Fine-Tuning of Modular Amino Alcohol Ligands for the Enantioselective Transfer Hydrogenation of Ketones

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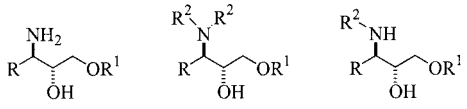
A family of stereodefined, modular amino alcohols (3-alkoxy-1-amino-1-phenyl-2-propanols), in which the steric bulk of the alkoxy and amino substituents varies smoothly, has been synthesized from enantiomerically pure phenylglycidol, prepared by Sharpless epoxidation. These amino alcohols have been evaluated as ligands in the catalyzed [(amino alcohol)-(arene)Ru^{II}] transfer hydrogenation of alkyl aryl ketones, with 2-propanol as the hydrogen source. Both the nitrogen substituent and the alkoxy group have been optimized for maximal enantioselectivity and catalytic activity in the process under consideration.

Introduction

One of the most attractive methods for the synthesis of optically active secondary alcohols, an important class of intermediates for fine chemicals and pharmaceuticals, is asymmetric transfer hydrogenation of prochiral ketones.[1]

The reaction conditions for this environmentally friendly process are relatively mild and do not involve the use of molecular hydrogen, since the organic solvent, often 2-propanol, serves as hydrogen donor. The most common catalysts for this reaction are ruthenium complexes, but derivatives of samarium,[2] rhodium,[3] and iridium[4] have also been used for the same purpose. R. Noyori has developed efficient versions of the reaction, by use of either diamines or amino alcohols possessing a *trans*-stilbene skeleton as chiral ligands.[5] Other chiral ligands incorporating phosphorus and/or nitrogen have also been reported.[6] Despite the high catalytic activities recorded for Noyori's Ru^{II} amino alcohol complexes in the transfer hydrogenation, there are only a few other reports on the use of amino alcohols as chiral ligands in the reaction.[7]

We have recently reported the synthesis of new families of enantiomerically pure β-amino alcohol ligands **I** and **II** from epoxy alcohols produced by Sharpless epoxidation,[8] through the regioselective and stereospecific ring-opening of the epoxide with nitrogen nucleophiles plus chemoselective protection of the primary alcohol.



I **II** **III**

The use of these substances as ligands offers the clear advantage of their modular construction, this characteristic being important for the fine-tuning of catalytic properties through structural variation. The results obtained with ligands **I** and **II** in some mechanistically diverse catalytic asymmetric processes[9] showed that all the different fragments in their structures were important both for catalytic activity and for enantioselectivity. Guided by these results, we decided to prepare the closely related amino alcohols **III**, with secondary amine moieties, and to test both **I** and **III** in the catalytic transfer hydrogenation process. The choice of these types of structures was based on previous results on the use of amino alcohols as ligands in ruthenium-catalyzed transfer hydrogenation, which showed that the presence of unsubstituted or *N*-substituted amino groups was crucially important for the acceleration of the process.[5e]

The work described here details our efforts in the preparation of optimized amino alcohol ligands **III** for the ruthenium-catalyzed transfer hydrogenation of ketones, through a modular optimization process involving both the alkoxy group R^1 and the substituent at nitrogen, R^2.

Results and Discussion

Synthesis of Amino Alcohol Ligands

As the starting point in our study we chose phenylglycidol, since its high crystallinity offered the clear advantage

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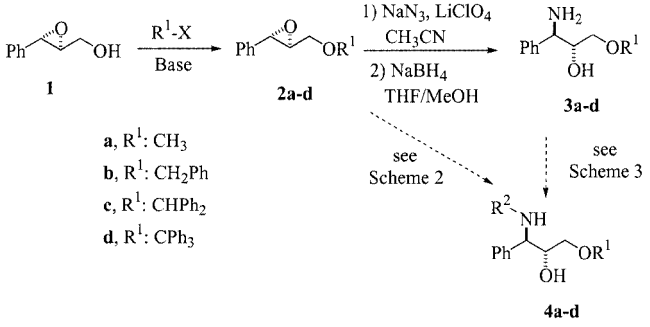
that its enantiomeric excess could be improved by successive crystallizations.[10] The synthetic methodology for the preparation of β-amino alcohols **3** (**I**, R = phenyl) from **1,** based on well established procedures, occurred in a totally stereospecific manner[9a] and is summarized in Scheme 1.

