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Enantioselective reduction of aromatic ketones catalysed by chiral ruthenium(II) complexes

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Abstract

The catalytic enantioselective reduction of aromatic ketones in 2-propanol is carried out by using ruthenium(II) complexes prepared from $[Ru(p\text{-cymene})Cl_2]_2$ and a variety of chiral diamines and β-amino-alcohols derived from α-amino acids. Good conversions (>99%) and enantioselectivities (=96%) are observed under mild reaction conditions.

1. Introduction

The asymmetric synthesis of chiral secondary alcohols, which play an important role as intermediates in organic chemistry, is a stimulating subject. Several methods for the asymmetric reduction of prochiral ketones have been used such as enantioselective 'hydride' reduction and enantioselective hydrogenation.[1–4] However, organic synthesis needs economically and technically more beneficial methods that are very general. Transition metal catalysed transfer hydrogenation with 2-propanol is a convenient method to reduce ketones since there is no need for high hydrogen pressure or hazardous reducing agents. It has only been over recent years that some satisfactory results in the enantioselective reductions using 2-propanol have been accomplished with some transition metal complexes, where pioneering efforts were made by Pfaltz (Ir),[5] Genet (Ru)[6] and Lemaire (Rh),[7] among others.[8,9]

However, these processes can still be improved for practical use in organic synthesis, being limited by low catalytic activity and low substrate/catalyst molar ratio (S/C). Excellent catalytic performance in asymmetric transfer hydrogenation of ketones with 2-propanol was achieved with ruthenium(II) complexes using chiral *N*-monosulfonylated C_2 symmetrical diamines as ligands.[10–12] However, their preparation, which takes several steps, sometimes needs a resolution.[13] These difficulties limit their use in asymmetric synthesis.

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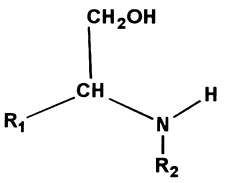
The use of chiral β-aminoalcohols as ligands in various areas of asymmetric synthesis has attracted great attention over recent years and stimulated their application as chiral auxiliaries in the enantioselective transfer hydrogenation of prochiral aromatic ketones catalysed by ruthenium(II) complexes.[10f,12,14–16]

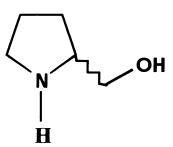
In this field, Noyori's group have found that ephedrine and ψ-ephedrine derivatives show a particulary high ligand-acceleration effect and high enantioselectivity.[14] Palmer et al. have also used (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol as a ligand in the same reaction and showed that a primary amine function in the ligand is essential.[15] The use of the *N*-methyl derivative resulted in lower asymmetric induction.[15] More recently, it has also been shown that amino acids could be used as chiral modifiers for the same reaction.[17] This communication prompts us to publish our recent results in this field, related to the use of a series of simple chiral aminoalcohols as ligands, following the pioneering work using ephedrines and related compounds.[10f,12,14–16] In line with other studies using this type of ligand,[14,16] we first used a series of simple acyclic aminoalcohols (derived from natural α-amino acids: leucine, I-leucine, alanine, valine and phenylglycine) in the ruthenium catalytic asymmetric reduction of acetophenone.

2. Ligand synthesis

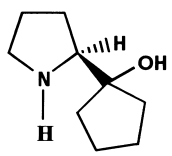
The interest of our catalytic system is the easy accessibility of the chiral ligands from natural α-amino acids. The aminoalcohols, (*R*)-leucinol (*R*)-**3**, (2*S*,3*S*)-isoleucinol (2*S*,3*S*)-**5**, (*R*)-phenylglycinol (*R*)-**7**, (*S*)- and (*R*)-pyrrolidinol **8** were commercially available, while the *N*-methyl derivatives were conveniently prepared from the corresponding commercial α-amino acids via an efficient three-step procedure. First, the amino acids were converted to the corresponding methyl ester hydrochlorides by treatment with methanol/$SOCl_2$. The salt was employed as such in the *N*-formylation step, where the α-amino acid methyl ester hydrochloride was added to formic acetic acid anhydride in chloroform and triethylamine. The *N*-formylamino acid methyl ester obtained was reduced with $LiAlH_4$ in THF to afford the *N*-methyl aminoalcohol in pure form.



