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Two Efficient Enantioselective Syntheses of 2-Amino-1-phenylethanol

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Abstract:

Two enantioselective methods for the synthesis of 2-amino-1-phenylethanol have been developed. The first utilizes an enantioselective oxazaborolidine-catalyzed borane reduction of 2-chloroacetophenone (phenacyl chloride) to give the chiral chloro alcohol in good yield with an ee in the 93−97% range. Reaction with dilute ammonium hydroxide produced the amino alcohol in good yield with a high ee. The second approach involved first the conversion of phenacyl chloride to the succinimido acetophenone which was then hydrogenated using a chiral ruthenium complex in conjunction with a base and an optically active amine (Noyori procedure). This gave the optically active succinimido alcohol in very good yield with an ee of 98%. Hydrolysis with dilute base produced the optically active amino alcohol in very good yield and excellent enantioselectivity.

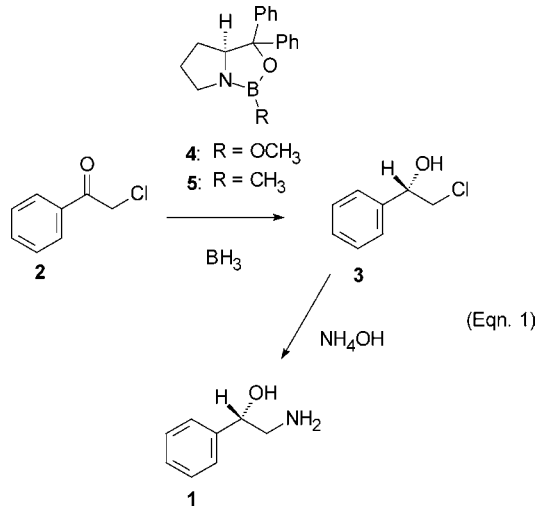
Introduction

Chiral β-amino alcohols such as (*R*)- or (*S*)-2-amino-1-phenylethanol (**1**) are important intermediates in the synthesis of a variety of pharmaceutically important compounds. Several years ago an evaluation of the more promising of those approaches known at that time led to the conclusion that the most practical method for preparing **1** in larger quantities was the resolution of the racemic amino alcohol using di-*O*-toluoyltartaric acid.[1] Each enantiomer was obtained in an overall yield of about 30% with a near 99% ee. Somewhat later, the resolution of racemic **1** using dehydroabietic acid was also reported, but the yields and ee's of the resulting enantiomers were somewhat lower.[2]

More recently, though, a number of different methods for the enantioselective reduction of substituted acetophenones have been developed and used for the synthesis of **1** or related precursors. These included enzyme reductions,[3] chiral borane reductions,[4] and enantioselective hydrosilylation.[5] Of more general usage, however, were the use of chiral oxazaborolidines as enantioselective catalysts for borane reductions, the CBS reduction,[6] and the enantioselective hydrogenation of ketones developed by Noyori.[7] These latter two procedures were selected as routes which could be used for the large-scale production of **1**.

Chiral Oxazaborolidene-Catalyzed Reductions

The first route explored for the potential large-scale synthesis of **1** involved the enantioselective reduction of 2-chloroacetophenone (**2**) with BH_3·THF (or BH_3·DMS) in the presence of an oxazaborolidine catalyst[6] to give the chloro alcohol, **3**, which then would be aminated to produce the amino alcohol, **1** (eq 1). This method seemed particularly attractive because it used commercially available catalyst precursors and stabilized borane solutions and frequently led to the formation of the corresponding alcohol at high ee with predictable stereochemistry. Typically, the reduction is quenched with excess methanol to deactivate any remaining BH_3·THF complex and is distilled to remove the boron from the products as the methyl borate/methanol azeotrope.



