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11 Asymmetric Reduction of Ketones Using Nonmetallic Catalysts

CONTENTS

11.1 INTRODUCTION

The amino alcohol–borane complex used in asymmetric reduction often consists of a boron hydride with one of a variety of chiral ligands based on vicinal amino alcohols derived from the corresponding amino acids (Figure 11.1). The complex is made by ligand exchange on treating a solution of amino alcohol with borane–tetrahydrofuran (BH_3.THF) or borane–dimethylsulfide (BH_3.SMe_2) complexes. The basicity of the nitrogen of the oxazaborolidine is considerably reduced, the boron is only loosely bound to the nitrogen.

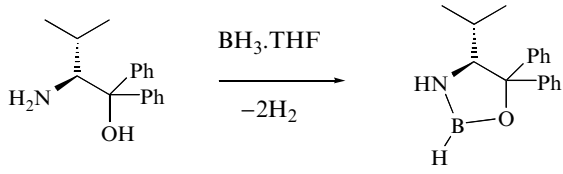


Figure 11.1 Complexation of borane with valinol[1].

Other nonmetallic catalysts were found to reduce ketones with high enantiomeric excess such as oxazaphospholidines (phosphorus analogues of oxazaborolidines), which were synthesized from (*S*)-prolinol and phenyl bis(dimethylamino)phosphine[2,3] Oxazaphosphinamide complexes, derived from oxazaphospholidines, react with borane to give a heterocycle in which the borane is activated by a strong donation from the oxygen atom of the N–P=O system coupled with a weaker interaction of the substrate carbonyl lone pair with the phosphorus atom[4]. Hydroxysulfoximines react with borane to give a six-membered heterocycle. The phenyl group and the electronic properties of the sulfoximine oxygen direct the coordination of the ketone[5].

Some of the above-mentioned catalysts or precursors are commercially available, such as the Corey catalyst (*S*)-3,3-diphenyl-1-methyltetrahydro-3H-pyrrolo[1,2-c] [1,3,2]oxazaborole (Me-CBS). The amino alcohol (*S*)-(−)-2-amino-3-methyl-1,1′-diphenylmethan-1-ol, used as the ligand in the Itsuno catalyst is also readily available. The ligand used to prepare the oxazaphospholidine or oxazaphosphinamide complex (from Wills) can be synthesized easily from commerically available material. The preparation of the Bolm β-hydroxysulfoximine catalyst will be described in this chapter (Figure 11.2).

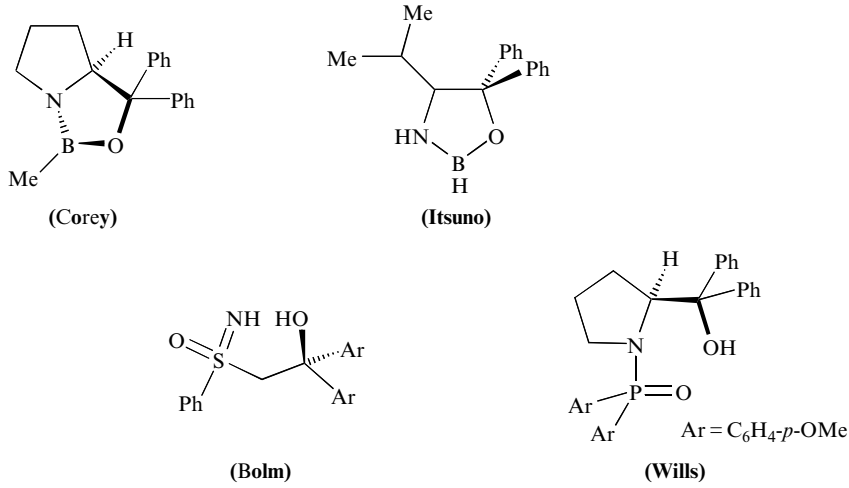


Figure 11.2 Catalysts and ligands for carbonyl reduction by borane.

As an example of a typical catalytic cycle, Figure 11.3 shows a mechanism suggested by Corey[6]. The reduction occurs by co-ordination of the oxazaborolidine electrophilic boron and the carbonyl oxygen. Then hydrogen transfer occurs from the amino borohydride anion unit (NBH_3^-) to the activated carbonyl via a six-membered ring transition state. Subsequent ligand exchange to form the alkoxy borane followed by displacement completes the catalytic cycle. For oxazaphosphinamide and hydroxysulfoximine catalysts, similar catalytic cycles have been suggested.

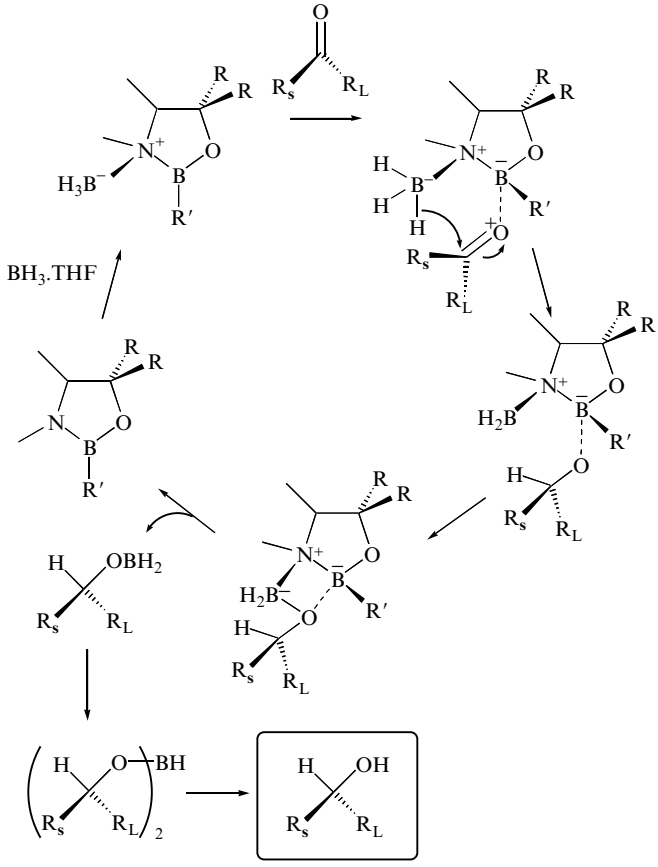
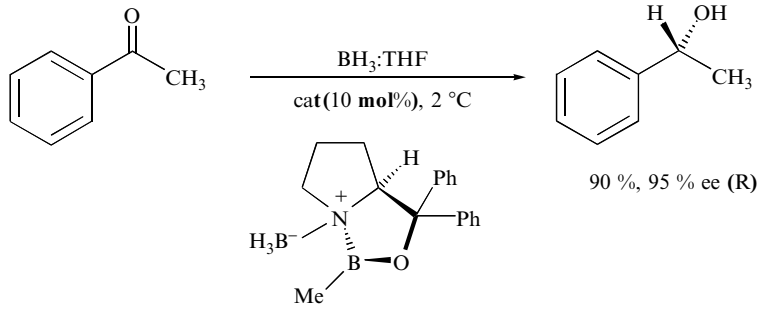


Figure 11.3 Mechanism of the reduction of ketone by borane catalysts[6].

11.2 OXAZABOROLIDINE BORANE REDUCTION OF ACETOPHENONE[7]



Materials and equipment

- (*S*)-3,3-Diphenyl-1-methyltetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaborole: (*S*)-Me-CBS, solution 1 *M* in toluene, 1.2 mL, 1.2 mmol, 0.12 eq

  The Me-CBS needs to be recently obtained and stored under argon; if a precipitate appears it can be due to the decomposition of the complex which is air and moisture sensitive.
- Anhydrous tetrahydrofuran, 15 mL
- Borane tetrahydrofuran complex, BH_3.THF, 1 *M* in tetrahydrofuran, 6.7 mL, 6.7 mmol, 0.67 eq.

