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Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation Using Unsymmetrical Vicinal Diamine-Based Ligands: Dramatic Substituent Effect on Catalyst Efficiency

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The use of unsymmetrical vicinal diamines as ligands for Ru-catalyzed asymmetric transfer hydrogenation is described. With a SmI_2-mediated cross-coupling protocol, a series of enantiomerically pure unsymmetrical vicinal diamines were readily prepared and examined in the asymmetric transfer hydrogenation. It was found that an aromatic substituent on the carbon bearing the –NHTs group and a bulky alkyl substituent on the other side, are both very important for the effectiveness of the ligand, suggesting that the substituent has a dramatic effect on the catalyst efficiency. With ligand **8**, excellent enantioselectivities that are comparable to *N*-tosyl-1,2-diphenylethane-1,2-diamine (TsDPEN) were achieved. The results provide some helpful information on the mechanism of Ru-catalyzed asymmetric transfer hydrogenation.

Introduction

Asymmetric transfer hydrogenation (ATH) of ketones, as an excellent method for the synthesis of enantiomerically pure alcohols, has attracted increasing attention in the last decade due to its great potential for applications in the fine chemicals, pharmaceuticals, and agrochemical industries and in new materials.[1] Of the ATH catalysts reported within the last decade, the most widely used ligands are those based on 1,2-amino alcohols, such as *cis*-aminoindanol **1**,[2] and monosulfonylated vicinal diamines, such as *N*-tosyl-1,2-diaminocyclohexane (TsDAC; **2**),[3] and *N*-tosyl-1,2-diphenylethane-1,2-diamine (TsDPEN; **3**).[4] In particular, TsDPEN-coordinated Ru^{II} complex (Ru-TsDPEN), which was first reported by Noyori and Ikariya in 1995,[4a] has become the catalyst of choice because of its excellent catalytic activity and easy accessibility (Figure 1).

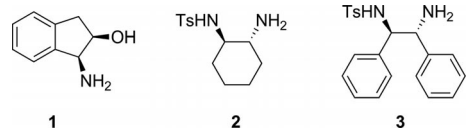

Figure 1. The most widely used ligands in ATH.

To understand the Ru-TsDPEN catalyzed hydrogen transfer process, Noyori and co-workers proposed a concerted pathway for the reduction of ketones in 2-propanol (Figure 2) that involved a concerted transfer of the protonic hydrogen on the NH_2 moiety and hydridic hydrogen on Ru-H from **4** to the substrate in a cyclic six-membered transition state to give the alcohol product and **4b**.[1a,4,5]

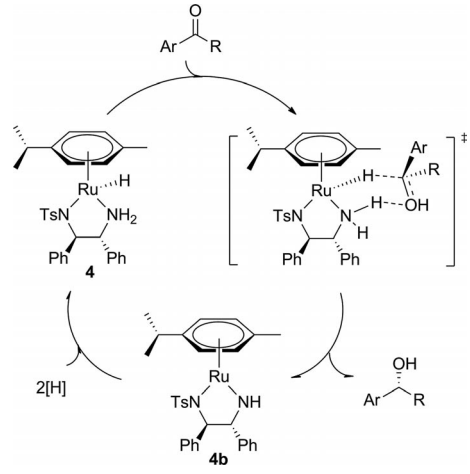

Figure 2. Proposed catalytic cycles.

This concerted mechanism was also supported by kinetic isotope effect studies from Casey's group,[6] which demonstrated a reversible, concurrent hydride and proton transfer from 2-propanol to the 16-electron species shown in Figure 1. The tosyl group at the diamine N-terminus was crucial for the reactivity; complexes with the CF_3SO_2, C_6H_5CO, and CH_3CO groups were much less reactive.[1a]

In our earlier work,[7] we documented a successful asymmetric synthesis of symmetrical and unsymmetrical vicinal

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diamines using a samarium diiodide-induced coupling protocol. Excellent enantioselectivities as well as high diastereoselectivities were achieved in both reactions. With symmetrical 1,2-bis(3,5-di-*tert*-butylphenyl)ethylenediamine, we recently discovered a new diamine ligand TsDBuPEN for the asymmetric transfer hydrogenation of 2-acylarylcarboxylates[8] that enables efficient access to a wide variety of 3-substituted phthalides in enantiomerically pure form. In 2004, Wills and co-workers[9] synthesized three derivatives of TsDPEN (**5**, **6**, and **7**) that contain, respectively, a *syn*-orientation between the phenyl groups, and a deleted phenyl group relative to TsDPEN **3**. They found that both disubstitution and the *anti* arrangement of substituents on the ligands were very important. However, the question of how the different kinds of substituent groups, as well as the chiral environments of the vicinal diamine ligand, affect the catalyst reactivity and enantioselectivity remains unanswered.

Considering the ready availability of a range of enantiomerically pure unsymmetrical vicinal diamines and their utility in asymmetric catalysis, we therefore wished to investigate whether the differences in the substituent on the carbon bearing the $-NH_2$/–NHTs group in the diamine was critical to its effectiveness as a ligand in asymmetric transfer hydrogenation. Towards this goal, we wanted to prepare compounds **8** and **9**, in which one phenyl group of TsDPEN is replaced with an isopropyl group (Figure 3).

