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Catalytic reduction of acetophenone with transition metal systems containing chiral bis(oxazolines)

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Abstract

The catalytic behaviour of several Ru, Rh and Ir systems containing bis(oxazoline) ligands (**1**–**6**) has been tested in the asymmetric reduction of acetophenone (**7**) to give 1-phenylethanol (**8**) by hydrogenation (Ir systems), transfer hydrogenation (Ir and Ru systems) and hydrosilylation (Ir and Rh systems). Ligands **1** and **3** gave good activities, obtaining the best asymmetric induction with Ir–**1** system in the hydrosilylation (ee up to 50% (*S*) of **8**). In order to identify the catalytic precursors, Ru (**9**–**11**) and Ir (**12**) complexes were synthesised and characterised. NMR studies of ruthenium complexes showed the existence of two main isomers in a ca. ratio 3/1, in agreement with the PM3(tm) calculations carried out for **10**.

Keywords: Homogenous catalysis; Chiral bis(oxazolines); Transition metals; NMR spectroscopy; PM3(tm) calculations

1. Introduction

Asymmetric synthesis of secondary alcohols from carbonyl compounds plays a singular role in homogeneous catalysis [1]. The catalytic process could be performed in three ways: hydrogenation, hydrogen transfer and hydrosilylation of prochiral ketones.

Although catalytic asymmetric hydrogenation of functionalised olefins and ketones have successfully been achieved, reduction of simple aryl alkyl prochiral ketones is more difficult, and only a limited number of chiral catalytic systems (Ru, Rh) have given excellent enantioselectivities, in particular Ru systems containing both chiral diphosphane and diamine [2], and Rh–chiral diphosphine systems [3].

Transfer hydrogenation [4,5] and hydrosilylation [6] using organic hydrogen donors have also been used for the synthesis of secondary alcohols. Recently some successful examples of catalytic asymmetric transfer hydrogenation have been reported using Rh, Ir and Ru catalysts with nitrogen-based chiral ligands. Excellent enantioface-discrimination ability has been obtained with different sources of hydrogen (formic acid [7] and 2-propanol [8]) using as molecular catalyst $[RuCl_2(arene)]_2$ with chiral *N*-tosylated diamines [9], diamines [10], and β-aminoalcohols [11], and also silica supported catalysts [12]. These results suggest that a NH group in the ligand backbone is crucial to obtain good enantioselectivities. The ligand may promote a cyclic transition state through hydrogen-bonding to the ketone and this fact should have a beneficial effect on the enantioselectivity. One example is the bis(oxazolinylmethyl)amine ligand, which allows the formation of the chiral 1-phenylethanol (**8**) with ee up to 97% [13] and β-aminoalcohols reported by Noyori getting ee up to 92% [8]. Recently, Moberg et al. has achieved high activities using microwave irradiation, but the enantioselectivities remained moderates [14].

In the last years C_2-symmetric chiral bis(oxazoline) ligands [15] and C_1-symmetric phosphino–oxazolines [16] have received a great attention for their successful

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use in various catalytic processes. In particular, Ir–bis(oxazolines) derived from oxalic and malonic acids have not revealed reactivity in either hydrogenation or hydrosilylation processes [17]. But rhodium complexes containing bis(oxazolines) derived from oxalic and malonic [18] and tartaric acids [19], pyridine–bis(oxazoline) [20], bipyridine–bis(oxazolines) [21], and bis(phosphinooxazolines) [22] have given good selectivities in hydrosilylation processes. Also mono(oxazoline) ligands as phenantroline–oxazoline [23] and pyridine–oxazoline [24] have been tested in this process, being better the last catalytic systems. On the another hand, in the hydrogen transfer reaction of carbonyl bonds, catalytic rhodium systems containing ligands led to high to moderate enantioselectivity (up to 97% ee in the case of bis(phosphino–oxazolines) [22]).

Although phosphino–oxazolines [25] and phosphino–pyrrolyl–oxazolines ligands [26], gave good asymmetric inductions in the Ir-catalysed enantioselective hydrogenation of olefins and imines, respectively, to the best of our knowledge, no studies about hydrogenation of carbonyl groups with bis(oxazolines) systems, have been reported.

The lack of these data prompted us to study the catalytic behaviour for the acetophenone reduction (hydrogenation, hydrogen transfer and hydrosilylation) of several C_2 symmetric chiral bis(oxazoline) ligands, containing aliphatic (**1** and **2**) and aromatic (**3**–**6**) backbones (Fig. 1). While for ligands **1** and **2**, the two oxazoline groups are connected by two or four C_{sp3}, respectively (aliphatic bridge), for **3**–**6**, two (phenyl) or four (biphenyl) C_{sp2}, separate both heterocycles. To identify the catalytic precursors, ruthenium (**9**–**11**) and iridium (**12**) complexes were prepared.

2. Results and discussion

2.1. Synthesis and characterisation of ruthenium and iridium complexes

'Aliphatic bridge' (**1**–**2**) and 'aromatic bridge' (**3**–**6**) bis(oxazolines) were prepared as previously described [15b,27,28] (Fig. 1). Ligands containing the biphenyl backbone (**4**–**6**) are obtained as a mixture of two diastereomers, (*Xc*, *Ra*, *Xc*) and (*Xc*, *Sa*, *Xc*) (*X* = *R* for **4** and *S* for **5** and **6**) due to the axial chirality of the skeleton. Upon *N,N*-bidentated coordination, the ligands can afford seven- (**1** and **3**) or nine-membered (**2**, **4** and **5**) metallic cycles. Ligand **6** can coordinate to the metal by sulphur atom, giving bimetallic species, as observed for palladium compounds [15b]. Because the best catalytic results have been obtained with systems containing **1** and **3** (see below), we synthesised their monometallic Ru (**9**–**11**) and Ir (**12**) complexes (Scheme 1).

