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Synthesis of (*R*)- and (*S*)-4-hydroxyisophorone by ruthenium-catalyzed asymmetric transfer hydrogenation of ketoisophorone

Michael Hennig, Kurt Püntener* and Michelangelo Scalone

Pharmaceuticals Division, Non-Clinical Development–Process Research and Chemical Technologies–Molecular Structure Research, F. Hoffmann-La Roche Ltd, CH-4070 Basel, Switzerland

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Abstract

The first synthesis of (*R*)- and (*S*)-4-hydroxyisophorone by catalytic transfer hydrogenation of ketoisophorone is reported. Ruthenium catalysts containing commercially available chiral amino alcohols afforded 4-hydroxyisophorone in up to 97% selectivity and 97% ee. (*R*)- or (*S*)-4-Hydroxyisophorones with >99% ee were isolated by crystallization. The catalyst precursors [$RuCl_2$((*S*,*R*)-ADPE)(η^6-*p*-cymene)] ((*S*,*R*)-ADPE = (1*S*,2*R*)-amino-1,2-diphenylethanol-*N*) and (R_{Ru})-[RuCl((*S*,*R*)-$ADPE^{-1}$)(η^6-*p*-cymene)] ($ADPE^{-1}$ = amino-1,2-diphenylethanolato-*N*,*O*) were isolated for the first time and the X-ray crystal structure of the latter determined.

1. Introduction

4-Hydroxyisophorone **2** (Scheme 1) is a volatile constituent of saffron,[1] a tobacco flavoring material[2] and an intermediate in the synthesis of pharmaceuticals[3] and natural pigments.[4] Whereas *rac*-**2** is easily accessible, e.g. by oxidation of β-isophorone (3,5,5-trimethyl-3-cyclohexen-1-one)[2,5] or by hydride reduction of ketoisophorone **1**,[6] an efficient synthesis of enantiomerically pure **2** is missing. The asymmetric hydrogenation of **1** for instance, afforded only a complex mixture of products, which contained phorenol **3** and levodione **4** as the main components.[7] On the other hand, the fermentation of **1** proceeded with high ee at low conversion, but suffered from loss of selectivity and partial racemization of **2** at high conversion.[8] Clearly, the presence of three reducible functional groups in conjugation with each other makes tremendous demands of the catalyst's selectivity.

Recently, new ruthenium catalysts containing chiral amino alcohols have been described to bring about the asymmetric transfer hydrogenation of acetophenone and derivatives to the corresponding

* Corresponding author. E-mail: kurt.puentener@roche.com

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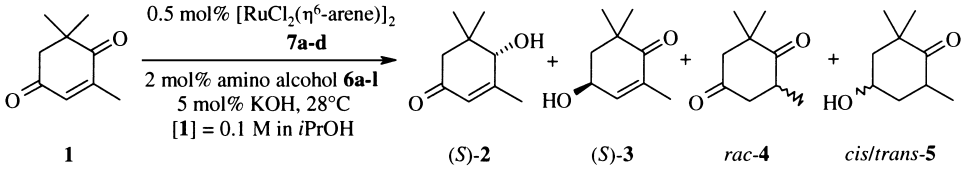


Scheme 1.

alcohols with up to 98% ees.[9] However, if prochiral ketones lacking an aryl or benzyl substituent were used as substrates, the ee values were at best moderate (7–75% ee).[9a,b] These catalyst precursors were formed in situ by treatment of $[RuCl_2(\eta^6\text{-arene})]_2$ with 4 molar equiv. of a chiral amino alcohol in 2-propanol. Then, the transfer hydrogenation was initiated by addition of a base (e.g. potassium hydroxide). Interestingly, at variance with the related and better understood Ru/Ts-DPEN (Ts-DPEN = *N*-tosyl-1,2-diphenylethylenediamine) system,[10] less is known about the structure of the catalyst precursors and the mechanism of the Ru/amino alcohol-catalyzed transfer hydrogenation. Quantum chemical calculations have predicted, for both types of catalytic systems, similar intermediate ruthenium species and a similar mechanism involving a concerted transfer of both a proton and a hydride.[11] Just recently, some of these proposed intermediates were found in the Ru/*cis*-1-amino-2-indanol system by electrospray ionization mass spectrometry.[12]

Herein, the application of the Ru/amino alcohol catalytic system to the asymmetric transfer hydrogenation of **1** is presented, which has resulted in an efficient method to prepare (*R*)- and (*S*)-hydroxyisophorone **2**. Moreover, the synthesis and characterization of the catalyst precursors $[RuCl_2((S,R)\text{-ADPE})(\eta^6\text{-}p\text{-cymene})]$ **8** and (R_{Ru})-$[RuCl((S,R)\text{-ADPE}^{-1})(\eta^6\text{-}p\text{-cymene})]$ **9** is reported.