Examination of the literature describing the CBS reduction of **2**[8] shows a wide range of conditions reported for this reaction. While most of these papers described the effect which a variety of chiral oxazaborolidines had on this reduction, the other reaction parameters remained relatively constant. The substrate to catalyst (S/C) molar ratios ranged from 1:1 to 50:1, but most were commonly in the 10−20:1 range. The substrate to borane (S/B) molar ratios ranged from

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1:2 to 1:0.6, but was generally 1:1. The reaction solvents were either THF or toluene, with THF being used for those reactions run near room temperature or lower, whereas toluene was used for reactions run at higher temperatures. The addition of the ketone to the preformed catalyst/borane mixture or the inverse addition of the borane solution to the catalyst/ketone mixture were the common methods of bringing the reactants into contact with each other. The successful scale-up of the CBS reductions of prochiral ketones have been reported by both Bayer[9] and Sepracor.[10]

The selectivity of the reaction depends on a number of parameters such as the nature of the substrate, the reaction temperature, the method of catalyst preparation, the nature of the solvated borohydride, the rate of addition of the ketone, and the sequence by which the ketone, the catalyst, and the reducing agent are brought into contact with each other.

Here, we report results obtained on optimizing the reduction of **2** using BH_3·DMS or BH_3·THF as the hydrogen source and two (*S*)-α,α-diphenyl-2-prolinol-based catalysts. The methoxy oxazaborolidine (**4**) was prepared in the reaction flask using a modification of a published procedure.[9] The methyl oxazaborolidine (**5**) was commercially available. The reaction parameters investigated were the substrate to catalyst ratio, the substrate to BH_3 ratio, the effect of the mode and the rate of addition of either the BH_3 or the ketone to the catalyst, and the effect of the temperature on the product ee and the ketone conversion.

Since the product ee depends on the relative rates of the enantioselective catalyzed reduction and the non-chiral borane reduction of the ketone, a high product ee can be obtained only if the non-chiral reduction is eliminated or, at least, minimized. In agreement with previous work,[9] the best results were obtained here using a slow addition of the ketone to a solution containing both the borane and the catalyst. More rapid addition of the ketone invariably caused a decrease in product ee (sometimes to a significant degree) since, under these conditions, there is probably an excess of ketone in the reaction mixture, thus increasing the probability of non-chiral reduction taking place. All reactions were usually run by adding the ketone solution to the borane/catalyst mixture at a rate of 0.15 cm^3/min (0.12 mmol/min) which was found to be the optimum for the 0.8 M solution of the ketone being used. The reaction temperature was 30 °C unless otherwise noted. The use of either (*S*)-α,α-diphenyl-2-prolinol-based catalyst **4** or **5** led to the formation of the (*S*)-(+)-2-chloro-1-phenylethanol enantiomer, **3**.

The first consideration was given to increasing the S/C ratio to a value more amenable for commercial use. Even though this reduction has been run on a large scale,[9,10] the reported S/C ratios in these reactions were only 20:1. In order to maximize the S/C ratio for this reduction a series of reactions were run in which the amount of ketone was kept constant at 8 mmol, while the quantity of the methoxy oxazaborolidine, **4**, was decreased systematically. The product ee, as shown in Table 1, decreased significantly when the S/C ratio dropped below 30:1, even though the reaction went to complete conversion. Attention then shifted to using the commercially available methyl oxazaborolidine, **5**, to catalyze the reduction. Here, too, the amount of **5** was decreased while keeping the quantity of ketone constant at 8 mmol. Two separate series of reactions were run using this catalyst, one involving the BH_3·DMS reducing agent and the other using BH_3·THF. The product ee's for these reactions are also listed in Table 1. All reactions went to 100% conversion. The methyl oxazaborolidine, **5**, was more reactive than **4** since with **5** the product ee remained fairly constant to S/C ratios of 320:1, a considerable improvement over the reactions reported in the literature. With the BH_3·DMS reducing agent, though, the ee did decline significantly at an S/C of 800:1 but using BH_3·THF at this S/C level resulted in only a slight decrease in ee. While it was possible that an intermediate S/C ratio could have given effective product ee's, all further reactions were run using the 320:1 ratio with the BH_3·THF reducing agent. This is 15−30 times greater than the S/C ratios reported in the literature for the reduction of **2**.

