**S2**	(*S*,*S*)-bppm	20	45	15	100	90	49[e]
9	**S2**	(*S*,*S*)-bppm	100	–4	20	40	22	23[e]
10	**S2**	(*S*,*S*,*R*,*R*)-tangphos	30	60	15	100	80	29[e]
11	**S2**	(*S*,*S*,*R*,*R*)-tangphos	95	–6	20	nd	33	7[e]
12	**S3**	(*S*,*S*)-bppm	45	20	15	nd	42	42[e]
13	**S3**	(*S*,*S*)-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 spectroscopy. [c] Yield of the isolated reduction products. [d] Determination of *ee* 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.

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 (Table 1, Entries 1–4). Two rhodium sources [$Rh(acac)(CO)_2$ and $Rh(H)(CO)(PPh_3)_3$] generated catalysts of similar efficiencies, whereas $[Rh(cod)Cl]_2$ proved to be less efficient for this transformation (Table 1, Entries 5–7). The temperature had a significant impact on the selectivity: the highest *ee* was reached at 20 °C (59%*ee* at 20 °C vs. 45%*ee* at 80 °C; Table 1, Entries 8–11). Among the four chiral ligands evaluated, (*S*,*S*)-bppm proved to be the most efficient, as 59%*ee* was obtained at 20 °C. In our hands, the use of the (*S*,*S*,*R*,*R*)-tangphos ligand at 60 °C led to the hydroformylated compound with a 53%*ee*, whereas a 60%*ee* was 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 (Table 1, Entries 11–14).

From analysis of the results obtained with substrate **S1** while varying the catalytic parameters, we selected the (*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 in the enantioselectivity when working on substrate **S1** (Table 2, Entries 1–4) and **S3** (Table 2, Entries 12, 13) with the bppm ligand, whereas it proved to be detrimental for both catalyst rate and selectivity for substrate **S2** (Table 2, Entries 7–9). A similar behaviour could be observed with the (*S*,*S*,*R*,*R*)-tangphos ligand for substrates **S1** and **S2** (Table 2, Entries 5,6 and 10, 11). Substrate **S3** was not very soluble in the reaction medium. Thus, the yield of the aldehyde was lower than that 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 with the use of catalytic asymmetric hydroformylation reactions is far from being straightforward and highly substrate dependent.



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

Conclusions

We showed 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 hydroboration, and its optimization is still a challenging task.

Experimental Section

^1H NMR and ^{13}C NMR spectra were recorded with 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 were performed under an atmosphere of nitrogen. THF was dried with $CaCl_2$, filtered through basic alumina, and distilled from Na under an atmosphere of nitrogen. Toluene was distilled from Na under an atmosphere of nitrogen. Substrates **S1**–**S3** were prepared following reported procedures.[15]

General Procedure for Hydroformylation: Under an atmosphere of 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 1 h. The substrate (1 mmol) was placed in a double-walled stainless steel autoclave equipped with a stir bar under an atmosphere of nitrogen. The solution containing the rhodium precatalyst was transferred into the autoclave by cannula under an atmosphere of nitrogen. The autoclave was then pressurized with syngas (CO/H_2, 1:1) at the selected pressure and placed at the desired temperature. At the end of the reaction, the autoclave was cooled to room temperature and depressurized. Toluene was evaporated under reduced pressure. The crude residue was dissolved in methanol, and the mixture was cooled to 0 °C. $NaBH_4$ (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 × 30 mL). The combined organic layers were washed with brine (20 mL) and dried with magnesium sulfate. After filtration and evaporation of the solvent, the crude residue was purified through silica gel flash chromatography.

Dibenzyl 5-Formyl-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (2): Yellow oil (330 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (d, J = 10.5 Hz, 1 H), 1.69 (d, J = 10.5 Hz, 1 H), 1.81–2.20 (m, 2 H), 2.99 (br. s, 1 H), 4.51–5.15 (m, 2 H), 5.10–5.27 (m, 4 H), 7.26–7.34 (m, 10 H), 9.46 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.3, 36.2, 52.3, 60.5, 68.3, 128.1, 128.4, 128.7, 135.9, 157.2, 199.1 ppm.