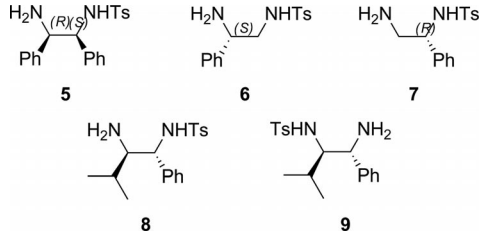
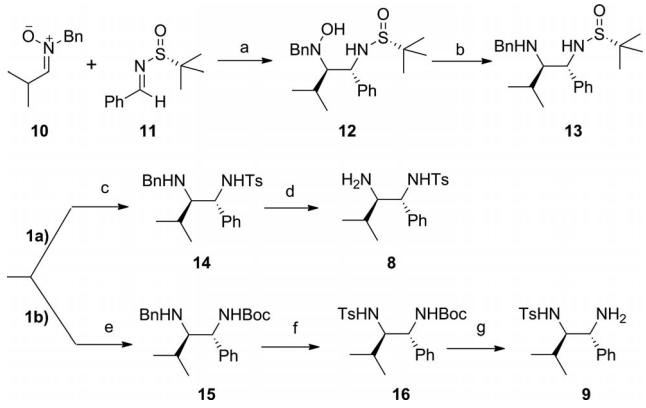


Figure 3. TsDPEN derivatives.

Results and Discussion

Following our reported procedure, the key intermediate **12** was easily prepared (Scheme 1). A solution of nitrone **10** and *N*-*tert*-butanesulfinyl imine **11** in tetrahydrofuran (THF) at –78 °C was treated with 3 equiv. of SmI_2 in the presence of 2 equiv. of *tert*-butyl alcohol to give **12** as the sole diastereomer in 75% yield.

Conversion of the cross-coupling product into the corresponding free diamine could be accomplished in a three-step reaction sequence. As shown in Scheme 1 (a), deoxygenation of the hydroxylamino function of the coupling product **12** by Zn/$Cu(OAc)_2$, followed by removal of the sulfinyl group and subsequent tosylation, gave **14**. Ligand **8** was finally obtained after removal of the benzyl group. The approach that was designed for the synthesis of ligand **9** is outlined in Scheme 1 (b). The sulfinyl group of **13** was removed to release the free amine, which was then protected by a Boc group. Debenzylation of **15** followed by tosylation

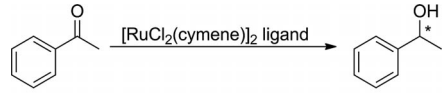


Scheme 1. *Reagents and conditions*: (a) SmI_2, *t*BuOH, THF, –78 °C, 75%; (b) Zn, $Cu(OAc)_2$, HOAc, 70 °C, 86%; (c) (1) HCl, MeOH; (2) TsCl, TEA, CH_2Cl_2, 95% for two steps; (d) H_2, $Pd(OH)_2$/C, 82%; (e) (1) HCl, MeOH; (2) $(Boc)_2O$, TEA, 82% for two steps; (f) (1) H_2, $Pd(OH)_2$/C; (2) TsCl, TEA, CH_2Cl_2, 76% for two steps; (g) CF_3COOH, CH_2Cl_2, 91%.

resulted in the formation of tosylate **16**, which underwent hydrolysis mediated by CF_3COOH to give the expected ligand **9**.

With ligands **8** and **9** in hand, we turned our attention to their applications in the asymmetric transfer hydrogenation of acetophenone. The reduction was carried out in 2-propanol, formic acid–triethylamine (TEA) azeotrope, and aqueous sodium formate (Table 1). As expected, both ligands **8** and **9** formed Ru-coordinated complexes that could be used as catalysts for the asymmetric transfer hydrogenation of acetophenone. When the two were compared, use of the complex with ligand **8** led to higher reactivity and gave

Table 1. Ru-Catalyzed ATH of acetophenone using ligand **3**, **8**, or **9**.[a]



Entry	L	Hydrogen donors	*T* [°C]	*t* [h]	Conv. [%][b]	*ee* [%][c]
1	**3**	*i*PrOH	28	10	98	97
2	**3**	HCOONa/H_2O	40	2	>99	94
3	**3**	HCOOH/TEA	28	20	99	98
4	**8**	*i*PrOH	40	40	83	82
5	**8**	HCOONa/H_2O	room temp.	12	83	70
6	**8**	HCOONa/H_2O	40	6	99	86
7	**8**	HCOONa/H_2O	50	2	98	83
8	**8**	HCOOH/TEA	room temp.	40	95	97
9	**8**	HCOOH/TEA	20	65	73	96
10	**8**	HCOOH/TEA	40	20	95	98
11	**9**	HCOONa/H_2O	28	20	56	65
12	**9**	HCOONa/H_2O	40	12	95	70
13	**9**	HCOOH/TEA	room temp.	40	–	–
14	**9**	HCOOH/TEA	40	7 d	trace	–

[a] Substrate/catalyst ratio: 100:1; the reaction was conducted on a 1.0 mmol scale, $[RuCl_2(cymene)]_2$ (0.005 mmol) and ligand (0.012 mmol) were added to the system. [b] Determined by ^1H NMR analysis. [c] Determined by HPLC on a Chiralcel OB-H column.

better enantioselectivity in aqueous sodium formate (Table 1, entries 6 vs. 12). The best result was obtained using **8** as ligand when the reaction was performed in formic acid–triethylamine (5:2) azeotrope at 40 °C (98% *ee*, Table 1, entry 10). In this case, the reactivity and enantioselectivity was comparable to that obtained using TsDPEN as ligand (Table 1, entry 3). However, when **9** was employed under the same reaction conditions, only a trace amount of product were observed, even when the reaction was allowed to proceed for 7 days at 40 °C (Table 1, entry 14).