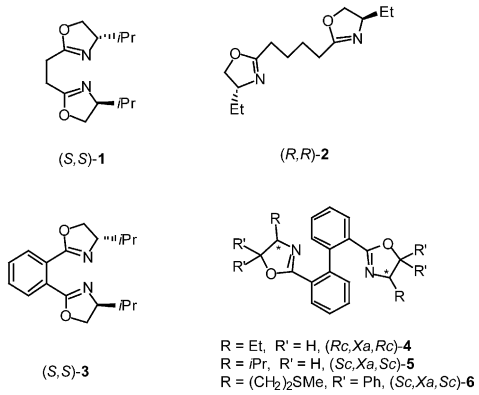


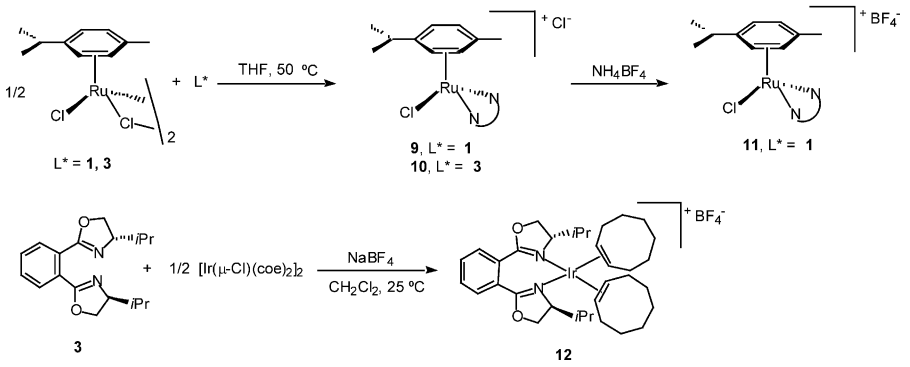
Fig. 1. Bis(oxazoline) ligands, (*S*,*S*)-**1**, (*R*,*R*)-**2**, (*S*,*S*)-**3**, (*Rc,Xa,Rc*)-**4**, (*Sc,Xa,Sc*)-**5** and (*Sc,Xa,Sc*)-**6** (*Xa* means the axial absolute configuration of the biphenyl backbone).

Complexes were prepared by reaction of the dimeric precursors ([Ru(*p*-cymene)Cl(μ-Cl)]$_2$ and [Ir(μ-Cl)(coe)$_2$]$_2$) with two equivalents of the appropriated ligand, following the methodology previously described [25,29]. In these compounds, the bis(oxazoline) acts as *N,N*-bidentate donor ligand. Addition of tetrafluoroborate salt decreases the solubility of the complexes in the reaction media. The complexes were characterised by IR and NMR spectroscopy, mass FAB spectrometry and elemental analysis.

Their infrared spectra show the C=N stretching vibration indicating the presence of the bis(oxazoline) ligand. The signal appears within a narrow interval between 1619 and 1628 cm^{-1}, shifted to lower frequencies compared with free ligands (1672 and 1654 cm^{-1} for **1** and **3**, respectively). Another strong band at 1054 cm^{-1} is observed for **11** and **12** complexes due to the tetrafluoroborate anion. Mass spectrometry data agree with monometallic compounds. FABMS spectra for Ru-complexes (**9**–**11**) show the same pattern of fragments, corresponding to [M], [M−Cl] and [M−*p*-cymene], where M means the cation fragment of the complex. FAB spectrum for **12** exhibits only one intense peak corresponding to [M+DMSO]$^+$ ($CHCl_3$–DMSO mixture was used as solvent for recording the spectra).

^{1}H-NMR spectra of Ru complexes were recorded in $CDCl_3$ at several temperatures (240–330 K). No isomeric composition change was observed in any compound in the temperature range studied. These spectra basically show the existence of two main species in a ca. 3/1 ratio, although other minor species (less than 10%) could be detected, probably dimeric species or diastereomers because of the metal chirality [30]. ^{1}H-NMR experiment (1D and 2D NOESY spectra) for **10** allowed us the structural determination of the main isomers. Complexes **9** and **11** show broader signals than **10**.

The main isomers are probably due to the relative position of the substituents on the *p*-cymene fragment and the bis(oxazoline) ligand, as stated in the literature



Scheme 1. Synthetic route for Ru (**9**–**11**) and Ir (**12**) complexes.

for analogous complexes [31]. Then two arrangements are possible: (i) the arene *iso*propyl and the chloride groups on the same side, ***Iso*-10**; and (ii) the arene methyl and the chloride groups on the same side, **Me-10** (Fig. 2).

Upon coordination, the two oxazoline fragments are not equivalent and therefore, the aromatic protons of the arene moiety appear as four signals. For the major isomer, signals at 5.51 and 5.44 ppm (protons in *ortho* position to the methyl group) and 5.24 and 5.11 ppm (protons in *ortho* position to the *iso*propyl group) are observed, due to the different donor electronic properties of both alkyl substituents (Table 1). The methyl group of the *p*-cymene unit for the major isomer of **10** resonates at higher-field (1.15 ppm) than the minor species (2.12 ppm) and the precursor ([Ru(*p*-cymene)Cl(μ-Cl)]$_2$ (2.13 ppm), because of the electronic effect of the oxazoline phenyl ring over this methyl group. In addition, 2D NOESY spectrum of **10** showed cross-peaks between the protons of one oxazoline heterocycle and the two aromatic protons (in *ortho* position to the methyl substituent) of the *p*-cymene moiety for the major isomer, while the minor isomer shows cross-peaks between one **4′b** and both aromatic protons in *ortho* position to the isopropyl group (Fig. 3). These facts suggest that the major isomer should be ***Iso*-10**, which shows the minor steric effects. Exchange signals between both isomers are also observed in the 2D NOESY spectrum, which demonstrates that these species are in equilibrium.