Attention was then directed to the S/B molar ratio. Since there are three hydrogens on the boron, ideally one might expect to be able to use one-third of an equivalent of the borane in the reduction. Most literature reports cite the use of at least one mole of the borane per mole of ketone, but a few have reported the successful use of 0.7 mole. Table 2 lists the conversion and product ee data for reactions run using decreasing amounts of BH_3·DMS or BH_3·THF as the reducing agent. These data show that the conversion and ee

Table 1. **Effect of substrate/catalyst (S/C) ratio on the product ee in the oxazoborolidine-catalyzed reduction of 2[a]**

BH_3·DMS					BH_3·DMS	BH_3·THF
4 (mmol)	S/C	% ee	**5** (mmol)	S/C	% ee	% ee
0.4	20	98	0.2	40	98	97
0.27	30	98	0.1	80	98	96
0.13	60	84	0.05	160	97	96
0.1	80	65	0.025	320	96	94
			0.01	800	74	90

[a] 8 mmol of **2**, BH_3/ketone = 1.05, T = 30 °C, ketone solution (0.8 M) added at 0.15 cm^3/min, 45 min post addition time, 100% conversion in all reactions.

Table 2. **Effect of BH_3/ketone ratio on the degree of conversion and the product ee in the oxazoborolidine-catalyzed reduction of 2[a]**

		BH_3.DMS		BH_3·THF	
BH_3 mmol	BH_3/**2**	% ee	% conv	% ee	% conv
8.4	1.05	96	100	94	100
8	1.0	96	100	94	100
7.2	0.9	95	100	94	100
6.4	0.8	95	100	95	100
5.6	0.7	95	100	96	100
4.8	0.6	93	99	96	100
4.0	0.5	90	88	90	88

[a] 8 mmol of **2**, 0.025 mmol of **5**, T = 30 °C, ketone solution (0.8 M) added at 0.15 cm^3/min, 45 min post addition time, 100% conversion in all reactions.

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Table 3. **Effect of temperature on the degree of conversion and the product ee in the oxazoborolidine catalyzed reduction of 2[a]**

T °C	% conv.	% ee	*T* °C	% conv.	% ee
20	85	86	45	91	93
30	88	90	50	99	95
40	93	93	65[b]	100	96

[a] 8 mmol of **2**, 0.025 mmol of **5**, BH_3/**2** = 0.5, ketone solution (0.8 M) added at 0.15 cm^3/min, 45 min post addition time, 100% conversion in all reactions. [b] Refluxing THF.

begin to decrease at a S/B molar ratio of 0.5. Again, BH_3·THF is more effective than BH_3·DMS.

The effect of increasing the temperature was then studied on reactions having a S/B ratio of 0.5. The results are presented in Table 3 which shows that increasing the reaction temperature resulted in an increase in product ee. Apparently, the higher temperature increases the rate of the enantioselective catalyzed reaction more than that of the non-chiral borane reduction. Of particular importance is that the reaction run in refluxing THF (65 °C) went to complete conversion with a product ee of 96%. Even with these results, we felt more comfortable using an S/B ratio of 0.6 in future reactions.

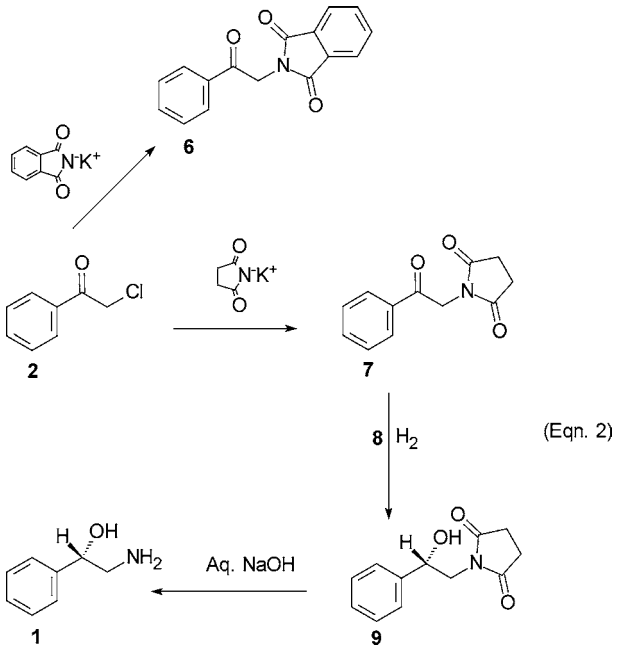
Another factor which was investigated was the effect on the amount of time between the completion of the ketone addition and the quenching of the reaction with methanol, the so-called post-addition time. An increase in the conversion and product ee was observed during the first 30 to 45 min after the ketone addition, but beyond that time, further changes were not seen.