These results indicate that changing the substituent on the carbon bearing the NH_2/NHTs group in ligands **8** and **9** resulted in a significant difference in catalyst reactivity and enantioselectivity. In comparison to TsDPEN, changing the substitution on the carbon bearing the $–NH_2$ group in ligand **8** did not cause much difference in enantioselectivity. In contrast, ligand **9** became less effective when the substitution on the carbon bearing the –NHTs group was changed to an aliphatic isopropyl group, suggesting the importance of an aromatic substituent at this position.

To further clarify the differences between ligand **8** and **9**, we then investigated the processes involved in coordination of the two ligands. At first, a coordination control experiment between TsDPEN and $[RuCl_2(cymene)]_2$ was carried out and monitored by ^1H NMR spectroscopy. The spectra had almost no change from 10 min to 6 h, with the coordinated complex and the free TsDPEN coexisting in a defined proportion. Similar spectra were observed when ligand **8** was mixed with $[RuCl_2(cymene)]_2$. To our surprise, ligand **9** coordinated with ruthenium completely in less than 10 min.[10] According to the different catalytic performances found in asymmetric transfer hydrogenations, we realized that the ligand (e. g. TsDPEN or **8**) did not react smoothly with $[RuCl_2(cymene)]_2$ but displayed higher catalytic activity and enantioselectivity in the reduction. Despite rapid complexation of the less effective ligand **9**, it is likely that the resulting complex was either relatively inactive, or difficult to convert into a more active form that was more capable of catalyzing the reaction. To better understand this catalytic difference as well as the reaction mechanism, we wished to compare the X-ray structures of ligands **8** and **9** as Ru complexes. After many trials, the Ru-**8** complex was obtained successfully (Figure 4),[11] however, we were unable to generate a suitable single crystal of the Ru-**9** complex. Not surprisingly, the crystal data of Ru-**8** was found to be similar to that of Ru-TsDPEN,[12] showing very similar bond lengths and bond angles.[13]

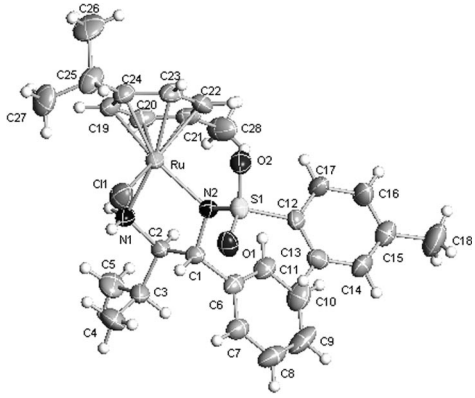


Figure 4. X-ray structure of the Ru-**8** complex.

To gain more information on the effect of the substituent, we designed and synthesized several new ligands **19**–**22** (Figure 5), in which the steric and electronic properties were

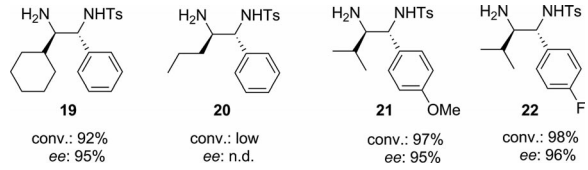
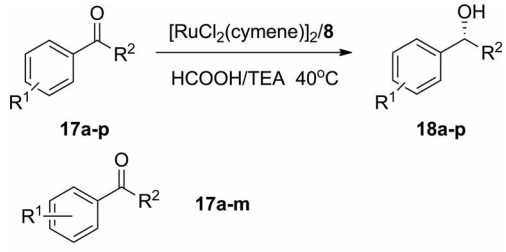
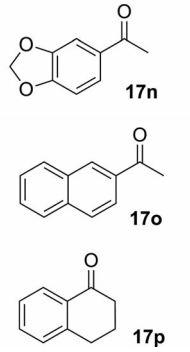


Figure 5. Ligands with modified substituents for ATH.