2. Results and discussion

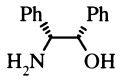
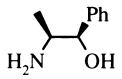
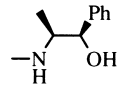
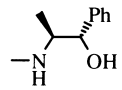
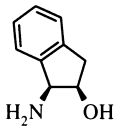
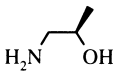
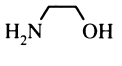
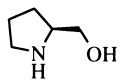
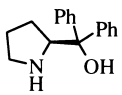
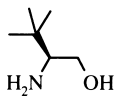
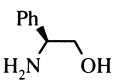
2.1. Asymmetric transfer hydrogenation of *1* with in situ-formed catalysts

Ruthenium catalysts containing chiral amino alcohols of the same type as those which were recently described to be very efficient in the asymmetric transfer hydrogenation of simple aryl ketones[9] were herein applied in the ruthenium-catalyzed transfer hydrogenation of ketoisophorone **1** (Scheme 1).

First, the influence of the amino alcohol's structure was investigated (Table 1). The catalyst precursors were formed in situ by treatment of $[RuCl_2(\eta^6\text{-benzene})]_2$ **7a** with commercially available amino alcohols **6a**–**l**. The results show that with all catalysts hydroxyisophorone **2** was formed in good to high selectivity (up to 97%). In general, the catalysts containing α,β-disubstituted amino alcohols were more active than those containing monosubstituted amino alcohols or ethanolamine, with prolinol **6h** and its α,α′-diphenylsubstituted analogue **6i** acting as exceptions to this rule. Interestingly, the α-substituent of the α,β-disubstituted amino alcohols **6a**–**e** controlled the configuration of **2** completely. This is clearly demonstrated by ephedrine **6c** and its epimer pseudoephedrine **6d**, which both resulted in the formation of **2** with 93% ee but with opposite configurations. The highest ees (97%) were achieved with the amino alcohols **6a** or **6b**. Again, the α-phenyl substituent in both **6a** and **6b** determined the configuration of **2**, independently

of the type of group present in β-position. If the phenyl group in the α-position in **6b** was replaced by a methyl group such as in **6f**, the ee was only slightly diminished. Nevertheless, the influence of the β-substituent on the asymmetric induction was not negligible, as indicated by the results obtained with **6k** and **6l**. Therein, **6k** containing a bulky *tert*-butyl group in the β-position gave **2** with higher ee than its phenyl analogue **6l**.

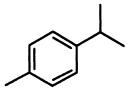
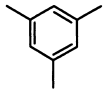
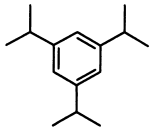
Table 1
Asymmetric transfer hydrogenation of **1** catalyzed by in situ-formed $[RuCl_2(\eta^6\text{-benzene})]_2$ **7a**/amino alcohol **6a–l** complexes[a)]

entry	amino alcohol		t [h]	conv[b)] [%]	**2**[b)] %GC / %ee	**3**[b,c)] %GC / %ee
1		**6a**	0.5	>99	92 / 97 (*S*)	7 / 63 (*S*)
2		**6b**	0.5	>99	94 / 97 (*R*)	4 / 47 (*R*)
3		**6c**	0.5	>99	94 / 93 (*R*)	5 / 48 (*R*)
4		**6d**	0.5	>99	95 / 93 (*S*)	4 / 55 (*S*)
5		**6e**	0.5	>99	97 / 89 (*R*)	2 / 17 (*R*)
6		**6f**	2	>99	94 / 92 (*R*)	5 / 56 (*R*)
7		**6g**	6	>99	92 / -	6 / -
8		**6h**	0.5	>99	95 / 77 (*R*)	4 / 62 (*R*)
9		**6i**	0.5	3	2 / 90 (*R*)	1 / n.d.
10		**6k**	3	48	40 / 86 (*S*)	7 / 82 (*S*)
11		**6l**	3	>99	89 / 57 (*S*)	11 / 68 (*S*)

[a)] Transfer hydrogenation conditions cf. experimental section.
[b)] Conversion and enantiomeric excess determined by GC analysis, cf. experimental section.
[c)] In addition to **3**, 1-2% of *rac*-**4** and *cis*/*trans*-**5** were formed as further by-products.