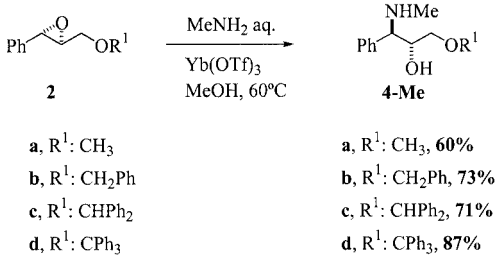


Scheme 1

It is worth noting that the initial protection step of **1** to give **2** is an interesting source of diversity, since groups R^1 with different steric and electronic characteristics can in principle be introduced onto a single epoxy alcohol. On the other hand, the free amino group in **3** originated from the reduction of an azide, which was in turn introduced onto epoxy ethers **2** by means of a regioselective ring-opening.

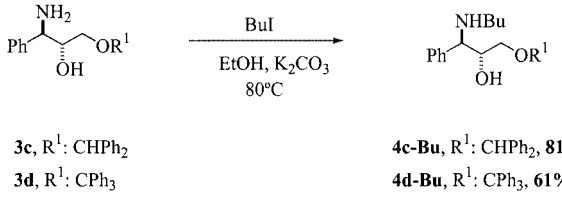
The preparation of *N*-alkylated amino alcohols **4** (**III**, R = phenyl) could be envisaged either from epoxy ethers **2**, by regioselective ring-opening with primary amines, or from **3**, by alkylation. Since preliminary experiments had shown that *N*-alkylated derivatives bearing bulky substituents were not suitable as ligands for the process under consideration,[11] we concentrated our efforts on *N*-methyl derivatives (**4-Me**).

The optimized reaction conditions involved the ring-opening of the epoxide ethers **2** by treatment with aqueous methylamine in a sealed tube in the presence of 0.2 equivalents of $Yb(OTf)_3$,[12] as shown in Scheme 2.



Scheme 2

As we discuss later, comparison of the behavior of **3** and **4-Me** as ligands for the transfer hydrogenation process suggested that related ligands incorporating a slightly bulkier substituent at nitrogen might produce enhanced enantioselectivities. To test this hypothesis, the *N*-butyl derivatives **4c-Bu** and **4d-Bu** were prepared in good yields by alkylation of the primary amine, by treatment of **3c** and **3d** with 1-iodobutane in the presence of potassium carbonate as shown in Scheme 3.



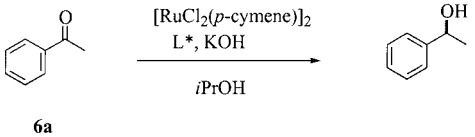
Scheme 3

Transfer Hydrogenation of Aromatic Ketones

As the starting point in the catalysis study, the transfer hydrogenation of acetophenone **6a** was used as a benchmark of ligand efficiency.

In this set of experiments, the chiral catalysts were prepared in situ by heating a mixture of $[RuCl_2(p\text{-cymene})]_2$ and the ligand in 2-propanol for 30 min. After the catalyst solution had cooled to room temperature, a solution of acetophenone in 2-propanol and a solution of KOH in 2-propanol were successively added (a ketone/Ru/ligand/KOH molar ratio of 15:1:2:3.5 was used), and the transfer hydrogenations were performed at room temperature. Results are summarized in Table 1.

Table 1. Asymmetric Transfer of Acetophenone



6a

Entry[a]	Ligand	Time (h)	Conversion (%)[b]	*e.e* (%)[b]	Configuration
1	**3a**	1	92	54	*S*
2	**3b**	1	91	51	*S*
3	**3c**	1.25	97	41	*S*
4	**3d**	1.25	97	23	*S*
5	**4a-Me**	2.25	93	54	*S*
6	**4b-Me**	3.50	93	57	*S*
7	**4c-Me**	1.25	90	65	*S*
8	**4d-Me**	2.25	96	57	*S*
9	**4c-Bu**	3.50	86	72	*S*
10	**4d-Bu**	2.25	68	67	*S*

[a] The reaction was carried out at room temperature by Procedure 1 in the Exp. Sect. [b] Determined by chiral GC analysis.