Table 2. Asymmetric transfer hydrogenation of aromatic ketones catalyzed by Ru-**8** complex.[a]



a: R^1 = H; R^2 = CH_3
b: R^1 = *p*-CH_3; R^2 = CH_3
c: R^1 = *p*-OCH_3; R^2 = CH_3
d: R^1 = *p*-CF_3; R^2 = CH_3
e: R^1 = *p*-Cl; R^2 = CH_3
f: R^1 = *p*-F; R^2 = CH_3
g: R^1 = *p*-Br; R^2 = CH_3
h: R^1 = *o*-OCH_3; R^2 = CH_3
i: R^1 = *o*-Cl; R^2 = CH_3
j: R^1 = *o*-F; R^2 = CH_3
k: R^1 = *m*-CH_3; R^2 = CH_3
l: R^1 = *m*-Cl; R^2 = CH_3
m: R^1 = H; R^2 = CH_2CH_3



Entry	Substrate	*t* [h]	Conv. [%][b]	*ee* [%] of **18**[c]
1	**17a**	20	95	98
2	**17b**	48	96	95
3	**17c**	96	63	92
4	**17d**	14	95	91
5	**17e**	30	90	95
6	**17f**	20	95	94
7	**17g**	20	99	91
8	**17h**	96	42	85
9	**17i**	36	98	87
10	**17j**	28	95	91
11	**17k**	48	98	94
12	**17l**	22	99	91
13	**17m**	36	49	90
14	**17n**	48	93	91
15	**17o**	22	99	93
16	**17p**	48	95	97

[a] Substrate/catalyst ratio: 100:1; the reaction was conducted on a 1.0 mmol scale, $[RuCl_2(cymene)]_2$ (0.005 mmol), Ligand **8** (0.012 mmol), HCOOH/Et_3N (5:2, 1.5 mL) were added to the system. [b] Determined by ^1H NMR analysis. [c] Determined by HPLC on a Chiralcel OD-H, OB-H, or OJ-H column.

considered. With these ligands, the catalytic transfer hydrogenation of acetophenone was carried out with sodium formate and TEA. As shown in Figure 5, ligand **20**, which contains a linear propyl group instead of a bulky isopropyl group, was inefficient in the reaction, with very low conversion being observed; the other ligands showed comparable reactivities and enantioselectivities to that of ligand **8**. As can be seen, whereas the electronic properties of the aryl substitution had nearly no influence on either the reactivity or enantioselectivity, a bulky alkyl group on the carbon bearing $-NH_2$ was important for the reaction. In general, ligand **8** was thus a better choice for asymmetric transfer hydrogenation of acetophenone.

With the identification of the optimal reaction conditions and ligand, the generality of the reaction was investigated (Table 2). In most cases, the products were obtained in high conversions and with good to excellent enantioselectivities. The *para*- and *meta*-substituted acetophenones gave products with 91–95% *ee* (Table 2, entries 2–7 and 11–13), which were comparable to results obtained by the group of Noyori. For the challenging *ortho*-substituted ketones, a slight decrease in the enantioselectivities were observed (85–91% *ee*) (Table 2, entries 8–10). The reduction of 3,4-methylenedioxyacetophenone, 1′-acetonaphthone, and α-tetralone also afforded the chiral alcohol products in excellent enantiomeric purities (91–97% *ee*) (Table 2, entries 14–16).

Conclusions

We have explored the use of unsymmetrical, vicinal diamine-based ligands in ruthenium-catalyzed asymmetric transfer hydrogenation and realized that **8** could be a suitable ligand; the use of this ligand as a complex with ruthenium leads to the desired alcohol products with good to excellent enantioselectivities (85–98% *ee*). It was found that the presence of an aromatic substituent on the carbon bearing the –NHTs group, and a bulky alkyl substituent on the other side, are both very important for the effectiveness of the ligand, suggesting a dramatic effect of the substituent on catalyst efficiency. These results might provide some helpful information for future ligand design. Further studies to gain a better understanding on the role of ligand substituents in asymmetric transfer hydrogenation are under investigation.

Experimental Section

General Remarks: All anaerobic and moisture-sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or argon. NMR spectra were recorded with a Varian or Bruker spectrometer (300 or 400 MHz for ^1H, and 75 or 100 MHz for ^{13}C). Chemical shifts are reported in δ units (ppm) referenced to internal $SiMe_4$ for ^1H NMR and $CDCl_3$ (δ = 77.00 ppm) for ^{13}C NMR spectroscopy. Optical rotations were measured with a JASCO P1-030 polarimeter.

General Procedure for the Cross-Coupling of Nitrones with *N*-*tert*-Butylsulfinyl Imines:[7a] Under argon, to a 10 mL Schlenk flask charged with Sm metal powder (230 mg, 1.5 mmol), was added diiodomethane (0.081 mL, 1.0 mmol) in freshly distilled THF (5 mL) at room temperature using a syringe. After approximately 5 min, the solution turned deep-blue, indicating the formation of samarium diiodide. The mixture was stirred at room temperature for 1 h and then cooled to –78 °C. A mixture of *tert*-butyl alcohol (1.0 mmol), nitrone (0.7 mmol), and chiral *N*-*tert*-butylsulfinyl imine (0.5 mmol) in THF (6 mL) was then added dropwise. The reaction was monitored by TLC and quenched by addition of saturated aqueous $Na_2S_2O_3$ (5 mL). Extraction with ethyl acetate and purification by flash column chromatography afforded the desired product.