Next, the influence of the ruthenium-coordinated arenes on the transfer hydrogenation of ketoisophorone **1** was investigated (Table 2). The catalysts were formed in situ as described above from $[RuCl_2(\eta^6\text{-arene})]_2$ **7a–d** and **6a**. It appears that the bulkier the coordinated arene, the lower the rate, the regio- and the enantioselectivity of the reduction. Analogously, sodium borohydride reduced **1** predominantly to **2** in 81% yield,[13,14] whereas the bulkier 9-BBN afforded exclusively **3** in 78% yield.[15] Evidently, sterically more demanding reducing agents have less access to the C(4) keto group of **1** and therefore preferentially reduce the C(1) keto group to give phorenol **3**.

Table 2
Asymmetric transfer hydrogenation of **1** catalyzed by in situ-formed $[RuCl_2(\eta^6\text{-arene})]_2$ **7a–d**/amino alcohol (*S*,*R*)-**6a** complexes[a)]

entry	$[RuCl_2(\eta^6\text{-arene})]_2$ arene:		t [h]	conv[b)] [%]	**2**[b)] %GC / %ee	**3**[b,c)] %GC / %ee
1		**7a**	0.5	>99	92 / 97 (*S*)	7 / 63 (*S*)
2		**7b**	1	>99	80 / 91 (*S*)	13 / 48 (*S*)
3		**7c**	4	84	55 / 89 (*S*)	29 / 76 (*S*)
4		**7d**	1	19	3 / 43 (*S*)	16 / 63 (*S*)

[a)] Transfer hydrogenation conditions cf. experimental section.
[b)] Conversion and enantiomeric excess determined by GC analysis, cf. experimental section.
[c)] In addition to **3**, 1-6% of *rac*-**4** and *cis*/*trans*-**5** were formed as further by-products.

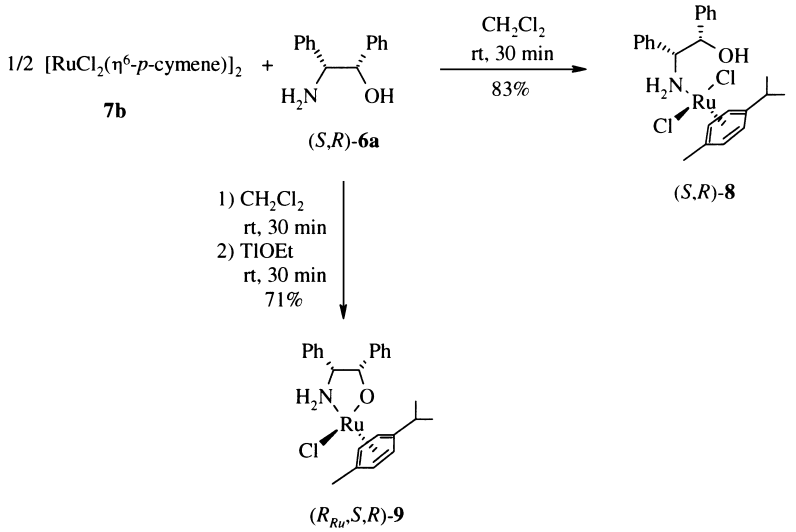
Transfer hydrogenation of **1** was also investigated using the catalyst precursor [RuCl((*S*,*S*)-Ts-$DPEN^{-1}$)(η^6-*p*-cymene)] **10**.[16] However, this catalytic system was less active and regioselective than its closely related **7b**/**6a** analogue (cf. Table 2, entry 2), affording after 6 h (conv. >99%) only 23% of **2**. Again, the lower regioselectivity might be explained by the presence of the sterically demanding tosyl group in **10**.