On the basis of these results it was concluded that reasonably optimum reaction conditions for the **5**-catalyzed BH_3·THF reduction of **2** are a reaction temperature of 65 °C, BH_3·THF/ketone/catalyst ratios of 0.6:1:0.003, an initial charge of the catalyst solution, the BH_3·THF hydride source and the THF solvent into the reactor followed by the metered addition of the solution of **2**. The optimum rate of addition of the ketone to the reducing mixture is apparently dependent on the concentration of the ketone solution and the amount of catalyst being used. For instance, with the standard reaction involving 8 mmol of a 0.8 M solution of **2** and 0.025 mmol of **5**, an addition rate of 0.15 cm^3/min (4.8 mmol of **2**/mmol of **5**/min) gave optimum conversion and product ee. Increasing the amount of **2** to 40 mmol in a 5.25 M solution and using 0.125 mmol of **5** required an addition rate of 0.0.75 cm^3/min (3.2 mmol of **2**/mmol of **5**/min) to obtain the best conversion and product ee. No other products were observed in the HPLC traces. Since reaction selectivity is dependent on the relative ease by which **2** can interact with the chiral borane as opposed to the non-chiral borane, stirring efficiency is also an important factor, but this aspect of the reaction was not examined here.

The amino alcohol (**1**) was produced by treating a methanol solution of **3** with a large excess of 30% aqueous NH_4OH at room temperature for 2−3 days.[9] After evaporation of the water and methanol, **1** was isolated as a crude product having an ee of 95% in 85% yield.

Enantioselective Catalytic Hydrogenation

Even though there are several examples in the literature of the enantioselective transfer hydrogenation of **2**,[11] because of the success reported in using the Noyori catalysts for the enantioselective catalytic hydrogenations of substituted acetophenones[7] it was decided to expend efforts in this area on the use of the Noyori hydrogenation procedure as another route for a commercial synthesis of **1** (eq 2). The first aspect



to be determined was the nature of the substrate to be used in this study. Using the classic Noyori hydrogenation for the hydrogenation of **2** was unsuccessful; thus, it was decided to introduce the amine moiety prior to the hydrogenation of the carbonyl group. It was thought that trying to hydrogenate a primary aminoketone would lead to self-condensation, particularly in a large-scale process; as a result, an amine with an easily removed blocking group was required. One such substrate is the phthalimido ketone, **6**, which could be prepared by reaction of **2** with potassium phthalimide. After hydrogenation, the phthalimido group could be removed using hydrazine in the classic Gabriel synthesis.[12] It has been reported that **6** was enantioselectively hydrogenated using a chiral rhodium catalyst, but the reaction only took place at high pressures,[13] something to be avoided, if possible, for a commercial application. Another problem with the use of **6** as a precursor in the preparation of **1** was the very low solubility of **6** in methanol or isopropyl alcohol, the solvents commonly used in Noyori hydrogenations. However, the succinimide, **7**, which was prepared by reacting **2** with potassium succinimide, was sufficiently soluble under our hydrogenation conditions. This material was therefore selected as the substrate to be used in this hydrogenation study.

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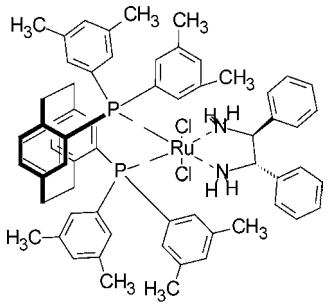
Table 4. **Effect of ligand and solvent on the hydrogenation of 1 mmol of 6 using 10 mmol of Ru(ligand)(*S*,*S*)-DPEN at 50 °C and 60 psig H_2 with 0.25 mmol of potassium *tert*-butoxide**

ligand	MeOH/iPrOH	% ee	rate[a]	% conv
(*S*)-Binap	30/70	19	30	100
(*S*)-Tol-Binap	30/70	73	408	87
(*R*)-Tol-Binap	30/70	−59	432	100
(*R*)-P-Phos	30/70	6	36	100
(*R*)-Xylyl P-Phos	30/70	7	120	100
(*R*)-Binam	60/40	55	180	100
(*R*)-Binam	100/0	68	120	100
(*S*,*S*)-Dipamp	30/70	93	30	95
(*R*)-Phanephos	30/70	64	420	100
(*R*)-Xylyl Phanephos	30/70	86	120	96
(*R*)-Xylyl Phanephos	60/40	>99	120	100
(*R*)-Xylyl Phanephos	100/0	>99	840	100
(*R*)-Xylyl Phanephos	EtOH	>99	234	22

[a] mol product/mol catalyst·h^{-1} (TOF).