Semi-empirical calculations (PM3(tm) level) were carried out for both isomers **Me-10** and ***Iso*-10** (Fig. 4)

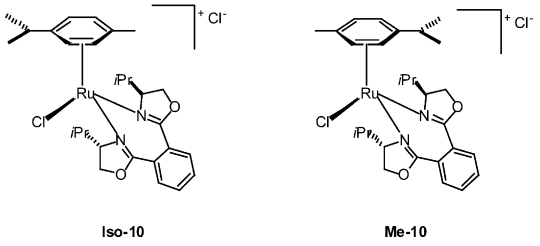


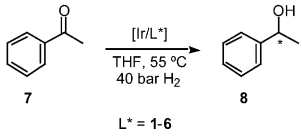
Fig. 2. Proposed isomers for Ru complex **10**.

[32]. ***Iso*-10** isomer showed lower formation enthalpy than the **Me-10** one (−62.082 vs. −61.509 kcal mol^{-1}). This result is in good accordance with the ratio observed in the ^{1}H-NMR spectrum (2.6/1 (calculated) vs. 3/1 (experimental)).

2.2. Catalytic acetophenone reduction

2.2.1. Asymmetric hydrogenation

The Ir–bis(oxazoline) systems (**1**–**6**) were tested in the hydrogenation of the acetophenone, using molecular hydrogen gas as hydride source (Eq. (1)). The catalyst–substrate ratio was 1/1000. The catalytic results are summarised in Table 2. Catalytic runs were performed either under in situ conditions (1 mol ‰ [Ir(cod)$_2$]BF$_4$ and 1.5 or 3 mol ‰ of L*) or using the precursor **12**, previously synthesised, but no differences were observed in both cases (entries 5 and 7, Table 2).



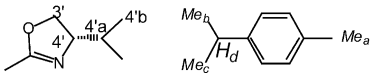
(1)

Activity is improved when the Ir–L* ratio decreases, when L* = **1**–**3**, suggesting a higher stability of the catalytic active species when the L* amount increases (entries 1 vs. 2, 3 vs. 4 and 5 vs. 6, Table 2). Ir–**1** system gave the best activity (up to 85% of conversion, entry 2, Table 2) but no asymmetric induction was observed. Under the same conditions, catalytic systems with ligands containing the biphenyl backbone (**4**–**6**) showed low activities (entries 8–12, Table 2), which are not dependent on the Ir–L* ratio. However, Ir–**6** system is slightly selective (ee = 21% (*S*), entry 12), probably due to the existence of other catalytic species because of the thioether substituent [15b].

In conclusion, we can state that the stability of the catalytic species is only achieved with excess of ligand probably due to the lability of the bis(oxazolines) in these Ir complexes. For the *N,N*-donor ligands (**1**–**5**), the lack of enantioselectivity could be associated to the monodentate coordination of the ligands, and only

Table 1
^{1}H-NMR data [a] (δ in ppm, $CDCl_3$, 298 K) for **10** (500 MHz), **3** and [Ru(*p*-cymene)Cl(μ-Cl)]$_2$ (250 MHz)

Compound	**4′b**	**4′a**	**4′**	**3′**	*p*-Cymene
***Iso*-10** *major* (75%)	0.40 (d, 7.0, 3H), 0.75 (d, 7.0, 3H), 0.96 (d, 7.0, 3H), 1.04 (d, 6.5, 3H)	2.43 (m, 1H), 2.66 (m, 1H)	4.42 (m, 1H), 4.83 (m, 1H)	4.24 (m, 2H), 4.27 (t, 10.0, 1H), 4.55 (pt, 7.5, 1H)	Me_a: 1.15 (s, 3H), Me_b, Me_c: 1.22 (d, 7.0, 3H), 1.40 (d, 6.5, 3H), H_d: 3.01 (m, 1H), *Aromatic protons*: 5.11 (d, 5.0, 1H), 5.24 (d, 5.5, 1H), 5.44 (d, 5.5, 1H), 5.50 (bs, 1H) [b]
Me-10 [b] *minor* (25%)	1.20 (d, 7.0, 3H), 1.31 (d, 6.5, 3H), 1.34 (d, 7.0, 3H), nd [c]	2.85 (m, 2H)	nd [c]	nd [c]	Me_a: 2.12 (s, 3H), Me_b, Me_c: nd [c], H_d: 3.16 (m, 1H), *Aromatic protons*: 5.20 (bs, 1H), 5.31 (d, 5.5, 1H), 5.50 (bs, 2H) [b]
3	0.87 (d, 6.7, 3H), 0.96 (d, 6.7, 3H)	1.79 (m, 1H)	3.99 (m, 2H)	3.99 (m, 2H), 4.29 (m, 1H)	
[Ru] [d]					Me_a: 2.13 (s, 3H), $Me_{b,c}$: 1.25 (d, 6.9, 6H), H_d: 2.13 (m, 1H), *Aromatic protons*: 5.31 (d, 5.9, 2H), 5.45 (d, 5.9, 2H)



[a] Multiplicity (d, doublet; m, multiplet; s, singlet; t, triplet; p, pseudo; bs, broad signal) and coupling constants (in Hz) in parentheses.
[b] Signals overlapped.
[c] Not distinguished.
[d] [Ru] = [Ru(*p*-cymene)Cl(μ-Cl)]$_2$.

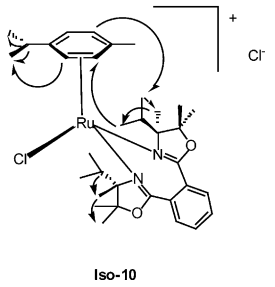


Fig. 3. Selected NOE contacts (indicated by arrows) for **Me-10**.