Pure (*S*)- and (*R*)-4-hydroxyisophorone **2** were isolated after transfer hydrogenation of ketoisophorone **1** (92% selectivity, 97% ee) and subsequent crystallization from diisopropyl ether in 54–55% yield with >99% ee (cf. Experimental section). The corresponding $[\alpha]_D^{22}$ values of –105.8 ($c = 1.00$, MeOH) for (*S*)-**2** and +105.9 ($c = 1.00$, MeOH) for (*R*)-**2** indicate that 4-hydroxyisophorone **2** prepared by fermentation of **1**, which had $[\alpha]_D^{23}$ values of –52.6 ($c = 0.90$, MeOH) and +42.6 ($c = 1.60$, MeOH), respectively,[8] was of much lower enantiomeric purity. Interestingly, (*R*)-**2** has a strong tobacco-like scent, whereas (*S*)-**2** is virtually odorless.

2.2. Synthesis and characterization of catalyst precursors

Surprisingly, very little is known about the structure of the catalyst precursors and the intermediates in the Ru/amino alcohol catalyzed transfer hydrogenation.[9,11,12]

In order to have an insight into the species formed during the in situ preparation of the catalyst solution, a sample of the reaction of **7b** with 4 molar equiv. of **6a** was evaporated to dryness. In the crude residue, beside some unknown by-products, mainly [$RuCl_2$((*S*,*R*)-ADPE)(η^6-*p*-cymene)] **8** was identified by ^{1}H NMR spectroscopy (Scheme 2). Pure **8** crystallized from this mixture upon standing at –15°C. Complex **8** was also prepared separately by treatment of [$RuCl_2(\eta^6$-*p*-cymene)]$_2$ **7b** with 2 molar equiv. of **6a** in 83% yield. The *N*-coordination of the amino alcohols **6a** in **8** is supported by the different chemical shifts of the two N–H protons in the ^{1}H NMR spectrum and is in accordance with the well known ability of amines to cleave dichloro bridged dimers such as **7b** to form monomeric [$RuCl_2$(amine-*N*)(η^6-arene)] complexes.[17]



Scheme 2.

Treatment of **8** with sodium hydroxide (Ru:OH^- molar ratio = 1:5) in 2-propanol at rt for 20 h and removal of the solvents afforded (R_{Ru})-[RuCl((*S*,*R*)-$ADPE^{-1}$)(η^6-*p*-cymene)] **9** as the main product. There was no evidence by ^{1}H NMR spectroscopy of the presence of [RuH((*S*,*R*)-$ADPE^{-1}$)(η^6-*p*-cymene)] or of the 16 electron complex [Ru((*S*,*R*)-$ADPE^{-2}$)(η^6-*p*-cymene)]. Pure **9** was better synthesized by treatment of **7b** with **6a** in the presence of thallium ethoxide (Scheme 2) affording, after removal of the solvents, virtually pure **9** as a single diastereomer. Subsequent crystallization from methanol/ether afforded the methanol adduct of **9** in 71% yield.

The ORTEP plot of the molecular structure of complex (R_{Ru},*S*,*R*)-**9**·MeOH is depicted in Fig. 1. The descriptor *R* for the ruthenium atom is assigned according to the proposals of Baird and Sloan.[18] The half sandwich complex **9** adopts a distorted three-legged 'piano stool' structure.[19] The Ru metal center occupies the idealized η^6-position with a distance of 1.66 Å from the planar arene unit. The average Ru–C distances (2.182(6) Å; range: 2.158(6)–2.217(6)) and both the Ru–N (2.137(5) Å) and the Ru–Cl (2.439(2) Å) bond lengths are comparable with those found in the related complex [RuCl((*S*,*S*)-Ts-$DPEN^{-1}$)(η^6-*p*-cymene)] **10**,[16] among others.[20] Furthermore, also

the N–Ru–O bond angle in **9** (78.3(2)°) is comparable with the N–Ru–N(Ts) bond angle in **10** (79.4(3)°). Interestingly, the Ru–O bond length in **9** (2.035(4) Å) is shorter than that found in closely related ruthenium α-aminocarboxylato-*N*,*O* complexes (2.07–2.09 Å).[21] The RuCl···HN distance in **9** (2.71 Å) is consistent with hydrogen bonding,[22] although it should be noted that this hydrogen atom has been included in a calculated position and was not found in the difference-Fourier map. Interestingly, the RuCl···HN distance in **10** (2.57 Å) is significantly shorter. This could reflect the observation that the HCl abstraction by a base in **10** proceeds easily to yield the stable 16 electron complex [Ru(Ts-DPEN^{-2})(η^6-*p*-cymene)],[10] whereas under the same conditions no reaction occurs with **9**.

