Remote Dipole Effects as a Means to Accelerate [Ru(amino alcohol)]-Catalyzed Transfer Hydrogenation of Ketones

Sofia J. M. Nordin,[a] Peter Roth,[a] Tibor Tarnai,[a] Diego A. Alonso,[b] Peter Brandt,[c] and Pher G. Andersson*[a]

Abstract: A new generation of 2-azanorbornyl amino alcohol ligands for the catalytic transfer hydrogenation reaction of aromatic ketones was synthesized. Extremely active catalysts were formed by introducing a ketal functionality at the rear end of the ligand. Acetophenone was reduced in 96% *ee* at low catalyst loading, substrate to catalyst ratio, S/C 5000, within 90 minutes with isopropyl alcohol as the hydrogen donor. It was found that the dioxolane substituent in the ligand increased the turnover frequency, TOF_{50}, from 1050 h^{-1} to 3000 h^{-1} at an S/C ratio of 1000. Introduction of a methyl group at the carbinol carbon resulted in TOF_{50} as high as 8500 h^{-1}. Transfer hydrogenation of a range of aromatic ketones was evaluated and found to reach completion within 30 minutes at room temperature, and excellent enantioselectivity, up to 99% *ee*, was obtained. A possible explanation for the enhanced activity was provided by density functional calculations, which showed that the presence of a remote dipole in the ligand lowered the transition state energy.

Keywords: amino alcohols · asymmetric catalysis · reduction · ruthenium

Introduction

Asymmetric transfer hydrogenation of multiple bonds has received great attention during the last two decades because it is an important complement to asymmetric hydrogenation. A number of Ru-, Ir-, Rh-, and Sm-based catalysts have been reported[1] and high asymmetric inductions have been obtained by using chiral N, O, and P ligands[1] with isopropyl alcohol or formic acid/triethylamine as the hydrogen source.[2] However, there is still room for improvement when it comes to reaction rate and catalyst loading. The activity of the catalyst is often just as important as high enantioselectivity, especially for industrial applications.[3] Many of the previously published catalysts for transfer hydrogenation that reduce aromatic ketones at high rates are associated with elevated reaction temperatures and high catalyst loading or low enantioselectivity.[4]

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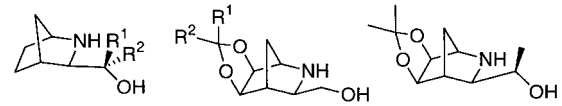
We reported earlier on the use of (1*S*,3*R*,4*R*)-2-azanorbornyl methanol and some analogues (**1a–c**, Figure 1) in the Ru-catalyzed transfer hydrogenation of aromatic ketones.[5]



1a: $R^1 = R^2 = H$
1b: $R^1 = CH_3$, $R^2 = H$
1c: $R^1 = H$, $R^2 = CH_3$

2a: $R^1 = R^2 = CH_3$
2b: $R^1 = R^2 = C_2H_5$
2c: $R^1 = CH_3$, $R^2 = Ph$
2d: $R^1 = R^2 = H$

5

Figure 1. Amino alcohol ligands evaluated in transfer hydrogenation.

The mechanism of the asymmetric transfer hydrogenation with [Ru(arene)(aminoalcohol)] as catalyst has been investigated by others and us.[5b, 6] We now report on further improvements concerning the activity and selectivity of [Ru(*p*-cymene)(azanorbornyl methanol)]-based catalysts with isopropyl alcohol as the hydrogen donor. To the best of our knowledge, this is the first catalyst to effect highly enantioselective transfer hydrogenation at low catalyst loading and high rate. This was accomplished by a modification of the azanorbornyl ligand backbone in a position remote from the catalyst active site. By employing DFT, density functional theory, we have been able to present a possible explanation for the increased activity of the new catalysts.

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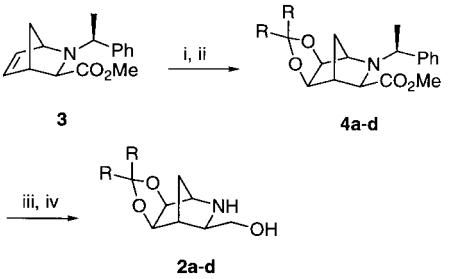
Results and Discussion

Synthesis of ligand 2a–d. The bicyclic structure of ligand **1a** can be easily modified, making this ligand well suited for optimization. The synthesis of ligand **2a–d** (Scheme 1) starts



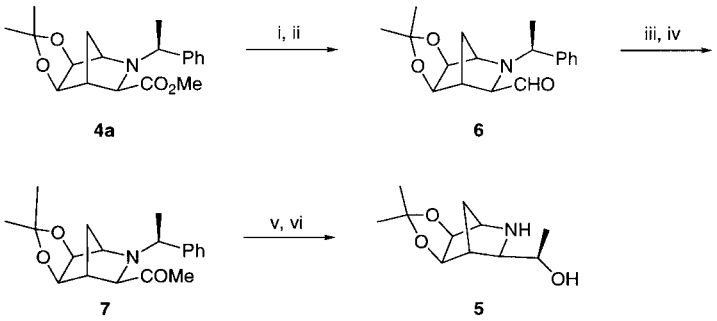
Scheme 1. Synthesis of ligands **2a–d**: i) 1 mol% OsO_4, NMO, *t*BuOH/H_2O, RT, 12 h; ii) *p*-TsOH, **4a**: $(CH_3O)_2C(CH_3)_2$, MeOH, 50 °C, 12 h, 89% (steps i and ii), **4b**: $(C_2H_5)_2CO$, MeOH, 50 °C, 20 h, 68% (steps i and ii), **4c**: $PhCOCH_3$, Dean–Stark trap, benzene, reflux, 12 h, 70% (steps i and ii), **4d**: $(CH_3O)_2CH_2$, P_2O_5, CH_2Cl_2, 50 °C, 12 h, 51% (steps i and ii); iii) 30 wt% $[Pd(OH)_2]$, H_2 (1 atm), MeOH, 50 °C; iv) $LiAlH_4$, THF, 0 °C then RT, 67–90% (steps iii and iv).

with a highly *exo*- and diastereoselective aza-Diels–Alder reaction between cyclopentadiene and the imine formed from methyl glyoxylate and (*S*)-1-phenylethylamine, affording the Diels–Alder adduct **3**.[7] This intermediate, which contains a double bond, was dihydroxylated by using OsO_4 and NMO in a *t*BuOH/H_2O mixture.[8] Protection of the diol with a ketone, or a corresponding dimethyl ketal, in the presence of *p*-TsOH afforded dioxolanes **4a–d**. Debenzylation with $[Pd(OH)_2]$ under atmospheric hydrogen pressure and subsequent reduction of the ester with $LiAlH_4$ afforded the corresponding β-amino alcohols, **2a–d**, in 46–80% overall yield from **3**.

