α-Amino-Oximes Based on Optically Pure Limonene: A New Ligands Family for Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation

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ABSTRACT A new family of bifunctional, optically pure α-amino-oxime ligands based on (*R*)-limonene has been synthesized and used as chiral inducers for enantioselective hydrogen transfer reactions on various ketones in the presence of ruthenium catalysts. The X-ray structures of Ru-amino-oxime complexes are also described. *Chirality 00:000–000, 2012.*

KEY WORDS: asymmetric transfer hydrogenation; limonene; amino-oxime; ruthenium

INTRODUCTION

The synthesis of chiral secondary alcohols by catalytic transfer hydrogenation of the corresponding ketones is a pivotal reaction in asymmetric synthesis because of its operational simplicity and its great potential for applications in the fine chemical industries.[1–3] As part of the development of this chemistry, the design and synthesis of enantiomerically pure ligands to produce chiral compounds with a maximal selectivity remain one of the key challenges of today's organic chemistry.[4–6] Among the different synthesis strategies of asymmetric ligands, precursors from the chiral pool still remain of interest because of their low cost and their availability in large quantities and as they avoid tedious resolution processes of the racemates.[7,8] As a former example in that field, the pioneering Kagan's DIOP synthesis started from naturally occurring L-(+)-tartaric acid.[9] Among naturally chiral compounds used for optically pure ligands synthesis, sugars,[10–12] amino acids,[13] or amino alcohols[14] are largely described. Terpenes such as limonene,[15–17] α-pinene and β-pinene,[18–26] or carene[27] as inexpensive available starting materials were also widely used.

Recently, we converted α-pinene into chiral β-amino alcohols and successfully used the corresponding ligands in ruthenium-catalyzed asymmetric hydrogen transfer reactions.[28] On the other hand, α-amino-oxime derivatives of terpenes have been described as "hemilabile" ligands of ruthenium carbonyl complexes.[29] In line with these former studies, it seemed interesting to us to develop and synthesize a series of ligands of this type, also bearing amino and hydroxyl functions, and to use them in asymmetric hydrogen transfer reactions in the presence of ruthenium arene complexes. Herein, we report on the synthesis of α-amino-oximes in two steps from optically pure limonene and their use in hydrogen transfer on various ketones.

EXPERIMENTAL

All manipulations were carried out under an inert nitrogen atmosphere by using standard Schlenk techniques. All reagents were commercially available and were used without further purification. Ligands **4a** and **4b** were prepared according to the published methods.[30–32] The different ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer (Bruker BioSpin, Wissenbourg, France) and referenced to TMS. Optical rotations were measured on a ZUZ: Modelo 412 polarimeter (Farmamundi, Valencia, Spain).

The X-ray intensity data were measured on an APEX II DUO system equipped with a mirror monochromator and a MoKα ImuS (λ = 0.71073 Å).

Conversions and enantiomeric excesses were determined on the crude mixture by gas chromatography (GC) analysis on a Chirasil-Dex CB capillary column. The absolute configurations of the alcohols have been assigned from comparison between the retention times observed using this Chirasil-Dex column in this work versus those described in the literature using the same stationary phase.[33–36]

Ligand 4c

A mixture of the nitrosochloride dimer **2** (2 g, 4.95 mmol) and *iso* propylamine **3c** (2 ml, 21.9 mmol) in ethanol (3 ml) was heated up to the formation of a clear solution. This latter was cooled at −5 °C, and HCl was added slowly. A white solid precipitate of chlorhydrate was formed, which was neutralized by the addition of Et_3N (up to strongly basic pH). The solution was washed with water (2 × 10 ml) then dried over $MgSO_4$. The solvent was evaporated, and a yellow oil was obtained. Upon addition of petroleum ether, the pure oxime **4c** was obtained as a light yellow solid.

Yield: 50% $[\alpha]_D^{20} = +12.41$ ($c = 0.4$, CH_3OH)

^{1}H NMR ($CDCl_3$): $\delta = 8.75$ (1H, O*H*); 4.76 (2H, CH_2); 3.30 (1H, $J = 11.3$ Hz); 2.86 (1H, t, $J = 6.3$ Hz, C$H(CH_3)_2$); 1.99 (1H, d, $J = 11.9$ Hz); 1.3–2.2 (m, 5H); 1.76 (3H, s, CH_3-CHCH$_2$); 1.28 (3H, s, CH_3-CNH); 1.06 (3H, d, $J = 6.3$ Hz, (CH_3)$_2$CH); 0.99 (3H, d, $J = 6.3$ Hz, (CH_3)$_2$CH).

^{13}C nuclear magnetic resonance (NMR) ($CDCl_3$): $\delta = 20.82$ (*C*H$_3$-C); 24.34 (*C*H$_3$-CHNH); 25.02 (2 CH$_3$); 25.57 (CH$_2$); 26.19 (CH); 41.08 (*C*H$_2$); 43.60 (*C*H-C); 44.68 (*C*H-(CH$_3$)$_2$); 56.85 (*C*q-NH); 109.47 (CH$_2$); 148.44 (Cq-CH$_2$); δ = 162.69 (CN).

Anal. calculated for $C_{13}H_{24}N_2O$: C, 69.60; H, 10.78; N, 12.49. Found : C, 69.48; H, 10.60; N, 12.21.