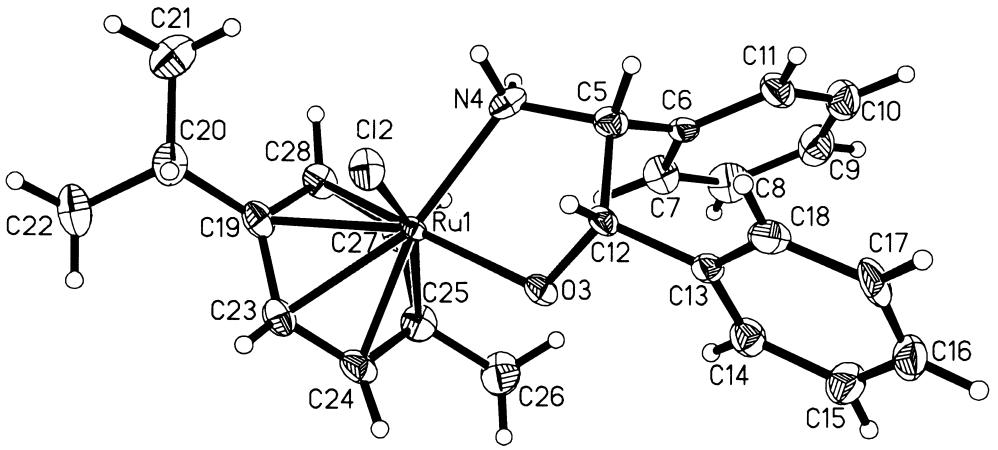


Figure 1. Molecular structure (50% thermal ellipsoids) and absolute configuration of (R_{Ru},*S*,*R*)-**9**·MeOH with arbitrary atom numbering scheme. For better clarity, the solvate methanol molecule is not included in the drawing. Selected bond lengths (Å) and angles (°): Ru(1)–O(3) 2.035(4), Ru(1)–N(4) 2.137(5), Ru(1)–Cl(2) 2.439(2), O(3)–C(12) 1.421(7), N(4)–C(5) 1.511(8), C(5)–C(12) 1.560(8); N(4)–Ru(1)–O(3) 78.3(2), N(4)–Ru(1)–Cl(2) 81.28(14), O(3)–Ru(1)–Cl(2) 89.19(12)

In the absence of a base, complexes **8** and **9** were inactive in the transfer hydrogenation of **1**. If **9** was used as a catalyst precursor in the presence of a base in the transfer hydrogenation of acetophenone,[23] (*S*)-phenylethanol was formed with identical yield (97%) and ee (56%) as reported with the in situ-formed catalyst precursor.[9a] However, if **8** or **9** were employed in transfer hydrogenation of **1**, 4-hydroxyisophorone **2** was formed more selectively and with higher ees than with the in situ-formed catalyst precursor (Table 3). Interestingly, the catalyst formed from **8** lost its activity during transfer hydrogenation. This was also observed when the catalyst precursor was prepared in situ from **7b**/**6a** with a molar ratio of Ru:**6a** = 1:1 only. Advantageously, no excess of **6a** was necessary to maintain the catalyst's activity, if the preformed catalyst precursor **9** was used directly.