In Table 4 are listed the ligands and methanol/isopropyl alcohol solvent mixtures screened for activity and selectivity in the hydrogenation of **7**. These hydrogenations were run at 50 °C and 60 psig with a S/C ratio of 100. It is obvious from these data that the ruthenium complex prepared from the xylyl Phanephos ligand and DPEN, dichloro[(*R*)-3,5-xylyl-Phanephos][DPEN]ruthenium (II) (**8**), was a superior catalyst as compared to the others tested, particularly when the solvent used is only methanol. When incomplete conversions are listed, it indicates that the reaction stopped at that point.



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While potassium *tert*-butoxide and potassium hydroxide are the most common bases associated with Noyori hydrogenations, other bases such as LiOtBu, K_2CO_3, Li_2CO_3, and DABCO were also tried here, but none of them was effective. It was also found that the presence of KOH was not compatible here since the base was apparently responsible for the partial hydrolysis of the succinimide with the concomitant deactivation of the catalyst. All subsequent hydrogenations were run using KOtBu as the base. It only remained to determine the optimum amount of the KOtBu to use for this reaction. The data listed in Table 5 indicate that at a S/C ratio of 1000 (2 mmol of ketone) the presence of 0.25 mmol of KOtBu in the reaction mixture gave the best reaction rate. The conversion and product ee were unchanged, regardless of the amount of base used. Further testing showed that the substrate/base ratio (S/B = 8) is the critical factor and not the catalyst/base ratio. At a S/C ratio of 2500 (5 mmol of ketone) 0.75 mmol of base (S/B = 6.7) was used to obtain the best results. In order to consistently run hydrogenations at the higher S/C ratios it is important that all oxygen be removed from the reaction system. This can be accomplished either by repeated application of a vacuum/purge or pressure/purge sequences as described in the Experimental Section.

Table 5. **Effect of the quantity of KOtBu on the degree of conversion and the product ee in the enantioselective hydrogenation of 7[a]**

tBuOK (mmol)	S/B	% ee	rate[b]	% conv
0.05	40	>99	1500	100
0.125	16	>99	2100	100
0.15	13	>99	1800	100
0.25	8	>99	3000	100
0.50	4	>99	2100	100
0.75	2.6	>99	2700	100

[a] 2 mmol of **7**, 2 μmol of catalyst (TON = 1000), T = 30 °C, 60 psig H_2. [b] mol product/mol catalyst·h^{-1}.

Table 6. **Effect of the temperature on the degree of conversion and the product ee in the enantioselective hydrogenation of 7[a]**

temp (°C)	% ee	rate[b]	% conv
30	>99	2400	100
40	>99	2400	96
50	>99	2640	92
60	>99	2565	72

[a] 5 mmol of **7**, 2 μmol of catalyst (TON = 2500), 0.75 mmol of KOtBu, 60 psig H_2. [b] mol product/mol catalyst·h^{-1}.

Table 7. **Effect of the hydrogen pressure on the degree of conversion and the product ee in the enantioselective hydrogenation of 7[a]**

pressure (psig)	% ee	rate[b]	% conv
30[c]	>99	810	98
40[c]	>99	1320	99
50[c]	>99	1710	98
60[c]	>99	2610	100
200[c,d]	>99	20,100	100

[a] 5 mmol of **7**, 2 μmol of catalyst (TON = 2500), 0.75 mmol of KOtBu, T = 30 °C. [b] mol product/mol catalyst·h^{-1}. [c] Reaction run in 75-mL glass reactor with suspended stirrer. [d] Reaction run in 40-mL stirred autoclave.

As shown by the data in Table 6, increasing the reaction temperature had little effect on the reaction rate, possibly because of a degree of diffusion control of the reaction. Increasing the temperature, however, did have an effect on the stability of the catalyst as shown by the decrease in the degree of conversion observed at higher temperatures. Increasing the pressure, on the other hand, had an effect on the reaction rate (Table 7). Even though the lower pressure reactions were run in a glass reactor whereas the 200 psig reaction was run in a stirred autoclave, this comparison is valid since hydrogenations run at 60 psig gave nearly identical results regardless of which reactor was used.