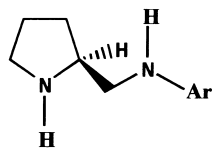
R_1= CH_3	R_2 = CH_3	(S)-1
R_1= $CH(CH_3)_2$	R_2 = CH_3	(S)-2
R_1= $CH_2CH(CH_3)_2$	R_2 = H	(R)-3
R_1= $CH_2CH(CH_3)_2$	R_2 = CH_3	(R)-4
R_1= $CH(CH_3)C_2H_5$	R_2 = H	(2S,3S)-5
R_1= $CH(CH_3)C_2H_5$	R_2 = CH_3	(2S,3S)-6
R_1= Ph	R_2 = H	(R)-7



(S)- 8
(R)-8



(S)-9



Ar = phenyl (S)-10
Ar = naphthyl (S)-1

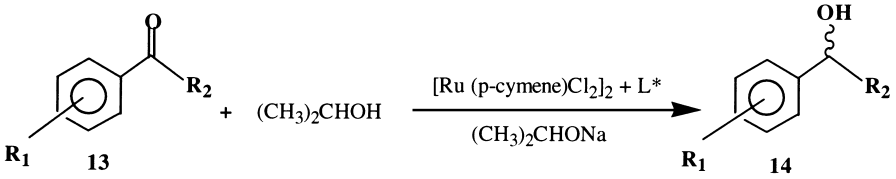
The cyclic aminoalcohol (*S*)-1-pyrrolidine-2-yl-cyclopentanol (*S*)-**9** has been prepared via an efficient two-step procedure from L-proline.[18] First, (*S*)-proline was converted to the corresponding

ethyl ester hydrochloride by treatment with ethanol/$SOCl_2$. The salt was employed as such in the Grignard reaction. Thus, (*S*)-proline ethyl ester hydrochloride was added to a fourfold excess of 1,4-bis(bromomagnesio)butane in ether to give (*S*)-1-pyrrolidine-2-yl-cyclopentanol (*S*)-**9** in 48% yield.

In order to maximise asymmetric inductions, we felt it valid that the use of stereochemically 'rigid' diamines, in particular (*S*)-2-anilinomethylpyrrolidine (*S*)-**10** and (*S*)-2-naphthylaminomethylpyrrolidine (*S*)-**11**, would be beneficial. We can notice here that diamine (*S*)-**10**, which is commercially available in enantiomerically pure form, has been used with success as the basic component for the synthesis of diaminodiphosphine chiral ligand for the catalytic asymmetric reduction of olefins.[19] Reduction of the commercial L-proline-2-naphthylamide by lithium aluminium hydride gave the diamine (*S*)-**11**.

3. Reduction results and discussion

In a typical experiment, the ruthenium(II) complexes were prepared in situ from [Ru(*p*-cymene)Cl_2]$_2$[20] and the chiral ligands (Ru atom:aminoalcohol: 1:2) at 80°C for 30 min under nitrogen using isopropanol as solvent. After introduction of the ketone into the catalyst solution at 0.1 M concentration (S/C = 100), the reduction was conducted at room temperature in the presence of sodium isopropoxide (*i*PrONa) (5 equiv. per Ru atom) freshly prepared using metallic sodium and isopropanol.



a: R_1 = H R_2 = Me
b: R_1 = p-Cl R_2 = Me
c: R_1 = o-OMe R_2 = Me
d: R_1 = H R_2 = CMe_3

R and S

Initial studies were conducted using acetophenone as substrate with different acyclic aminoalcohol ruthenium(II) complexes. The results are summarised in Table 1.

Table 1
Reduction of acetophenone catalysed by Ru(II)–acyclic aminoalcohol complexes

entry	L*	t/h		yield [a] / %		e.e.[b] %		config.
1	(*S*)-**1**	1.5	(3)	88	(95)	34	(30)	(*S*)
2	(*S*)-**2**	3	(6)	72	(92)	**50**	(**45**)	(*S*)
3	(*R*)-**3**	1	(3.5)	97	(97)	19	(09)	(*R*)
4	(*R*)-**4**	0.5	(3)	90	(95)	38	(30)	(*R*)
5	(2*S*,3*S*)-**5**	0.5	(3)	85	(95)	31	(20)	(*S*)
6	(2*S*,3*S*)-**6**	1	(3)	77	(93)	**53**	(**50**)	(*S*)
7	(*R*)-**7**	1	(3)	94	(96)	28	(25)	(*R*)

Conditions: reactions were carried out using a 0.1 M solution of ketone (4.0 mmol) in 2-propanol; ketone: Ru: ligand: iPrONa = 100:1:2:5:, room temperature. (a) Yields were determined by GLC analysis. (b) Determined by capillary GLC analysis using a chiral column (FS-cyclodex beta-I/P). (c) Values in parentheses refer to results obtained after prolonged reaction time.