If **9** was applied in the transfer hydrogenation of acetophenone with formic acid:triethylamine (5:2) in lieu of 2-propanol as solvent and hydride source, no conversion was observed. In contrast, [RuCl(Ts-DPEN^{-1})(η^6-*p*-cymene)] **10** also effectively catalyzed the transfer hydrogenation of acetophenone in other systems, such as in formic acid:triethylamine (5:2),[20a] sodium formate:DMSO[24] or hypophosphorous acid:triethylamine (1:1).[25] Evidently, the two ruthenium complexes **9** and **10** have a different propensity to generate the catalytically active species. In this respect, we noticed that when a CD_2Cl_2-solution of **10** was treated with a D_2O-solution of sodium

Table 3
Performance of the in situ-formed **7b**/(*S*,*R*)-**6a** versus the preformed catalyst precursors **8** and **9** in the transfer hydrogenation of **1**[a)]

entry	catalyst precursor	t [h]	conv[b)] [%]	**2**[b)] %GC / %ee	**3**[b,c)] %GC / %ee
1	**7b**/(*S*,*R*)-**6a**	1	>99	80 / 91 (*S*)	13 / 48 (*S*)
2	(*S*,*R*)-**8**	4[d)]	80	67 / 95 (*S*)	12 / 62 (*S*)
3	(R_{Ru},*S*,*R*)-**9**	1	>99	84 / 96 (*S*)	14 / 62 (*S*)

[a)] Transfer hydrogenation conditions cf. experimental section.
[b)] Conversion and enantiomeric excess determined by GC analysis, cf. experimental section.
[c)] In addition to **3**, 1-6% of *rac*-**4** and *cis*/*trans*-**5** were formed as by-products.
[d)] A sample taken after 1 h showed 76% conversion.

formate (10 molar equiv.), the catalytic active hydride complex [RuH(Ts-DPEN^{-1})(η^6-*p*-cymene)] was exclusively formed in the organic layer, whereas no hydride resonance was detected by ^{1}H NMR spectroscopy if **9** was subjected to the same conditions.

3. Conclusions

We demonstrated that the Ru/amino alcohol-catalyzed asymmetric transfer hydrogenation of ketoisophorone **1** is a powerful tool to prepare (*S*)- and (*R*)-4-hydroxyisophorone **2** with high selectivity and ee. The catalysts are easily prepared in situ from commercially available components and, advantageously, the transfer hydrogenation can be carried out in standard laboratory equipment using Schlenk techniques. For the first time, the so far proposed ruthenium catalyst precursor (R_{Ru})-[RuCl((*S*,*R*)-ADPE^{-1})(η^6-*p*-cymene)] **9** has been isolated and characterized by X-ray analysis. Further work will aim at identifying the catalytic active species in the Ru/amino alcohol system as already done in the Ru/Ts-DPEN one.[10]

4. Experimental

All manipulations were carried out routinely under an argon atmosphere using Schlenk techniques. The solvents were dried before use and distilled under argon. The amino alcohols **6a**–**l** and the ruthenium precursors **7a**–**b** were purchased from Aldrich, Strem or Fluka AG. The ruthenium complexes **7c**–**d** were prepared according to the literature.[26] Melting points were determined on a Büchi 510 and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 spectrometer. IR spectra were recorded on a Perkin–Elmer FTIR 1750 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AC 250E spectrometer by using TMS as an internal standard. Chemical shifts are given in ppm (δ) and *J* values in hertz. ESI-MS spectra were measured on a Perkin–Elmer Sciex API III. Elemental analyses were determined with a Carlo Erba 1160 elemental analyzer. Gas chromatographic analyses were carried out on a Perkin–Elmer Mod. AutoSystem equipped with a fused silica column (30 m) with Permaphase

PE-wax as the stationary phase. Enantiomeric excess was determined by GC using a Hewlett–Packard 5890 II equipped with a fused silica column (30 m) with BGB-176 as the stationary phase.

4.1. General procedure for the transfer hydrogenation of **1**

4.1.1. Method A: with in situ prepared catalyst precursors

In a typical experiment, **7b** (14.8 mg, 0.024 mmol) and (*S*,*R*)-**6a** (20.8 mg, 0.10 mmol) were dissolved in a 100 ml Schlenk tube containing 2-propanol (10 ml). The red solution was stirred for 1 h at 80°C and, after cooling to 28°C, **1** (0.73 ml, 4.8 mmol), 0.1 M sodium hydroxide in 2-propanol (2.42 ml, 0.24 mmol) and 2-propanol (38 ml) were added. After stirring the resulting mixture for 1 h at 28°C, the GC analysis of a sample filtered through a short silica gel path showed the conversion to be complete. The product consisted of 80% (*S*)-**2** with 91% ee, 13% (*S*)-**3** with 48% ee and 6% *cis*/*trans*-**5**.