Ligand 4d

The same procedure as for **4c** was applied using 2-picolylamine. Yield : 63% $[\alpha]_D^{20} = +54.61$ (c = 0.4, CH_3OH)

Additional Supporting Information may be found in the online version of this article.

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^{1}H NMR ($CDCl_3$) : δ = 9.82 (1H, O*H*); 8.52 (1H, d, J = 4.5 Hz, C_6H_4N); 7.61 (1H, td, J = 1.1 Hz, C_6H_4N); 7.30 (1H, d, J = 7.8 Hz, C_6H_4N); 7.13 (1H, t, J = 5.8 Hz, C_6H_4N); 4.77 (2H, d, J = 8.1 Hz, CH_2); 3,88 (1H, d, J = 14.2 Hz, CH_2Py), 3.62 (1H, d, J = 14.3 Hz, CH_2Py); 3.30 (1H, d, J = 13.1 Hz, CH_2); 1.98 (1H, d, J = 12.3 Hz, CH_2); 1.6–2.4 (m, 5H); 1,77 (s, 3H, CH_3-CCH$_2$); 1,34 (s, 3H, CH_3-CNH).

^{13}C NMR ($CDCl_3$) : δ = 20.69 (*C*H$_3$-C); 23.25 (*C*H$_3$-CNH); 25.31 (*C*H$_2$); 26.12 (*C*H$_2$); 40.37 (*C*H$_2$); 44.71 (*C*H-C); 47.86 (*C*H$_2$NH); 56.49 (*C*q-NH); 109.46 (*C*H$_2$); 121.82, 122.38, 136.51, 148.60 (4 *C*H); 148.92 (Cq-CH); 159.91 (*C*q (Py)); 162.19 (*C*N).

Anal. calculated for $C_{16}H_{23}N_3O$: C, 70.30; H, 8.48; N, 15.37. Found: C, 69.75; H, 8.85; N, 14.97.

Complex 5a

Phenylamino-oxime **4a** ligand (136 mg; 0.527 mmol) and [RuCl$_2$(*p*-cymene)]$_2$ (0.161 g; 0.263 mmol) were stirred for 30 min in 7 ml of anhydrous dichloromethane. Diethyl ether (7 ml) was then added drop by drop, and the mixture was stirred overnight at −5 °C. After filtration, the crude product was concentrated under vacuum to give complex **5a** as a yellow powder. Yield: 65%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 12.46 (s, 1H, O*H*); 6.90–7.95 (m, 5H, C_6H_5); 6.44 (d, J = 6Hz, 1H, C*H* (*p*-cym)); 6.31 (d, *J* = 6 Hz, 1H, C*H* (*p*-cym)); 5.99 (d, *J* = 6 Hz, 1H, C*H* (*p*-cym)); 5.40 (s, 1H, N*H*); 4.74 (d, 1H, *J* = 8 Hz, C*H* (*p*-cym)); 4.72 (s, 1H, CH$_2$); 4.57 (s, 1H, CH$_2$); 3.7 (d, *J* = 15Hz, 1H, C*H*$_2$); 2.79 (st, 1H, C*H*(CH$_3$)$_2$); 2.49 (m, 1H, C*H*); 2.35–2.41 (m, 1H, C*H*$_2$); 2.36 (s, 3H, C*H*$_3$); 1.3–1.9 (m, 4H); 1,81 (s, 3H, C*H*$_3$); 1,56 (s, 3H, C*H*$_3$); 1.07 (d, *J* = 6 Hz, 3H, (C*H*$_3$)$_2$CH); 0,57 (d, *J* = 6 Hz, 3H, (C*H*$_3$)$_2$CH).

^{13}C NMR ($CDCl_3$, 300 MHz) : δ = 171.93 (*C*N); 167.25 (*C*$_6$H$_5$); 143.28 (*C*-NH); 142.70 (*C*CH$_2$); 105.80 (*p*-cym); 124.00; 124.73; 127.89; 129.46; 130.15 (Ph); 113.83 (*C*H$_2$); 105,8 (*p*-cym)); 97.56 (*p*-cym); 81.07; 84.81; 86.33; 86.55 (*p*-cym); 39.21 (CH); 34.60 (CH$_2$); 30.48 (*C*H(CH$_3$)$_2$); 28.43 (CH$_2$); 24.09 ((*C*H$_3$)$_2$CH); 23.94 (CH$_2$); 22.86 (*C*H$_3$); 22.07 (CH$_3$); 18.79 (CH$_3$); 18.41 ((CH$_3$)$_2$*C*H).

X-ray crystallography, a lustrous pale yellow plate-like specimen of C28H38Cl8N2ORu, approximate dimensions of 0.07 × 0.23 × 0.27 mm, was used for the X-ray crystallographic analysis. The integration of the data using an orthorhombic unit cell yielded a total of 32,454 reflections to a maximum angle of 23.46°, of which 5163 were independent (completeness = 98.8%, R_{int} = 6.59%). The final cell constants of a = 9.5362 (15) Å, b = 15.604(3) Å, c = 23.905(4) Å, and volume = 3557.1(10) Å^3 are based upon the refinement of the XYZ centroids of 229 reflections above 20 σ(I) with 4.338° < 2 < 30.68°. Data were corrected for absorption effects by using the multiscan method (SADABS).