With the amino alcohol ligands **3**, each bearing an unsubstituted amino group (entries 1−4), equilibrium was approached after only 1 h of reaction, the level of conversion in all cases being higher than 90%. In any case, this set of experiments showed that the steric bulk of the alkoxy group in **3** affected catalytic efficiency and enantioselectivity in a conflicting manner. Whereas the level of conversion increased with the bulk of R^1 (**3c**−**d** vs. **3a**−**b**), the *ee* of the alcohol decreased from 54% (with **3a**) to 23% (with **3d**).

Interestingly enough, when the *N*-methyl derivatives **4-Me** were studied as ligands (entries 5−8) a different effect

was observed. With a progressive increase of the steric bulk of the alkoxy group, enantioselectivity increased until a point of maximal enantioselectivity, reached when ligand **4c-Me** was used (entry 7), after which selectivity started to decrease again.

To explore the influence of the alkyl substituent on the amino group in more depth, and in the hope that a slightly bulkier substituent at nitrogen might deliver enhanced selectivities, *N*-butyl ligands also incorporating a bulky alkoxy substituent, **4c-Bu** and **4d-Bu** (entries 9−10), were then tested. The best enantioselectivity in the whole series was found for ligand **4c-Bu** (72% *ee*), but a prolonged reaction time was required to achieve good conversion. It is worth noting that longer reaction times did not result in better conversions, while slight drops in the enantiomeric purity of the resulting alcohol were observed.

The influence of the catalyst precursor, the ligand stoichiometry, and the reaction temperature were also studied. The use of another ruthenium arene complex, the (benzene)-ruthenium(II) chloride dimer in combination with ligand **4c-Me**, resulted in a large decrease in the enantiomeric excess and in a faster reaction rate (96% conversion after 1 h 15 min and 29% *ee*). Such an increase in reactivity, accompanied by a decrease in enantioselectivity, with decreasing steric bulk in the arene has been observed in other systems.[5e,7i] We also found that the use of 2 equivalents of ligand per ruthenium atom was necessary to maintain high selectivity.

For the best ligands (**4c-Me** and **4c-Bu**), we tried an alternative reaction procedure[7e] in which the chiral catalyst was prepared simply by stirring the $[RuCl_2(p\text{-cymene})]_2$ precursor with the chiral ligand at room temperature. This catalyst solution was then transferred to the solution of the ketone and KOH in 2-propanol. With this methodology, better results were obtained, as shown in Table 2. We also investigated the effect of the temperature on the turnover and stereoselectivity of the reaction under these conditions. As the temperature was reduced from room temperature to 0 °C, the turnover of the system decreased, but the enantioselectivity improved slightly (entries 3 and 4).

Table 2.

Entry[a]	Ligand	*T* (°C)	Time (h)	Conversion (%)[b]	*ee* (%)[b]	Configuration
1	**4c-Me**	25	2.0	97	70	*S*
2	**4c-Bu**	25	3.5	92	73	*S*
3	**4c-Me**	0	6.0	53	74	*S*
4	**4c-Bu**	0	17.0	93	76	*S*

[a] The reaction was carried out by Procedure 2 in the Exp. Sect. [b] Determined by chiral GC analysis.

To investigate the scope of the transfer hydrogenation system presented above, ketones other than acetophenone were subjected to reduction in the presence of ligands **4c-Me** and **4c-Bu**. The results are presented in Table 3.

The enantioselectivity outcome of the reaction was significantly influenced by the electronic and steric properties of the substrate. Aliphatic ketones were not reactive under these reaction conditions.

Conclusions

In summary, we have developed a new family of modular amino alcohol ligands and we have analyzed the influence of the different fragments constituting the ligand molecules on catalytic efficiency and enantioselectivity. In this way, enantiomeric ratios of up to 88:12 have been attained. Future work along these lines will involve the systematic variation of the main chain substituent. The information gained in these investigations into the optimization of the primary alcohol protecting group and the nitrogen substituent should contribute to the identification of fully optimized ligands for ruthenium-catalyzed transfer hydrogenation.