  Borane complexes are water and air sensitive and need to be stored under argon in anhydrous conditions.
- Acetophenone, 1.2 g, 10 mmol

  Acetophenone was previously distilled under vacuum and stored under nitrogen.
- Aqueous solution of hydrochloric acid 1 N, 10 mL
- Petroleum ether, ethyl acetate, methanol, diethyl ether
- Brine
- Magnesium sulfate
- *p*-Anisaldehyde

- 100 mL Two-necked round-bottomed flask with a magnetic stirrer bar
- Magnetic stirrer hot plate with a thermostatically controlled oil bath and thermometer
- Addition funnel, 20 mL
- Ice-bath
- Separating funnel, 250 mL
- Rotary evaporator
- Kugelrohr apparatus

Procedure

1. A 100 mL two-necked round-bottomed flask equipped with a magnetic stirrer bar and an addition funnel were dried in an oven at 120 °C overnight. The dry flask, equipped with the addition funnel, was placed under vacuum until cool and then flushed with nitrogen.
2. The flask was charged with (*S*)-Me-CBS (1 *M* solution in toluene, 1.2 mL) in 10 mL of tetrahydrofuran. The mixture was cooled with an ice-bath and then BH_3.THF (6.7 mL) was added. The solution was stirred for 15 minutes.
3. The addition funnel was filled with acetophenone (1.16 mL) and dry tetrahydrofuran (5 mL); this solution was then added over 2 hours to the cold reaction mixture.
4. After completion, the reaction was stirred for an additional 30 minutes at room temperature.
5. The reaction was followed by TLC (eluent: petroleum ether–ethyl acetate; 75:25). The acetophenone was UV active, stained yellow with *p*-anisaldehyde, R_f 0.68. Phenylethanol had a low UV activity, stained purple with *p*-anisaldehyde, R_f 0.46.
6. The reaction was quenched by careful addition of methanol (5 mL, hydrogen evolution). An aqueous solution of hydrochloric acid 1N (10 mL) was then added and a white suspension appeared. The mixture was stirred for 15 minutes.
7. Diethyl ether was added (30 mL) and the two-phase solution was transferred into a separating funnel. The organic phase was separated and the aqueous layer extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with water (4 × 30 mL) and with brine (2 × 30 mL), dried over magnesium sulfate, filtered and concentrated to give a yellow oil (1.64 g).
8. The residue was purified by Kugelrohr distillation giving the phenylethanol as a colourless oil (1.1 g, 90 %).

   The ee (95 %) was determined by chiral GC (Lipodex® E, 25 m, 0.25 mm ID, temperatures: column 80 °C isotherm, injector 250 °C, detector 250 °C, mobile phase helium). R_t (*S*)-enantiomer: 68.3 min, R_t (*R*)-enantiomer: 71.1 min.

   ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.18–7.36 (m, 5H, Ph); 4.87 (qd, *J* 6.6 Hz, *J* 3.3 Hz, 1H, C*H*OH); 2.25 (br s, 1H, O*H*); 1.48 (d, *J* 6.6 Hz, 3H, CH_3).

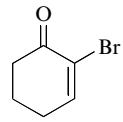
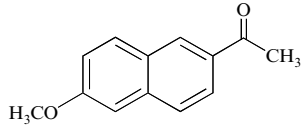
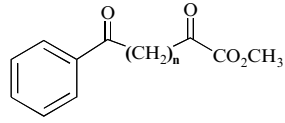
   IR ($CHCl_3$, cm^{-1}): 3611, 3458 (O–H), 3011, 2981 (C–H Ar), 2889 (C–H aliphatic), 1603 (Ar), 1493, 1453 (Ar), 1379 (Ar), 1255, 1075 (O–H), 895, 693 (Ar).

   Mass: calculated for $C_8H_{10}O$: *m/z* 122.07317, found $[M]^+$ 122.07293.

Conclusion

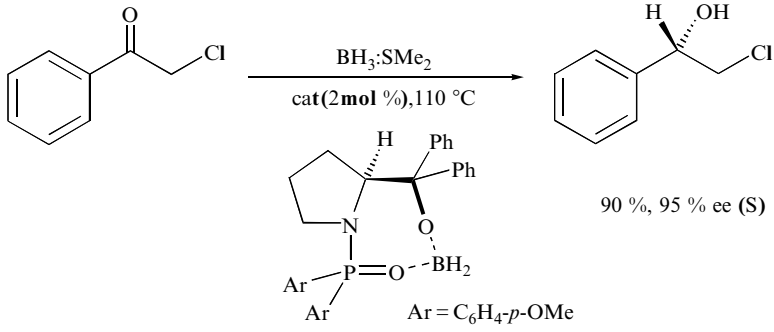
The reduction using oxazaborolidine borane needs to be done in anhydrous conditions to avoid the decomposition of the catalyst. The addition of acetophenone has to be as slow as possible to obtain a good enantiomeric excess. However, the reaction is easy to handle, the catalyst is commercially available

Table 11.1 Asymmetric reduction of ketones catalysed by (*S*)-Me-CBS[7] (results according to the literature).

	ee % **(configuration)**
	91 **(R)**
	97.6 **(R)**
	**n** = 2; 94 **(R)** **n** = 3; 96.7 **(R)**

although it has to be stored under argon to avoid decomposition. Table 11.1 gives some examples of the different substrates that can be reduced by oxazaborolidine borane complex, using the procedure described; other examples are given in Table 11.4. Some modifications of this method, using other hydrogen donor and/or other amino alcohols as catalyst ligands have been reported [6,8–12].

11.3 OXAZAPHOSPHINAMIDE BORANE REDUCTION OF CHLOROACETOPHENONE[13]



Materials and equipment

- 2-Chloroacetophenone, 154 mg, 1 mmol
- Anhydrous toluene, 16 mL

- Oxazaphosphinamide (*N*-(di-*p*-anisylphosphoryl)-(*S*)-α, α-diphenyl-2-pyrrolidine methanol), 50 mg, 0.1 mmol, 0.1 eq*

  The catalyst was prepared by reaction of (*S*)-diphenylprolinol with dimethylphosphinite and triethylamine in the presence of carbon tetrachloride. The N-(O,O-dimethylphosphoryl) derivative obtained was treated with an excess of *p*-anisylmagnesium bromide to give the oxazaphosphinamide catalyst[13].
- Borane dimethyl sulfide complex 2 *M* solution in tetrahydrofuran, 0.5 mL, 1 mmol, 1 eq
- Petroleum ether, ethyl acetate, triethylamine
- Saturated aqueous solution of NH_4Cl, 10 mL
- Brine
- Magnesium sulfate
- Silica gel 60 (0.063–0.04 mm)
- *p*-Anisaldehyde dip

- 50 mL Two-necked dry round-bottomed flask with a magnetic stirrer bar
- Magnetic stirrer hot plate with a thermostatically controlled oil bath and thermometer
- Dean and Stark apparatus
- Condenser
- Syringe, 3 mL
- Syringe pump
- Separating funnel, 250 mL
- Rotary evaporator
- Kugelrohr apparatus

Procedure

1. A 50 mL two-necked round-bottomed flask (dried overnight at 150 °C and cooled under vacuum) was equipped with a Dean and Stark apparatus and flushed with nitrogen.
2. The flask was filled with the catalyst (50 mg) and anhydrous toluene (4 mL). The mixture was refluxed until 3.5 mL of solvent was recovered. The catalyst was azeotroped twice with toluene (4 mL) and then cooled to room temperature under argon.

   Precautions were taken whilst azeotroping the catalyst with toluene: thus the use of freshly dried toluene and flame-dried glassware were necessary to ensure anhydrous conditions.
3. The Dean and Stark apparatus was removed, replaced by a condenser (the solution was flushed continuously with nitrogen) and the catalyst dissolved in anhydrous toluene (2 mL). Borane–dimethylsulfide (0.5 mL of a 2 *M* solution in tetrahydrofuran) was added to the mixture, which was heated to 110 °C.

* *The catalyst was kindly provided by Prof. M. Wills (University of Warwick, Coventry, UK).*

4. When the reaction was at reflux, a solution of chloroacetophenone (154 mg) in toluene (2 mL) was added via a syringe pump over 10 minutes. After completion of the addition the reaction was stirred for a further 20 minutes.
5. The reaction was followed by TLC (eluent: petroleum ether–ethyl acetate; 85:15). The chloroacetophenone was UV active and stained grey with *p*-anisaldehyde dip, R_f 0.5. 2-Chloro-1-phenylethanol was UV active and stained green-grey with *p*-anisaldehyde, R_f 0.39.
6. The mixture was cooled to room temperature and the borane–dimethylsulfide was slowly hydrolysed by water (10 mL) and then by a saturated solution of NH_4Cl (10 mL).
7. The mixture was transferred into a separating funnel and the two phases were separated. The aqueous layer was extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with water (3×30 mL), brine (3×30 mL) and then dried over magnesium sulfate, filtered and concentrated to give a crude oil (620 mg).
8. The crude material was purified by flash chromatography on silica gel (30 g) using petroleum ether–ethyl acetate–triethylamine (89:10:1) as eluent to give 2-chloro-1-phenylethanol as an oil (140 mg, 90 %).

   The ee (95 %) was determined by chiral GC (Lipodex® E, 25 m, 0.25 mm ID, temperatures: column 105 °C isotherm, injector 250 °C, detector 250 °C, mobile phase helium). R_t (*R*)-enantiomer: 102.4 min; R_t (*S*)-enantiomer: 106.7 min.

   ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–7.31 (m, 5H, Ph); 4.88 (ddd, *J* 8.8 Hz, *J* 3.3 Hz, *J* 3.3 Hz, 1H, C*H*); 3.74 (dd, *J* 3.3 Hz, *J* 11.5 Hz, 1H, CH_aH$_b$); 3.70 (dd, *J* 8.8 Hz, *J* 11.8 Hz, 1H, CH$_a$$H_b$); 2.78 (br s, 1H, O*H*).