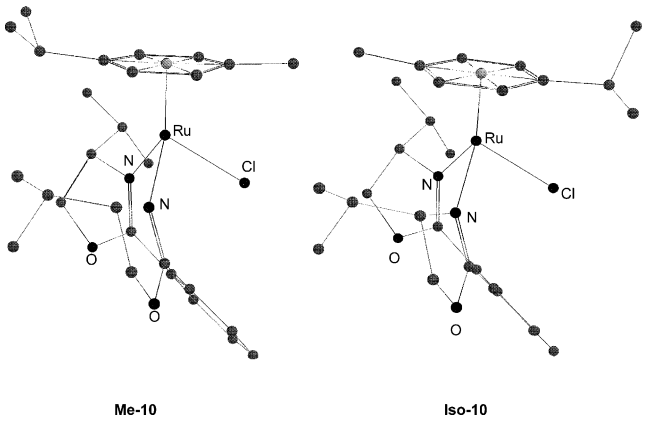


Fig. 4. Optimised structures (PM3(tm)) for **Me-10** and ***Iso*-10**.

Table 2
Enantioselective hydrogenation of acetophenone using $[Ir(cod)_2]BF_4$–bis(oxazoline) systems [a]

Entry	L*	Ir–L*	Conversions (%) [b]
1	**1**	1/1.5	65
2	**1**	1/3	85
3	**2**	1/1.5	7
4	**2**	1/3	14
5	**3**	1/1.5	26
6	**3**	1/3	40
7	**3** [c]	1/1	32
8	**4**	1/1.5	17
9	**4**	1/3	18
10	**5**	1/1.5	11
11	**6**	1/1.5	9
12	**6**	1/3	10 (21%(*S*))

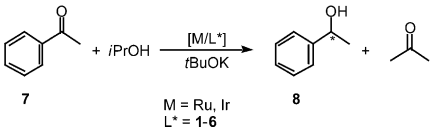
[a] Results from duplicated experiments. Reaction conditions: 0.020 mol of acetophenone, 2×10^{-5} mol of $[Ir(cod)_2]BF_4$, 3×10^{-5} mol (or 6×10^{-5}) of ligand, 40 bar of H_2 in 10 ml of THF at 50 °C for 15 h.
[b] Conversions and enantiomeric excesses determined by GC on chiral column.
[c] Preformed complex **12**. Reaction conditions: 0.020 mol of acetophenone, 2×10^{-5} mol of **12**, 40 bar of H_2 in 10 ml of THF at 50 °C for 15 h.

enantiomeric excess is achieved when the *N,S*-donor ligand **6** is used, suggesting the stabilisation of chelate metallic rings in the catalytic species.

Rh–**3** system gave a similar catalytic behaviour than the analogous iridium catalyst (39% conversion, without asymmetric induction), under the same conditions [33].

2.2.2. Asymmetric hydrogen transfer

Ru- (L* = **1**–**5**) and Ir- (L* = **1**–**6**) bis(oxazoline) systems were tested in the asymmetric hydrogen transfer process of acetophenone, using *iso* propanol under basic conditions as hydrogen source (Eq. (2)). The catalyst–substrate ratio was 1/20. The catalytic results are summarised in Table 3 (for Ru) and Table 4 (for Ir).



(2)

Concerning the ruthenium catalytic systems, Ru–**2** was the most active, giving 91% of 1-phenylethanol (**8**) in 10 h (entry 5, Table 3). As observed for the Ir-catalysed hydrogenations (see above), an excess of ligand induces higher activity (entries 1 vs. 2 and 6 vs. 7, Table 3), although the selectivity was practically unchanged. Comparing 'aliphatic backbone' (**1** and **2**) and 'aromatic backbone' (**3**–**5**) ligands, we observe that the former systems are most active than the latter ones (entries 2 and 5 vs. 7, 10 and 11, Table 3). Then, this feature seems to indicate that a more flexible metallic cycle induces better activities. When **9** and **10** were used as preformed precursors, the catalytic behaviour was similar to the catalyst generated in situ (entries 1 and 4; 6 and 9, Table 3).

Table 3
Enantioselective transfer hydrogenation of acetophenone using Ru–bis(oxazoline) catalytic systems [a]

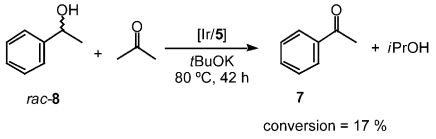
Entry	L*	Ru–L*	Time (h)	Conversions (%) [b]	ee (%) [b]
1	**1**	1/1	20	40	24(*S*)
2	**1**	1/2	20	88	25(*S*)
3	**1** [c]	1/2	24	38	38(*S*)
4	**1** [d]	1/1	23	39	28(*S*)
5	**2**	1/2	10	91	11(*R*)
6	**3**	1/1	24	10	24(*S*)
7	**3**	1/2	20	42	29(*S*)
8	**3** [c]	1/2	24	21	32(*S*)
9	**3** [d]	1/1	24	6	22(*S*)
10	**4**	1/2	96	90	5(*R*)
11	**5**	1/2	96	60	3(*S*)

[a] Results from duplicated experiments. Reaction conditions: 12×10^{-5} mol of acetophenone, 2.4×10^{-5} mol of *t*BuOK, 3×10^{-6} mol of $[Ru(p\text{-cymene})Cl(\mu\text{-}Cl)]_2$ and 6×10^{-6} mol (or 12×10^{-6} mol) of ligand in 4 ml of *i*PrOH.
[b] Conversions and enantiomeric excesses determined by GC on chiral column.
[c] Reaction at 0 °C.
[d] Reaction conditions: 12×10^{-5} mol of acetophenone, 2.4×10^{-5} mol of *t*BuOK, 6×10^{-6} mol of **9** or **10** in 4 ml of *i*PrOH.