Experimental Section

General Remarks: Optical rotations were measured at room temperature on a Perkin−Elmer 241MC automatic polarimeter (concentration in g/100 mL). Melting points were determined on a Gallenkamp apparatus and have not been corrected. Infrared spectra were recorded on a Nicolet 510FT-IR instrument, by NaCl film or KBr pellet techniques. NMR spectra were acquired on Varian XL 200 or Varian Unity 300 instruments. ^{1}H NMR were obtained at 200 or 300 MHz (s = singlet, d = doublet, t = triplet, dt = double triplet, m = multiplet, and b = broad) ^{13}C NMR were obtained at 50.3 MHz or 75.4 MHz. ^{1}H chemical shifts are quoted relative to TMS, and ^{13}C shifts relative to solvent signals. Carbon multiplicities were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. High-resolution mass spectra (CI) were measured by the Servicio de Espectrometría de Masas de la Universidad de Santiago de Compostela. Chromatographic separations were carried out on NEt_3-pretreated (2.5% v/v) SiO_2 (70−230 mesh) and by elution with hexane/ethyl acetate mixtures of increasing polarity. *i*PrOH was distilled over magnesium under nitrogen

Table 3. Asymmetric Transfer of Aromatic Ketones

Ketone[a]	Ligand	*T* (°C)	Time (h)	Conversion (%)[b]	*ee* (%)[b]	Configuration
1-(3-Methoxyphenyl)ethanone (**6b**)	**4c-Bu**	25	2.25	96	72	*S*
6b	**4c-Me**	25	4.0	97	58	*S*
1-(4-Chlorophenyl)ethanone (**6c**)	**4c-Bu**	0	17.0	79	53	*S*
1-(2-Methoxyphenyl)ethanone (**6d**)	**4c-Me**	25	4.0	99	46	*S*
1-Phenylpropan-1-one (**6e**)	**4c-Bu**	0	17.0	73	57	*S*
1,2,3,4-Tetrahydronaphthalen-1-one (**6f**)	**4c-Me**	25	4.0	59	74	*S*

[a] The reaction was carried out by Procedure 2 in the Exp. Sect. [b] Determined by chiral GC analysis.

prior to use. Catalytic reactions were performed under nitrogen by standard Schlenk techniques. (2*S*,3*S*)-2,3-Epoxy-3-phenylpropanol (**1**) was prepared by the procedure described by Sharpless et al.;[8a] epoxy ethers **2a**−**d** were prepared by the procedure described by Vidal−Ferran et al.,[9b] and β-amino alcohols **3a**−**d** were prepared by the procedure described by Puigjaner et al.[9a]

(1*R*,2*R*)-3-Methoxy-1-methylamino-1-phenylpropan-2-ol (4a-Me): A solution of epoxide **2a** (80 mg, 0.49 mmol), $Yb(OTf)_3$ (60 mg, 0.1 mmol), and $MeNH_2$ (1.7 mL of a 40% solution in water, 20.1 mmol) in MeOH (2 mL) was stirred at 65 °C in a sealed tube for 1 h 30 min. H_2O (2 mL) was added, and the reaction mixture was extracted with dichloromethane. The combined organic extracts were dried and concentrated in vacuo to give 90 mg of an oil that was chromatographed through a SiO_2 column with hexane/EtOAc (90:10) as eluent to give 60 mg (60%) of **4a-Me** as a white solid: M.p. 52−53 °C. $[\alpha]_D^{20} = -75$ (c = 0.76 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 2.6 (br. s, 2 H, NH + OH), 3.24 (m, 2 H), 3.29 (s, 3 H), 3.76 (d, J = 4.8 Hz, 1 H), 3.97 (m, 1 H), 7.2−7.4 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.2 (CH_3), 59.0 (CH_3), 67.0 (CH), 72.0 (CH), 73.6 (CH_2), 127.4 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 139.0 (C) ppm. IR (film): $\tilde{\nu}$ = 2896, 1456, 1128, 1076, 960, 702 cm^{-1}. MS (CI, NH_3): m/z = 196 (100) [$C_{11}H_{17}NO_2 \cdot H^+$]. HRMS (CI, CH_4) for $C_{11}H_{18}NO_2$ [M + H^+] 196.1337 found 196.1336.