4.1.2. Method B: with preformed catalyst precursors

In a typical experiment, (R_{Ru},*S*,*R*)-**9** (5.2 mg, 0.01 mmol) and **1** (0.15 ml, 1.0 mmol) were dissolved in a 50 ml Schlenk tube containing 2-propanol (10 ml). At 28°C, 0.1 M sodium hydroxide in 2-propanol (0.50 ml, 0.05 mmol) were added and the red solution stirred for 1 h. The GC analysis of a sample filtered through a short silica gel path showed the conversion to be complete. The product consisted of 84% (*S*)-**2** with 96% ee, 14% (*S*)-**3** with 62% ee and 2% *cis*/*trans*-**5**.

4.2. Preparation of (S)-4-hydroxyisophorone, (S)-**2**

Compounds **7a** (103.8 mg, 0.21 mmol) and (*S*,*R*)-**6a** (177.2 mg, 0.83 mmol) were dissolved in a 250 ml round-bottomed flask containing 2-propanol (50 ml). After stirring the red solution for 30 min at 80°C, 2-propanol (365 ml) was added and after cooling to 28°C, **1** (6.13 ml, 41.5 mmol) and 0.1 M sodium hydroxide in 2-propanol (20.8 ml, 2.08 mmol) were added. After 30 min, the red solution was filtered through a silica gel path and the filtrate was evaporated to dryness. The black oily residue was distilled under high vacuum (0.5 mbar, 200°C) to afford crude (*S*)-**2** (5.37 g, 83%) with 92% purity and 95% ee as a yellow oil which solidified on standing. After two crystallizations from diisopropyl ether, (*S*)-**2** (3.50 g, 55%) was isolated as a white solid with 99.6% purity and 99.7% ee. Mp 72°C, $[\alpha]_D^{22} = -105.8$ ($c = 1.00$, methanol). IR (KBr): $\nu_{max} = 3411$ (m), 1655 (s), 1621 (m), 1374 (s), 1080 (s). ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.02$ (s, 3H), 1.08 (s, 3H), 2.05 (t, 3H, $J = 1.2$), 2.21 (d, 1H, $J = 16.3$), 2.27 (d, 1H, $J = 6.8$), 2.41 (d, 1H, $J = 16.4$), 4.04 (d, 1H, $J = 6.8$), 5.86 (m, 1H). MS (EI) *m*/*z*: 154 (M^+, 5%). Anal. calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.94; H, 8.90.

4.3. Preparation of (R)-4-hydroxyisophorone, (R)-**2**

Compound (*R*)-**2** was prepared from **7a** (111.9 mg, 0.22 mmol), (*R*,*S*)-**6a** (190.9 mg, 0.89 mmol), **1** (6.59 ml, 44.7 mmol) and 0.1 M solution of sodium hydroxide in 2-propanol (22.4 ml, 2.24 mmol) in 2-propanol (420 ml) in analogy to the procedure described for (*S*)-**2**. Two crystallizations of the crude (*R*)-**2** from diisopropyl ether afforded (*R*)-**2** (3.72 g, 54%) with 99.3% purity and 99.3% ee. Mp 72°C, $[\alpha]_D^{22} = +105.9$ ($c = 1.00$, methanol). Anal. calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.82; H, 8.99. The spectroscopic data were in agreement with those of (*S*)-**2**.