Dibenzyl 5-(Hydroxymethyl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (3, P1): Yellow oil (364 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00–1.30 (m, 1 H), 1.50–1.70 (m, 2 H), 1.80–2.00 (m, 1 H), 2.10–2.40 (m, 2 H), 3.20–3.40 (m, 1 H), 3.40–3.60 (br. s, 1 H), 4.40–4.80 (m, 2 H), 5.10–5.30 (m, 4 H), 7.26–7.32 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.5, 35.3, 42.7, 60.5, 62.1, 64.2, 68.1, 128.1, 128.3, 128.6, 136.1, 157.7 ppm. HRMS: calcd. for $C_{22}H_{25}N_2O_5$ 397.1763; found 397.1765. HPLC (concentration = 0.1 g L^{-1} in a 20-mL injection loop; Chiralpack AD column, 0.46 cm I.D. × 25 cm, equipped with a precolumn, 0.46 cm I. D. × 5 cm; λ = 220 nm; flow = 0.8 mL min^{-1}; eluent = hexane/*i*PrOH, 70:30): 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%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70 (d, J = 11.0 Hz, 1 H), 1.91 (d, J = 11.0 Hz, 1 H), 2.15 (dd, J = 11.5, 9.0 Hz, 1 H), 2.29 (m, 1 H), 3.26 (m, 1 H), 4.99 (s, 1 H), 5.31 (s, 1 H), 7.40 (m, 1 H), 7.47 (m, 4 H), 9.78 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7, 36.9, 52.4, 60.1, 125.5, 128.6, 129.4, 131.4, 157.0, 198.2 ppm.

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. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (ddd, J = 13.0, 5.0, 3.0 Hz, 1 H), 1.94 (m, 2 H), 2.11 (m, 2 H), 2.41 (m, 1 H), 3.44 (m, 1 H), 3.64 (m, 1 H), 4.68 (br. s, 1 H), 4.88 (br. s, 1 H), 7.40 (m, 1 H), 7.47 (m, 2 H), 7.49 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.5, 36.2, 43.0, 60.3, 61.9, 63.7, 125.6, 128.5, 129.3, 131.6, 157.0 ppm. MS (ES): m/z = 296 [M + Na]$^+$. HPLC (concentration: 0.1 g L^{-1} in a 20-mL injection loop; Chiralpack AD column. 0.46 cm I.D. × 25 cm, equipped with a precolumn, 0.46 cm I. D. × 5 cm; λ = 220 nm, flow = 0.8 mL min^{-1}; eluent = hexane/*i*PrOH, 70:30): t_{R1} = 11.9 min, t_{R2} = 13.8 min.

2-(Hydroxymethyl)-1,4-methano-1,2,3,4-tetrahydropyridazino-[1,2-*b*]phthalazine-6,11-dione (P3): Yellow oil (125 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (m, 1 H), 2.08 (s, 2 H), 2.15 (m, 1 H), 2.45 (m, 1 H), 3.53 (m, 1 H), 3.69 (br. s, 1 H), 3.75 (m, 1 H), 5.37 (br. s, 1 H), 5.43 (br. s, 1 H), 7.76 (m, 2 H), 8.26 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.8, 35.4, 43.7, 58.6, 60.4, 63.9, 127.3, 129.9, 133.1, 153.4, 153.7 ppm. MS (ES): m/z = 281 [M + Na]$^+$. HPLC (concentration = 0.1 g L^{-1} in a 20-mL injection loop; Chiralpack AD column, 0.46 cm I.D. × 25 cm, equipped with a precolumn, 0.46 cm I. D. × 5 cm; λ = 220 nm; flow = 0.8 mL min^{-1}; eluent = hexane/*i*PrOH, 80:20): 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 Torr) for 1 h, and then placed under an atmosphere of 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. The solvent and the excess amount of reagent were then carefully removed under vacuum (0.1 Torr, 3 h) to give intermediate borane **4** as a dark-yellow foam. A solution of **4** in THF (6 mL) under an atmosphere of argon was then added over a 2-M solution of trimethylsilyldiazomethane in Et_2O (2.5 mL, 5 mmol). After heating at reflux overnight, freshly prepared mixture of 2 N aqueous sodium hydroxide and 30% hydrogen peroxide (1:1, 10 mL) were then added dropwise at 0 °C, which turned the solution to black. The mixture was stirred for an additional 4 h at room temperature. After extraction with EtOAc (3 × 20 mL), the combined organic layers was washed with 1 M HCl (20 mL), dried with $MgSO_4$, filtered, and concentrated. The crude reaction mixture was then purified by silica gel flash chromatography (cyclohexane/ethyl acetate, 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**.[7]

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