Transfer hydrogenation with ligands 1a and 2a–d: The reduction of acetophenone with [Ru(*p*-cymene)(**2a**)] as catalyst showed a threefold increase in reaction rate combined with an increase in enantioselectivity relative to [Ru(*p*-cymene)(**1a**)] (Table 1, entries 1 and 2). To determine how different substituents on the ketal affect the activity of the catalyst, ligands **2b–d** were synthesized by protecting the hydroxyl groups with diethyl ketone, acetophenone and dimethoxy methane, respectively. The enantioselectivity in the transfer hydrogenations with ligands **2b–d** was almost identical to that found with **2a**, whereas the activity of the catalyst was slightly lower for **2b** and **2d** (Table 1, entries 2–5).

Synthesis of ligand 5: We showed earlier that a (*R*)-methyl substituent at the carbinol carbon on 2-azanorbornyl methanol causes a significant increase in the activity of the catalyst.[5b,c] If the positive effect of this modification was transferable to a ligand with a remote dimethyl dioxolane structure, we would obtain an extremely efficient catalyst.

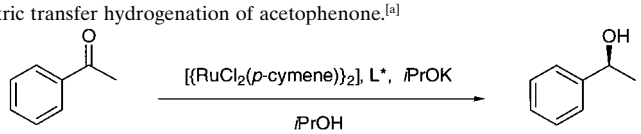
The synthesis of ligand **5** (Scheme 2) starts with the reduction of the ester **4a** with $LiAlH_4$ followed by Swern oxidation to afford aldehyde **6** in 84% yield. Grignard

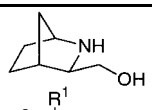
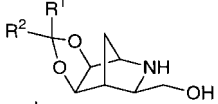
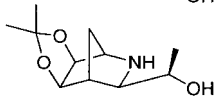


Scheme 2. Synthesis of ligand **5**: i) $LiAlH_4$, THF, 0 °C, 1 h; ii) DMSO, oxalyl chloride, TEA, CH_2Cl_2, −78 °C, 84% (steps i and ii); iii) MeMgBr, $CeCl_3$, THF, −78 °C, 89%; iv) DMSO, oxalyl chloride, TEA, CH_2Cl_2, −78 °C, 86%; v) $LiAlH_4$, THF, 0 °C, 1 h, and separation of the diastereomers; vi) 30 wt% $[Pd(OH)_2]$, H_2 (1 atm), MeOH, 50 °C, 12 h, 38% (steps v and vi).

reaction with MeMgBr and $CeCl_3$ affords the two diastereomeric alcohols in 95:5 mixture with the desired isomer **5** as the minor product. Therefore, it was necessary to oxidize the diastereomeric mixture to the corresponding ketone **7** and then reduce it back to a 1:1 mixture of diastereomers, by using $LiAlH_4$ as the reducing agent. This route allows recycling of the undesired diastereomer. Debenzylation of the alcohols affords ligand **5** in 38% yield.

Table 1. Asymmetric transfer hydrogenation of acetophenone.[a]



Entry	Chiral ligand (L*)		*t* [h]	Conv. [%][b]	Product TOF [h^{-1}][c]	*ee* [%][d]
1		**1a**	3	90	1050	94
2		**2a**: $R^1 = R^2 = CH_3$	1	92	3000	96
3		**2b**: $R^1 = R^2 = C_2H_5$	1	72	1900	95
4		**2c**: $R^1 = CH_3$, $R^2 = Ph$	1	90	2800	96
5		**2d**: $R^1 = R^2 = H$	1	73	1500	96
6		**5**	0.25	97	8500	96

[a] S/C = 1000. [b] Determined by ^1H NMR spectroscopy. [c] Turnover frequencies [(mol product/mol catalyst)/h] were calculated at 50% conversion. [d] Determined by chiral HPLC analysis.

Transfer hydrogenation with ligand 5: When reducing acetophenone with **5** at an S/C ratio of 200 (Ru/ligand/base/substrate 1:4:5:200), the reaction was completed within six minutes (Table 2, entry 1) with 96% *ee*. This result encouraged us to decrease the catalyst loading and it was found that at an

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Table 2. Catalyst-loading study of asymmetric transfer hydrogenation of acetophenone with [Ru(*p*-cymene)(**5**)].[a]

Entry	S/C	*t* [min]	Product Conv. [%][b]	*ee* [%][c]
1	200	6	96	96
2	1000	15	97	96
3	3000	45	96	96
4	4000	70	95	96
5	5000	90	96	96
6	7000	110	85	96

[a] See Experimental Section for the transfer hydrogenation procedure. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral GC analysis.

S/C ratio of 1000 the reaction was finished in less than 15 minutes, with a TOF_{50} as high as 8500 h^{-1} (Table 1, entry 6). Even at an S/C ratio of 5000 the reaction proceeded to full conversion after 90 minutes, but at an S/C ratio of 7000 the reaction stopped at 85% conversion. The enantioselectivity was unaffected by lowering the amount of catalyst, and no decrease in *ee* was detected as a result of prolonged reaction times. Increasing the substrate concentration to 0.4 M solution, however, resulted in 3% lower *ee* (93%) and only 85% conversion after one hour reaction time at an S/C ratio of 1000.

The reason for the apparent deactivation of the catalyst is not fully understood, but formation of styrene as a side reaction has been detected when reducing acetophenone, an indication of the possible formation of water. To remove any water formed, different drying agents such as molecular sieves and $MgSO_4$, were added to the reaction. However, the presence of drying agents caused the reaction to stop at lower conversion, probably due to interactions between the catalyst and the drying agent. To find out whether styrene itself was deactivating the catalyst, styrene was initially added to the reaction, which continued unaffected. One possible explanation for the low yields is dissociation of the [Ru(ligand)(arene)] complex. This could be excluded, since stirring the catalyst in isopropyl alcohol for two hours before adding the substrate gave the same conversion as when the reaction is carried out according to the normal procedure. The possibility of product inhibition was investigated by adding (*R*)- and (*S*)-1-phenylethanol to two separate reaction mixtures prior to the catalyst. The enantiomerically pure alcohols did not affect the reaction. Since the reaction is known to be both moisture and air sensitive it is possible that water is the cause of catalyst deactivation, but deactivation by other by-products formed in the catalytic cycle can not be excluded.