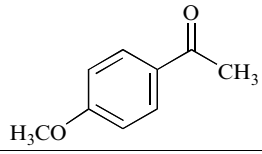
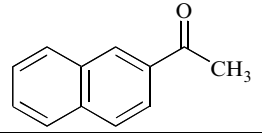
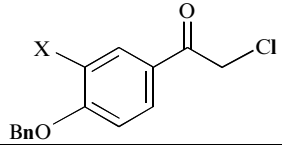
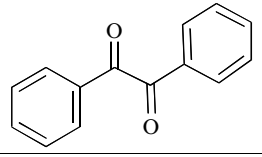
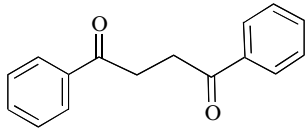
   IR ($CHCl_3$, cm^{-1}): 3586, 3460 (O–H), 3070, 3012, (C–H Ar), 2961, 2897 (C–H aliphatic), 1603 (Ar), 1494, 1454 (Ar), 1428, 1385, 1254, 1187, 1062, 1012, 870, 690.

   Mass: calculated for C_8H_9OCl: *m/z* 156.03419, found $[M]^+$ 156.03385.

Conclusion

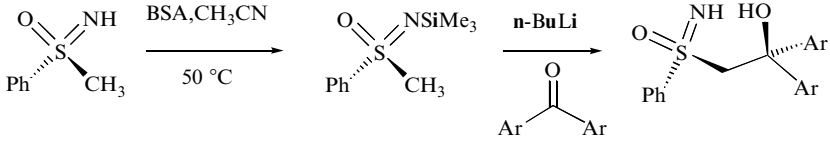
The reduction using the oxazaphosphinamide is easy to reproduce and the results correlate with the published material. During the reaction the addition of the chloroacetophenone solution needs to be as slow as possible; this is an essential factor for obtaining a good enantiomeric excess. According to the publication, the reaction could be performed without the prescribed precautions to work under anhydrous conditions with only a small drop in selectivity and no change to the reaction time. This is due to the stability of the phosphinamide reagent, which is not sensitive to water or oxygen. Another advantage of using this catalyst is that it does not decompose under the reaction conditions and could be recovered and re-used without any decrease in the reactivity. In Table 11.2 different results obtained by oxazaphosphinamide catalysts are reported. Some other examples are given in Table 11.4.

Table 11.2 Reduction of aromatic ketones using oxazaphosphinamide catalyst[13] (results according to the literature).

	Yield %	ee %
	89	90
	82	90
	X = H; 8 X = CH_2OBn; 84	94 93
	83	>90
	71	>90

11.4 ASYMMETRIC REDUCTION OF CHLOROACETOPHENONE USING A SULFOXIMINE CATALYST [S]

11.4.1 PREPARATION OF β-HYDROXYSULFOXIMINE BORANE



Materials and equipment

- (*S*S)-Methyl-S-phenylsulfoximine, 523 mg, 3.4 mmol*

* *(SS)-Methyl-S-phenylsulfoximine was kindly provided by Prof. C. Bolm (Technische RWTH Aachen)*

- *N, O*-Bis-(trimethylsilyl)-acetamide (BSA), 924 μL, 3.74 mmol, 1.1 eq
- Dry acetonitrile, 15 mL
- Dry tetrahydrofuran, 18 mL
- *n*-Butyl lithium, 1.6 *M* in hexane, 2.1 mL, 3.4 mmol, 1 eq
- Benzophenone, 682 mg, 3.74 mmol, 1.1 eq
- Aqueous saturated solution of NH_4Cl and methanol (10:1), 2 mL
- Petroleum ether, ethyl acetate
- *p*-Anisaldehyde dip
- Silica gel 60 (0.063–0.04 mm)

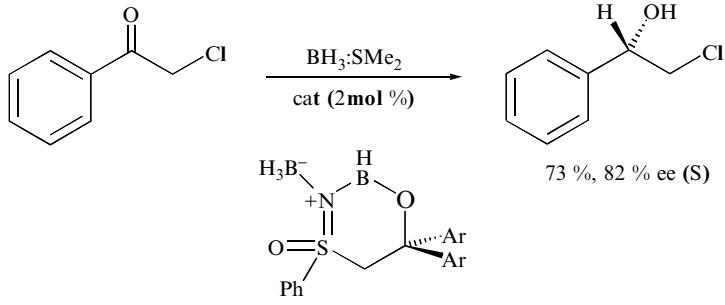
- 50 mL Two-necked round-bottomed flask with a magnetic stirrer bar
- 50 mL Schlenk tube with a magnetic stirrer bar
- Condenser
- Cannula (double-tipped needle)
- Magnetic stirrer hot plate with a thermostatically controlled oil bath and thermometer
- Ice-bath
- Syringe
- Solid carbon dioxide/ethanol cooling bath (−78 °C)
- Kugelrohr apparatus

Procedure

1. A 50 mL two-necked flask equipped with a magnetic stirrer bar was dried overnight at 150 °C, cooled under vacuum and flushed with nitrogen.
2. Under a nitrogen atmosphere, the flask was charged with (*S*S)-methyl-S-phenylsulfoximine (523 mg) and placed under vacuum. The flask was flushed with nitrogen, then dry acetonitrile (15 mL), and *N, O*-bis-(trimethylsilyl)-acetamide (924 μL) were added.
3. The flask was equipped with a condenser and the mixture was heated under nitrogen at 50 °C and stirred for 45 minutes at this temperature (it was not necessary for the solvent to reflux).
4. After 45 minutes, the mixture was cooled to room temperature under nitrogen. The solvent was evaporated under high vacuum.
5. The residue was placed under nitrogen in a Kugelrhor apparatus and the impurities were distilled at a temperature less than 70 °C at 0.3 mbar. The purity of N-(trimethylsilyl)-*S*-methyl-S-phenylsulfoximine was verified by NMR.
   - ^{1}H NMR(200 MHz, $CDCl_3$): δ 7.97–7.93 (m, 2H, Ph); 7.57–7.451 (m, 3H, Ph); 3.01 (s, 3H, CH_3); 0.11 (s, 9H, Si (CH_3)$_3$).
6. A 50 mL Schlenk tube equipped with a magnetic stirrer bar, dried overnight at 150 °C, was cooled under vacuum and then flushed with nitrogen.
7. N-(Trimethylsilyl)-*S*-methyl-S-phenylsulfoximine (prepared as above) was dissolved in 15 mL of dry tetrahydrofuran and transferred by cannula into the Schlenk tube under nitrogen.

8. The mixture was cooled to 0 °C with an ice-bath and then 2.1 mL of *n*-BuLi (1.6 *M* in hexane) was added carefully via a syringe. The solution became yellow.
9. The mixture was cooled to −78 °C using an ethanol cooling bath. A solution of benzophenone (682 mg) in dry tetrahydrofuran (3 mL) was then added dropwise. The mixture was stirred for 2 hours at −78 °C.
10. The reaction was followed by TLC (eluent: petroleum ether–ethyl acetate; 9:1). The benzophenone was UV active and stained yellow with permanganate, R_f 0.58. β-Hydroxysulphoximine was UV active and stained yellow with *p*-anisaldehyde, R_f 0.11.
11. The reaction was quenched with aqueous saturated solution of NH_4Cl and methanol (10:1, 2 mL). The mixture was stirred overnight at room temperature and the solvent was evaporated under reduced pressure.
12. The alcohol was obtained by flash chromatography on silica gel eluting with petroleum ether–ethyl acetate (9:1) to eliminate the benzophenone and then with an eluant ratio 6:4, giving (S*S*)-1,1-diphenyl-2-(S-phenylsulfonimidoyl)-ethanol (790 mg, 2.3 mmol, 77 %).
    - The yield of the reaction is variable (33–77 %), especially if the reaction is not carried out under strictly anhydrous conditions or if the flash chromatography takes an excessive amount of time.
    - ^{1}H NMR(200 MHz, $CDCl_3$): δ 7.6–7.09 (m, 15H, Ph); 4.11 (s, 2H, CH_2); 2.96 (br s, 1H, NH).

11.4.2 REDUCTION OF CHLOROACETOPHENONE USING THE SULFOXIMINE BORANE



Materials and equipment

- Sulfoximine catalyst, (*S*S)-1, 1-diphenyl-2-(S-phenylsulfonimidoyl)-ethanol, 68 mg, 0.2 mmol, 0.1 eq
- Dry toluene, 6 mL

  The toluene was distilled from sodium and benzophenone and then stored over activated molecular sieves.

- Borane dimethylsulfide, 2 *M* in THF, 1.2 mL, 2.4 mmol, 1.2 eq
- Chloroacetophenone, 310 mg, 2 mmol

Chloroacetophenone is toxic and needs to be manipulated using gloves and eye protection in a well-ventilated fume-hood.