The structure was solved by Charge Flipping Method using Superflip software[37] and refined using the CRYSTALS Software Package,[38] using the space group P2$_1$2$_1$2$_1$, with *Z* = 4 for the formula unit, C28H38Cl8N2ORu. In the final cycles of refinements, the contribution to electron density suggested that part of solvent was highly disordered; attempts to model this disorder were unsuccessful. In the final cycles of refinement, the contribution to electron density corresponding to the disordered solvent was removed from the observed data using the SQUEEZE option in PLATON.[39] The resulting data significantly improved the accurateness of the geometric parameters for the remaining structure. The final anisotropic full-matrix least-squares refinement on *F* with 281 variables converged at *R* = 0.091 for the observed data and *wR* = 0.087 for all data. The goodness-of-fit was 1.02.

Complex 5b

Similar procedure as **5a** using benzylamino-oxime **4b**. Yield : 81%

^{1}H NMR ($CDCl_3$) : δ = 12.19 (s, 1H, *OH*); 7.2–7.6 (m, 5H, C_6H_5), 5.96 (d, 1H, J = 5.9 Hz, *p*-cym); 5.86 (d, 1H, J = 5.7 Hz, *p*-cym); 5.76 (d, 1H, J = 6.5 Hz, *p*-cym); 5.39 (d, 1H, J = 5.97 Hz, *p*-cym); 4.68 (m, 2H, C*H*$_2$-); 4.58 (m, 2H, C*H*$_2$-NH); 4.05 (singlet large, 1H, N*H*); 3.64 (d, 1H$_1$, J = 16.6 Hz, C*H*$_2$); 2.67 (spt, 1H, J = 7.2 Hz, C*H*(CH$_3$)$_2$); 2.41 (singlet large, 1H, C*H*-CH$_2$); 2.29 (dd, 1H$_1$, J = 6 Hz, C*H*$_2$); 2.7 (s, 3H, C*H*$_3$ (p-cym)); 1.30–2.01 (m, 4H, CH$_2$); 1.59 (s, 3H, C*H*$_3$-CCH$_2$); 1.51 (s, 3H, C*H*$_3$-C-NH); 1.16 (d, 3H, J = 7 Hz, (CH$_3$)$_2$-C*H* (*p*-cym); 0.90 (d, 3H, J = 6.9 Hz, (C*H*$_3$)$_2$-CH).

NMR ^{13}C (APT, $CDCl_3$) : δ = 171.58 (CN); 142.85 (Cq-CH$_2$); 135.25 (Cq-Ph); 129.17, 128.66, 128.21 (C_6H_5); 114.24 (Cq (*p*-cym); 109.89 (CH$_2$); 96.46 (Cq (*p*-cym)); 87.46, 84.70, 81.36, 80.82 (4 CH (*p*-cym)); 68.86 (Cq-NH); 55.04 (CH$_2$-Ph); 39.22 (CH$_2$-CH-CH$_2$); 34.15 (CH$_2$); 31.26 (*C*H(CH$_3$)$_2$); 29.41 (CH$_2$); 24.36 (CH$_2$); 23.47 (CH(*C*H$_3$)$_2$); 22.05 (*C*H$_3$-CNH); 21.15 (*C*H$_3$-C); 20.50 (*C*H(CH$_3$)$_2$); 18.98 (*C*H$_3$ (*p*-cym)).

Complex 6b

To a mixture of [Ru(*p*-cymene)Cl$_2$]$_2$ (76.5 mg, 0.125 mmol) and benzylamino-oxime **4b** ligand (68 mg, 0.25 mmol) in 10 ml of dichloromethane, KOH (0.275 mmol) was added. After 4 h stirring at ambient temperature, the orange solution was filtered, and KCl was eliminated. Upon evaporation of the solvent, **6b** was obtained as an orange powder. Yield: 70%

NMR ^{1}H ($CDCl_3$) : δ = 7.2–7.6 (5H, m, C_6H_5); 6.11 (1H, d, *J* = 6 Hz, C*H* (*p*-cym)); 5.92 (1H, d, *J* = 6 Hz, C*H* (*p*-cym)); 5.62 (1H, d, *J* = 6 Hz, C*H* (*p*-cym); 5.44 (1H, d, *J* = 6 Hz, C*H* (*p*-cym)); 4.85 (2H, m, C*H*$_2$NH); 4.66 (2H, d, *J* = 15 Hz, CH$_2$); 4.03 (1H, s, N*H*); 3.61 (1H, d, *J* = 18 Hz, C*H*$_2$); 2.66 (1H, spt, C*H*(CH$_3$)$_2$); 2.39 (1H, m, CH); 2.17 (1H, dd, *J* = 6.1 Hz, C*H*$_2$); 2.00 (3H, s, CH$_3$ (*p*-cym)); 1.2–1.9 (4H, m, 2 C*H*$_2$); 1.58 (3H, s, C*H*$_3$); 1.51 (3H, s, C*H*$_3$); 1.09 (3H, d, *J* = 9 Hz, (C*H*$_3$)$_2$CH); 0.87 (3H, d, *J* = 9 Hz, (C*H*$_3$)$_2$CH).