The substrate study (Table 3) shows that it is possible to perform transfer hydrogenation on a range of different aromatic ketones with a catalyst loading as low as S/C = 1000 (Table 3, entries 1, 2, 4, 8, 10, and 12). Lowering the amount of catalyst does not affect the enantioselectivity and the reaction rates are still high. This system is capable of reducing aromatic ketones that contain both electron-donating and -withdrawing substituents in *ortho*, *meta*, and *para* positions with excellent enantioselectivity.

Density functional calculations: Enzyme catalysis partly relies on the stabilization of transition states and high-energy intermediates by fixed pre-oriented dipoles. In ligand **2a** we replaced two remote C–H bonds in **1a** with oppositely polarized C–O bonds, by introducing a dioxolane structure in the ligand. This functionalization does not change the geometry of the Ru–hydride complex[9] and there is no van der Waals contact between the dioxolane and the substrate in the transition state (TS). Nevertheless, catalyst **2a** proved to be about three times faster than the parent compound **1a**. Possible explanations for the rate enhancement include through-bond electronic effects, changes in long-range electrostatics, or solvent effects. To distinguish between these factors, we did a series of calculations.

Table 3. Asymmetric transfer hydrogenation of aromatic ketones catalyzed by [Ru(*p*-cymene)(**5**)].[a]

Entry	Ketone	S/C	*t* [min]	Product Conv. [%][b]	*ee* [%][c]
1	isobutyrophenone	200	30	93	90
2	α,α,α-trimethyl acetophenone	200	30	83	85
3	2-methyl acetophenone	1000	15	100	94
4	2-bromo acetophenone	1000	10	98	95
5	3-methyl acetophenone	200	4	100	96
6	3-methyl acetophenone	1000	15	90	96
7	3-methoxy acetophenone	200	4	100	98
8	3-amino acetophenone	200	4	98	99
9	3-nitro acetophenone	200	4	100	91
10	3-nitro acetophenone	1000	15	100	90
11	4-bromo acetophenone	200	3	98	91
12	4-chloro acetophenone	1000	15	90	92
13	1-acetonaphthone	200	4	100	>99
14	1-acetonaphthone	1000	15	98	>99
15	4-methyl acetophenone	200	6	92	93
16	2-acetyl pyridine	200	15	90	91
17	3-acetyl pyridine	200	4	98	89
18	4-acetyl pyridine	200	3	97	91

[a] See Experimental Section for the transfer hydrogenation procedure. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral GC analysis.

The size of the system forced us to devise a scheme where we started from B3PW91/LANL2DZ structures of the non-functionalized system (**1a**) and optimized the dioxolane structure using PM3(tm) with frozen co-ordinates of other atoms (part **C** in Figure 2).[10] This generated a set of reactant

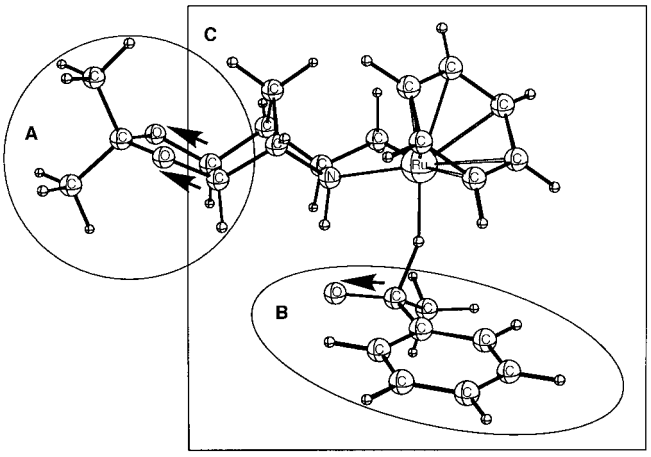

Figure 2. Computational scheme used in the evaluation of the dioxolane effects.

and TS structures suitable for an analysis of the cause of the increased rate. By using these structures, single-point calculations at B3PW91[11] gave an almost perfect fit to the expected reaction barrier difference between the two catalysts (0.8 kcal mol^{-1} vs. the experimental estimate of 0.7 kcal mol^{-1}). This suggests that the effect of the dioxolane substituent is described well by the computational method employed. To differentiate between through-bond effects and electrostatic effects, we calculated the interaction energy between the truncated subsystems **A** and **B** (Figure 2). In this case, system **A** was end-capped with hydrogens. Single-point calculations at the B3LYP/6-311 + G** level for the separated systems and for the interacting systems of the TS geometry indicated a repulsion of 0.4 kcal mol^{-1} in the TS of catalyst **1a** and an attraction of 0.9 kcal mol^{-1} in the TS of catalyst **2a**. Adding these effects, a contribution to the net lowering of the TS energy of catalyst **2a** could be estimated at 1.3 kcal mol^{-1}.[12] Therefore, it is most likely that the observed rate enhancement is caused by the interaction of the new bond dipoles, introduced at the rear end of the azanorbornyl skeleton, with the substrate dipole.[13] By presenting this analysis, we would like to encourage the use of van der Waals attractions in the design of new catalysts.

Conclusion

In conclusion, we have shown that the introduction of a dioxolane ring in the amino alcohol ligand lowers the energy in the transition state owing to van der Waals attractions between the dipole in the dioxolane ring and the dipole in the substrate. This results in a transfer hydrogenation catalyst that can be used at low catalyst loading with high TOF_{50} and which induces excellent enantioselectivity. To the best of our knowledge, no other asymmetric catalyst for transfer hydrogenation is capable of reducing acetophenone in a S/C ratio exceeding 5000.

Experimental Section

For general experimental information see reference [14]. *i*PrOH was dried over CaH_2 and freshly distilled under nitrogen prior to use. Acetophenone was distilled and stored over activated molecular sieves. *i*PrOK (1M) was prepared prior to use from freshly distilled *i*PrOH and potassium. Flash chromatography was performed on silica gel (Matrex 60A, 37–70 μm). Deactivated silica gel means that it was treated with 5% Et_3N in pentane, and the column was eluted with the same solvent mixture until the eluent was basic when tested with pH indicator paper. HPLC analysis was carried out with a chiral column (ChiralCel OD-H) and a diode-array detector with a flow rate of 0.5 mL min^{-1} with 5% *i*PrOH in hexane as solvent. GC analysis was performed on a Varian 3400 capillary gas chromatograph with a CP-Chirasil-Dex CB column (25 m with 0.25 mm inner diameter), nitrogen as carrier gas, and a flame ionization detector. MS-analysis was carried out on a Finnigan MAT GCQ PLUS system. Infrared spectra were recorded on a Perkin–Elmer 1760 FT-IR spectrometer.