It is of interest that all of the hydrogenations of **7** run using **8** as the catalyst produced products with ee's in excess of 99% regardless of the other reaction conditions employed. Obviously, the only factor of importance in determining the enantioselectivity of this reaction was the ligand present on the catalyst.

Either enatiomer of **1** could be prepared using this procedure. Hydrogenation of **7** using dichloro[(*R*)-xylyl-Phanephos][1*S*,2*S*-DPEN]ruthenium (II) gave the S enantiomer of **9** with 99% ee at 100% conversion. Using (*S*)-xylyl-Phanephos and (1*R*,2*R*)-DPEN resulted in the formation of the R enantiomer of **9**, again with 99% ee at 100% conversion.

It was originally thought that one should be able to remove the succinic acid group by treatment of **9** with hydrazine in the same way one is able to produce a primary amine by treating a phthalimide with hydrazine in the classical Gabriel synthesis.[12] This was not the case, though, since **9** did not react with hydrazine. However, it was found that treatment of **9** with dilute sodium hydroxide readily hydrolyzed the succinimide to produce the amino alcohol, **1**, in 90% yield with an ee of 98−99%.

Conclusions

While both approaches to the preparation of **1** are adaptable to large-scale synthesis, a number of factors need to be considered before selecting one over another. One of these is concerned with the IP of the process be it the Corey oxazaborolidine process (CBS reactio)[14] or the use of the Noyori hydrogenation[15] using the xylyl-Phanephos ligand.[16] Another factor is the type of apparatus available for use in the scale-up. The oxazaborolidine approach needs only a standard reactor system, but the Noyori procedure requires the use of a pressure reactor. Further, while the solvents used by us were purified following our routine procedures, this is not necessary for a large-scale oxazaborolidine-catalyzed reaction. However, to be successful, the Noyori reaction used here requires the strict exclusion of oxygen from the reactor system throughout the entire reaction sequence.

One must also consider the substrate/catalyst ratios as well as the cost of the catalysts themselves. The oxazaborolidine catalyst is considerably less expensive than the xylyl-Phanephos catalyst, but the oxazaborolidine reaction proceeds at only a moderate S/C ratio. The Noyori hydrogenation, though, can be run at a more reasonable S/C ratio. Finally, the hydrogenation produces an almost enantiomerically pure product, whereas the oxazaborolidine-catalyzed reaction gives a product having an ee in the mid-90% range.

If the oxygen-free pressure equipment is available and **1** is needed in nearly enantiomerically pure form with minimal purification, the hydrogenation route should be considered. On the other hand, if **1** is going to be converted into a larger molecule which can then be purified, the oxazaborolidine-catalyzed reaction may be the one to use.

Experimental Section

All reagents and ligands were obtained from Aldrich, Acros, or Strem and were used without further purification. The methanol, isopropyl alcohol, and DMF were distilled over calcium hydride under an argon atmosphere and stored in sealed flasks under argon. The THF was purified by distillation over sodium ketyl under an argon atmosphere and stored in a sealed flask under argon. The (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (**5**) was purchased from Aldrich as a 1 M solution in toluene [(*S*)-2-methyl-CBS-oxazaborolidine]. An authentic sample of (*S*)-2-amino-1-phenylethanol (**1**) was purchased from Alfa Aesar. All gases used were zero grade. The HPLC analyses were accomplished using a 250 mm × 4.6 mm Chiracel OJ column with an 8% v/v isopropyl alcohol in hexane solvent, isocratic at 0.8 cm^3/min and room temperature with 2,6-dimethylnaphthalene as the internal standard.

(*S*)-5,5-Diphenyl-2-methoxy-3,4-propano-1,3,2-oxazaborolidine (4). A dry, 75-mL jacketed reactor equipped with a magnetic stir bar, two addition ports, and two purge ports was charged with 101.3 mg of (*S*)-α,α-diphenylprolinol (0.4 mmol) and 5 cm^3 of dry THF. The mixture was stirred in an inert atmosphere for 2 min until the solid was completely dissolved. A solution, made by dissolving 55 mg (0.53 mmol) of $B(OMe)_3$ in 5 mL of dry THF, was added dropwise to the reactor, with stirring, under nitrogen. The mixture was stirred for 1 h at 20 °C. A bleach scrubber was connected to the vent line of the reactor, and an argon flow of 5 cm^3/min was passed through the reactor.