- Aqueous solution of hydrochloric acid, 1 N, 3 mL
- Diethyl ether
- Aqueous solution of sodium hydroxide, 2 N, 20 mL
- Sodium sulfate
- *p*-Anisaldehyde dip

- 50 mL Two-necked round-bottomed flask with a magnetic stirrer bar
- Magnetic stirrer hot plate with a thermostatically controlled oil bath and thermometer
- Syringe pump
- Syringe, 3 mL
- Separating funnel, 250 mL
- Kugelrohr apparatus

Procedure

1. A 50 mL round-bottomed flask equipped with a magnetic stirrer was dried overnight at 150 °C and placed under vacuum and then flushed with nitrogen.
2. The flask was charged with the sulfoximine catalyst (68 mg) and dry toluene (4 mL). To this white suspension was added borane dimethylsulfide (1.2 mL). The mixture became clear with the evolution of hydrogen.
3. After 15 minutes a solution of chloroacetophenone (310 mg) in dry toluene (2 mL) was added via a syringe pump over a period of 3 hours at room temperature.
4. After completion of the addition the mixture was stirred for a further 10 minutes. The reaction was quenched with an aqueous solution of HCl (1 N, 3 mL) and water (10 mL).
5. The mixture was transferred into a separating funnel and the two phases separated. The aqueous layer was extracted with diethyl ether (3×30 mL) and the combined organic layers washed with an aqueous solution of sodium hydroxide (2 N, 20 mL) and then dried over sodium sulfate, filtered and concentrated.
6. The alcohol was obtained by distillation of the residue using a Kugelrohr apparatus (120 °C, 3 mmHg) to give (*S*)-2-chloro-1-phenylethanol (233 mg, 1.49 mmol, 73 %).

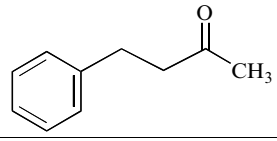
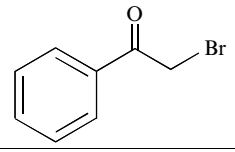
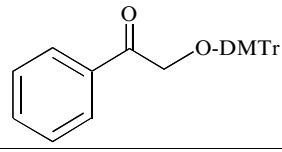
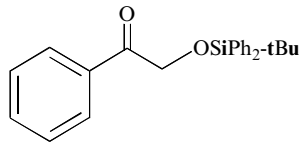
   The ee (82 %) was determined by chiral GC analysis (Lipodex® E, 25 m, 0.25 mm ID, temperatures: column 120 °C isotherm, injector 250 °C, detector 250 °C, mobile phase helium) R_t (*R*)-enantiomer: 45.3 min, R_t (*S*)-enantiomer: 46.5 min.

^{1}H NMR(200 MHz, $CDCl_3$): δ 7.39–7.31 (m, 5H, Ph); 4.88 (ddd, *J* 8.8 Hz, *J* 3.3 Hz, *J* 3.3 Hz, 1H, C*H*); 3.74 (dd, *J* 3.3 Hz, *J* 11.5 Hz, 1H, CH_aH$_b$); 3.70 (dd, *J* 8.8 Hz, *J* 11.8 Hz, 1H, CH$_a$$H_b$); 2.78 (br s, 1H, O*H*).

Conclusion

To obtain a good enantiomeric excess, the ligand synthesis and the reduction reaction need to be carried out under strictly anhydrous conditions. The addition of the substrate needs to be as slow as possible. Table 11.3 gives some examples of the different substrates that can be reduced by the hydroxysulfoximine-borane catalyst described. Other examples are given in the comparative Table 11.4. Concerning the synthesis of the catalyst, the yield can dramatically decrease if the reaction conditions are not strictly anhydrous.

Table 11.3 Reduction of ketones by hydroxysulfoximine-borane catalyst[14] (results according to the literature).

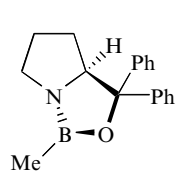
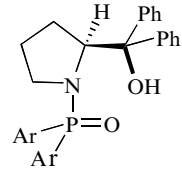
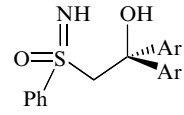
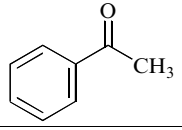
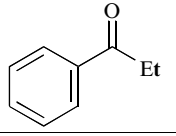
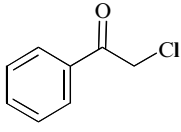
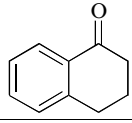
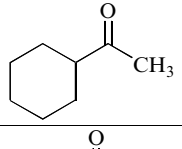
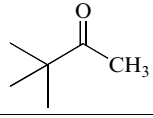
	ee % **(configuration)**
	70 **(R)**
	81 **(S)**
	93 **(S)**
	92 **(S)**

11.4.3 SUMMARY

All the different methods using nonmetallic catalysts are similar in terms of procedure; they all require anhydrous conditions to obtain high enantiomeric excesses. However, the oxazaphosphinamide catalysts can give relatively high enantiomeric excess without all the precautions of reactions conducted under

strictly anhydrous conditions. Table 11.4 gives some substrates that can be reduced by the three catalysts described above. Each catalyst can give good results depending on the nature of the substrate. However, considering the results and the commercially availability, the reduction of ketones with Corey's catalyst is the easiest method to use.

Table 11.4 Catalytic reduction of ketones by nonmetallic catalysts (results according to the relevant publications).

	 Oxaza **borolidines**[7] ee % **(configuration)**	 Oxaza *phosphinamides*[13] **Yield** %, ee % **(configuration)**	 **Hydroxy sulfoximines**[14] ee % **(configuration)**
	96.5 **(R)***	83, 88 **(R)**	76 **(R)**
	96.7 **(R)**	76, 77 **(R)**	73 **(R)**
	95.3 **(S)**	91, 94.4 **(S)***	84 **(S)***
	86 **(R)**	81, 82 **(R)**	–
	84 **(R)**	87, 67 **(R)**	–
	97.3 **(R)**	65-86 **(R)**	–

* Reaction validated

11.5 ASYMMETRIC REDUCTION OF BROMOKETONE CATALYZED BY *CIS*-AMINOINDANOL OXAZABOROLIDINE

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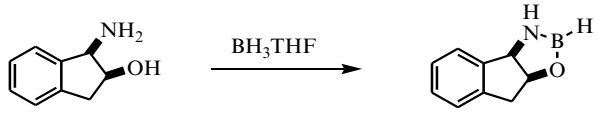
Chemical Research and Development, Sepracor Inc., 111 Locke Drive, Marlbrough, MA 01752, USA

11.5.1 SYNTHESIS OF AMINOINDANOL OXAZABOROLIDINE[15]



1 2a

Materials and equipment

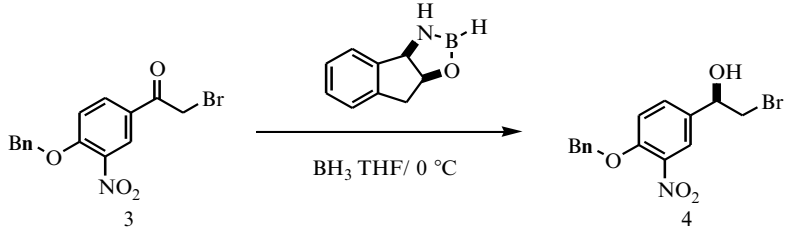
- (1*R*,2*S*)-Aminoindanol, 2.0 g
- Anhydrous tetrahydrofuran, 100 mL
- Borane-THF (1.0 M), 290 mL

- 2000 mL Round-bottomed flask with an overhead stirrer
- Mechanical stirrer

Procedure

1. A 2 L dried round-bottomed flask under an inert atmosphere was charged with aminoindanol (2.0 g) and anhydrous tetrahydrofuran (100 mL).
2. Borane–THF (1.0 M, 290 mL) was added while the temperature was maintained between 0–25 °C.
3. The mixture was stirred for 30 minutes at 20 °C.