General procedure for transfer hydrogenation of aromatic ketones: Amino alcohol ligand (20 μmol) and [{$RuCl_2$(*p*-cymene)}$_2$] (1.53 mg, 2.5 μmol) were added to a round-bottomed flask. Moisture was azeotropically removed by evaporation with benzene (3 × 4 mL) at reduced pressure. Stirring the ligand and [{$RuCl_2$(*p*-cymene)}$_2$] at RT for 10 minutes in *i*PrOH (2 mL) generated the pre-catalyst. The substrate (5 mmol) was dissolved in *i*PrOH (48 mL), and the base (25 μL, 1M *i*PrOK in *i*PrOH), was added at RT, followed by the pre-catalyst. The resulting solution was stirred at RT, and the reaction was monitored by ^{1}H NMR.

Compound 3: Compound **3** was prepared according to a literature procedure.[7]

(1*R*,2*R*,6*S*,7*R*,9*R*)-4,4-Dimethyl-8-[(*S*)-1-phenylethyl]-3,5-dioxa-8-azatricyclo[5.2.1.0^{2,6}]decane-9-carboxylic acid methyl ester (4a): Compound **3** (6.6 g, 26 mmol) was dissolved in *t*BuOH (72 mL) and water (9.8 mL). NMO (40 mL, 60% solution in water, 230 mmol) was added at RT, followed by addition of OsO_4 (0.2 g, 0.6 mmol). The reaction was stirred overnight, diluted with H_2O (50 mL), and quenched with $Na_2S_2O_5$. The organic solvent was removed under reduced pressure, and the residue was washed with CH_2Cl_2 (3 × 100 mL). Drying ($MgSO_4$) and evaporation afforded the diol in quantitative yield (7.4 g). The diol, was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.40$ (d, $J = 6.4$ Hz, 3H), 1.77 (d, $J = 10.8$ Hz, 1H), 1.92 (d, $J = 10.8$ Hz, 1H), 2.21 (br s, 1H) 2.44 (br s, 1H), 3.45 (s, 3H), 3.54 (q, $J = 6.4$ Hz, 1H), 3.55 (br s, 1H), 3.79 (d, $J = 5.2$ Hz, 1H), 4.25 (d, $J = 5.2$ Hz, 1H), 7.12–7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.2$, 29.6, 48.8, 51.5, 60.1, 61.6, 65.6, 67.2, 73.2, 127.4, 127.9, 128.0, 143.8, 173.9.

The diol (7.4 g, 26 mmol) was dissolved in MeOH and *p*-toluenesulfonic acid (5.4 g, 29 mmol) was added, followed by addition of 2,2-dimethoxy propane (7.9 mL, 65 mmol). The reaction mixture was warmed to 40–50 °C and stirred overnight. The solvent was removed under reduced pressure, and the residue was washed with aqueous NaOH (50 mL, 2M) and CH_2Cl_2 (3 × 100 mL). Drying ($MgSO_4$), evaporation, and purification by flash chromatography (deactivated silica) afforded pure **4a** in 89% yield (8.4 g). $R_f = 0.25$ (EtOAc/ pentane 1:9); m.p. 82–83 °C; $[\alpha]_D^{30} = +1.9$ ($c = 1.0$ in CH_2Cl_2); IR (CH_2Cl_2): $\tilde{\nu} = 2976$, 1746, 1494, 1455, 1375 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.33$ (s, 3H), 1.46 (d, $J = 6.4$ Hz, 3H), 1.46 (s, 3H), 1.74 (d, $J = 10.4$ Hz, 1H), 1.91 (d, $J = 10.4$ Hz, 1H), 2.34 (s, 1H), 2.42 (s, 1H), 3.25 (s, 3H), 3.60 (q, $J = 6.4$ Hz, 1H), 3.71 (s, 1H), 4.15 (d, $J = 5.6$ Hz, 1H), 4.55 (d, $J = 5.6$ Hz, 1H), 7.18–7.23 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.4$, 24.3, 25.4, 29.3, 45.9, 51.4, 59.0, 60.1, 64.2, 75.6, 80.5, 109.6, 127.4, 127.8, 128.0, 144.0, 173.6; MS (EI): *m*/*z* (%): 332 (59) $[M]^+$, 299 (22), 272 (25), 230 (63), 126 (47), 105 (100), 73 (32); elemental analysis calcd (%) for $C_{19}H_{25}NO_4 \cdot 0.4\,H_2O$: C 67.39, H 7.68, N 4.14; found C 67.28, H 7.33, N 4.34.

(1*R*,2*R*,6*S*,7*R*,9*R*)-4,4-Dimethyl-3,5-dioxa-8-azatricyclo[5.2.1.0^{2,6}]dec-9-ylmethanol (2a): Compound **4a** (8.4 g, 25 mmol) was dissolved in MeOH and added to dried [$Pd(OH)_2$] (2.5 g, 30 wt%). The flask was placed under hydrogen atmosphere, and the reaction mixture was heated to 50 °C and stirred overnight. The suspension was filtered through a pad of Celite, dried ($MgSO_4$), and evaporated to afford the ester in quantitative yield (5.8 g). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.25$ (d, $J = 10.8$ Hz, 3H), 1.26 (s, 3H), 1.71 (d, $J = 10.8$ Hz, 1H), 2.04 (br s, 1H) 2.63 (br s, 1H), 3.05 (br s, 1H) 3.41 (br s, 1H), 3.72 (s, 3H), 4.07 (d, $J = 5.6$ Hz, 1H), 4.07 (d, $J = 5.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.2$, 25.5, 28.8, 44.4, 52.5, 57.24, 57.47, 80.6, 81.6, 110.1, 174.2.