NMR ^{13}C ($CDCl_3$) : δ = 164.37 (CN); 143.79 (*C*qCH$_2$); 136.01 (*C*q-C$_6$H$_5$); 128.88, 128.42, 128.16 (*C*H(*p*-cym)); 113.49 (*C*H$_2$); 108.32 (*C*q(*p*-cym)); 96.37 (*C*q(*p*-cym)); 87.74, 83.59, 81.79, 81.55 (*C*H(*p*-cym)); 68.45 (*C*q-NH); 54.93 (*C*H$_2$NH); 39.34 (*C*H); 34.33 (*C*H$_2$); 31.10 (*C*H(CH$_3$)$_2$); 29.69 (*C*H$_2$); 24.62 (*C*H$_2$); 23.98 (CH(*C*H$_3$)$_2$); 22.20 (*C*H$_3$); 21.18 (*C*H$_3$); 20.10 (CH(*C*H$_3$)$_2$); 18.60 (*C*H$_3$ (*p*-cym)).

X-ray crystallography, an irregular yellow plate-like specimen of C54H74N4O2Ru2, approximate dimensions of 0.12 × 0.14 × 0.16 mm, was used for the X-ray crystallographic analysis. The integration of the data using an orthorhombic unit cell yielded a total of 14,148 reflections to a maximum angle of 26.3°, of which 10,577 were independent (completeness = 98.3%, R_{int} = 5.50%). The final cell constants of a = 8.8793 (11) Å, b = 22.171 (3) Å, c = 18.394 (2) Å, β = 90.627 (5)°, and volume = 3620.8 (8) Å^3 are based upon the refinement of the XYZ centroids of 9823 reflections with 6° < 2 < 52°. Data were corrected for absorption effects using the multiscan method (SADABS).

The structure was solved by Charge Flipping Method using Superflip software[37] and refined using the CRYSTALS Software Package[38], using the space group P2$_1$, with *Z* = 4 for the formula unit, C54H74N4O2Ru2. In the final cycles of refinements, the contribution to electron density suggested that part of solvent was highly disordered; attempts to model this disorder were unsuccessful. In the final cycles of refinement, the contribution to electron density corresponding to the disordered solvent was removed from the observed data using the SQUEEZE option in PLATON.[39] The resulting data significantly improved the accurateness of the geometric parameters for the remaining structure. The final anisotropic full-matrix least-squares refinement on *F* with 578 variables converged at *R* = 0.062 for the observed data and *wR* = 0.056 for all data. The goodness-of-fit was 0.99.

Complexes 7b/7b′

[Ru(*p*-cymene)Cl$_2$]$_2$ (76.5 mg; 0.125 mmol) and benzylamino-oxime **4b** ligand (68 mg; 0.25 mmol) in 5 ml *iso*PrOH were stirred for 30 min at 80 °C. A solution of KOH in *i*PrOH (4.13 ml, 0.12 M) was added to the reaction mixture. After stirring for 15 min, the solution was evaporated under vacuum at 0 °C to give a red powder. Yield: 91%.

NMR ^{1}H (C_6D_6): δ = 7.00–7.40 (5H, m, C_6H_5); 5.29, 5.02, 4.86, 4.64 (4H, 4d, *J* = 6 Hz, (*p*-cym)); 5.00 (1H, N*H*); 4.05–4.45 (4H, m, C*H*$_2$Ph + C*H*$_2$); 2.46 (1H, spt, C*H*(CH$_3$)$_2$); 2.18 (1H, m, C*H*); 1.83 (3H, s, *CH*$_3$ (*p*-cym); 1.15–1.65 (4H, m, 2 CH$_2$); 1.48 (3H, dd, *J* = 1.5, 6 Hz, CH$_3$); 1.14 (3H, d, *J* = 4.5 Hz (C*H*$_3$)$_2$CH)); 1.12 (3H, d, *J* = 4.5 Hz, (C*H*$_3$)$_2$CH)); −5.10 and −6.15 (Ru-*H*).

Typical Transfer Hydrogenation Procedure

The catalysts were generated *in situ* prior to catalysis by heating a mixture of the [RuCl$_2$(arene)$_2$]$_2$ complex (0.01 mmol) with the desired amino-oxime (0.04 mmol, 2 eq per Ru) at 80 °C for 20 min in dry propan-2-ol (5 ml). Then, a solution of the substrate (2 mmol) in propan-2-ol was

added, immediately followed by 0.33 ml of a 0.12-M solution of KOH in *i*PrOH, and the mixture was heated at the desired temperature. The reaction course was monitored versus time using GC analysis of aliquots on a Chirasil-Dex column to assess conversions and enantioselectivities.

RESULTS AND DISCUSSION

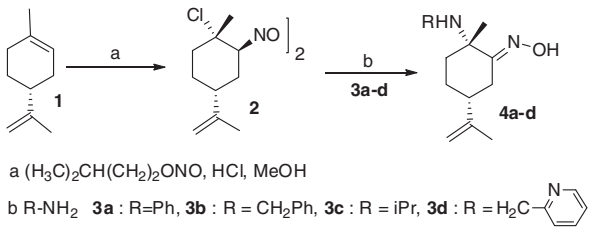
Synthesis of Chiral Ligands and Complexes

As described previously,[30–32] the synthesis of α-amino-oximes derived from (*R*)-limonene proceeds via the (1*S*,2*S*,4*R*)-nitroso chloride intermediate formation followed by the addition of amines (Scheme 1). Thus, (*R*)-limonene **1** was reacted with *iso*pentylnitrite in a hydrochloric acid solution to form the nitrosochloride dimer **2**. The amines **3a–d** were then reacted into methanol with **2** at 50 °C to afford the desired α-amino-oximes **4a–d**, from which series **4c** and **4d** are new compounds. These latter were obtained respectively in 50% and 63% yield and were fully characterized. As described in the literature,[30–32] the configurations of these compounds were assumed to be (1*S*,4*R*) and confirmed by NMR analysis.