Coupling Product 12: M.p. 122–124 °C. $[\alpha]_D^{20}$ = –142.6 (*c* = 1.05, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.56 (d, *J* = 5.4 Hz, 3 H), 1.17 (m, 12 H), 2.30 (m, 1 H), 2.82 (dd, *J* = 10.2, 1.2 Hz, 1 H), 3.93 (d, *J* = 13.8 Hz, 1 H), 4.29 (d, *J* = 13.4 Hz, 1 H), 4.59 (d, *J* = 10.2 Hz, 1 H), 5.68 (s, 1 H), 6.64 (s, 1 H), 7.24–7.34 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.48, 22.14, 22.44, 26.01, 55.16, 57.06, 60.87, 72.25, 127.22, 127.67, 128.17, 128.31, 128.91, 129.12, 138.23, 141.15 ppm. FTIR (KBr): $\tilde{\nu}$ = 3580, 3223, 3062, 3034, 2965, 1475, 1031, 1010, 702 cm^{-1}. MS (EI): *m*/*z* (%) = 331 (5.71) [$M^+ - C_4H_9$], 313 (0.59) [$M^+ - C_4H_9 - H_2O$], 179 (12.75), 178 (100.00), 162 (5.92), 106 (8.67), 92 (8.39), 91 (97.72), 57 (8.14). HRMS: calcd. for $C_{22}H_{32}N_2O_2S$ 389.2257; found 389.2295.

General Procedure for the Preparation of Chiral Diamine Ligands 8 and 19–22: Under argon, to a 25 mL flask charged with AcOH (1 mL) was added $Cu(OAc)_2$ (9 mg, 0.05 mmol) and zinc powder (162 mg, 2.5 mmol). The mixture was stirred for 15 min, followed by the addition of a mixture of AcOH (1 mL) and distilled water (0.35 mL) containing the obtained cross-coupling product (0.5 mmol). The resulting mixture was heated to 70 °C and stirred for 1 h. After cooling to room temperature, the reacting system was mixed with EDTA-2Na (0.5 g) and stirred for 10 min. 3 N aqueous KOH solution was then added until the mixture reached pH 10. The resulting solution was extracted with ethyl acetate, and the combined organic layer was successively washed with saturated aqueous EDTA-2Na and brine. Purification by flash column chromatography afforded the deoxygenation product **13** as a white solid in quantitative yield.

The obtained deoxygenation product **13** (1.0 mmol) was dissolved in methanol (2.0 mL), to which was added 4 N HCl (2.0 mL) in 1,4-dioxane (8.0 mmol). The mixture was stirred for 30 min at room temperature and then concentrated. The residual acid was removed by concentrating three times with further portions of methanol (5 mL). The resulting solid and triethylamine (5.0 mmol) were dissolved in CH_2Cl_2 (20 mL), and TsCl (1.2 mmol) in CH_2Cl_2 (10 mL) was added dropwise with magnetic stirring. The reaction was monitored by TLC and purified by flash column chromatography to give the monosulfonylated diamine **14** in 95% yield.

The monosulfonylated diamine **14** was dissolved in methanol (5 mL) containing 10% $Pd(OH)_2$/C. The mixture was reacted for 24 h under a H_2 atmosphere (1 atm) then filtered through a pad of Celite. Purification by flash column chromatography afforded the corresponding ligand.

Ligand 8: Yield 82%; m.p. 115–116 °C. $[\alpha]_D^{20}$ = –61.1 (*c* 0.64, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.6 Hz, 3 H), 0.86 (d, *J* = 6.6 Hz, 3 H), 1.32 (br., 2 H), 1.48 (m, 1 H), 2.33 (s, 3 H), 2.60 (t, *J* = 6.0 Hz, 1 H), 4.27 (d, *J* = 6.3 Hz, 1 H), 7.02–7.15 (m, 7 H), 7.45–7.48 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.66, 20.24, 21.33, 28.74, 59.51, 61.91, 126.99, 127.05, 127.08, 128.16, 128.99, 137.93, 139.75, 142.54 ppm. FTIR (film): $\tilde{\nu}$ = 3200, 2962, 2843, 1598, 1456, 1323, 1156, 1093, 1058, 970, 919,

882, 815, 755, 703, 648, 555, 535 cm^{-1}. MS (ESI): *m*/*z* = 333.2 [M^+ + H]. HRMS: calcd. for $C_{18}H_{24}N_2O_2SNa$ [M^+ + Na] 355.1451; found 355.1468.

Ligand 19: Yield 62%; m.p. 86–88 °C. $[\alpha]_D^{21}$ = –55.2 (*c* 0.78, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89–1.13 (m, 6 H), 1.62–1.70 (m, 5 H), 2.33 (s, 3 H), 2.61 (m, 1 H), 4.38 (d, *J* = 6.3 Hz, 1 H), 7.07–7.15 (m, 7 H), 7.49–7.53 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.38, 25.92, 25.98, 26.27, 27.88, 30.25, 38.73, 58.30, 61.45, 126.92, 127.03, 127.06, 128.24, 129.12, 138.11, 140.25, 142.62 ppm. FTIR (film): $\tilde{\nu}$ = 3129, 2928, 2852, 1599, 1495, 1455, 1325, 1155, 1093, 1063, 706, 650, 545 cm^{-1}. MS (ESI): *m*/*z* = 373 [M^+ + H]. HRMS: calcd. for $C_{21}H_{29}N_2O_2S$ [M^+ + H] 373.1944; found 373.1944.