As shown in Table 1, fast and quantitative reductions to phenylethanol were achieved with Ru(II) complexes prepared in situ from $[Ru(p\text{-cymene})Cl_2]_2$ combined with chiral aminoalcohols **1**–**7**. However, the asymmetric induction is low to moderate for the reduction of acetophenone, the highest being 53% using (2*S*,3*S*)-**6** as ligand.

The use of aminoalcohols with a primary amine function results in low e.e.s (entries 3 and 5). In contrast with other works showing that the presence of a primary amino group is necessary to reach good activities,[14,15] the *N*-methyl derivatives (*R*)-**4** and (2*S*,3*S*)-**6** tend to increase significantly the enantioselectivity and show activities of the same order as their unsubstituted amino precursors (*R*)-**3** and (2*S*,3*S*)-**5** (entries 4 and 6).

The sense of asymmetric induction is determined by the configuration of the amine-bearing carbon, the (*S*)-aminoalcohols afford (*S*)-phenylethanol preferentially, whereas the (*R*) auxiliary gives (*R*)-enriched alcohols. As already observed,[14,15] a decrease in selectivity is observed after prolonged reaction times (Table 1, see values in parentheses).

We have also examined the transfer hydrogenation of aromatic ketones **12a**–**c** using rigid cyclic aminoalcohols, derived from L-proline, under the same conditions. The results are presented in Table 2.

Table 2
Reduction of ketones **12a**–**c** catalysed by Ru(II)–cyclic aminoalcohol complexes

entry	ketone	L*	t/h		yield [a] / %		e.e. % [b]		config.
8	**12a**	(*S*)-**8**	1	(3)	75	(95)	51	(48)	(*R*)
9	**12a**	(*R*)-**8**	1.5	(3)	80	(95)	51	(47)	(*S*)
10	**12a**	(*S*)-**9**	2	(5)	63	(85)	78	(70)	(*R*)
11	**12b**	(*S*)-**8**	2	(5)	70	(99)	40	(40)	(*R*)
12	**12b**	(*S*)-**9**	2	(3)	83	(96)	53	(49)	(*R*)
13	**12c**	(*S*)-**8**	2	(7)	96	(99)	52	(52)	(*R*)
14	**12c**	(*S*)-**9**	2	(3)	51	(94)	68	(60)	(*R*)

Conditions: same as in Table 1. (a) Yields were determined by GLC analysis. (b) Determined by capillary GLC analysis using a chiral column (FS-cyclodex beta-I/P). (c) Values in parentheses refer to results obtained after prolonged reaction time.

As shown in Table 2, when aminoalcohol (*S*)-**9** was used as ligand, we noticed that steric hindrance acts favourably on the enantioselectivity, we also note here that the enantiomeric purity of the alcohols depended on the nature of the aromatic ketones. Thus, acetophenone **12a** and *o*-methoxyacetophenone **12c** were reduced with significant e.e.s. (>68%) (entries 10 and 12). However, the *p*-chloro group on acetophenone significantly decreases the enantioselectivity. When aminoalcohol (*S*)-**8** was used, the enantioselectivity was almost the same using the three substrates (entries 8, 11 and 13).

As revealed from the results shown in Table 1, phenylethanol was obtained with the same absolute configuration as that of the acyclic aminoalcohol. However, with (*S*)-cyclic aminoalcohols, (*R*)-alcohols were obtained predominantly (Table 2).

Reduction of ketones **12a**–**d** under identical condition using ligands (*S*)-**10** and (*S*)-**11** led to the corresponding alcohols in good to excellent yields (59–99%) and high e.e.s (74–96%) (Table 3).

Substitution in ligand (*S*)-**10** of the phenyl by the naphthyl group acts in a favourable way on the activity and enantioselectivity of the reaction (entries 16, 18 and 20).