(1*R*,2*R*)-1-Methylamino-1-phenyl-3-(phenylmethoxy)propan-2-ol (4b-Me): Epoxide **2b** (40 mg, 0.16 mmol), $Yb(OTf)_3$ (20 mg, 0.03 mmol), and $MeNH_2$ (0.52 mL of a 40% solution in water, 6.2 mmol) in MeOH (0.6 mL) were stirred at 60 °C in a sealed tube for 3 h 45 min. After workup as described for **4a-Me**, 33 mg (73%) of **4b-Me** were obtained as a white solid: M.p. 55 °C. $[\alpha]_D^{20} = -50.5$ (c = 1.5 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 2.4−2.6 (m, 2 H, NH + OH), 3.36 (d, J = 5.2 Hz, 2 H), 3.75 (d, J = 4.8 Hz, 1 H), 4.02 (dd, J = 5.0, 5 Hz, 1 H), 4.44 (s, 2 H), 7.1−7.4 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.2 (CH_3), 66.9 (CH), 71.4 (CH_2), 72.0 (CH), 73.4 (CH_2), 127.4 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.4 (CH), 137.9 (C), 138.8 (C) ppm. IR (film): $\tilde{\nu}$ = 3029, 2861, 1495, 1454, 1092, 1028, 737, 700 cm^{-1}. MS (CI, NH_3): m/z = 272 (100) [$C_{17}H_{21}NO_2 \cdot H^+$]. HRMS (CI, CH_4) for $C_{17}H_{22}NO_2$ [M + H^+] 272.1650 found 272.1648.

(1*R*,2*R*)-3-(Diphenylmethoxy)-1-methylamino-1-phenylpropan-2-ol (4c-Me): Epoxide **2c** (0.2 g, 0.63 mmol), $Yb(OTf)_3$ (59 mg, 0.09 mmol), and $MeNH_2$ (1.85 mL of a 40% solution in water, 21.4 mmol) in MeOH (2.5 mL) were stirred at 60 °C in a sealed tube for 17 h. After workup as described for **4a-Me**, 0.15 g (71%) of **4c-Me** were obtained as a white solid: M.p. 108−110 °C. $[\alpha]_D^{20} = -45.5$ (c = 1.1 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 2.4−2.6 (br. m, 2 H, NH + OH), 3.35 (d, J = 5.0 Hz, 2 H), 3.76 (d, J = 4.4 Hz 1 H), 4−4.2 (m, 1 H), 5.25 (s, 1 H), 7−7.4 (m, 15 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.5 (CH_3), 67.1 (CH), 70.3 (CH_2), 72.4 (CH), 84.2 (CH), 126.8 (CH), 126.9 (CH), 127.3 (CH), 127.4 (CH), 127.5 (CH), 127.8 (CH), 128.3 (CH), 128.4 (CH), 139.2 (C) 141.8 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3083, 2903, 1493, 1452, 1184, 1030, 600 cm^{-1}. MS (CI, NH_3): m/z = 348 (30) [$C_{23}H_{25}NO_2 \cdot H^+$], 347 (100) [$C_{23}H_{25}NO_2{}^+$]. HRMS (CI, CH_4) for $C_{23}H_{26}NO_2$ [M + H^+] 348.1963 found 348.1951.