Ligand 20: Yield 88%; m.p. 85–86 °C. $[\alpha]_D^{23}$ = –76.1 (*c* 0.83, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 6.8 Hz, 3 H), 1.10–1.39 (m, 4 H), 2.34 (s, 3 H), 2.87–2.91 (m, 1 H), 4.15 (d, *J* = 4.8 Hz, 1 H), 7.06–7.11 (m, 4 H), 7.15–7.17 (m, 3 H), 7.53 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.83, 19.23, 21.35, 36.35, 56.04, 61.14, 126.80, 126.95, 127.06, 128.19, 129.08, 137.80, 139.93, 142.64 ppm. FTIR (film): $\tilde{\nu}$ = 3300, 2957, 1451, 1343, 1317, 1151, 1093, 1058, 676, 547 cm^{-1}. MS (ESI): *m*/*z* = 333.2 [M^+ + H]. HRMS: calcd. for $C_{18}H_{25}N_2O_2S$[M^+ + H] 333.1631; found 333.1634.

Ligand 21: Yield 75%; m.p. 70–72 °C. $[\alpha]_D^{21}$ = –59.5 (*c* 0.54, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H), 1.48 (m, 1 H), 2.34 (s, 3 H), 2.58 (t, *J* = 6.0 Hz, 1 H), 3.74 (s, 3 H), 4.17 (d, *J* = 6.9 Hz, 1 H), 6.65 (d, *J* = 8.7 Hz, 2 H), 6.95 (d, *J* = 8.7 Hz, 2 H), 7.07 (d, *J* = 7.8 Hz, 2 H), 7.46 (d, *J* = 7.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.24, 20.36, 21.38, 28.51, 55.22, 59.23, 61.78, 113.64, 127.10, 128.26, 129.00, 131.62, 137.99, 142.49, 158.80 ppm. FTIR (film): $\tilde{\nu}$ = 3260, 2962, 1612, 1514, 1438, 1321, 1248, 1161, 1093, 1054, 1034, 812, 678, 560 cm^{-1}. MS (ESI): *m*/*z* = 363.2 [M^+ + H]. HRMS: calcd. for $C_{19}H_{26}N_2O_3SNa$ [M^+ + Na] 385.1556; found 385.1576.

Ligand 22: Yield 63%; m.p. 70–72 °C. $[\alpha]_D^{21}$ = –59.5 (*c* 0.54, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.0 Hz, 3 H), 0.85 (d, *J* = 6.0 Hz, 3 H), 1.48 (m, 1 H), 2.35 (s, 3 H), 2.56 (m, 1 H), 4.22 (d, *J* = 6.3 Hz, 1 H), 6.81 (m, 2 H), 7.02 (m, 2 H), 7.08 (d, *J* = 7.8 Hz, 2 H), 7.46 (d, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.37, 20.31, 21.38, 28.60, 58.91, 61.84, 114.94, 115.16, 127.07, 128.75, 128.83, 129.08, 135.47, 135.51, 137.88, 142.82, 160.75, 163.20 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –110.85 (m) ppm. FTIR (film): $\tilde{\nu}$ = 3344, 3293, 3084, 2965, 1604, 1512, 1324, 1227, 1155, 1091, 1075, 973, 902, 832, 812, 666, 570, 540 cm^{-1}. MS (ESI): *m*/*z* = 351.2 [M^+ + H]. HRMS: calcd. for $C_{18}H_{24}N_2O_2SF$ [M^+ + H] 351.1537; found 351.1553.

General Procedure for the Preparation of Chiral Diamine Ligand 9: The obtained diamine **13** (1.0 mmol) was dissolved in methanol (2.0 mL), to which was added 4 N HCl (2.0 mL) in 1,4-dioxane (8.0 mmol). The mixture was stirred for 30 min at room temperature and then concentrated. The residual acid was removed by concentrating three times with added methanol (5 mL). The resulting solid and triethylamine (3.0 mmol) were dissolved in CH_2Cl_2 (20 mL) and $(Boc)_2O$ (1.5 mmol) was then added slowly with magnetic stirring. The reaction was monitored by TLC and purified by flash column chromatography to give **15** in 82% yield.

The Boc-protected diamine **15** was dissolved in methanol (10 mL) containing 10% $Pd(OH)_2$/C. The mixture was reacted for 24 h under a H_2 atmosphere (1 atm) and was filtered through a pad of Celite. The resulting solid and triethylamine (2.4 mmol) were dissolved in CH_2Cl_2 (20 mL), and TsCl (0.97 mmol) in CH_2Cl_2 (10 mL) was then added dropwise with magnetic stirring. DMAP (5% mmol) was added as catalyst and the progress of the reaction was monitored by TLC. Purification by flash column chromatography gave **16** in 76% yield.