2-Chloro-1-phenylethanol (3). A 75-mL jacketed reaction flask equipped with an addition port, reflux condenser and a magnetic stir bar was first purged with argon for 10 min and then charged with a solution of 0.025 mmol of **5** in 5 mL of THF. A BH_3·THF solution containing 4.8 mmol of BH_3 (10 mL) was added portionwise over 10 min. The reaction flask was heated to 30 °C and a solution of 1.24 g (8 mmol) of **2** in 10 mL of THF was added via syringe pump at a rate of 0.15 mL/min. After the addition was complete, the reaction mixture was stirred for 45 min and cooled to ambient, and the remaining hydride was decomposed by the addition of 2 mL of dry methanol. The reaction mixture was passed through a short bed of SiO_2 and the solvent evaporated giving the chloro alcohol, **3**, in 95% yield; HPLC purity >95%, HPLC ee = 95%.

Large-Scale Preparation of 3. The reaction was run as described above but using a 100-mL jacketed reaction flask to which was added a solution of 0.125 mmol of **5** in 11 mL of THF. A BH_3·THF solution containing 24 mmol of BH_3 (34 mL) was then added portionwise over 10 min, the reaction flask was heated to 65 °C, and a solution of 6.19 g (40 mmol) of **2** in 7.6 mL of THF was added via syringe pump at a rate of 0.075 mL/min. After the addition was complete, the reaction mixture was stirred for 45 min and cooled to ambient, and the remaining hydride was decomposed by the addition of 5 mL of dry methanol. The reaction mixture was passed through a short bed of SiO_2 and the

(14) Corey, E. J. U.S. Patent 4,943,635, 1990.
(15) Ohkuma, T.; Koizumi, M.; Muniz, K.; Noyori, R. U.S. Patent 6,720,439, 2004.
(16) Burk, M. J.; Hems, W.; Zanotti-Gerosa, A. U.S. Patent 6,486,337, 2002.

solvent evaporated, giving the chloro alcohol, **3**, in 95% yield; HPLC purity >95%, HPLC ee = 95%.

(*S*)-2-Amino-1-phenylethanol (1). Five and a half grams of **3** was dissolved in 30 mL of methanol followed by the addition of 100 mL of 30% aqueous ammonium hydroxide. The resulting mixture was stirred at room temperature for 2−3 days after which time the light precipitate which formed was removed by filtration and the methanol only removed by evaporation. To the cold water phase was added 15 g of sodium chloride and 30% aqueous ammonium hydroxide to pH 12.5. This solution was extracted twice with 50 mL portions of ether. The organic phase was dried over magnesium sulfate and evaporated giving 3.4 g (83%) of the amino alcohol, **1**, ee = 95%, which had IR and NMR spectra and HPLC retention times identical to those of an authentic sample.

2-Succimidoacetophenone (7). To 17.22 g (0.17 mol) of succinimide in a 1000-mL round-bottomed flask was added 150 mL of THF and the suspension stirred at 65 °C until the succinimide was dissolved. In a separate 250-mL flask 20.4 g (0.18 mol) of potassium *tert*-butoxide was suspended in 120 mL of THF and the suspension sonicated for 10 min to give a cloudy suspension which was added dropwise to the stirred succinimide solution at such a rate that the internal temperature remained below 20 °C. After the addition was complete, the mixture was sonicated for an additional 1 h. To this suspension was added dropwise over a period of 1 h, with stirring, a solution of 27.84 g (0.18 mol) of **2** in 120 mL of DMF. After this addition, the reaction mixture was stirred overnight during which time the initial red solution changed color to orange. Water (2.5 L) was added dropwise to the stirred suspension, and the pale-yellow precipitate was filtered and dried in a vacuum oven at 45 °C/3−4 mmHg to give 30 g of the crude succinimido ketone (79% yield). This material was recrystallized twice from ethanol to produce a white solid which, after drying in a vacuum oven at 40 °C, gave 20 g (67%) of the succinimido ketone, **7**, of sufficient purity for the hydrogenation step: HPLC purity >95%; ^{1}H NMR (500 MHz, $DCCl_3$), δ (ppm): 7.54−8.06 (m, 5H), 4.84 (s, 2H), 2.84 (s, 4H); GC−MS MW = 217, calc = 217.