The ester (5.8 g, 25 mmol) dissolved in dry THF (50 mL) was added dropwise to a suspension of $LiAlH_4$ (6.6 g, 0.18 mol) in THF at 0 °C. The reaction mixture was allowed to reach RT, and after 25 min the reaction was quenched by slow addition of H_2O (6.6 mL), aqueous NaOH (6.6 mL, 1M), and H_2O (20 mL). The reaction mixture was filtered, dried ($MgSO_4$), and the solvent was removed under reduced pressure. Precipitation of the oil in EtOAc/pentane afforded **2a** in 90% yield (4.7 g). M.p. 98–101 °C; $[\alpha]_D^{24} = -2.9$ (c = 0.5 in CH_2Cl_2); IR: $\tilde{\nu} = 3357$, 2974, 1458, 1168 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.31$ (s, 3H), 1.44 (d, $J = 10.4$ Hz, 1H) 1.46 (s, 3H) 1.70 (d, $J = 10.4$ Hz, 1H), 2.28 (s, 1H), 2.61 (dd, $J = 8.0$, 5.6 Hz, 1H), 3.28 (dd, $J = 10.4$, 8.0 Hz, 1H), 3.35 (br s, 1H), 3.50 (dd, $J = 10.4$, 6.0 Hz, 1H), 4.00 (d, $J = 5.6$ Hz, 1H), 4.15 (d, $J = 5.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.2$, 25.5, 27.9, 42.0, 55.6, 57.0, 65.1, 80.8, 82.5, 109.6; MS (EI): *m*/*z* (%): 200 (71) $[M]^+$, 184 (30), 124 (17), 110 (17), 98 (30), 82 (36), 68 (100); elemental analysis calcd (%) for $C_{10}H_{17}NO_3$: C 60.28, H 8.60, N 7.03; found C 60.06, H 8.59, N 7.00.

(1*R*,2*R*,6*S*,7*R*,9*R*)-4,4-Diethyl-8-[(*S*)-1-phenylethyl]-3,5-dioxa-8-azatricyclo[5.2.1.0^{2,6}]decane-9-carboxylic acid methyl ester (4b): Compound **4b** was prepared by following the same procedure as described for **4a**, except for the protection of the diol. The diol (0.70 g, 2.4 mmol) was dissolved in MeOH (50 mL), and *p*-toluenesulfonic acid (0.51 g, 2.6 mmol) was added

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followed by diethyl ketone (0.60 mL, 9.6 mmol). The reaction mixture was heated under reflux overnight. The solvent was removed, and the residue was washed with aqueous NaOH (5 mL, 2M) and CH_2Cl_2 (3×20 mL). Drying ($MgSO_4$), evaporation, and purification by flash chromatography (deactivated silica) afforded the pure product in 68% yield (0.59 g). R_f = 0.4 (pentane/EtOAc 1:10); m.p. 82–83 °C; $[\alpha]_D^{24} = +0.4$ ($c = 1.9$ in CH_2Cl_2); IR: $\tilde{\nu}$ = 2971, 1743, 1492, 1458, 1379 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.6 Hz, 3H), 0.95 (t, J = 7.6 Hz, 3H) 1.46 (d, J = 6.4 Hz, 3H), 1.59 (q, J = 7.6 Hz, 2H), 1.70 (q, J = 7.6 Hz, 2H), 1.81 (d, J = 10.4 Hz, 1H), 1.88 (d, J = 10.4 Hz, 1H), 2.37 (s, 1H), 2.41 (s, 1H), 3.25 (s, 3H), 3.58 (q, J = 6.4 Hz, 1H), 3.74 (s, 1H), 4.12 (d, J = 5.6 Hz, 1H), 4.51 (d, J = 5.6 Hz, 1H), 7.18–7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.2, 8.2, 22.4, 27.3, 27.9, 29.4, 46.0, 51.5, 59.0, 60.1, 64.3, 75.5, 80.4, 113.7, 127.4, 127.8, 128.0, 144.0, 173.6; MS (EI): m/z (%): 358 (20) $[M]^+$, 329 (32), 300 (18), 229 (100), 225 (43), 126 (60), 105 (79), 79 (17); elemental analysis calcd (%) for $C_{21}H_{29}NO_4$: C 70.16, H 8.13, N 3.90; found C 70.00, H 8.21, N 3.97.

(1*R*,2*R*,6*S*,7*R*,9*R*)-4,4-Diethyl-3,5-dioxa-8-azatricyclo[5.2.1.0^{2,6}]dec-9-ylmethanol (2b): Debenzylation of **4b** by the procedure given for **2a** afforded the corresponding product in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 8 Hz, 3H), 0.93 (t, J = 8.0 Hz, 3H), 1.27 (d, J = 10.8 Hz, 1H), 1.55 (q, J = 8.0 Hz, 2H) 1.66 (q, J = 8.0 Hz, 2H), 1.81 (d, J = 10.8 Hz, 1H), 2.69 (s, 1H), 3.08 (s, 1H), 3.48 (s, 1H), 3.74 (s, 3H), 4.09 (d, J = 5.2 Hz, 1H), 4.17 (d, J = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.0, 8.6, 27.3, 27.8, 28.9, 44.4, 52.4, 57.2, 57.4, 80.4, 81.4, 114.1 and 174.1. Reduction of the ester according to the procedure given for **2a** afforded ligand **2b** in 68% yield. M.p. 53–54 °C; $[\alpha]_D^{24} = -23.5$ (c = 0.4 in CH_2Cl_2); IR: $\tilde{\nu}$ = 3360, 2975, 1458, and 1169 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, J = 7.6 Hz, 3H), 0.89 (t, J = 7.6 Hz, 3H), 1.32 (d, J = 10.4 Hz, 1H), 1.50 (q, J = 7.6 Hz, 2H), 1.60 (q, J = 7.6 Hz, 2H), 1.68 (d, J = 10.4 Hz, 1H), 2.24 (s, 1H), 2.49 (dd, J = 8.0, 5.4 Hz, 1H), 3.22 (dd, J = 10.2, 8.0 Hz, 1H), 3.27 (brs, 1H), 3.39 (dd, J = 10.2, 5.4 Hz, 1H), 3.89 (d, J = 5.2 Hz, 1H), 4.02 (d, J = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.0, 8.6, 27.3, 27.9, 28.0, 41.8, 56.1, 60.0, 64.9, 80.6, 82.0, 113.6; MS (EI): m/z (%): 228 (48) $[M]^+$, 198 (67), 124 (63), 110 (20), 106 (24), 97 (38), 80 (92), 68 (100); elemental analysis calcd (%) for $C_{12}H_{21}NO_3 \cdot 0.5\,H_2O$: C 60.99, H 9.38, N 5.93; found C 60.76, H 9.39, N 5.93.