Both the activity and selectivity are dependent on temperature. At 273 K, the activity decreases but the selectivity increases. Under these conditions the best selectivities are showed by systems containing seven-membered cycles, Ru–**1** and Ru–**3**. The former is the most selective (ee up to 38%, entry 3, Table 3).

For Ir-catalysed transfer hydrogenation, the most active and selective system was Ir–**3** (85% conversion with 33% of ee, entry 5, Table 4). Systems containing biphenyl backbone show lower activities and worse selectivities (entries 8–10, Table 4), but the catalytic system Ir–**4** is slightly enantioselective (18% of ee, entry 8, Table 4). With these systems the selectivity does not depend on the temperature (entries 6 and 7, Table 4). Comparing analogous systems, Ir catalysts are more active than the Ru ones (Tables 3 and 4).

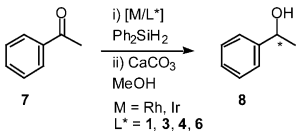
An inherent problem of transfer hydrogenation is the reversibility of the reaction, which prevents complete conversion and also causes a decrease of the enantiomeric purity of the chiral alcohol (**8**). To avoid this problem, other hydrogen donor systems as HCOOH–NEt_3, are described in the literature, but oxazoline ligands are not stable under these conditions [34]. In order to know the existence of the unfavourable reverse process with our systems, control experiments using *rac*-**8** and acetone in 2-propanol (under the same basic conditions), revealed that the reaction is negligible for ruthenium and iridium systems except, for Ir–**5** system which afforded acetophenone (**7**), with 17% conversion after 42 h of reaction (Eq. (3)). No kinetic resolution of *rac*-**8** was observed in any case.



(3)

2.2.3. Asymmetric hydrosilylation

Catalytic behaviour of Rh and Ir–bis(oxazoline) systems (L* = **1**, **3**, **4** and **6**) were studied in the asymmetric hydrosilylation process of acetophenone with diphenylsilane in the presence of $[Rh(\mu\text{-}Cl)(cod)]_2$ and $[Ir(\mu\text{-}Cl)(cod)]_2$ as metallic precursors (Eq. (4)). This catalytic reaction was performed in toluene at 50 °C. The catalyst–substrate ratio was 1/100. The results are summarised in Table 5.



(4)

Concerning the Rh-catalysed reactions, the most active system was Rh–**3** (entry 3, Table 5), while Rh–**1** showed the best selectivity (ee = 33%, entry 1, Table 5).

The Ir systems gave better activities (Ir–**3**, 95% of conversion, entry 4, Table 5) and better enantioselectivities (Ir–**1**, 50% of ee, entry 2, Table 5) than the Rh analogous systems. Rh and Ir containing **4** and **6** ligands gave very low activities (up to 6%, entries 5–8, Table 5).

Table 4
Enantioselective transfer hydrogenation of acetophenone using Ir–bis(oxazoline) catalytic systems [a]

Entry	L*	Ir–L*	Time (h)	Conversions (%) [b]	ee (%) [b]
1	**1**	1/3	2.5	91	9(*S*)
2	**2**	1/3	5	91	11 (*R*)
3	**3**	1/1	3	95	18 (*S*)
4	**3**	1/2	3	96	32 (*S*)
5	**3**	1/3	1.5	85	33 (*S*)
6	**3** [c,d]	1/1	3	10	31 (*S*)
7	**3** [c]	1/1	3	100	32 (*S*)
8	**4**	1/3	3	77	18 (*R*)
9	**5**	1/3	6	67	5 (*S*)
10	**6**	1/3	8	90	5 (*S*)

[a] Results from duplicated experiments. Reaction conditions: 12×10^{-5} mol of acetophenone, 2.4×10^{-5} mol of *t*BuOK, 3×10^{-6} mol of $[Ir(\mu\text{-}Cl)(coe)_2]_2$ in 4 ml of *i*PrOH at 80 °C.
[b] Enantiomeric exces and conversions determined by GC with chiral columns.
[c] Reaction conditions: 12×10^{-5} mols of acetophenone, 2.4×10^{-5} mol of *t*BuOK, 6×10^{-6} mol of preformed complex **12** in 4 ml of *i*PrOH.
[d] Reaction carried out at room temperature.

Table 5
Enantioselective hydrosilylation of acetophenone with diphenylsilane using Rh and Ir–bis(oxazoline) catalytic systems [a]

Entry	Precursor	Time (h)	Conversions (%) [b]	ee (%) [b]
1	Rh–**1** [c]	6	32	33(*S*)
2	Ir–**1** [c]	6	89	50(*S*)
3	Rh–**3** [c]	6	48	0
4	Ir–**3** [c]	5	95	0
5	Rh–**4** [c]	60	6	nd
6	Ir–**4** [c]	25	5	nd
7	Rh–**6** [c]	60	0	
8	Ir–**6** [c]	60	1	
9	Rh–**1** [d]	24	60	20(*S*)
10	Rh–**3** [d]	24	65	0
11	Rh–**4** [d]	24	8	nd
12	Rh–**6** [d]	24	8	nd

[a] Results from duplicated experiments.
[b] Enantiomeric excess and conversions determined by GC with chiral column.
[c] Reaction conditions: 2 mmol of acetophenone, 0.01 mmol of $[Rh(\mu\text{-}Cl)(cod)]_2$ or $[Ir(\mu\text{-}Cl)(cod)]_2$, 0.08 mmol of ligand and 3.2 mmol of diphenylsilane at 50 °C in 1 ml of toluene.
[d] Reaction conditions: 2 mmol of acetophenone, 0.01 mmol of $[Rh(\mu\text{-}Cl)](cod)_2$, 0.08 mmol of ligand and 3.2 mmol of diphenylsilane at r.t. in 0.1 ml of CCl_4.