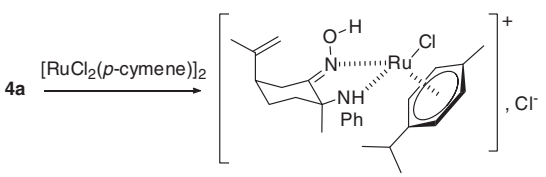
Reaction of the α-amino-oxime **4a** with the $[RuCl_2(p\text{-cymene})]_2$ precursor leads to the clean formation of complex **5a** in 65% yield. Single crystals were isolated as brown needles after recrystallization by slow diffusion of chloroform in an ether solution (Scheme 2). The electrospray ionization mass spectrum of **5a** in MeOH solution showed an isotope cluster at $m/z = 529$. The mass peaks observed for this cluster and the intensity ratio of the various isotope peaks were in excellent agreement with the calculated pattern for the expected molecule $C_{26}H_{36}ClN_2ORu$. X-ray analysis of this complex (Figure 1) confirms the (1*S*,4*R*) configuration onto the amino-oxime.

The main bond lengths and bond angles are given in Table 1. This cationic complex has a highly distorted octahedral coordination environment. A cationic complex of the type [Ru(arene)Cl(neutral amino-amino)]$^+$ had already been crystallographically described.[40]

The ruthenium atom has the characteristic of a three-legged "piano-stool" arrangement. The amino-oxime is coordinated by the two nitrogen atoms that are involved in a five-membered



Scheme 1. Synthesis of α-amino-oxime ligands from (*R*)-limonene.



Scheme 2. Synthesis of the cationic ruthenium complex **5a**.

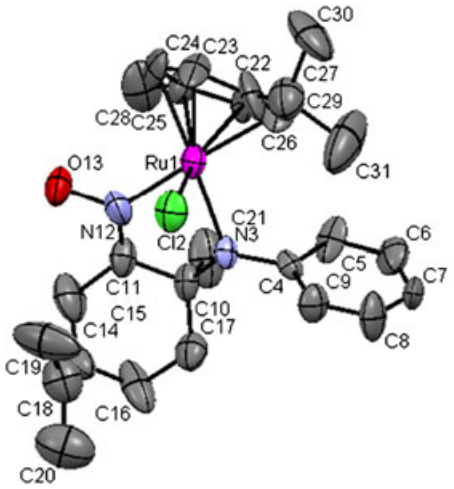


Fig. 1. Molecular structure of the ruthenium complex **5a**, $2CHCl_3$ (the solvate molecules and hydrogen atoms have been omitted for clarity).

TABLE 1. Selected bond lengths (Å) and angles (°) for 5a

Bond lengths		Angles	
Ru-N_3	2.192	N_{oxime}-Ru-N_3	74.0
Ru-N_{oxime}	2.103	Cl-Ru-N_3	79.2
Ru-Cl	2.405	N_{oxime}-Ru-Cl	85.7
N_3-C10	1.517	C4-N_3-C10	119.0
N_{oxime}-C11	1.207	C10-C11-N_{oxime}	117.2
C10-C11	1.498		

chelated ring displaying an envelope conformation with C10 and C11. A chloride anion and the arene complete the coordination sphere on ruthenium. A second chloride anion is present as a non coordinating counterion. Both the Ru-N_{oxime} [2.103 Å] and Ru-N3 [2.192 Å] as well as the Ru-Cl [2.405 Å] and the Ru-$(C)_{arene}$ distances (range 2.17–2.23 Å) are comparable with those reported in the literature.[41]

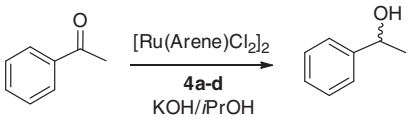
The same procedure was used with the amino-oxime **4b** and $[RuCl_2(p\text{-cymene})]_2$, but suitable crystals for X-Ray analysis of the cationic complex **5b** could not be obtained. A description of the NMR data of the two complexes **5a** and **5b** are given in the Experimental section. The presence of the OH hydroxy moieties is clearly identified at 12.46 and 12.19 ppm (respectively, for **5a** and **5b** complexes).

Results of Catalysis

The four synthesized α-amino-oximes were applied in the ruthenium-catalyzed transfer hydrogenation of acetophenone (Scheme 3). We used the *in situ* technique to check the catalytic performance of each ligand on different precursors by varying the arene moiety on ruthenium from *p*-cymene to benzene and hexamethylbenzene.

These catalysts were formed by mixing $[RuCl_2(arene)]_2$ with one or two equivalents of the desired amino-oxime in *iso*propanol in the presence of potassium hydroxide; the substrate was then added and the mixture heated up to 80 °C.

As shown in Table 2, hydrogen transfer is effective because all the conversions are rather high, up to 97% after at most 24 h. The best activity is obtained using $[RuCl_2(benzene)]_2$



Scheme 3. Hydrogen transfer of acetophenone using Ru catalysts.

as precursor coordinated by the picolylamino-oxime **4d** with 94% conversion after only 7 h. (entry 8, Table 2) On the other hand, for all these reactions, the selectivities are very variable, with a maximal *ee* of 80%. In that latter case, the ligand used was **4b** with a 92% conversion after 19 h. (entry 6, Table 2). Comparing the different results in Table 2 also tells us that the benzene ruthenium complexes are the most active, as shown earlier[41] within this series, and that ligands **4a** and **4b** lead to the best enantioselectivities.