(1*R*,2*R*)-1-Methylamino-1-phenyl-3-(triphenylmethoxy)propan-2-ol (4d-Me): Epoxide **2d** (0.1 g, 0.25 mmol), $Yb(OTf)_3$ (30 mg, 0.05 mmol), and $MeNH_2$ (0.82 mL of a 40% solution in water, 9.5 mmol) in MeOH (1 mL) were stirred at 65 °C in a sealed tube for 5 h 30 min. After workup as described for **4a-Me**, 0.10 g (87%) of **4d-Me** were obtained as a colorless oil: $[\alpha]_D^{20} = -35$ (c = 2.8 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 2.2−2.4 (br. m, 2 H, NH + OH), 2.9−3.1 (m, 2 H), 3.79 (d, J = 4.8 Hz, 1 H), 3.91 (q, J = 4.8 Hz, 1 H), 7−7.6 (m, 20 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.5 (CH_3), 64.4 (CH_2), 67.3 (CH), 72.5 (CH), 126.9 (CH), 127.1 (CH), 127.4 (CH), 127.6 (CH), 127.7 (CH), 128.0 (CH), 128.1 (CH), 128.5 (CH), 139 (C), 143.7 (C) ppm. IR (film): $\tilde{\nu}$ = 3060, 2932, 1597, 1491, 1221, 908, 648 cm^{-1}. MS (CI, NH_3): m/z = 424 (100) [$C_{29}H_{29}NO_2 \cdot H^+$]. HRMS (CI, CH_4) for $C_{29}H_{30}NO_2$ [M + H^+] 424.2276 found 424.2269.

(1*R*,2*R*)-1-Butylamino-3-(diphenylmethoxy)-1-phenylpropan-2-ol (4c-Bu): A mixture of amino alcohol **3c** (0.2 g, 0.6 mmol), iodobutane (0.22 g, 1.2 mmol), K_2CO_3 (0.17 g, 1.24 mmol), and absolute ethanol (5.5 mL) was heated at 80 °C for 23 h under N_2. The reaction mixture was allowed to cool to room temperature and filtered, and the precipitate was washed with ethanol. The solution was concentrated under reduced pressure, and the residue was purified by column chromatography to afford 29 mg (11%) of (1*R*,2*R*)-1-dibutylamino-3-(diphenylmethoxy)-1-phenylpropan-2-ol and 0.19 g (81%) of **4c-Bu** as an oil: $[\alpha]_D^{20} = -38.9$ (c = 1.7 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.0 Hz, 3 H), 1.2−1.6 (m, 4 H), 2.3−2.6 (m, 2 H), 2.6−2.8 (br. m, 2 H, NH + OH), 3.33 (m, 2 H), 3.89 (d, J = 4.8 Hz, 1 H), 3.98 (dd, J = 4.4, 4.4 Hz, 1 H), 5.24 (s, 1 H), 7−7.4 (m, 15 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0 (CH_3), 20.4 (CH_2), 32.4 (CH_2), 47.2 (CH_2), 65.4 (CH), 70.4 (CH_2), 72.3 (CH), 84.3 (CH), 126.7 (CH), 126.8 (CH), 127.1 (CH), 127.3 (CH), 127.4 (CH), 127.6 (CH), 128.2 (CH), 128.3 (CH), 139.8 (C), 141.8 (C) ppm. IR (film): $\tilde{\nu}$ = 3062, 2871, 1653, 1186, 1030, 742 cm^{-1}. MS (EI): m/z = 162 (100) [$C_{11}H_{16}N^+$]. HRMS (CI, CH_4) for $C_{26}H_{32}NO_2$ [M + H^+] 390.2433 found 390.2430.

(1*R*,2*R*)-1-Butylamino-1-phenyl-3-(triphenylmethoxy)propan-2-ol (4d-Bu): A mixture of amino alcohol **3d** (70 mg, 0.17 mmol), iodobutane (0.11 g, 0.6 mmol), K_2CO_3 (50 mg, 0.36 mmol), and absolute ethanol (1.5 mL) was heated at 80 °C for 23 h under N_2 and treated as described for **4c-Bu** to afford, after purification by column chromatography, 12 mg (17%) of starting material and 40 mg (61%) of **4d-Bu** as an oil: $[\alpha]_D^{20} = -20.4$ (c = 1.7 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.9 (t, J = 7.0 Hz, 3 H), 1.2−1.6 (m, 4 H), 2.3−2.6 (m, 2 H), 2.85 (dd, J = 4, 9.6 Hz, 1 H), 3.12 (dd, J = 4, 9.7 Hz, 1 H), 3.85 (q, J = 4.6 Hz, 1 H), 3.92 (d, J = 4.8 Hz, 1 H), 7−7.6 (m, 20 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 20.5 (CH_2), 32.5 (CH_2), 47.4 (CH_2), 64.5 (CH_2), 65.8 (CH), 72.4 (CH), 86.9 (C), 126.9 (CH), 127.0 (CH), 127.8 (CH), 128.2 (CH), 128.6 (CH), 139.7 (C), 143.8 (C) ppm. IR (film): $\tilde{\nu}$ = 3060, 2929, 1491, 1449, 1072, 744, 702, 632 cm^{-1}. MS (EI): m/z = 162 (100) [$C_{11}H_{16}N^+$]. HRMS (CI, CH_4) for $C_{32}H_{36}NO_2$ [M + H^+] 466.2746 found 466.2741.