(1*R*,2*R*,4*S*,6*S*,7*R*,9*R*)-4-Methyl-4-phenyl-8-[(*S*)-1-phenylethyl]-3,5-dioxa-8-azatricyclo[5.2.1.0^{2,6}]decane-9-carboxylic acid methyl ester (4c): Compound **4c** was prepared by following the same procedure as described for **4a**, except for the protection of the diol. The diol (0.70 g, 2.4 mmol) was dissolved in benzene (50 mL), and *p*-toluenesulfonic acid (0.51 g, 2.6 mmol) was added followed by acetophenone (0.80 mL, 6.8 mmol). The reaction was heated under reflux overnight with azeotropic removal of water by using a Dean–Stark apparatus. The solvent was removed under reduced pressure, and the residue was washed with aqueous NaOH (5 mL, 2M) and CH_2Cl_2 (3×20 mL). Drying ($MgSO_4$), evaporation, and purification by flash chromatography (deactivated silica) afforded the pure product in 70% yield (0.77 g): R_f = 0.38 (pentane/EtOAc 1:10); m.p. 118 °C; $[\alpha]_D^{24} = +7.1$ (c = 1.4 in CH_2Cl_2); IR: $\tilde{\nu}$ = 3425, 2972, 1746, 1639 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49 (d, J = 6.4 Hz, 3H), 1.60 (d, J = 9.2 Hz, 1H), 1.64 (s, 3H), 1.84 (d, J = 9.2 Hz, 1H), 2.44 (s, 1H), 2.48 (s, 1H), 3.25 (s, 3H), 3.65 (q, J = 6.4 Hz, 1H), 3.78 (s, 1H) 4.34 (d, J = 5.2, 1H), 4.74 (d, J = 5.2 Hz, 1H) 7.20–7.38 (m, 8H), 7.51–7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 25.5, 29.3, 46.0, 51.4, 59.0, 60.1, 64.1, 75.8, 80.6, 110.1, 124.7, 127.4, 127.8, 127.97, 128.0, 141.4, 143.8, 174.1; MS (EI): m/z (%): 393 (1) $[M]^+$, 180 (16), 172 (18), 162 (17), 149 (68), 136 (17), 105 (34), 95 (55), 91 (54), 81 (67), 67 (66), 55 (100); elemental analysis calcd (%) for $C_{24}H_{27}NO_4$: C 73.25, H 6.92, N 3.56; found C 73.06, H 6.81, N 3.49.

(1*R*,2*R*,4*S*,6*S*,7*R*,9*R*)-4-Methyl-4-phenyl-3,5-dioxa-8-aza-tricyclo-[5.2.1.0^{2,6}]dec-9-ylmethanol (2c): Debenzylation of **4c** by the procedure given for **2a** afforded the corresponding product in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, J = 10.8 Hz, 1H), 1.57 (s, 3H), 1.60 (d, J = 10.8 Hz, 1H), 2.13 (brs, 1H), 2.74 (s, 1H), 3.12 (s, 1H), 3.50 (s, 1H), 3.72 (s, 3H), 4.28 (d, J = 5.2 Hz, 1H), 4.38 (d, J = 5.2 Hz, 1H), 7.24–7.36 (m, 8H), 7.49–7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 28.9, 44.5, 52.5, 57.3, 57.4, 80.8, 81.8, 110.7, 124.7, 128.1, 141.6, 174.1.

Reduction of the ester according to the given procedure for **2a** afforded ligand **2c** in 67% yield. $[\alpha]_D^{25} = +71.4$ (c = 1.4 in CH_2Cl_2); IR (KBr): $\tilde{\nu}$ = 2927, 1138, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, J = 10.8 Hz, 1H), 1.56 (m, 1H), 1.58 (s, 3H), 2.34 (s, 1H) 2.62 (dd, J = 8.0, 5.6 Hz, 1H), 3.26 (dd, J = 10.8, 8.0 Hz, 1H), 3.39 (s, 1H), 3.47 (dd, J = 10.8, 5.6 Hz, 1H) 4.15 (d, J = 5.2 Hz, 1H), 4.31 (d, J = 5.2 Hz, 1H), 7.25–7.60 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 28.0, 41.8, 56.0, 56.9, 64.9, 80.9, 82.1, 110.0, 124.7, 125.2, 127.9, 128.1, 141.5; MS (EI): m/z (%): 262 (14) $[M]^+$, 220 (48), 205 (27), 152 (14), 1124 (21), 105 (100), 80 (55); elemental analysis calcd (%) for $C_{15}H_{19}NO_3$: C 68.94, H 7.33, N 5.36; found C 69.06, H 39, N 5.28.

(1*R*,2*R*,6*S*,7*R*,9*R*)-8-[(*S*)-1-Phenylethyl]-3,5-dioxa-8-azatricyclo-[5.2.1.0^{2,6}]decane-9-carboxylic acid methyl ester (4d): The diol (5.0 g, 17 mmol) was dissolved in a solution of CH_2Cl_2 (80 mL) and dimethoxymethane (80 mL), followed by addition of P_2O_5 (40 g). The resulting suspension was stirred at RT overnight and partitioned in a mixture of saturated aqueous $NaHCO_3$ (100 mL) and CH_2Cl_2 (100 mL) at 0 °C. The organic phase was separated and washed with saturated aqueous $NaHCO_3$ and brine. Drying ($MgSO_4$), evaporatiion, and purification by flash chromatography (deactivated silica, EtOAc/pentane; 1/10) afforded pure **4d** in 51% yield (2.67 g). R_f 0.46 (EtOAc/pentane 1:4), m.p. 127–128 °C; $[\alpha]_D^{25} = +11.1$ (c = 1.0 in CH_2Cl_2); IR (KBr): $\tilde{\nu}$ = 2970, 2866, 1742, 1438, 1369 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (d, J = 6.4 Hz, 3H), 1.72 (d, J = 10.8 Hz, 1H), 1.93 (d, J = 10.8 Hz, 1H), 2.42 (s, 1H), 2.44 (s, 1H), 3.58 (q, J = 6.4 Hz, 1H), 3.79 (s, 1H), 4.06 (d, J = 5.6 Hz, 1H), 4.44 (d, J = 5.6 Hz, 1H), 4.62 (s, 1H), 5.07 (s, 1H), 7.17–7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7, 29.4, 46.0, 51.8, 59.2, 60.5, 64.4, 76.3, 80.8, 95.3, 127.7, 128.1, 128.3, 144.2, 173.9; MS (EI): m/z (%): 303 (4) $[M]^+$, 272 (38), 171 (19), 172 (40), 105 (100); elemental analysis calcd (%) for $C_{17}H_{21}NO_4$: C 67.31, H 6.98, N 4.62; found C 67.35, H 7.10, N 4.72.