Attempts were made to improve the selectivity upon changing the L/Ru ratio. In all cases, when the ratio was decreased to 1, the activity was improved with conversion ranging from 85% to 100% after 4–6 h. Nevertheless, the enantioselectivity generally dropped drastically. For example, in the case of $[RuCl_2(benzene)]_2$ coordinated by **4a**, an 81% conversion and a 43% *ee* were observed after 21 h, whereas at L/Ru = 1, the conversion was 88% after 6 h but to the detriment of the enantioselectivity (17%). The same trend was observed with ligand **4b**, but to a much less extent, as using a Ligand/Ru ratio of 1, the *ee* remained much more stable (84% and 80% *ee* after 4 h and 9 h at 82% and 93% conversion, respectively). This racemization process has already been reported, because of the reversibility of the reaction, and found to be subtantially ketone and ligand dependent.[42] Conversely, when the ratio L/Ru was increased to 4, the activity largely decreases as expected with no change in the *ee*.

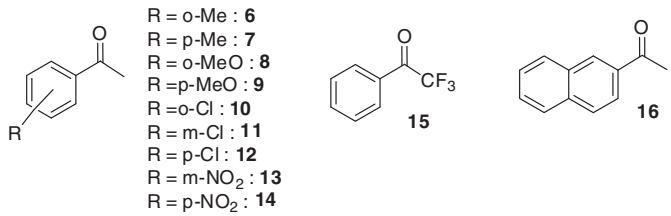
Lowering the temperature to 60 °C using standard conditions with **4a** led to a decrease in the reaction rate but did not improve the enantioselectivity (80% *ee* at 50% conversion after 2 h, 74% *ee* at 94% conversion after 16 h).

Generalization of this reaction to other ketones was next performed. Considering the above results on acetophenone, the $[RuCl_2(benzene)]_2$/**4a** and **4b** catalysts were then applied on substrates **6–16** (Scheme 4), at a ligand/ruthenium ratio of 2 to avoid or limit the racemization process. The results are reported in Table 3.

In the case of substituted aromatic ketones (substrates **6–14**), for a given catalytic system, the reaction rate is generally sensitive to the electronic properties of the phenyl ring substituent. By using **4a** as ligand, reaction rates of substrates with electrodonating substituents (-CH_3: **6**, **7** and -OCH_3: **8** and **9**) are similar to those observed with acetophenone; 90% conversions were reached after 20 h (entries 13, 15, 17, Table 3 versus entry 5, Table 2). On the other hand, by using electron-withdrawing groups as -Cl or -NO_2, the reactions proceed at much higher rate (up to 99% conversion after only 1–10 h, entries 21–34). These differences in reactivity of various substrates were already described by Gladiali with the same trend.[43] The extent of the enantioselectivity appears to be also strongly dependent on the aromatic ring substituents. Enantioselectivities between 6% and 75% were obtained, and it is more difficult to rationalize these *ee* values. The best result is observed with the *m*-chloroacetophenone (74–75% *ee*, entries 23 and 24, Table 3) The same observation has already been reported by Noyori who found that the best activity and enantioselectivity were also reached with this substrate.[44] In the case of trifluoroacetophenone **15**, the result was rather disappointing with a maximal *ee* of 46% (entries 31–32). The asymmetric reduction of 2-acetonaphtone **16** led to the best result in terms of activity (90% yield after 2 h) and enantioselectivity (78% *ee*) with the catalytic system $[Ru(benzene)Cl_2]_2$/**4b**/KOH (entry 34).

As these ligands are bearing both NH and OH moieties, attempts were made to look at the mechanism of the hydrogen transfer, which may occur via pathways involving a ruthenium hydride as already described for amino alcohols.[42,45]

To confirm this hypothesis, we followed Noyori's procedure, that is, via stoichiometric reactions step by step from the



Scheme 4. Aromatic ketones used for asymmetric transfer hydrogenation.

TABLE 2. Transfer hydrogenation of acetophenone using ruthenium complexes $[RuCl_2(arene)]_2$ of amino-oxime ligands 4a–d[a]

Entry	Arene	Ligand	*T* (h)	Conversion (%)	Ee (%)	Configuration
1	*p*-cymene	**4a**	21	97	24	(*S*)
2		**4b**	21	93	12	(*R*)
3		**4c**	22	64	5	(*S*)
4		**4d**	22	96	35	(*S*)
5	Benzene	**4a**	21	84	43	(*S*)
6		**4b**	19	92	80	(*S*)
7		**4c**	23	93	28	(*S*)
8		**4d**	7	94	20	(*S*)
9	HMB	**4a**	20	85	53	(*S*)
10		**4b**	21	97	40	(*R*)
11		**4c**	23	93	28	(*S*)
12		**4d**	24	26	39	(*S*)

HMB, hexamethylbenzene.

[a]All reactions were performed using 2 mmol of acetophenone in 20 ml of *i*PrOH. S/Ru = 100, Ligand/Ru = 2, Base/Ru = 2, *T* = 80 °C.