As already stated, the nature and position of substituents in the aromatic ketone results in significant effects on the activity and enantioselectivity of the reaction.[10a,10c,14] Thus, the reduction

Table 3
Reduction of ketones **12a–d** catalysed by Ru(II)–diamine complexes

entry	ketone	L*	t/h		yield [a] / %		e.e. %[b]		config.
15	**12a**	(*S*)-**10**	1.	(2)	80	(93)	89	(89)	(*R*)
16	**12a**	(*S*)-**11**	0.5	(2)	89	(96)	91	(85)	(*R*)
17	**12b**	(*S*)-**10**	0.5	(1)	83	(98)	93	(87)	(*R*)
18	**12b**	(*S*)-**11**	0.5	(2)	98	(99)	88	(83)	(*R*)
19	**12c**	(*S*)-**10**	1.5	(3)	98	(99)	95	(96)	(*R*)
20	**12c**	(*S*)-**11**	0.25	(1)	99	(100)	95	(93)	(*R*)
21	**12d**	(*S*)-**10**	48	(96)	63	(83)	81	(80)	(*R*)
22	**12d**	(*S*)-**11**	24	(48)	59	(71)	74	(72)	(*R*)
23[c]	**12a**	(*S*)-**10**	5	(8)	87	(90)	87	(83)	(*R*)
24[d]	**12a**	(*S*)-**10**	1	(3)	75	(79)	78	(62)	(*R*)

Conditions: same as in Table 1. (a) Yields were determined by GLC analysis. (b) Determined by capillary GLC analysis using a chiral column (FS-cyclodex beta-I/P). (c) Result of the reaction conducted with S/C=500 and [S]= 0.2M. (d) S/C= 500 and [S]= 1M. (e) Values in parentheses refer to results obtained after prolonged reaction time.

of *p*-chloroacetophenone **12b** and *o*-methoxyacetophenone **12c** resulted in the corresponding alcohols with excellent conversion and e.e.s (entries 17–20). The introduction of a bulky alkyl group like *tert*-butyl (ketone **12d**) led to a decrease in activity, but still a rather good enantioselectivity.

Again, a decrease in enantioselectivity was observed after prolonged reaction times. This arises presumably as a result of the known reversibility of the reaction.[14] To overcome this problem, the use of formic acid/triethylamine as hydrogen transfer reagent has been reported for certain catalytic systems,[10c] with the interest to lead to a non reversible transfer reaction: it has to be noticed that upon using this hydride source with diamines (*S*)-**10** and (*S*)-**11**, no reaction was observed.

This study reveals that the use of disymmetric diamines (*S*)-**10** and (*S*)-**11** derived from L-proline gives excellent results in asymmetric transfer hydrogenation for a variety of ketones. Studies are in progress to improve the enantioselectivity and determine the mode of induction of chirality in this reaction.

4. Experimental

All the commercial products were used as received without any further purification. Isopropanol was distilled over magnesium under nitrogen. The ketones (Aldrich) were degassed and purged under nitrogen prior to use. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker (AM 200) Fourier transform spectrometer. Optical rotations were measured using a Perkin–Elmer 298 polarimeter. The enantiomeric excesses were measured by capillary gas chromatography using a chiral column (FS-cyclodex beta-I/P). The catalyst precursor $[RuCl_2(p\text{-cymene})]_2$ was prepared according to the procedure already described.[20] (*R*)-Leucinol (*R*)-**3**, (2*S*,3*S*)-isoleucinol (2*S*,3*S*)-**5**, (*R*)-phenylglycinol (*R*)-**7**, (*S*)- and (*R*)-pyrrolidinol **8**, (*S*)-2-anilonomethyl-pyrrolidine (*S*)-**10** and L-proline-2-naphthylamide are commercially available (Aldrich or Fluka) in enantiomerically pure form.

4.1. Ligand synthesis

4.1.1. (S)-N-*Methyl-alaninol (S)-**1***

To a solution of (*S*)-alanine (0.5 mol.) in 350 ml of anhydrous methanol was added at 0°C 6.5 ml of thionyl chloride. The solution was stirred at room temperature for 2 h, then 90 min at reflux.

After removal of the solvent, the (*S*)-alanine methyl ester hydrochloride obtained was recrystallised from ethyl acetate. Yield 93%; mp 88°C; $[\alpha]_D^{25}$ +5.8 (c = 1, H_2O); ^1H NMR (D_2O): δ (ppm): 1.3 (d, J = 7 Hz, 3H), 3.7 (s, 3H), 4.6 (q, J = 7 Hz, 1H), 4.5 (s, 3H).

To a solution of (*S*)-alanine methyl ester hydrochloride (0.1 mol) in 200 ml of chloroform was added 0.1 mol of triethylamine in an equal volume of the same solvent. The temperature was kept betwen 0°C and 10°C during the addition. Then were added simultanously 0.1 mol of formic acetic acid anhydride and 0.1 mol of triethylamine. The reaction mixture was stirred for 3 h at room temperature. The mixture was then washed twice with 100 ml of water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. *N*-Formylalanine methyl ester was obtained as an oil, yield 73%, $[\alpha]_D^{25}$ +31.6 (c = 2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm): 1.4 (d, J = 7 Hz, 3H), 3.8 (s, 3H), 4.7 (q, J = 7 Hz, 1H), 7.7 (s, 1H), 8.3 (s, 1H).