(1*R*,2*R*,6*S*,7*R*,9*R*)-3,5-Dioxa-8-azatricyclo[5.2.1.0^{2,6}]dec-9-ylmethanol (2d): Debenzylation of **4d** according to the procedure given for **2a** afforded the corresponding product in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (d, J = 10.8 Hz, 1H), 1.71 (d, J = 10.8 Hz, 1H), 2.28 (brs, 1H), 2.75 (s, 1H), 3.09 (s, 1H), 3.53 (s, 1H), 3.75 (s, 1H), 4.02 (d, J = 5.6 Hz, 1H), 4.10 (d, J = 5.6 Hz, 1H), 4.60 (s, 1H), 5.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.0, 44.5, 52.9, 57.4, 57.7, 80.9, 81.9, 95.8, 174.2.

Reduction of the ester according to the procedure given for **2a** afforded ligand **2d** in 75% yield. M.p. = 110–111 °C; $[\alpha]_D^{25} = -31.8$ (c = 1.0 in CH_2Cl_2); IR (KBr): $\tilde{\nu}$ = 3299, 2929, 1408, 1161 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (d, J = 10.8 Hz, 1H), 1.64 (d, J = 10.8 Hz, 1H), 1.85 (brs, 2H), 2.37 (s, 1H), 2.59 (dd, J = 6.8, 5.6 Hz, 1H), 3.28 (dd, J = 10.4, 8.0 Hz, 1H), 3.41 (s, 1H), 3.49 (dd, J = 10.4, 6.0 Hz, 1H), 3.88 (d, J = 5.6 Hz, 1H), 4.01 (d, J = 5.6 Hz, 1H), 4.59 (s, 1H), 5.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0, 42.1, 55.7, 57.0, 65.3, 81.1, 82.7, 95.3; MS (EI): m/z (%): 172 (29) $[M]^+$, 140 (14), 110 (15), 105 (85), 98 (12), 68 (100); elemental analysis calcd (%) for $C_8H_{13}NO_3$: C 56.13, H 7.65, N 8.18; found C 56.03, H 7.77, N 8.15.

(1*R*,2*R*,6*S*,7*R*,9*R*)-4,4-Dimethyl-8-[(S)-2-phenylethyl]-3,5-dioxa-8-azatricyclo[5.2.1.0^{2,6}]decane-9-carbaldehyde (6): Compound **4a** (11 g, 35 mmol) was dissolved in dry THF (80 mL) and added drop-wise to a suspension of $LiAlH_4$ (1.3 g, 35 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then quenched by slow addition of H_2O (1.3 mL), aqueous NaOH (1.3 mL, 1M), and H_2O (3.9 mL). The reaction mixture was filtered and dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford the product in 94% crude yield (10 g). The product was oxidized without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 3H), 1.45 (d, J = 6.4 Hz, 3H), 1.46 (s, 3H), 1.64 (m, 2H) 1.93 (dd, J = 6.4, 2.4 Hz, 1H), 2.27 (s, 1H), 2.43 (dd, J = 10.8, 6.4 Hz, 1H), 2.76 (d, J = 10.8 Hz, 1H) 3.58 (q, J = 6.4 Hz, 1H), 3.61 (s, 1H), 4.14 (d, J = 5.4 Hz, 1H), 4.56 (d, J = 5.4 Hz, 1H), 7.20–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 24.3, 25.5, 29.1, 45.2, 59.7, 60.0, 63.6, 63.8, 75.7, 80.6, 109.3, 127.3, 127.7, 128.5, 145.6.

DMSO (4.2 mL, 79 mmol) was added to a solution of oxalylchloride (3.1 mL, 36 mmol) in dry CH_2Cl_2 (200 mL) for a period of 10 min at −78 °C. The reaction mixture was stirred for 15 min, and the alcohol (10 g, 33 mmol), dissolved in dry CH_2Cl_2 (50 mL), was added over a period of 10 min. The reaction mixture was stirred for 15 min and triethylamine (16 mL, 120 mmol) was subsequently added over a period of 10 min. The reaction mixture was allowed to reach RT and then washed with brine (100 mL) and CH_2Cl_2 (3×200 mL). The combined organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (deactivated silica) affording **6** in 89% yield (8.9 g). R_f = 0.2 (pentane/EtOAc 1:9); $[\alpha]_D^{30} = +10.2$ (c = 2.3, CH_2Cl_2); IR (neat): $\tilde{\nu}$ = 2980, 1723, 1382, 1207 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3H), 1.43 (s,

3H), 1.45 (m, 1H) 1.47 (d, $J = 6.4$ Hz, 3H), 1.75 (d, $J = 10.8$ Hz, 1H), 2.26 (d, $J = 2.8$ Hz, 1H), 2.44 (s, 1H), 3.58 (q, $J = 6.6$ Hz, 1H), 3.72 (s, 1H), 4.16 (d, $J = 5.4$ Hz, 1H) 4.56 (d, $J = 5.4$ Hz, 1H), 7.12–7.30 (m, 5H), 8.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.0$, 24.1, 25.3, 29.6, 44.8, 59.2, 59.7, 69.6, 75.8, 80.2, 109.4, 127.5, 127.8, 128.4, 144.0, 203.2; MS (EI): *m/z* (%): 302 (7) $[M]^+$, 272 (100), 172 (59), 105 (91), 68 (84); elemental analysis calcd (%) for $C_{18}H_{25}NO_3 \cdot 0.3\,H_2O$: C 70.47, H 7.75, N 4.57; found C 70.35, H 7.93, N 4.94.