For Rh catalytic systems, the reaction were also carried out in CCl_4 at room temperature (entries 9–12, Table 5), which is, for the Rh–oxazoline systems, the best solvent to get excellent enantioselectivities in the hydrosilylation reaction as stated by Brunner [24]. At 0 °C, these Rh systems were not active, in contrast to other analogous catalysts described in the literature [23]. Comparing both solvents, we can conclude that Rh–bis(oxazoline) systems in toluene show better activities and similar selectivities than in CCl_4 (entries 1 vs. 9 and 3 vs. 10, Table 5).

3. Conclusions

In summary, the catalytic systems containing two carbon spacers (ligands **1** and **3)** show the best results in activity and enantioselectivity for the reduction of acetophenone (**7**) to its corresponding secondary alcohol (**8**). This fact suggests that *N,N*-bidentated coordination of L* is necessary to stabilise the catalytic species. The most of catalytic systems containing biphenyl backbone ligands (**4**–**6**) are the less active. If we compare the three described reduction processes, hydrosilylation seems to be the process of choice in order to obtain asymmetric induction for **8** (up to 50% ee).

4. Experimental

4.1. General data

All compounds were prepared under a purified nitrogen atmosphere using standard Schlenk and vacuum-line techniques. Solvents were purified by standard procedures and distilled under nitrogen [35]. *t*-BuOK, [Ru(η^6-*p*-cymene)Cl(μ-Cl)]$_2$, [Ir(cod)$_2$]BF$_4$, [Rh(cod)$_2$]BF$_4$, [Ir(μ-Cl)(coe)$_2$]$_2$, [Rh(μ-Cl)(cod)]$_2$ and [Ir(μ-Cl)(cod)]$_2$ were purchased and used without previous purification. NMR spectra were recorded on Varian XL-500 (^{1}H), Varian Gemini (^{1}H, 200 MHz), and Bruker DRX 250 (^{13}C, 63 MHz) spectrometers. Chemical shifts were reported downfield from $SiMe_4$ as standard. IR spectra were recorded on a Nicolet 520 FTIR spectrometer. FAB mass spectra were obtained on a Fisons V6-Quattro instrument. The GC analyses, for chiral substances, was performed on a Hewlett–Packard 5890 Series II gas chromatograph (25 m FS-cyclodex-β-I/P column: heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin–polysiloxan; 25 m Lipodex α from Macherey–Nagel and 30 m Cyclodex β from J&W Scientifique) with a FID detector. Elemental analyses were carried out by the Serveis Científico-Tècnics of the University of Barcelona in an Eager 1108 microanalyser. Melting and decomposition points were determined in a 510-Büchi apparatus. The molecular mechanics calculations were performed using the SPARTAN program, version 5.0 (Wave function Inc., Irvine, CA, 1997).

4.2. Preparation of chloro-(η^6-*p*-cymene)-{1,2-bis[(4′*S*)-(4′-isopropyl-3′,4′-dihydrooxazol-2′-yl)]ethane-*N,N*}ruthenium(II) chloride (**9**)

[RuCl(*p*-cymene)(μ-Cl)]$_2$ (110 mg (0.18 mmol)), 100 mg (0.39 mmol) of (*S,S*)-**1** were dissolved in 13 ml of THF and stirred at 55 °C for 3 h. The solvent was removed and the residue washed with pentane. The product was recrystallised from CH_2Cl_2 and hexane giving an orange solid (129 mg, 88%). IR (KBr) = 1619 (C=N) cm^{-1}. ^{1}H-NMR (500 MHz, 298 K, $CDCl_3$): δ major isomer (75%), 0.83 (d, $J_{HH} = 6.0$ Hz, 3H, CH*Me*$_2$), 0.86 (d, $J_{HH} = 7.0$ Hz, 3H, CH*Me*$_2$), 0.93 (d, $J_{HH} = 7.0$ Hz, 3H, CH*Me*$_2$), 1.01 (d, $J_{HH} = 7.0$ Hz, 3H, CH*Me*$_2$), 1.22 (d, $J_{HH} = 6.0$ Hz, 3H, CH*Me*$_2$), 1.27 (d, $J_{HH} = 6.0$ Hz, 3H, CH*Me*$_2$), 1.68 (m, 1H, C*H*Me$_2$), 1.87 (m, 2H, CH$_2$), 1.97 (m, 1H, C*H*Me$_2$), 2.20 (m, 1H, C*H*Me$_2$), 2.24 (s, 3H, CH$_3$), 4.00 (m, 2H, CH$_2$), 4.20 (m, 6H, CH$_2$ *i*CH), 5.31 (d, $J_{HH} = 5.5$ Hz, 2H, C$_6$*H*$_4$), 5.44 (d, $J_{HH} = 6.0$ Hz, 1H, C$_6$*H*$_4$) ppm; *minor isomer* (25%), 2.12 (s, 3H, CH*Me*$_2$), 5.45 (sa, 2H, C$_6$*H*$_4$) ppm. Anal. Found: C, 51.61; H, 6.81; N, 5.02; Cl, 12.70. Calc. for $C_{24}H_{38}Cl_2N_2O_2Ru$: C, 51.77; H, 7.00; N, 5.09; Cl, 12.10%. MS (FAB positive) *m/z* 523 ([M−Cl]$^+$), 487 ([M−Cl]$^+$), 353 ([M−*p*-cymene]$^+$). Melting point: 90 °C.