TABLE 3. Transfer hydrogenation of various ketones using ruthenium complexes of amino-oxime ligands 4a and 4b[a]

Entry	Substrate	Ligand	*T* (h)	Conversion (%)[b]	Ee (%)[b]	Configuration[c]
13	**6**	**4a**	22	98	6	(*S*)
14		**4b**	23	99	24	(*S*)
15	**7**	**4a**	22	96	12	(*S*)
16		**4b**	23	97	55	(*S*)
17	**8**	**4a**	22	84	28	(*S*)
18		**4b**	5	88	66	(*S*)
19	**9**	**4a**	7	94	6	(*S*)
20		**4b**	18	84	39	(*S*)
21	**10**	**4a**	8	71	30	(*S*)
22		**4b**	2	95	56	(*S*)
23	**11**	**4a**	23	87	74	(*S*)
24		**4b**	3	97	75	(*S*)
25	**12**	**4a**	6	93	17	(*S*)
26		**4b**	2	92	65	(*S*)
27	**13**	**4a**	24	59	47	(*S*)
28		**4b**	1	99	66	(*S*)
29	**14**	**4a**	24	27	34	(*S*)
30		**4b**	0.5	95	64	(*S*)
31	**15**	**4a**	10	99	37	(*R*)
32		**4b**	3	99	46	(*R*)
33	**16**	**4a**	8	92	59	(*S*)
34		**4b**	2	90	78	(*S*)

[a]All reactions were performed by using 2 mmol of ketone in 20 ml of *i*PrOH. S/Ru = 100, Ligand/Ru = 2, Base/Ru = 2, $T = 80°C$.
[b]Determined using chiral gas chromatography with a Chirasil-Dex CB column.
[c]Determined by comparison of the retention times of the enantiomers on the gas chromatography traces with literature values.

ruthenium precursor and the amino-oxime **4b**. Next are the observations made during these reactions, allowing to support the mechanism and intermediates described in Figures 2 and 4.

i. To a mixture of $[Ru(p\text{-cymene})Cl_2]_2$ and **4b** (1:2) in dichloromethane, 2.2 equivalents of KOH were added. After stirring for 4 h at ambient temperature, the orange solution was filtered, and KCl was eliminated. Evaporation of solvent led to an orange powder. The ^1H NMR analysis of this complex shows the complete disappearance of the OH signal, which is due to the more acidic character of the hydrogen of the oxime than that of the amine. Thereafter, two coordination modes could be envisaged, either via the oxygen moiety to form an oximato complex or with the nitrogen atom. The molecular structure of this complex **6b** has been determined by single crystal X-ray diffraction analysis and is depicted in Figure 3, which shows the nitrogen coordination with a pendent O^- moiety as already described by Pandey.[46] In the asymmetric unit of **6b**, there are two independent molecules that are almost identical. As previously for **5a** complex, the Ru-N (2.171 Å), Ru-N_{oxime} (2.066 Å), and Ru-Cl (2.401 Å) distances and N-Ru-N_{oxime}, N_{oxime}-Ru-Cl, and N-Ru-Cl angles (respectively, 74.8, 82.45, and 82.62°) support a three-legged "piano-stool" arrangement. Noteworthy is also the absence of OH proton in the ^1H NMR spectrum, confirming the abstraction of the oxime proton by the base.

ii. In the presence of a second equivalent of base, HCl should be eliminated to form the active 16-electrons species. In spite of numerous attempts, no clean complex suitable for NMR analysis could be obtained. The use of three or four equivalents of NaOH or NaH as bases led to untractable results as well.

iii. The same procedure was then performed in *i*PrOH instead of CH_2Cl_2. After addition of two equivalents of KOH, the solution turned rapidly red. After 15 min stirring at room temperature, the solvent was evaporated, and a red powder was obtained and analyzed by ^1H NMR. Two resonances at −5.10 and −6.15 ppm in a 1:2 ratio were observed, which would correspond to Ru-H units according to the literature.[41,47] These two signals could be assigned to the presence of the expected two ruthenium diastereoisomers **7b** and **7b'** as already observed by Sirlin and Pfeffer.[47]

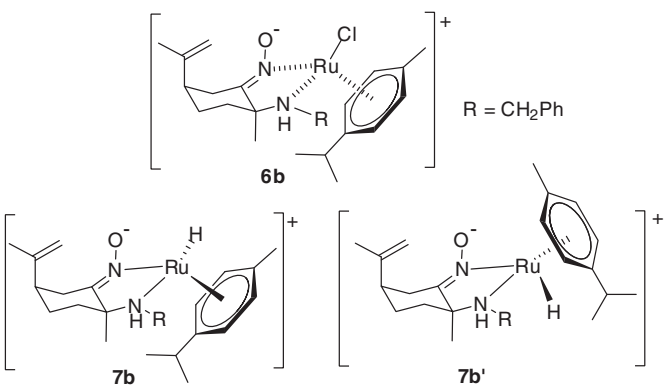


Fig. 2. Proposed intermediates for **3b** amino-oxime-based hydrogen transfer.

These data are in line with the hypothesis that from a mechanistic point of view, the amino-oxime ligands behave similarly as amino alcohols in these transfer reactions.

We then propose the following mechanism (Figure 4).