1-{(1*R*,2*R*,6*S*,7*R*,9*R*)-4,4-Dimethyl-8-[(*S*)-1-phenylethyl]-3,5-dioxa-8-azatricyclo[5.2.0^{2,6}]dec-9-yl}ethanone (7): MeMgI (29 mL, 3M in Et_2O) was added to a suspension of dry $CeCl_3$ (22 g, 88 mmol) in Et_2O at $-78\,^\circ$C. After stirring for 1 h at $-78\,^\circ$C, compound **6** (8.9 g, 29 mmol) in Et_2O (50 mL) was added. The reaction mixture was allowed to reach RT overnight. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (400 mL) and washed with H_2O (200 mL) and CH_2Cl_2 (3×400 mL). Drying ($MgSO_4$) and evaporation of the solvent afforded the alcohol (95:5 diastereomeric mixture) in 98% crude yield (9.3 g). The product was used without further purification. The diastereomeric mixture of alcohols was transformed to the methyl ketone by Swern oxidation according to the same procedure as described above for preparation of compound **6**. Purification by flash chromatography (deactivated silica) afforded the methyl ketone **7**, in 86% yield. $R_f = 0.18$ (pentane/EtOAc 1:9); m.p. 98–99 °C; $[\alpha]_D^{25} = +3.8$ ($c = 0.8$ in CH_2Cl_2); IR (KBr): $\tilde{\nu} = 2978$, 1702, 1382, 1206 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 1.35 (s, 3H), 1.45 (s, 3H), 1.47 (d, $J = 6.8$ Hz, 3H), 1.53 (s, 3H), 1.68–1.77 (m, 2H), 2.24 (s, 1H), 3.50 (s, 1H) 3.56 (q, $J = 6.6$ Hz, 1H), 3.74 (s, 1H), 4.20 (d, $J = 5.6$ Hz, 1H) 4.59 (d, $J = 5.6$ Hz, 1H), 7.15–7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.8$, 24.3, 25.4, 27.3, 28.9, 45.3, 59.4, 60.0, 70.5, 75.6, 80.9, 109.7, 127.7, 128.2, 128.3, 144.0, 209.3; MS (EI): *m/z* (%): 316 (9) $[M]^+$, 272 (89), 172 (43), 105 (100), 68 (57); elemental analysis calcd (%) for $C_{19}H_{25}NO_3$: C 72.35, H 7.99, N 4.44; found C 72.24, H 8.06, N 4.40.

(*R*)-1-{(1*R*,2*R*,6*S*,7*R*,9*R*)-4,4-Dimethyl-3,5-dioxa-8-azatricyclo[5.2.1.0^{2,6}]-dec-9-yl}ethanol (5): Reduction of **7** by $LiAlH_4$ by the same procedure as described for **6** afforded the alcohols in a 1:1 diastereomeric mixture. The diastereomers were separated by flash chromatography (EtOAc/pentane 1:4, deactivated silica) to afford the (*S*)-methyl diastereomer ($R_f = 0.3$) in 45% yield and the (*R*)-methyl diastereomer ($R_f = 0.2$) in 46% yield.

(S)-Methyl diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.80$ (d, $J =$ 6.6 Hz, 3H), 1.35 (s, 3H), 1.46 (s, 3H), 1.48 (d, $J = 6.6$ Hz, 3H), 1.61 (d, $J = 10.4$ Hz, 1H), 1.69 (d, $J = 10.4$ Hz, 1H) 1.72 (d, $J = 3.6$ Hz, 1H), 2.29 (m, 1H), 2.41 (s, 1H), 3.61 (q, $J = 6.4$ Hz, 1H), 3.66 (s, 1H) 4.08 (d, $J = 5.8$ Hz, 1H), 4.58 (d, $J = 5.8$ Hz, 1H), 7.20–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.0$, 22.6, 24.4, 25.5, 29.6, 40.3, 59.8, 60.2, 65.3, 67.6, 76.0, 81.2, 109.3, 127.0, 127.8, 128.7, 145.6.

(R)-Methyl-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.56$ (d, $J =$ 6.6 Hz, 3H), 1.34 (s, 3H), 1.45 (s, 3H), 1.47 (d, $J = 6.6$ Hz, 3H), 1.51 (d, $J = 10.4$ Hz, 1H), 1.67 (d, $J = 10.4$ Hz, 1H,) 1.88 (d, $J = 4.4$ Hz, 1H,), 2.23 (s, 1H), 2.83 (m, 1H), 3.58 (q, $J = 6.4$ Hz, 1H), 3.61 (s, 1H) 4.15 (d, $J = 5.4$ Hz, 1H), 4.58 (d, $J = 5.4$ Hz, 1H), 7.20–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.9$, 22.4, 24.3, 25.5, 29.0, 44.4, 59.9, 60.2, 67.4, 68.3, 76.0, 80.3, 109.3, 127.8, 128.0, 128.5, 145.3.

Debenzylation of the (*R*)-methyl-diastereomer by the procedure given for **2a** afforded **5** in 98% yield. The oil was precipitated in Et_2O/pentane and recrystallized in EtOH. $[\alpha]_D^{25} = -19.2$ ($c = 0.8$ in CH_2Cl_2); m.p. 53 °C; IR (KBr): $\tilde{\nu} = 3317$, 2987, 2881, 1385, 1206, 1060 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.12$ (dd, $J =$ 6.0, 2.4 Hz, 3H), 1.28 (s, 3H), 1.41 (d, $J = 10.8$ Hz, 1H), 1.42 (s, 3H), 1.66 (d, $J = 10.8$ Hz, 1H), 2.13 (m, 1H), 2.24 (s, 1H), 3.26 (m, 1H) 3.32 (s, 1H), 3.97 (brs, 1H), 4.12 (d, $J = 5.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.1$, 24.2, 25.5, 28.0, 42.2, 57.0, 61.3, 68.8, 80.7, 82.5, 109.7; MS (EI): *m/z* (%): 214 (5) $[M]^+$, 198 (16), 138 (16), 110 (15), 82 (21), 68 (100); elemental analysis calcd (%) for $C_{11}H_{19}NO_3$: C 61.94, H 8.98, N 6.57; found C 61.81, H 9.03, N 6.54.

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[9] Evaluated by B3PW91/LANL2DZ calculation.

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[11] SDD with an added set of f functions was used for Ru, whereas 6–311 + G was used for other atoms.

[12] MM3* in MacroModel 6.5 gives the difference in interaction energy as 0.8 kcal mol^{-1}. BSSE in the B3PW91 calculation could cause an overestimation of the interaction energy.

[13] Solvation free energies calculated in Gaussian 98 by using the PCM method with parameters for ethanol together with B3PW91 and SDD for ruthenium and 6–31G* for other atoms indicate a possible rate difference for ligand **2a**. However, the small energy difference is probably without the accuracy of this method.

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