4.3. Preparation of chloro-(η^6-*p*-cymene)-{1,2-bis[(4′*S*)-(4′-isopropyl-3′,4′-dihydrooxazol-2′-yl)]benzene-*N,N*}ruthenium(II) chloride (**10**)

[RuCl(*p*-cymene)(μ-Cl)]$_2$ (118 mg (0.19 mmol)), 115 mg (0.39 mmol) of (*S,S*)-**3** were dissolved in 13 ml of THF and stirred at 55 °C for 3 h. The solvent was removed and the residue washed with pentane. The product was recrystallised from CH_2Cl_2 and hexane giving an orange solid (163 mg, 70%). IR (KBr) = 1628 (C=N) cm^{-1}. ^{1}H-NMR (500 MHz, 298 K, $CDCl_3$): δ major isomer, 0.40 (d, $J_{HH} = 7.0$ Hz, 3H, CH*Me*$_2$), 0.75 (d, $J_{HH} = 7.0$ Hz, 3H, CH*Me*$_2$), 0.96 (d, $J_{HH} = 7.0$ Hz, 3H, CH*Me*$_2$), 1.04 (d, $J_{HH} = 6.5$ Hz, 3H, CH*Me*$_2$), 1.15 (m, 3H, C*H*$_3$), 1.22 (d, $J_{HH} = 7.0$ Hz, 3H, CH*Me*$_2$), 1.40 (d, $J_{HH} = 6.5$ Hz, 3H, CH*Me*$_2$), 2.43 (m, 1H, C*H*Me$_2$), 2.66 (m, 1H, C*H*Me$_2$), 3.01 (m, 1H, C*H*Me$_2$), 4.24 (m, 2H, C*H*$_2$), 4.27 (t, $J_{HH} = 10.0$ Hz, 1H, C*H*$_2$), 4.42 (m, 1H, C*H*), 4.55 (pt, $J_{HH} = 7.5$ Hz, 1H, C*H*$_2$), 5.11 (d, $J_{HH} = 5.5$ Hz, 2H, C$_6$*H*$_4$), 5.24 (d, $J_{HH} = 5.5$ Hz, 1H, C$_6$*H*$_4$), 5.44 (d, $J_{HH} = 5.5$ Hz, 2H, C$_6$*H*$_4$), 5.51 (m, 1H, C$_6$*H*$_4$) ppm; *minor isomer*, 1.00 (m, 1H, C*H*Me$_2$), 1.20 (d, $J_{HH} = 7.0$ Hz, 3H, CH*Me*$_2$), 1.31 (d, $J_{HH} = 6.5$ Hz, 3H, CH*Me*$_2$), 1.34 (d, $J_{HH} = 7.0$ Hz, 3H, CH*Me*$_2$), 3.16 (m, 1H, C*H*Me$_2$), 2.12 (s, 3H, C*H*$_3$), 5.20 (bs, 1H, C$_6$*H*$_4$), 5.31 (d, $J_{HH} = 5.5$ Hz, 1H, C$_6$*H*$_4$), 5.51 (bs, 1H,

C_6H_4) ppm. Anal. Found: C, 55.42; H, 6.27; N, 4.62; Cl, 11.69. Calc. for $C_{28}H_{38}BCl_2F_4N_2O_2Ru$: C, 55.93; H, 6.35; N, 4.52; Cl, 11.78%. MS (FAB positive) *m/z* 571 ($[M-Cl]^+$). 533 ($[M-Cl]^+$), 397 ($[M-p$-cymene$]^+$). M.p.: 115 °C.

4.4. Preparation of chloro-(η^6-p-cymene)-{1,2-bis[(4′S)-(4′-isopropyl-3′,4′-dihydrooxazol-2′-yl)]ethane-N,N}ruthenium(II) tetrafluoroborate (**11**)

Compound **9** (94 mg (0.168 mmol)) was dissolved in 19 ml of CH_2Cl_2 and washed with an aqueous solution of $NaBF_4$ (256 mg, 2.34 mmol). The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, affording an orange solid; (87.2 mg, 85%). IR (KBr) = 1620 (C=N), 1054 (BF_4) cm^{-1}. ^{1}H-NMR (250 MHz, 298 K, $CDCl_3$): δ 0.92 (d, $J_{HH} = 7.0$ Hz, 6H, CH*Me*$_2$), 0.94 (d, $J_{HH} = 7.0$ Hz, 3H, CH*Me*$_2$), 1.01 (d, $J_{HH} = 7.0$ Hz, 3H, CH*Me*$_2$), 1.25 (d, $J_{HH} = 6.0$ Hz, 6H, CH*Me*$_2$), 1.68 (m, 1H, C*H*Me$_2$), 1.89 (m, 2H, CH_2), 1.99 (m, 1H, C*H*Me$_2$), 2.15 (s, 3H, CH_3), 2.22 (m, 1H, C*H*Me$_2$), 4.00 (m, 2H, CH_2), 4.20 (m, 6H, CH_2 and CH), 5.35 (d, $J_{HH} = 5.5$ Hz, 2H, C_6H_4), 5.46 (d, $J_{HH} = 5.9$ Hz, 1H, C_6H_4) ppm. Anal. Found: C, 47.11; H, 6.23; N, 4.59. Calc. for $C_{24}H_{38}BClF_4N_2O_2Ru$: C, 47.77; H, 6.10; N, 4.49%. MS (FAB positive) *m/z* 523 ($[M-BF_4]^+$), 487 ($[M-Cl]^+$), 353 ($[M-p$-cymene$]^+$). Melting point: 102 °C.