Dichloro[(*R*)-3,5-xylyl-Phanephos][*S*,*S*-DPEN]ruthenium (II) (8). Five milligrams (0.02 mmol of Ru) of $[RuCl_2(benzene)]_2$ and 14 mg (0.02 mmol) of CTH-(*R*)-3,5-xylylphanephos were placed in a 50-mL Schlenk flask. After completely replacing all of the air with argon, 2 mL of degassed DMF was added to the flask via cannula and the mixture heated to 100 °C for 10 min with stirring to give a reddish brown solution. After cooling to ambient, 4 mg (0.19 mmol) of *S*,*S*-DPEN, dissolved in 2 mL of degassed DMF, was added and the mixture stirred for 3 h. The DMF was removed under a vacuum of 1 mmHg at 25 °C and then at 50 °C to give a light-yellow solid containing 20 μmol of Ru. This was dissolved in 10 mL of degassed methanol to give a stock catalyst solution containing 2 μmol of Ru/mL. This solution was kept in a completely deaerated, airtight, septum-sealed flask until use.

The enantiomeric catalyst was prepared from CTH-(*S*)-3,5-xylyl-Phanephos and (*R*,*R*)-DPEN in this procedure.

A second stock solution containing 0.25 mmol/mL potassium *tert*-butoxide in methanol was prepared using 700 mg (6.25 mmol) of potassium *tert*-butoxide dissolved in 25 mL of degassed methanol. This was also kept in a deaerated, airtight, septum-sealed flask until use.

(*S*)-2-Succinimido-1-phenylethanol (9). Twenty mmol (4.34 g) of **7** was placed in a 250-mL jacketed, glass reactor vessel,[14] and the air in the reactor was completely replaced by argon using multiple fill/release cycles. Degassed methanol (250 mL) was added to the reactor via cannula and the mixture stirred at 30 °C to dissolve the ketone. Four milliliters of the catalyst solution (8 μmol of Ru) and 12 mL of the K-OtBu solution (3 mmol) were injected into the reactor using gastight syringes. The argon in the reactor was replaced with hydrogen (fill/release cycles) and the reactor pressurized to 60 psig with hydrogen. The reaction mixture was stirred at 1000 rpm overnight at 30 °C with the hydrogen uptake recorded as described previously.[17] The reaction mixture was passed through a short alumina column and the solvent removed to give **9**, with an HPLC ee of 99% at 100% conversion. HPLC purity >97%; ^{1}H NMR (500 MHz, $DCCl_3$), δ (ppm): 7.26−7.41 (m, 5H), 4.84−4.97 (d, 1H), 3.31−3.80 (m, 2H), 2.49−2.674 (m, 4H); GC−MS: MW = 219, calc = 219.

(*R*)-2-Succinimido-1-phenylethanol was prepared using dichloro [(*S*)-3,5-xylyl-Phanephos][*R*,*R*-DPEN]ruthenium (II) as the catalyst.

(*S*)-2-Amino-1-phenylethanol (1). The succinimido alcohol, **9** (1.74 g), was dissolved in 60 mL of 95% ethanol followed by the addition of 36 mL of 20% aqueous sodium hydroxide. The resulting solution was the refluxed for 18 h and then cooled to ambient which resulted in the separation of two layers. The top organic layer was separated and evaporated to dryness to give a solid material which was refluxed with 30 mL of MTBE and 10 mL of methylene chloride for 30−40 min to extract the amino alcohol from the solid sodium succinate. After cooling to ambient the solid was removed by filtration through a Celite pad and the filtrate decolored by stirring with Norit. Filtration gave a clear solution which, after evaporation, produced 980 mg of the white, amorphous amino alcohol, **1** (90% yield, ee = 98+%). The NMR and IR spectra and the HPLC traces of **1** were identical to those of an authentic sample of (*S*)-(+)-2-amino-1-phenylethanol.

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