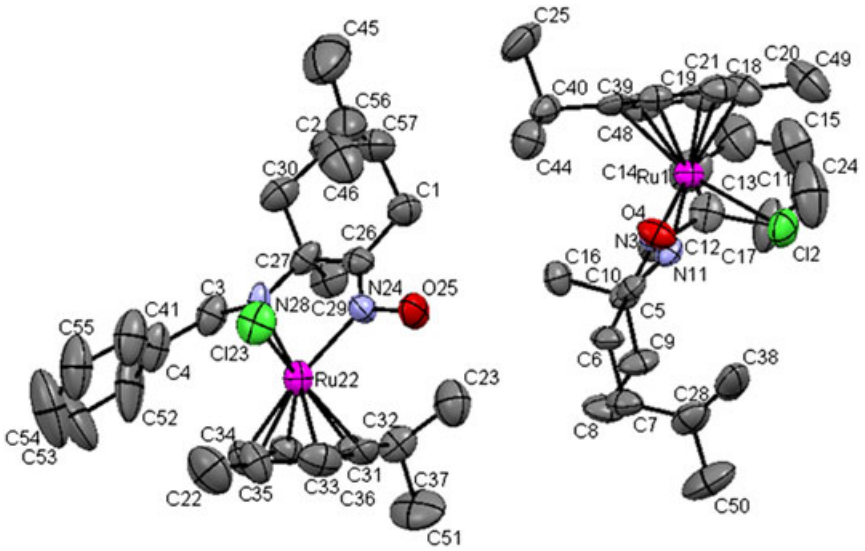


Fig. 3. Molecular structure of the ruthenium complex **6b** (the hydrogen atoms have been omitted for clarity).

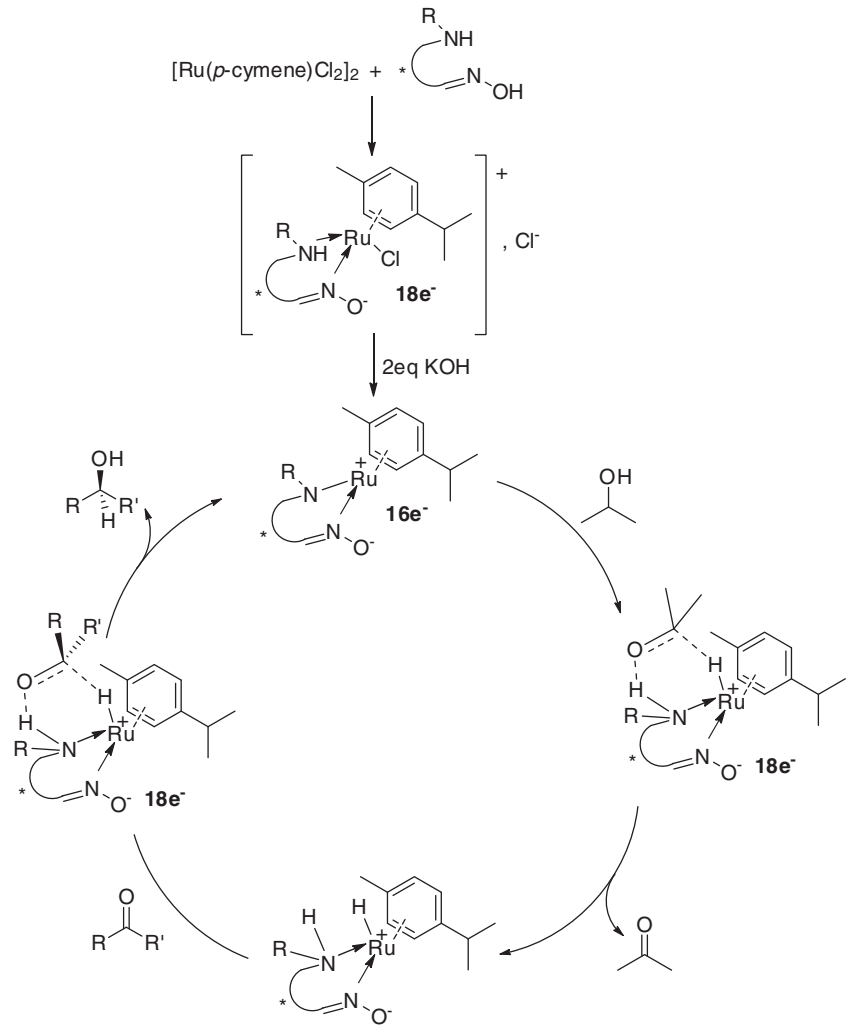


Fig. 4. Proposed mechanism for the asymmetric transfer reaction of ketones over Ru(arene)(aminooxime)-based catalysts.

CONCLUSION

Although their propensity to induce asymmetric induction is by far lower than that of amino alcohols, the use of amino-oxime as ligands for hydrogen transfer reactions using ruthenium catalysts is here proposed for the first time and been shown to probably occur via an outer sphere, six-membered ring catalytic mechanism.

The main advantage that may be found in this chemistry is the straightforward synthesis of these ligands from natural, enantiomerically pure compounds, especially when, as in the present case, both enantiomeric forms are available from the chiral pool, resulting in the possibility to synthesize both enriched enantiomeric mixtures of a desired alcohol at will. Keeping in mind that the chiral terpene sources are renewable and both in large varieties and quantities, these results may open the way to the synthesis of new chiral ligands that may be used in this reaction and many others in asymmetric catalysis.

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