11.5.2 ASYMMETRIC REDUCTION OF 2-BROMO-(3-NITRO-4-BENZYLOXY)ACETOPHENONE[16]



3 4

Materials and equipment

- 2-Bromo-(3-nitro-4-benzyloxy)acetophenone, 100 g
- Anhydrous tetrahydrofuran, 800 mL
- (1*R*,2*S*)-Aminoindanol-oxazaborolidine
- Acetone, 100 mL
- Toluene, 700 mL
- Aqueous 2 % sulfuric acid solution, 350 mL
- Aqueous 20 % NaCl solution, 160 mL
- Heptane, 200 mL
- Heptane, 200 mL

- 1 L Round-bottomed flask with a magnetic stirrer bar
- Magnetic stirrer
- Separatory funnel (2 L)
- Rotary evaporator
- Buchner funnel

Procedure

1. The oxazaborolidine solution was cooled to 0 °C.
2. A solution of bromoketone **3** in tetrahydrofuran (100 g in 800 mL THF, 0.35 M) was slowly added over 1 hour to the oxazoborolidine solution while the temperature was maintained between 0–5 °C. The mixture was stirred for 30 minutes at 0 °C.
3. Acetone (100 mL) was slowly added to quench the excess borane. The reaction mixture was concentrated to 300 mL and toluene (700 mL) was added. The solution was washed with 2 % sulfuric acid (350 g) then with 20 % NaCl (120 g). The organic phase was concentrated to 300 mL and cooled to 5 °C.
4. The resulting slurry was stirred at 5 °C for 1 hour, heptane (200 mL) was slowlyadded and the mixture was stirred an additional 1 hour at 5 °C.
5. The slurry was filtered and the solid was washed with heptane (200 mL). The off-white solid was dried *in vacuo* to give 89 g (93 % ee, >99 % cp) of the desired alcohol.

Recrystallization of 2-bromo-(3-nitro-4-benzyloxyphenyl)ethanol

Materials and equipment

- 2-Bromo-(3-nitro-4-benzyloxy)acetophenone, 48 g
- Toluene, 100 mL
- Heptane, 125 mL

- 500 mL Round-bottomed flask with a magnetic stirrer bar

- Magnetic stirrer
- Buchner funnel

Procedure

1. 2-Bromo-(3-nitro-4-benzyloxyphenyl) ethanol (93 % ee, 48 g) and 100 mL of toluene were placed in a 500 mL flask. The mixture was warmed until all the alcohol dissolved. The mixture was cooled to 5 °C and stirred for 1 hour.
2. Heptane (100 mL) was slowly added to the stirring mixture and that solution was stirred for 1 hour at 5 °C.
3. The slurry was filtered and the solid washed with heptane (25 mL).
4. The solid was dried in a vacuum oven to yield 45 g of 2-bromo-(3-nitro-4-benzyloxyphenyl) ethanol (>99 % ee).

   ^{1}H NMR (300 MHz DMSO-d6): δ 7.88 (m, 1H), 7.65 (d, 1H), 7.3–7.5 (m, 6 H), 6.01 (d, 1H), 5.35 (s, 2 H), 4.83 (m, 1H), 3.64 (ddd, 2H).

   ^{13}C NMR (MHz DMSO-d6): δ 151.94, 140.15, 135.52, 133.24, 131.73, 128.95, 128.51, 127.51, 123.62, 115.47, 72.40, 71.45, 39.75.

   IR: (KBr): 3381 (OH), 3091, 3067, 2961, 2893 (C–H), 1532, 1296, 1026, 729 cm^{-1}.

11.5.3 CONCLUSIONS

This procedure has been developed through the evaluation of several reaction parameters (catalyst, temperature, borane source, additives) and has been successfully used on large scale. The chemical purity of the product is excellent and the enantiomeric purity of the product can be increased by crystallizing from toluene/heptane.

The temperature has a significant effect on the selectivity of the reaction, with the optimal temperature being dependent on the borane source. The optimal range of temperature was 25 °C when borane–dimethylsulfide was used and 0–5 °C when borane–tetrahydrofuran was used as the reducing agent (Table 11.5).

Table 11.5 Optimization of enantioselectivity as a function of borane source and temperature using aminoindanol oxazaborolidine.

Borane	Temperature	er (% *R*)	ee (%)
$BH_3 - Me_2S$	40	89.0	78
	25	**95.0**	**90**
	0	91.0	82
	−10	66.0	32
BH_3 – THF	25	95	90
	0	**96.5**	**93**
	−10	94	88

Table 11.6 Effect of catalyst ratio and additives on % ee.

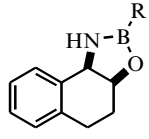
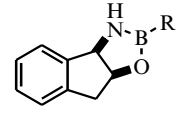
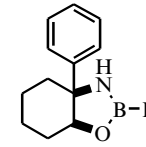
Entry	Mol % Catalyst	Additive	% ee
1	1	None	88
2	5	None	93
3	10	None	93
4	10	H_2O (5)	85
5	10	H_2O (20)	50
6	10	CH_3CN (20)	92
7	10	2-propanol (20)	91

The minimum amount of catalyst needed to obtain maximum selectivity was determined to be 5 mol%. Larger quantities had no effect. Consistent with other literature reports[17], very small quantities of water (5 mol% = 2.5 mg H_2O/g **3**) lowered the selectivities (Table 11.6, entry 4). Water sensitivity required thorough drying of the equipment, the starting materials and the solvents. In the case of tetrahydrofuran, drying was achieved by using activated 5 Å molecular sieves (KF titration >0.005%). On the other hand, solvents used for crystallization of the starting material (**3**), such as 2-propanol and acetonitrile showed little effect on the enantioselectivities of the reaction (entries 6 and 7).

After finding the optimal condition for catalyst **2a** in the reduction process, studies were aimed at understanding the role of the rigid indane platform, which behaves as a conformationally restricted phenyl glycinol equivalent. The use of the homologous six-membered[18] catalyst **5** in the asymmetric reduction process was examined. Surprisingly, the less rigid B–H catalyst **5a** displayed a higher degree of enantioselection than the corresponding indane catalyst **2a** (Table 11.6), while B–Me catalyst **5b** displayed similar selectivity compared to B–Me catalyst **2b**. The increased selectivity of catalyst **5a** may be due to the closer proximity of the $C_{ortho}-H$ to the N–BH_3 moiety when compared to catalyst **2a**.

This study has clearly shown that B–H and B–Me catalysts have different optimal conditions for each catalyst system in the reduction of prochiral

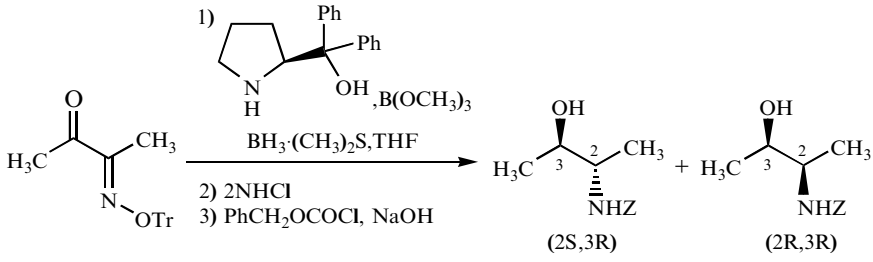
Table 11.7 Comparison of rigid aminoalcohols and catalyst types (B-methyl vs. B–H).

			
Catalyst b R = H	**(R)**-5a, 96 % ee, 0 °C, BH_3•THF	**(R)**-2a, 93 % ee, 0 °C, BH_3•THF	**(R)**-6a, 26 % ee, 25 °C, BMS*
Catalyst a R = Me[20]	**(R)**-5b, 95 % ee −10 °C, BMS	**(R)**-2b, 96 % ee, 0 °C, BH_3•THF	**(R)**-6b, 12 % ee, −10 °C, BH_3•THF*

*Un*o*ptimi*zed

ketones. The highest selectivities are observed with catalyst **5a** (tetralin platform) and catalyst **2b**, and the lowest with catalysts **6a** and **6b**. From a practical point of view, B–H catalyst systems are much more preferred than B–alkyl systems. Therefore, the use of highly effective B–H oxazaborolidine catalysts from readily accessible tetralin and aminoindanol is recommended.

11.5.4 STEREOSELECTIVE REDUCTION OF 2,3-BUTADIONE MONOXIME TRITYL ETHER



Materials and equipment

- Anhydrous tetrahydrofuran, 10 mL
- 2,3-Butadionemonoxime trityl ether, 1.72 g, 5.0 mmol
- (*S*)-α, α-Diphenylpyrrolidinemethanol, 127 mg, 0.5 mmol
- Trimethyl borate, 62 mg, 0.6 mmol
- 10 M Borane–dimethylsulfide complex, 2.0 mL, 20 mmol
- 2 N Hydrochloric acid, 15 mL, 30 mmol
- Sodium hydroxide, 2.4 g, 60 mmol
- Benzyl chloroformate, 3.41 g, 20 mmol
- Diethyl ether, 30 mL
- Methylene chloride, 60 mL
- Magnesium sulfate
- Silica gel
- *n*-Hexane, ethyl acetate

- 25 mL Three-necked flask with a magnetic stirrer bar
- 200 mL Round-bottomed flask with a magnetic stirrer bar
- Magnetic stirrer
- Ice-bath
- Oil-bath
- Separating funnel, 100 mL
- Rotary evaporator