To a suspension of lithium aluminium hydride (0.215 mol) in dry THF (100 ml) was added dropwise a suspension of *N*-formylalanine methyl ester (0.1 mol) in 100 ml of THF over 0.5 h at room temperature. The mixture was stirred at reflux for 3 h and 12 h at room temperature. The reaction was hydrolysed with a 30% KOH solution. The solution was filtered off and extracted with a diethyl ether:THF mixture (1:1). The organic layer was dried over anhydous $MgSO_4$. Evaporation of the solvent and distillation of the residue afforded the pure aminoalcohol. Yield 50%, bp 80°C (15 mmHg), $[\alpha]_D^{25}$ +54 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm): 1.0 (d, J = 7 Hz, 3H), 2.4 (s, 3H), 2.4–2.9 (m, 1H), 3.3–3.7 (m, 2H).

The same procedure has been used for the synthesis of ligands (*S*)-**2**, (*R*)-**4** and (2*S*,3*S*)-**6**.

*4.1.2. (*S*)-N-Methyl-valinol (*S*)-**2***

(*S*)-Valine methyl ester hydrochloride: yield 95%, mp 180°C (ethyl acetate), $[\alpha]_D^{25}$ +14.1 (c = 1, H_2O); ^1H NMR ($CDCl_3$): δ (ppm): 0.9 (d, J = 7 Hz, 6H), 2.2 (m, 1H), 3.7 (s, 3H), 3.9 (d, J = 5 Hz, 1H), 4.65 (s, 3H).

(*S*)-*N*-Formylvaline methyl ester: yield 98%, mp 72°C (ethyl acetate/$CHCl_3$), $[\alpha]_D^{25}$ +28.2 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm): 0.95 (d, J = 7, 6H), 2.2 (m, 1H), 3.8 (s, 3H), 4.7 (m, 1H), 6.8 (s, 1H), 8.3 (s, 1H).

(*S*)-*N*-Methyl-valinol **2**: Yield 72%, bp 90°C (15 mmHg), $[\alpha]_{589}$ +53 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm): 0.95 (d, J = 7 Hz, 6H), 1.9 (m, 1H), 2.45 (s, 3H), 3.35 (s, 2H), 3.4–3.8 (m, 3H).

*4.1.3. (*R*)-N-Methyl-leucinol (*R*)-**4***

(*R*)-Leucine methyl ester hydrochloride: yield 85%, mp 155°C (ethyl acetate), $[\alpha]_D^{25}$ –11.7 (c = 1, 2% HCl); ^1H NMR ($CDCl_3$): δ (ppm): 0.8–1.1 (m, 6H), 1.6–1.9 (m, 3H), 3.8 (s, 3H), 3.9–4.3 (m, 1H), 4.75 (s, 3H).

(*R*)-*N*-Formylleucine methyl ester: yield 97%, $[\alpha]_D^{25}$ –4.1 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm): 0.95 (d, J = 7, 6H), 1.6 (m, 3H), 3.7 (s, 3H), 4.6 (q, J = 7 Hz, 1H), 7.5 (d, J = 7 Hz,1H), 8.2 (s, 1H).

(*R*)-*N*-Methyl-leucinol **4**: yield 69%, bp 90°C (15 mmHg), $[\alpha]_D^{25}$ –40.5 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm): 0.9 (d, J = 7 Hz, 6H), 1.25 (t, J = 7 Hz, 2H), 1.5–1.9 (m, 1H), 2.4 (s, 3H), 3.3–3.7 (m, 3H), 3.8 (s, 2H).

*4.1.4. (2*S*,3*S*)-N-Methyl-iso-leucinol **6***

(2*S*,3*S*)-Isoleucine methyl ester hydrochloride: yield 87%, mp 80°C (ethyl acetate), $[\alpha]_D^{20}$ +18 (c = 1, H_2O); ^1H NMR ($CDCl_3$): δ (ppm): 1.08 (t, J = 7 Hz, 3H), 1.33 (t, J = 7 Hz, 3H), 1.5 (m, 5H), 2.2 (m, 1H), 4.1 (m, 1H), 4.5 (q, J = 7 Hz, 2H), 9.0 (m, 3H).