Monosulfonylated diamine **16** (0.25 mmol) was dissolved in CH_2Cl_2 (5 mL), and CF_3COOH (2 mL) was added slowly at 0 °C. CH_2Cl_2 (20 mL) was added to dilute the system after 30 min, and the pH was adjusted to pH 7 by addition of $NH_3{\cdot}H_2O$. Extraction with CH_2Cl_2 and purification by flash column chromatography afforded the desired ligand **9** in 91% yield.

Ligand 9: $[\alpha]_D^{21}$ = –23.7 (*c* = 0.59, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.73 (d, *J* = 6.9 Hz, 3 H), 0.81 (d, *J* = 6.6 Hz, 3 H), 1.67 (m, 1 H), 2.37 (s, 3 H), 3.30 (dd, *J* = 6.3, 5.1 Hz, 1 H), 3.92 (d, *J* = 6.0 Hz, 1 H), 7.11–7.26 (m, 7 H), 7.60–7.63 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.53, 19.86, 21.41, 30.44, 56.01, 65.10, 126.42, 126.80, 127.14, 128.56, 129.35, 138.60, 142.65, 143.60 ppm. FTIR (film): $\tilde{\nu}$ = 3296, 2964, 2930, 2876, 1599, 1454, 1325, 1157, 1094, 1039, 914, 703, 667, 546 cm^{-1}. MS (ESI): *m*/*z* = 333.1 [M^+ + H]. HRMS: calcd. for $C_{18}H_{25}N_2O_4S$ [M^+ + H] 333.1631; found 333.1642.

General Procedure for the Asymmetric Transfer Hydrogenation Catalyzed by Ru-8 Complex: A 5 mL Schlenk tube was loaded with $[RuCl_2(p\text{-cymene})]_2$ (3 mg, 0.005 mmol) and diamine ligand **8** (4 mg, 0.012 mmol), and purged with argon. The vessel was charged with distilled CH_2Cl_2 (2 mL) and then stirred at 40 °C. After 30 min, the solvent was removed and HCOOH/Et_3N (5:2, 1.5 mL) and substrate **1** (1.0 mmol) were added sequentially. The reaction was continually stirred at 40 °C until full conversion of **1** was observed (determined by ^1H NMR spectroscopy). The reaction mixture was diluted with H_2O (5 mL) and then extracted with diethyl ether. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography afforded the corresponding alcohols. This procedure was based on a report by Xiao and co-workers,[4h] similar results were obtained with Noyori's procedure.[4b]

Compound 18a: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (d, *J* = 6.6 Hz, 3 H), 2.41 (br., 1 H), 4.85 (q, *J* = 6.6 Hz, 1 H), 7.26–7.36 (m, 5 H) ppm. HPLC: Chiralcel OB-H; detected at 254 nm; hexane/2-propanol = 90:10, flow rate = 0.7 mL/min, retention time: t_{minor} = 11.6 min, t_{major} = 10.7 min.

Compound 18b: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (d, *J* = 6.6 Hz, 3 H), 2.35 (s, 3 H), 4.86 (m, 1 H), 7.16 (d, *J* = 6.9 Hz, 2 H), 7.26 (d, *J* = 7.2 Hz, 2 H) ppm. HPLC: Chiralcel OD-H; detected at 254 nm; hexane/2-propanol = 99:1, flow rate = 0.7 mL/min, retention time: t_{minor} = 14.7 min, t_{major} = 17.4 min.

Compound 18c: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46 (d, *J* = 6.0 Hz, 3 H), 3.77 (s, 3 H), 4.84 (q, *J* = 6.3 Hz, 1 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H) ppm. HPLC: Chiralcel OB; detected at 254 nm; hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, retention time: t_{minor} = 11.2 min, t_{major} = 13.8 min.

Compound 18d: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (d, *J* = 6.6 Hz, 3 H), 4.91 (q, *J* = 6.3 Hz, 1 H), 7.43 (d, *J* = 8.4 Hz, 2 H), 7.57 (d, *J* = 7.8 Hz, 2 H) ppm. HPLC: Chiralcel OB; detected at 254 nm; hexane/2-propanol = 95:5, flow rate = 0.7 mL/min, retention time: t_{minor} = 10.8 min, t_{major} = 11.7 min.

Compound 18e: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 6.6 Hz, 3 H), 2.22 (br., 1 H), 4.83 (q, *J* = 6.6 Hz, 1 H), 7.26 (m, 4 H) ppm. HPLC: Chiralcel OB-H; detected at 254 nm; hexane/2-propanol = 95:5, flow rate = 0.7 mL/min, retention time: t_{minor} = 13.5 min, t_{major} = 14.4 min.

Compound 18f: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (dd, J = 1.2, 6.3 Hz, 3 H), 2.17 (br., 1 H), 4.89 (q, J = 6.2 Hz, 1 H), 7.03 (t, J = 8.4 Hz, 2 H), 7.34 (t, J = 6.3 Hz, 2 H) ppm. HPLC: Chiralcel OB-H; detected at 254 nm; hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, retention time: t_{minor} = 9.3 min, t_{major} = 10.1 min.