General Procedure for Transfer Hydrogenation of Aromatic Ketones. Procedure 1: The appropriate amount of ligand (0.04 mmol) was added to the catalyst precursor [Ru(*p*-cymene)Cl_2]$_2$ (0.01 mmol) (Ru atom/Ligand = 1:2) in 1.5 mL of 2-propanol and stirred at 80 °C for 30 min under nitrogen. After the mixture had cooled to room temperature, a solution of ketone in dry, degassed 2-propanol (0.5 M, 0.6 mL, 0.3 mmol) was added, followed by KOH (0.08 M in *i*PrOH, 0.9 mL). The resulting mixture was stirred at the temperature specified and time indicated in Table 1. The reaction was quenched by the addition of 3 drops of a 1 M HCl solution, and concentrated in vacuo. The residue was diluted with dichloromethane and the organic solution was washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pres-

sure. The enantiomeric excesses were determined from the crude mixture by GC analysis.

Procedure 2: Amino alcohol (0.04 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (0.01 mmol) were dissolved in 1.5 mL of 2-propanol. Stirring under nitrogen at room temperature for 40 min generated the precatalyst. The substrate (0.3 mmol) was dissolved in 0.6 mL of 2-propanol, and the base (0.9 mL of a 0.08 M in *i*PrOH) was added. The resulting mixture was stirred for 5 min. The light brown solution of the precatalyst was transferred to this solution by cannula, and the mixture was stirred at the temperature specified and the time indicated in Table 2 or 3. The workup was identical to that described for Procedure 1. The enantiomeric excesses were determined from the crude mixture by GC analysis.

Conditions of the GC analyses: β-DEX 120, 30m length, 0.25 mm internal diameter, isotherm temperature program, He as carrier gas (2.4 mL/min). For 1-phenylethanol: β-DEX 120, 100 °C, t_R (*R* isomer) = 52.1 min, t_R (*S* isomer) = 55.7 min. For 1-(3-methoxyphenyl)ethanol: β-DEX 120, 122 °C, t_R (*R* isomer) = 78.4 min, t_R (*S* isomer) = 82.3 min. For 1-(4-chlorophenyl)ethanol: β-DEX 120, 125 °C, t_R (*R* isomer) = 60.6 min, t_R (*S* isomer) = 65.8 min. For 1-(2-methoxyphenyl)ethanol: β-DEX 120, 122 °C, t_R (*S* isomer) = 58.6 min, t_R (*R* isomer) = 64.0 min. For 1-phenylpropan-1-ol: β-DEX 120, 112 °C, t_R (*R* isomer) = 47.4 min, t_R (*S* isomer) = 49.1 min. For 1,2,3,4-tetrahydronaphthol: β-DEX 120, 125 °C, t_R (*S* isomer) = 89.2 min, t_R (*R* isomer) = 93.3 min.

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[10] The enantiomeric purity of this epoxy alcohol, as checked by optical rotation ($[\alpha]_D^{20} = -50.9$, (c = 1.0, $CHCl_3$), ref.[8a] $[\alpha]_D^{20} = -51.0$, c = 1.1, $CHCl_3$) and by GC (β-DEX), was >99.9%.

[11] When (1*R*,2*R*)-1-cyclohexylamino-1-phenyl-3-(triphenylmethoxy)propan-2-ol and (1*R*,2*R*)-1-benzhydrylamino-1-phenyl-3-(triphenylmethoxy)propan-2-ol were used as ligands in the transfer hydrogenation process for acetophenone with $[RuCl_2(p\text{-benzene})]_2$, the degrees of conversion were 5% and 14%, respectively, after 19 h reaction time.

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