(2*S*,3*S*)-*N*-Formylisoleucine methyl ester: yield 60%, $[\alpha]_D^{25}$ +32.5 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ (ppm): 0.9 (d, J = 7, 6H), 1.0 (m, 2H), 1.3 (t, J = 7 Hz, 6H), 1.9 (m, 1H), 4.3 (q, J = 7 Hz, 2H), 4.7 (m, 1H), 6.9 (m, 1H), 8.6 (s, 1H).

(2*S*,3*S*)-*N*-Methyl-isoleucinol **6**: yield 84%, bp 90°C (5 mmHg), $[\alpha]_D^{25}$ +19.3 (c = 1, EtOH); ^1H NMR ($CDCl_3$): δ (ppm): 1.06 (m, 6H), 1.48 (m, 2H), 1.93 (m, 1H), 2.83 (m, 3H), 3.16 (m, 1H), 3.95 (d, J = 6, 2H), 4.8 (s, 1H), 8.9 (m, 2H).

*4.1.5. (S)-1-Pyrrolidine-2-yl-cyclopentanol (S)-**9***

To a solution of L-proline (43.3 mmol) in absolute ethanol was added at 0°C 8 ml of thionyl chloride. The mixture was stirred at room temperature for 1 h and 2 h at reflux. After removal of the solvent, L-proline ethyl ester hydrochloride was obtained as oil.

To a Grignard reagent, prepared from magnesium (148 mmol) and 1,4-dibromobutane (73 mmol) in diethyl ether (250 ml), was added L-proline ethyl ester hydrochloride (18.4 mmol) over 30 min at 0°C. After the addition, the reaction mixture was allowed to warm to room temperature. The solution was then heated at reflux for 4 h. The mixture was poured with stirring into crushed ice (150 g) and conc. hydrochloric acid (10 ml). The filtrate was concentrated under reduced pressure to remove diethyl ether. The residue was extracted with light petroleum and the water layer was concentrated under reduced pressure. The residue was intensively extracted with dichloromethane and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained crude product was treated with 2N aqueous sodium hydroxide in dichloromethane. Evaporation of the solvent afforded (*S*)-1-pyrrolidine-2-ylcyclopentanol (*S*)-**9** as a white solid, yield 48%, $[\alpha]_D^{20} = -30$ (c = 0.3, CH_2Cl_2); ^1H NMR (DMSO): δ (ppm): 1.4–1.9 (m, 12H), 2.6 (broad s, 1H), 2.9–3.0 (m, 1H), 3.05–3.10 (m, 1H).

*4.1.6. (S)-2-Naphtylaminomethylpyrrolidine (S)-**10***

L-Proline-2-naphthylamide (2.72 mmol) in 100 ml of dry diethyl ether was added to a suspension of lithium aluminium hydride (18 mmol) in 100 ml of diethyl ether. The mixture was stirred at reflux for 3 h and 12 h at room temperature. The reaction was hydrolysed with a 30% KOH solution. The solution was filtered off and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$. Evaporation of the solvent gave (*S*)-2-naphtylaminomethylpyrrolidine **10**, yield 80%, $[\alpha]_D^{20}$ +13 (c = 1, EtOH); ^1H NMR ($CDCl_3$): δ (ppm): 1.5–2 (m, 4H), 3 (m, 2H), 3.15 (dd, J = 8.4, 12.3 Hz, 1H), 3.35 (dd, J = 12.6, 4.4 Hz, 1H), 3.55 (m, 1H), 4.20–4.35 (m, 2H), 6.8–7.7 (m, 7H).

4.2. Reduction of ketones (typical procedure)

The appropriate amount of ligand was added to the catalyst precursor $[Ru(p\text{-cymene})Cl_2]_2$ (Ru atom:ligand: 1:2) in 5 ml of 2-propanol and stirred at 80°C for 30 min under nitrogen after cooling to room temperature. A freshly prepared solution (5 ml) of sodium isopropoxide (*i*PrONa) (5 equiv. per Ru atom) was added under nitrogen. The solution was stirred for 15 min at room temperature. After introduction of the ketone into the catalyst solution at 0.1 M concentration (S/C = 100), the reduction was conducted at room temperature under nitrogen for the time indicated (monitored by GC). The resulting solution was neutralised with 1 M HCl solution and concentrated in vacuo to give the crude product, which was purified by flash chromatography (SiO_2, hexane:EtOAc: 90:10).

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