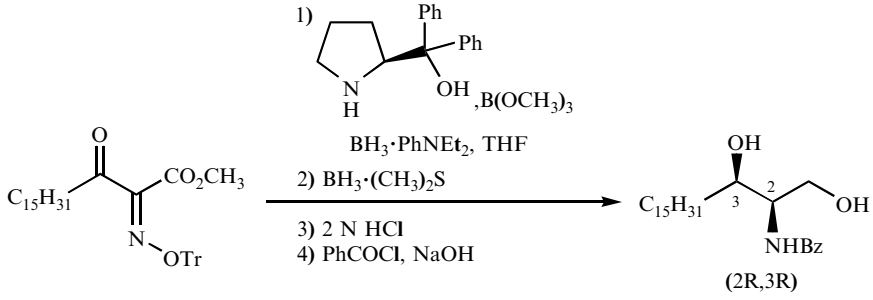
Procedure

1. (*S*)-α, α-Diphenylpyrrolidinemethanol (127 mg) was placed in a 25 mL three-necked flask equipped with a magnetic stirrer bar, under nitrogen. A solution of trimethyl borate (62 mg) in dry tetrahydrofuran (5 mL) was added. The mixture was stirred for 1 hour at room temperature.
2. 10 M Borane–dimethylsulfide complex (2.0 mL) was added to the resulting solution. The mixture was cooled to 0–5 °C with an ice-bath, and then a solution of 2,3-butadione monoxime trityl ether (1.72 g) in dry tetrahydrofuran (5 mL) was added dropwise via a syringe pump over 1 hour at that temperature.
3. After being stirred for 0.5 hour at 0–5 °C, the mixture was allowed to warm to room temperature and heated under reflux for 18 hours. The resulting mixture was cooled to room temperature and cautiously transferred into 2 N hydrochloric acid (15 mL) in a 200 mL round-bottomed flask equipped with a magnetic stirrer bar using diethyl ether (10 mL).
4. After being stirred for 5 hours at room temperature, the mixture was made basic with sodium hydroxide (2.4 g). The organic solvents were removed under reduced pressure using a rotary evaporator. The aqueous residue was washed with diethyl ether (2 × 10 mL) and then benzyl chloroformate (3.41 g) was added. The mixture was stirred for 20 hours at room temperature.
5. The resulting mixture was transferred into a separating funnel with methylene chloride (20 mL) and the phases were separated. The aqueous layer was extracted with methylene chloride (2 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated using a rotary evaporator.
6. The residue was purified by silica gel column chromatography using *n*-hexane–ethyl acetate (3:1 → 1:1) as an eluent to give as a white solid 3-benzyloxyamino-2-butanol (1.03 g, 92 %) as a mixture of diastereomers.

   The *anti/syn* ratio (86:14) and the respective ee (*anti* 99 %, *syn* 97 %) were determined by HPLC (Chiralcel OJ chiral column (i.d. 4.6 × 250 mm), flow 0.5 mL/min, eluent *n*-hexane–isopropanol 9:1, detection UV 230 nm); 22.9 min for (2*S*, 3*S*)-isomer, 26.8 min for (2*S*, 3*R*)-isomer, 29.8 min for (2*R*, 3*R*)-isomer, 36.1 min for (2*R*, 3*S*)-isomer.

   ^{1}H NMR (270 MHz, $CDCl_3$) for *anti* isomer δ 1.11 (d, *J* 6.7 Hz, 3H), 1.15 (d, *J* 6.7 Hz, 3H), 2.18 (br, 1H), 3.74 (m, 1H), 3.88 (m, 1H), 4.94 (br, 1H), 5.10 (s, 2H), 7.35 (m, 5H); for *syn* isomer δ 1.18 (d, *J* 6.7 Hz, 3H), 1.20 (d, *J* 6.1 Hz, 3H), 1.88 (br, 1H), 3.70 (m, 2H), 4.94 (br, 1H), 5.10 (s, 2H), 7.35 (m, 5H).

11.5.5 STEREOSELECTIVE REDUCTION OF METHYL 3-OXO-2-TRITYLOXYIMINOSTEARATE



Materials and equipment

- Anhydrous tetrahydrofuran, 10 mL
- Methyl 3-oxo-2-trityloxyiminostearate, 1.46 g, 2.5 mmol
- (*S*)-α,α-Diphenylpyrrolidinemethanol, 63 mg, 0.25 mmol
- Trimethyl borate, 31 mg, 0.3 mmol
- Borane-diethylaniline complex, 815 mg, 5.0 mmol
- 10 M Borane–dimethylsulfide complex, 2.0 mL, 20 mmol
- 2 N Hydrochloric acid, 10 mL, 20 mmol
- Sodium hydroxide, 1.4 g, 35 mmol
- Benzoyl chloride, 0.70 g, 5.0 mmol
- Diethyl ether, methanol, methylene chloride, tetrahydrofuran
- Magnesium sulfate
- Silica gel

- 25 mL Three-necked flask with a magnetic stirrer bar
- 200 mL Round-bottomed flask with a magnetic stirrer bar
- Magnetic stirrer
- Oil-bath
- Separating funnel, 100 mL
- Rotary evaporator

Procedure

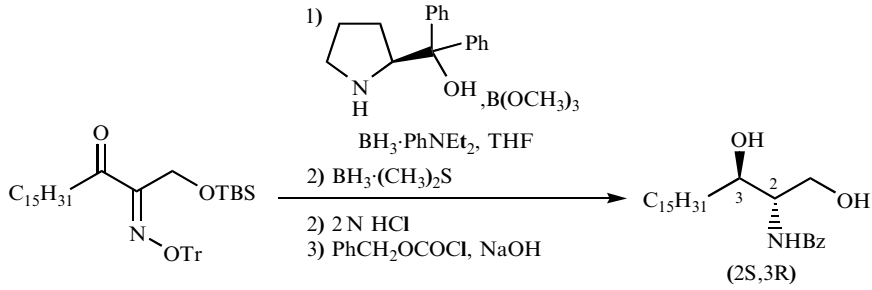
1. (*S*)-α,α-Diphenylpyrrolidinemethanol (63 mg) was placed in a 25 mL three-necked flask equipped with a magnetic stirrer bar, under nitrogen. A solution of trimethyl borate (31 mg) in dry tetrahydrofuran (5 mL) was added. The mixture was stirred for 1 hour at room temperature.
2. Borane–diethylaniline complex (815 mg) was added to the resulting mixture. A solution of methyl 3-oxo-2-trityloxyiminostearate (1.46 g) in dry tetrahydrofuran (5 mL) was added dropwise via a syringe pump over 1 hour at room temperature.

3. After being stirred for 2 hours at room temperature, 10 M borane–dimethylsulfide complex (2.0 mL) was added. The mixture was heated under reflux for 65 hours. The resulting mixture was cooled to room temperature and cautiously transferred into 2 N hydrochloric acid (10 mL) in a 200 mL round-bottomed flask equipped with a magnetic stirrer bar using diethyl ether (10 mL).
4. After being stirred for 1 hour at 60 °C, the mixture was cooled to room temperature and then made basic with sodium hydroxide (1.4 g). Benzoyl chloride (0.70 g) was added, and the mixture was stirred for 1 hour at room temperature and subsequently stirred for 2 hour at 60 °C with methanol (10 mL).
5. The organic solvents were removed under reduced pressure using a rotary evaporator. The residue was transferred into a separating funnel with methylene chloride–tetrahydrofuran (2:1, 40 mL) and the phases were separated. The aqueous layer was extracted with methylene chloride–tetrahydrofuran (2:1, 2 × 40 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated using a rotary evaporator.
6. The residue was purified by silica gel column chromatography using methylene chloride–methanol (50:1 → 30:1) as an eluent to give a white solid *N*-benzoylsphingamine (0.93 g, 92 %) as a mixture of diastereomers.

   The *anti/syn* ratio (13:87) and the respective ee (*anti* 75 %, *syn* 89 %) were determined by HPLC (YMC Chiral NEA® chiral column (i.d. 4.6 × 250 mm) and Chiralcel OJ-R chiral column (i.d. 4.6 × 150 mm) connected in series, flow 0.3 mL/min, eluent acetonitrile–water 3:7, detection UV 254 nm); 65.6 min for (2*S*, 3*R*)-isomer, 68.0 min for (2*R*, 3*S*)-isomer, 71.8 min for (2*R*,3*R*)-isomer, 74.2 min for (2*S*,3*S*)-isomer.

   ^{1}H NMR (270 MHz, $CDCl_3$) for *syn* isomer δ 0.88 (t, *J* 6.7 Hz, 3H), 1.25 (br, 26H), 1.50 (m, 2H), 3.32 (br, 2H), , 3.88 (m, 2H), 4.03–4.14 (m, 2H), 6.97 (d, *J* 8.6 Hz, 1H), 7.40 (t, *J* 7.3 Hz, 2H), 7.48 (d, *J* 7.3 Hz, 1H), 7.78 (d, *J* 7.3 Hz, 2H).