4.5. Preparation of bis(cis-cyclooctene)-{1,2-bis[(4′S)-(4′-isopropyl-3′,4′-dihydrooxazol-2′-yl)]benzene-N,N}iridium(I) chloride (**12**)

[Ir(μ-Cl)(coe)$_2$]$_2$ (228 mg (0.25 mmol)), 153 mg (0.51 mmol) of (*S,S*)-**3** were dissolved in 10 ml of diclormethane and stirred at room temperature (r.t.) for 1 h. The solution was washed with an aqueous solution of $NaBF_4$ (128 mg, 0.17 mmol). The organic phase was dried over anhydrous Na_2SO_4. The product was recrystallised from CH_2Cl_2 and hexane giving an orange solid (183 mg, 45%). IR (KBr) = 1622 (C=N), 1054 (BF_4) cm^{-1}. Anal. Found: C, 51.06; H, 6.51; N, 3.50. Calc. for $C_{34}H_{32}BF_4N_2O_2Ir$: C, 51.23; H, 6.65; N, 3.60%. MS (FAB positive) *m/z* 793.5 ($[M+DMSO]^+$). M.p.: 185 °C.

4.6. General procedure for iridium-catalysed hydrogenation with preformed complex

The precursor (10 mg, 2×10^{-5} mol of **12**) and the substrate (2.40 g, 0.0200 mol of acetophenone) were dissolved in 10 ml of THF in the autoclave. Then, molecular hydrogen was introduced until 40 bar. The reaction was stirred at 50 °C for 15 h. Then the solution was filtered over celite and purified by column chromatography (SiO_2; ethyl acetate). Enantiomeric excesses and conversions were determined by GC on a chiral column.

4.7. General procedure for iridium and rhodium catalysed in situ hydrogenation

The precursor (2×10^{-5} mol, 10 mg of complex [Ir(cod)$_2$]BF_4 or 8.2 mg of [Rh(cod)$_2$]BF_4) and the substrate (2.40 g, 0.0200 mol of acetophenone) were dissolved in 10 ml of THF in the autoclave. Then, molecular hydrogen was introduced until 40 bar. The reaction was stirred at 55 °C for15 h. Then the solution was filtered over celite and purified by column chromatography (SiO_2; ethyl acetate). Enantiomeric excesses and conversions were determined by GC on a chiral column.

4.8. General procedure for iridium and ruthenium catalysed hydrogen transfer with preformed complex

The precursor (complexes **10**–**12**) (3×10^{-3} mmol) were dissolved in 2 ml of a solution 0.012 M of *t*BuOK in *iso*propanol at r.t.. The resulted solution was stirred during 30 min. Then 2 ml of a solution 0.06 M of acetophenone in *iso*propanol was added. The reaction was stirred at r.t. (for ruthenium-catalysed) or at 80 °C (for iridium-catalysed) until the substrate was totally consumed (unless stated otherwise), and monitored by GC.

4.9. General procedure for iridium and ruthenium catalysed in situ hydrogen transfer

The precursor (3×10^{-3} mmol) (1.8 mg of [Ru(*p*-cymene)Cl(μ-Cl)]$_2$, 2.7 mg of [Ir(coe)$_2$Cl]$_2$) and 6, 12 or 18×10^{-3} mmol of ligand were dissolved in 2 ml of a solution 0.012 M of *t*BuOK in *iso*propanol at r.t.. The resulted solution was stirred during 30 min. Then 2 ml of a solution 0.06 M of acetophenone in *iso*propanol was added. The reaction was stirred at r.t. (for ruthenium-catalysed) or at 80 °C (for iridium-catalysed) until the substrate was totally consumed (unless stated otherwise), and monitored by GC.

4.10. Ruthenium catalysed hydrogen transfer of acetone and rac-8

[Ru(*p*-cymene)Cl(μ-Cl)]$_2$ (3×10^{-3} mmol) (1.8 mg) and 12×10^{-3} mmol (4.5 mg) of **5** were dissolved in 2 ml of a solution 0.012 M of *t*BuOK in *iso*propanol at r.t.. The resulted solution was stirred during 30 min. Then 2 ml of an equimolar solution 0.06 M in *rac*-**8** and acetone in *iso*propanol were added. The reaction was monitored by GC.

4.11. General procedure for rhodium catalysed in situ hydrosilylation

4.11.1. In CCl_4

A solution of ligand (0.08 mmol), $[Rh(\mu\text{-}Cl)(cod)]_2$ (5 mg, 0.01 mmol), and acetophenone (240 mg, 2 mmol) in tetrachloromethane (0.1 ml) was stirred for 1 h at r.t. under argon atmosphere. After diphenylsilane (590 mg, 3.2 mmol) was added to the solution at −5 °C, the reaction mixture was stirred at r.t. and monitored by GC. The reaction solution was quenched with methanol and a small amount of $CaCO_3$ during 30 min. The solution was washed with water and extracted with diethyl ether. Enantiomeric excesses and conversions were determined by GC on a chiral column.

4.11.2. In toluene

A solution of ligand (0.08 mmol) and $[Rh(\mu\text{-}Cl)(cod)]_2$ (5 mg, 0.01 mmol), in toluene (1 ml) was stirred for 1 h at 50 °C under argon atmosphere. After acetophenone (240 mg, 2 mmol) and diphenylsilane (590 mg, 3.2 mmol) were added to the solution at r.t., the reaction mixture was stirred at 50 °C and monitored by GC. The reaction solution was quenched with methanol and a small amount of $CaCO_3$ during 30 min. The solution was washed with water and extracted with diethyl ether. Enantiomeric excesses and conversions were determined by GC on a chiral column.

4.12. General procedure for iridium catalysed in situ hydrosilylation

A solution of ligand (0.08 mmol) and $[Ir(\mu\text{-}Cl)(cod)]_2$ (2.6 mg, 0.01 mmol), in toluene (1 ml) was stirred for 1 h at 50 °C under argon atmosphere. After acetophenone (240 mg, 2 mmol) and diphenylsilane (590 mg, 3.2 mmol) were added to the solution at r.t., the reaction mixture was stirred at 50 °C and monitored by GC. The reaction solution was quenched and analysed as described above (see Section 4.11).

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