4.4. Preparation of [$RuCl_2$((S,R)-*ADPE*)(η^6-p-*cymene*)], (S,R)-**8**

In a 50 ml Schlenk tube, **7b** (719.3 mg, 1.2 mmol) and (*S*,*R*)-**6a** (501 mg, 2.4 mmol) were dissolved in dichloromethane (30 ml). After stirring the red solution for 30 min at rt, diethyl ether (20 ml) was added dropwise and the resulting voluminous jelly suspension was stored at 0–5°C overnight. After filtration, the residue was dried under high vacuum at rt to afford (*S*,*R*)-**8** (1.01 g, 83%) as a yellow solid. IR (KBr): ν_{max} = 3400 (m), 1500 (m), 852 (w), 756 (m), 699 (s). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.19 (d, 3H, J = 6.9), 1.23 (d, 3H, J = 6.9), 2.07 (s, 3H), 2.89 (sept., 1H, J = 6.9), 3.2–3.4 (br, 1H), 3.52 (br d, 1H, J = 9.1), 3.67 (br t, 1H, J = 11.1), 4.4–4.5 (m, 1H), 4.76 (d, 1H, J = 5.8), 4.94 (d, 1H, J = 5.8), 5.01 (d, 1H, J = 5.8), 5.13 (d, 1H, J = 5.8), 5.15 (s, 1H), 6.9–7.0 (m, 2H), 7.1–7.2 (m, 5H), 7.3–7.4 (m, 3H). Anal. calcd for $C_{24}H_{29}N\,OCl_2Ru$: C, 55.49; H, 5.63; N, 2.70; Cl, 13.65. Found: C, 55.28; H, 5.62; N, 2.70; Cl, 13.55.

4.5. Preparation of (R_{Ru})-[*RuCl*((S,R)-*ADPE*$^{-1}$)(η^6-p-*cymene*)], (R_{Ru},*S*,*R*)-**9**

In a 100 ml Schlenk tube, **7b** (1.42 g, 2.32 mmol) and (*S*,*R*)-**6a** (0.999 g, 4.64 mmol) were dissolved in dichloromethane (75 ml). After stirring the red solution for 30 min at rt, thallium ethoxide (1.18 g, 4.64 mmol) was added dropwise and the resulting suspension was stirred for an additional 30 min. After removal of the solids by filtration, the filtrate was evaporated to dryness under reduced pressure. The crude (R_{Ru},*S*,*R*)-**9** was crystallized from methanol/diethyl ether to afford (R_{Ru},*S*,*R*)-**9**·MeOH (1.68 g, 71%) as orange crystals. IR (KBr): ν_{max} = 3330 (m), 2787 (s), 1610 (m), 1500 (m), 1042 (s), 852 (w), 750 (m), 700 (s). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.31 (d, 6H, J = 6.7), 2.33 (s, 3H), 2.85 (sept., 1H, J = 6.7), 3.43 (s, 3H), 3.87 (br t, 1H, J = 4.6), 4.04 (br d, 1H, J = 9.2), 4.2–4.4 (br, 1H), 4.81 (d, 1H, J = 5.7), 5.16 (d, 1H, J = 5.3), 5.22 (d, 1H, J = 4.3), 5.29 (d, 1H, J = 5.7), 5.51 (d, 1H, J = 5.7), 6.93 (t, 1H, J = 7.1), 7.0–7.1 (m, 2H), 7.1–7.2 (m, 3H), 7.32 (d, 2H, J = 7.1), 7.4–7.5 (m, 2H). MS (ESI) m/z: 448 (M–Cl$^+$, 100%). Anal. calcd for $C_{25}H_{32}NO_2ClRu$: C, 58.30; H, 6.26; N, 2.72; Cl, 6.88. Found: C, 58.33; H, 6.31; N, 2.79; Cl, 7.03.

4.6. X-Ray crystal structure of (R_{Ru},S,R)-**9**

Crystals of (R_{Ru},*S*,*R*)-**9** suitable for X-ray diffraction were grown by storing a methanolic solution of **8** at –15°C for 1 week under argon. Crystal data: $C_{25}H_{32}ClNO_2Ru$, M = 515.04, red prisms, crystal size: 0.6×0.6×0.6 mm, orthorhombic, space group: $P222(1)$; a = 13.214 Å, b = 16.865 Å, c = 10.436 Å, Z = 4, V = 2325.7 Å^3, Dc = 1.471 g cm^{-3}, $F(000)$ = 1064, μ(Cu-K$_\alpha$) = 0.810 mm^{-1}. Data collection: all measurements were made on a Siemens P4 diffractometer equipped with a graphite monochromator using Cu-K$_\alpha$ radiation (λ = 1.54 Å). The data were collected at –90(1)°C. The Θ range for data collection was 1.96–55.94°. The structure was refined without restrains using 3086 independent reflections. The Flack parameter was refined to –1.32(5). The final R-value for all data was 0.0403 (R_w = 0.1062). The structure was solved by direct methods and all non-hydrogen atoms were refined anisotropically using full-matrix least-square technique and Fourier synthesis based on F^2 (SHELX-package).[27]

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