11.5.6 STEREOSELECTIVE REDUCTION OF 1-(TERT-BUTYLDIMETHYLSILYLOXY)-3-OXO-2-TRITYLOXYIMINOOCTADECANE



Materials and equipment

- Anhydrous tetrahydrofuran, 10 mL
- 1-(*tert*-Butyldimethylsilyloxy)-3-oxo-2-trityloxyiminooctadecane, 1.68 g, 2.5 mmol
- (*S*)-α,α-Diphenylpyrrolidinemethanol, 63 mg, 0.25 mmol
- Trimethyl borate, 31 mg, 0.3 mmol
- Borane–diethylaniline complex, 815 mg, 5.0 mmol
- 10 M Borane–dimethylsulfide complex, 0.5 mL, 5.0 mmol
- 2 N Hydrochloric acid, 10 mL, 20 mmol
- Sodium hydroxide, 1.4 g, 35 mmol
- Benzoyl chloride, 0.70 g, 5.0 mmol
- Diethyl ether, methanol, methylene chloride, tetrahydrofuran
- Magnesium sulfate
- Silica gel

- 25 mL three-necked flask with a magnetic stirrer bar
- 200 mL round-bottomed flask with a magnetic stirrer bar
- Magnetic stirrer plate
- Oil-bath
- Separating funnel, 100 mL
- Rotary evaporator

Procedure

1. (*S*)-α,α-Diphenylpyrrolidinemethanol (63 mg) was placed in a 25 mL three-necked flask equipped with a magnetic stirrer bar, under nitrogen. A solution of trimethyl borate (31 mg) in dry tetrahydrofuran (5 mL) was added. The mixture was stirred for 1 hour at room temperature.
2. Borane–diethylaniline complex (815 mg) was added to the resulting mixture. A solution of 1-(*tert*-butyldimethylsilyloxy)-3-oxo-2-trityloxyiminooctadecane (1.68 g) in dry tetrahydrofuran (5 mL) was added dropwise using a syringe pump over 1 hour at room temperature.
3. After being stirred for 1 hour at room temperature, 10 M borane–dimethylsulfide complex (0.5 mL) was added. The mixture was heated under reflux for 18 hours. The resulting mixture was cooled to room temperature and cautiously transferred into 2 N hydrochloric acid (10 mL) in a 200 mL round-bottomed flask equipped with a magnetic stirrer bar using diethyl ether (10 mL).
4. The same procedure described for the stereoselective reduction of methyl 3-oxo-2-trityloxyiminostearate gave a white solid *N*-benzoylsphingamine (0.96 g, 94%) as a mixture of diastereomers.

   The *anti/syn* ratio (97:3) and the respective ee (*anti* 87%, *syn* 58%) were determined by chiral HPLC.

   ^{1}H NMR (270 MHz, $CDCl_3$) for *anti* isomer δ 0.88 (t, *J* 6.7 Hz, 3H), 1.26 (br, 26H), 1.60 (m, 2H), 2.55 (d, *J* 6.7 Hz, 1H), 2.63 (br, 1H), 3.82–3.98 (m,

2H), 4.02–4.18 (m, 2H), 7.10 (brd, 1H), 7.42–7.56 (m, 3H), 7.82 (d, *J* 6.7 Hz, 2H).

11.6 ENANTIOSELECTIVE REDUCTION OF KETONES USING N-ARYLSULFONYL OXAZABOROLIDINES

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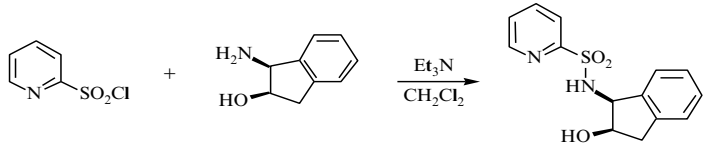
11.6.1 SYNTHESIS OF N-(2-PYRIDINESULFONYL)-1-AMINO-2-INDANOL



Materials and equipment

- Methylene chloride, 160 mL
- Triethylamine, 6.7 mL
- 2-Chlorosulfonyl pyridine, 7.1 g[21]
- (1*S*,2*R*) (*Z*)-Amino indanol, 5.97 g.
  Both enantiomers of (*Z*)-1-amino-2-indanol are available commercially.

- 250 mL Three-necked round-bottomed flask with a magnetic stirrer bar
- Magnetic stirrer
- Ice-bath

Procedure

1. The amino indanol was placed in a 250 mL three-necked round-bottomed flask equipped with a magnetic stirrer bar under nitrogen. Dry methylene chloride (110 mL) and triethylamine (6.7 mL) were then added. The reaction mixture was allowed to cool to 0 °C before adding a solution of 2-chlorosulfonyl pyridine (7.1 g in 50 mL CH_2Cl_2) over 20 minutes. The mixture was stirred at this temperature for 1 hour.
2. Water (60 mL) was added. The organic layer was separated. The aqueous layer was extracted with methylene chloride (4 ×100 mL). The organic layers

were combined and washed with brine, dried over magnesium sulfate and concentrated to give a white solid. The solid was purified by crystallization using ethyl acetate to give the product as white crystals (10 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, *J* 4.8 Hz, 1H), 8.10 (d, *J* 8 Hz, 1H), 8.00 (m, 1H), 7.57 (m, 1H), 7.41 (dd, *J* 5.2, 7.6 Hz, 1H), 7.3–7.2 (m, 4H), 5.69 (d, *J* 8 Hz, 1H), 4.95 (dd, *J* 4.8, 9.7 Hz, 1H), 4.27 (m, 1H), 3.06 (dd, *J* 5.6, 16.7 Hz, 1H), 2.94 (d, *J* 16.6 Hz, 1H).

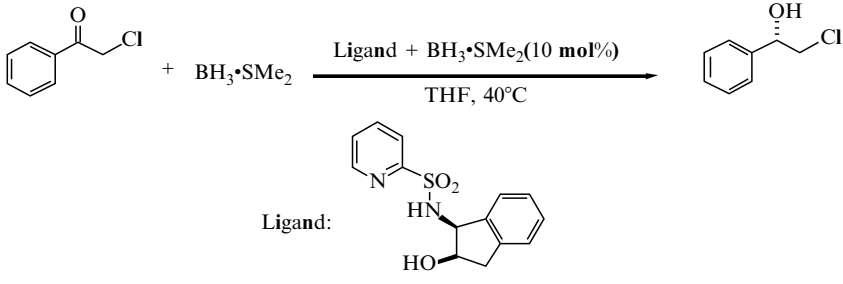
^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 149.2, 140.0, 139.4, 139.1, 128.7, 127.3, 127.3, 125.3, 124.9, 122.5, 72.1, 62.3, 38.8.

Rotation was recorded on a JASCO-DIP-370 instrument: $[\alpha]_D^{25}$ − 37.0 (*c* 1.0, $CHCl_3$).

Analysis calculated for $C_{14}H_{14}N_2O_3S$: C, 57.92, H, 4.86, N, 9.65, Found: C, 57.67, H, 4.57, N, 9.65.

The quality of the ligand can be determined by performing an asymmetric reduction reaction on prochiral ketones according to the following procedure.

11.6.2 ASYMMETRIC REDUCTION OF A PROCHIRAL KETONE (CHLOROACETOPHENONE)



Materials and equipment

- Tetrahydrofuran, 71 mL
- 2-Chloroacetophenone, 1.02 g
- Borane-methyl sulfide complex (2 M in THF), 4.62 mL
- Ligand *N*-(2-Pyridinesulfonyl)-1-amino-2-indanol, 191.4 mg

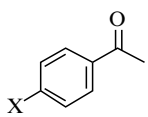
- 100 mL Round-bottomed flask with a magnetic stirrer bar
- Magnetic stirrer hot plate
- Oil-bath
- Thermometer
- Syringe pump

Procedure

1. The ligand (191.4 mg) was placed in a 100 mL round-bottomed flask equipped with a magnetic stirrer bar in an oil-bath at 40 °C, under nitrogen. Dry tetrahydofuran (66 mL) was then added. After the solution turned clear, borane–methyl sulfide complex (1.32 mL) was added dropwise. The mixture was stirred at this temperature for 2.5 hours.
2. Borane–methyl sulfide complex (3.3 mL) was added to the reaction mixture. After stirring for an additional 1.5 hour at 40 °C, a solution of 2-chloroacetophenone (1.02 g in 5 mL of THF) was added over 2 hours using a syringe pump. The reaction was monitored by TLC and after completion (1.5 hour), it was cooled to 0 °C and quenched carefully with methanol. Solvent was removed on a rotary evaporator. 1 M HCl (15 mL) was added followed by extraction with dichloromethane (3 × 50 mL). The organic layers were combined and washed with brine, dried over magnesium sulfate, and concentrated to give a liquid.
3. The crude reaction mixture was purified by flash column chromatography (10 % ethyl acetate in hexane) to give the product as a colourless liquid (0.9 g, 90 % yield).
   - The ee (86–89 %) was determined by HPLC (Chiralcel OD column, flow rate 1 mL/min, eluent *i*-propanol–*n*-hexane 2:98), *S*-enantiomer: R_t 22.2 min, *R*-enantiomer: R_t 26.1 min.
   - ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4–7.3 (m, 5H), 4.89 (dd, *J* 13.2, 5.4 Hz, 1H), 3.8–3.6 (m, 2H), 2.62 (broad, 1H).
   - ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.0, 128.8, 128.6, 126.2, 74.2, 51.0.