Compound 18g: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (d, J = 6.3 Hz, 3 H), 2.32 (br., 1 H), 4.88 (q, J = 6.5 Hz, 1 H), 7.26 (d, J = 6.9 Hz, 2 H), 7.47 (d, J = 7.8 Hz, 2 H) ppm. HPLC: Chiralcel OB-H; detected at 254 nm; hexane/2-propanol = 95:5, flow rate = 0.8 mL/min, retention time: t_{minor} = 9.0 min, t_{major} = 10.1 min.

Compound 18h: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (d, J = 6.3 Hz, 3 H), 3.83 (s, 3 H), 5.12 (q, J = 6.3 Hz, 1 H), 6.85–7.36 (m, 4 H) ppm. HPLC: Chiralcel OB; detected at 254 nm; hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, retention time: t_{minor} = 15.3 min, t_{major} = 27.2 min.

Compound 18i: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (d, J = 6.3 Hz, 3 H), 5.26 (q, J = 6.3 Hz, 1 H), 7.18–7.56 (m, 4 H) ppm. HPLC: Chiralcel OB; detected at 254 nm; hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, retention time: t_{minor} = 10.0 min, t_{major} = 14.3 min.

Compound 18j: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (d, J = 6.6 Hz, 3 H), 2.26 (br., 1 H), 5.18 (q, J = 6.2 Hz, 1 H), 6.97–7.03 (m, 1 H), 7.11–7.16 (m, 1 H), 7.20–7.27 (m, 1 H), 7.45–7.50 (m, 1 H) ppm. HPLC: Chiralcel OB; detected at 254 nm; hexane/2-propanol = 95:5, flow rate = 0.7 mL/min, retention time: t_{minor} = 7.7 min, t_{major} = 10.1 min.

Compound 18k: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (d, J = 6.3 Hz, 3 H), 4.87 (q, J = 6.3 Hz, 1 H), 7.20–7.36 (m, 4 H) ppm. HPLC: Chiralcel OB; detected at 254 nm; hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, retention time: t_{minor} = 8.0 min, t_{major} = 9.8 min.

Compound 18l: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (d, J = 6.6 Hz, 3 H), 2.35 (s, 3 H), 4.86 (m, 1 H), 7.07–7.26 (m, 4 H) ppm. HPLC: Chiralcel OJ-H; detected at 254 nm; hexane/2-propanol = 95:5, flow rate = 0.7 mL/min, retention time: t_{minor} = 12.7 min, t_{major} = 13.7 min.

Compound 18m: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.2 Hz, 3 H), 1.75 (m, 2 H), 2.40 (br., 1 H), 4.56 (t, J = 7.5 Hz, 1 H), 5.92 (s, 2 H), 7.23–7.31 (m, 5 H) ppm. HPLC: Chiralcel OD; detected at 254 nm; Hexane/*i*-propanol = 95:5, flow rate = 0.7 mL/min, retention time: t_{major} = 12.5 min, t_{minor} = 13.9 min.

Compound 18n: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (d, J = 6.6 Hz, 3 H), 2.40 (br., 1 H), 4.77 (m, 1 H), 5.92 (s, 2 H), 6.72–6.89 (m, 3 H) ppm. HPLC: Chiralcel OD-H; detected at 254 nm; hexane/2-propanol = 97.5:2.5, flow rate = 0.7 mL/min, retention time: t_{major} = 23.5 min, t_{minor} = 25.3 min.

Compound 18o: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.54 (d, J = 6.6 Hz, 3 H), 5.00 (m, 1 H), 4.75 (m, 1 H), 7.43–7.48 (m, 3 H), 7.75–7.81 (m, 4 H) ppm. HPLC: Chiralcel OD; detected at 254 nm; hexane/2-propanol = 95:5, flow rate = 0.5 mL/min, retention time: t_{major} = 13.8 min, t_{minor} = 15.2 min.

Compound 18p: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72–1.99 (m, 4 H), 2.72–2.85 (m, 2 H), 4.75 (m, 1 H), 7.06–7.42 (m, 4 H) ppm. HPLC: Chiralcel OD; detected at 254 nm; hexane/2-propanol = 98:2, flow rate = 0.7 mL/min, retention time: t_{minor} = 21.7 min, t_{major} = 24.1 min.

Supporting Information (see footnote on the first page of this article): NMR spectra of the ligands and coordination study, and selected X-ray data comparison.

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[10] For NMR spectra obtained in the coordination study, see the Supporting Information.
[11] Crystallographic X-ray data for Ru-**8** complex ($C_{28}H_{37}ClN_2O_2RuS$): T = 293(2) K; wavelength: 0.71073 Å; crystal system: orthorhombic; space group: $P2(1)2(1)2(1)$; unit cell dimensions: a = 12.7969(15) Å, b = 13.0758(15) Å, c = 17.124(2) Å, α = 90°, β = 90°, γ = 90°; V = 2865.3(6) Å^3; Z = 4; ρ_{calc} = 1.396 Mg/m^3; $F(000)$ = 1248; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0409, wR_2 = 0.0787; R indices (all data), R_1 = 0.0586, wR_2 = 0.0831; 16845 reflections measured, 6210 were unique [$R_{(int)}$ = 0.1011]. CCDC-813453 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[12] For X-ray crystallographic data of the Ru-TsDPEN complex, see ref.[4b]
[13] For selected X-ray data comparison, see the Supporting Information.

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