Conclusions

Oxazaborolidine-mediated reduction of ketones is very popular for the synthesis of enantiomerically pure secondary alcohols[22]. The present work illustrates an example of delivery of the hydride by borane coordinated to a remote Lewis basic site. The procedure is easy to reproduce. Slow addition of the ketone helps increase the enantioselectivity. The methodology is general and a variety of ketones can be reduced in high chemical yield and good enantioselectivity. The following table presents results from the reduction of a variety of ketones using the chiral ligand derived from amino indanol[23].



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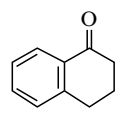

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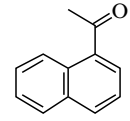

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Table 11.8 Reduction of ketones using *N*-(2-pyridinesulfonyl)-1-amino-2-indanol as a ligand.

Compound	X	Yield (%)	% ee (config.)
1	H	85	80 (*R*)
2	Br	91	87 (*R*)
3	OMe	90	77 (*R*)
4	–	90	87 (*R*)
5	–	83	71 (*R*)

11.7 REDUCTION OF KETONES USING AMINO ACID ANIONS AS CATALYST AND HYDROSILANE AS OXIDANT

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One of the fundamental operations in organic synthesis remains the stereoselective reduction of carbonyl groups[24]. In a process related to that reported by Hosomi *et al.*[25], using hydrosilanes as the stoichiometric oxidant and amino acid anions as the catalytic source of chirality, a variety of ketones were reduced in good to excellent yield and with good stereoselectivity[26]. This process reduces the amount of chiral catalyst needed and utilizes catalysts from the chiral pool that can be used directly in their commercially available form.

Materials and equipment

- L-Histidine, 50 mg, 0.3 mmol
- Dry tetrahydrofuran, 30 mL
- Distilled tetramethylethylene diamine, 1.0 mL, 6 mmol
- *n*-Butyllithium, 2 M solution in hexane, 0.32 mL, 0.6 mmol
- Trimethoxysilane (or triethoxysilane) 0.38 mL, 3 mmol
- Acetophenone 0.35 mL, 3 mmol
- Sodium hydrogen carbonate, 1 M solution, 20 mL
- Pentane (360 mL), diethyl ether (240 mL)
- Silica gel 60 (1 × 15 cm)
- Sand

- Two 100 mL one-neck round-bottomed flask
- Magnetic stirrer and stirrer bar
- Separatory funnel, 250 mL
- Rotary evaporator

Procedure

1. The 100 mL round-bottomed flask, equipped with a magnetic stirrer bar, was dried in an oven at 120 °C overnight. The flask was removed, sealed, cooled and flushed with nitrogen.
2. L-Histidine (50 mg) was placed in the flask. The flask was again flushed with nitrogen. Tetrahydrofuran (30 mL) was added and the mixture was stirred.

   L-Histidine is sparingly soluble in tetrahydrofuran.
3. To this stirring mixture at ambient temperature was added *n*-butyllithium (0.32 mL of a 2 M solution in hexane) dropwise. The resulting solution was stirred at ambient temperature for 30 minutes.
4. The clear mixture was cooled to 0 °C, and freshly distilled tetramethylene diamine (1 mL) was added. The system was stirred for 10 minutes after the addition.

   Tetramethylethylene diamine is hygroscopic.
5. Trimethoxysilane (0.38 mL) was added and the solution allowed to stir for an additional 10 minutes.

   Triethoxysilane and especially trimethoxysilane are rather toxic compounds (they may cause blindness if allowed to get into contact with eyes) and therefore care must be taken in their handing. Both need to be manipulated very carefully with suitable gloves, eyes face protection, in a well ventilated fume-hood. However, both can be handled without problems via syringe techniques.

   Although both triethoxysilane and trimethoxysilane are useful in these reactions, the latter reacts much more rapidly and, therefore is more convenient than the former.
6. Acetophenone (0.35 mL) was added and the resulting system was allowed to stir overnight at 0 °C.
7. The reaction was removed from the cooling bath and quenched with the addition of sodium hydrogen carbonate (20 mL), with vigorous stirring that was continued for 30 minutes at room temperature.

   Care must be taken in controlling the quenching time of the reaction. It was found that longer quenching times resulted in crude reaction mixtures that were difficult to effectively separate (lower product yields were obtained).
8. The biphasic system was transferred to a separatory funnel (250 mL) and extracted with ether (3 × 40 mL). The organic fractions were combined. The solvent was removed using a rotary evaporator, to produce a yellow oil and a white solid (polymerized trimethoxysilane).
9. The crude material was purified using flash silica gel chromatography eluting with pentane/ether (3:1). This provided 0.31 g (85 %) phenethanol.

   ^{1}H NMR and/or ^{19}F NMR analysis of the Mosher ester of the resulting alcohol was used to determine the ee (25–30 %).

General experimental procedure for preparation of Mosher esters[27]

For (*S*)-1-phenylethanol: (*S*)-1-phenylethanol (2 mg, 0.02 mmol) and MTPA-Cl (+) (4 mL, 0.02 mmol) were mixed with carbon tetrachloride (3 drops) and dry pyridine (3 drops). The reaction mixture was allowed to stand in a stoppered flask for 12 hours at ambient temperature. Water (1 mL) was added and the reaction mixture transferred to a separatory funnel and extracted with ether (20 mL). The ether solution, after washing successively with HCl (1 M, 20 mL), and saturated sodium carbonate solution (20 mL), and water (20 mL), was dried over sodium sulfate, filtered and solvents were removed *in vacuo*. The residue was dissolved in deuteriated chloroform for NMR analysis. The relative integration of the hydrogen on the carbon bearing the hydroxyl group was used to calculate the ee.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.56 (d, 3H, J = 6.5 Hz, PhCH(OH)*C*H_3), 2.76 (bs, 1H, PhCH(*O*H)CH_3), 4.94 (q, 1H, J = 6.5 Hz, Ph*C*H(OH)CH_3), 7.32–7.45 (m, 5H_{arom}).

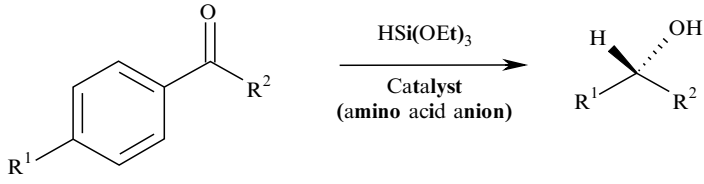
^{13}C NMR ($CDCl_3$, 200 MHz): δ 24.97, 69.99, 125.24, 127.14, 128.24, 145.75.

FTIR (neat, KBr disc) ν (cm^{-1}) 3364, 3065, 3031, 2974, 2929, 1728, 1603, 1494, 1452, 1371, 1287, 1204, 1077, 1030, 1011, 900, 762, 700, 607, 541.

Conclusion

The stereoselective reduction may be applied to a variety of ketones. Some examples of reductions, as a function both of ketone substrate and amino acid catalyst are provided in Table 11.9. The full scope of this procedure[26–28] has

Table 11.9 Reduction of Ketones Using $HSi(OEt)_3$ and amino acid anions.



R^1	R^2	Amino acid anion (mol%)	Yield %	ee%
H	Me	Li_2-His (10)	85	26 (S)
H	Me	Li-His (10)	75	26 (S)
CF_3	Me	Li_2-His (10)	86	30 (*S*)
Me	Me	Li_2-His (10)	80	40 (*S*)
Me	Ph	Li_2-His (10)	82	5 (*S*)
CF_3	Ph	Li_2-His (10)	95	30 (*S*)
H	Me	Li-Phe (100)	70	25 (S)

not been completely mapped out and, in particular, the use of other amino acids such as proline, which are known to be particularly useful chiral catalysts[29], must be examined.

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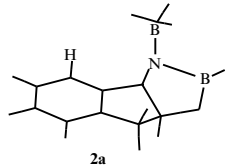
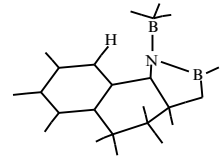
19. Inspection of molecular model of oxazaborolidine **2a** and **5a** indicated that the distance of hydrogen (C_{ortho} – H) to boron (N-BH_3) of **5a** is closer than **2a**.



2a



5a

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