New Chiral Ruthenium(II) Catalysts Containing 2,6-Bis(4′-(*R*)-phenyloxazolin-2′-yl)pyridine (Ph-pybox) Ligands for Highly Enantioselective Transfer Hydrogenation of Ketones

Darío Cuervo, M. Pilar Gamasa, and José Gimeno*[a]

Dedicated to Professor José Vicente on the occasion of his 60th birthday

Abstract: Treatment of complex *trans*-[$RuCl_2(\eta^2\text{-}C_2H_4)\{\kappa^3\text{-}N,N,N\text{-}(R,R)\text{-Ph-pybox}\}$] [(*R*,*R*)-Ph-pybox = 2,6-bis{4′-(*R*)-phenyloxazolin-2′-yl}pyridine] with phosphines or phosphites in dichloromethane at 50°C leads to the formation of novel ruthenium(II)-pybox complexes *trans*-[$RuCl_2(L)\{\kappa^3\text{-}N,N,N\text{-}(R,R)\text{-Ph-pybox}\}$] [L = PPh_3 (**1a**), PPh_2Me (**2a**), $PPh_2(C_3H_5)$ (**3a**), $PPh_2(C_4H_7)$ (**4a**), PMe_3 (**5a**), P*i*Pr$_3$ (**6a**), $P(OMe)_3$ (**7a**) and $P(OPh)_3$ (**8a**)]. Likewise, reaction of *trans*-[$RuCl_2(\eta^2\text{-}C_2H_4)\{\kappa^3\text{-}N,N,N\text{-}(R,R)\text{-Ph-pybox}\}$] with PPh_3 or P*i*Pr$_3$ in refluxing methanol leads to the complexes *cis*-[$RuCl_2(L)(\kappa^3\text{-}N,N,N\text{-}(R,R)\text{-Ph-pybox}$] [L = PPh_3 (**1b**), P*i*Pr$_3$ (**6b**)]. No *trans–cis* isomerisation of complexes **1a**–**8a** has been observed. Complexes **1a**–**8a**, **1b**, **6b** together with the analogous *trans*-[$RuCl_2\{P(OMe)_3\}\{\kappa^3\text{-}N,N,N\text{-}(S,S)\text{-}i\text{Pr-pybox}\}$] (**10a**) and the previously reported *trans*- and *cis*-[$RuCl_2(PPh_3)\{\kappa^3\text{-}N,N,N\text{-}(S,S)\text{-}i\text{Pr-pybox}\}$] (**9a** and **9b**, respectively) are active catalysts for the transfer hydrogenation of acetophenone in 2-propanol in the presence of NaOH (ketone/cat/NaOH 500:1:6). *cis*-Ph-pybox derivatives are the most active catalysts. In particular, *cis* complexes **1b** and **6b** led to almost quantitative conversions in less than 5 min with a high enantioselectivity (up to 95%). A variety of aromatic ketones have also been reduced to the corresponding secondary alcohols with very high TOF and *ee* up to 94%. The overall catalytic performance seems to be a subtle combination of the steric and/or electronic properties both the phosphines and the ketones. A high TOF (27300 h^{-1}) and excellent *ee* (94%) have been found for the reduction of 3-bromoacetophenone with catalyst **6b**. Reductions of alkyl ketones also proceed with high and rapid conversions but low enantioselectivities are achieved.

Keywords: asymmetric catalysis · hydrogen transfer · ketones · N ligands · ruthenium

Introduction

The role of nitrogen-containing ligands in the catalytic activity of transition-metal complexes has become an important feature in both homogeneous and heterogeneous catalysis. Many new catalysts have incorporated N ligands as a choice to compete with those containing phosphines.[1,2] It is well established that the use of polydentate imino and amino ligands has provided a considerable improvement in catalyst performance in the catalytic hydride transfer reduction of ketones.[3] Among other catalytic asymmetric processes,[4] asymmetric transfer hydrogenation[5] has emerged as a reliable synthetic tool for chiral alcohols, which proves the high efficiency and stereoselectivity of transition metal complexes containing chiral nitrogen ligands. Monotosylated 1,2-diamine ligands **A** and **B** have promoted outstanding conversions and enantioselectivities, mostly using either ruthenium[6] or rhodium and iridium[7] complexes.

Although C_2 chiral ligands have been widely used in a series of catalytic processes because of their ability to generate high chiral inductions,[8] only a few ruthenium complexes containing C_2 polydentate N ligands have been reported in transfer hydrogenations. As far as we know, only examples bearing diaminoferrocenyl derivatives[6e,9] (**C**), bis(oxazolines)[10] (**D**, **E**), aromatic substituted diimines[11] (**F**) and diamines[12] (**G**) have been described.[13] In particular, only one ruthenium complex, containing the tridentate N,N,N ligand bis(oxazolinylmethyl)amine (**D**), has been reported (prepared in situ from [$RuCl_2(PPh_3)$] and **D**).[10a] This fact

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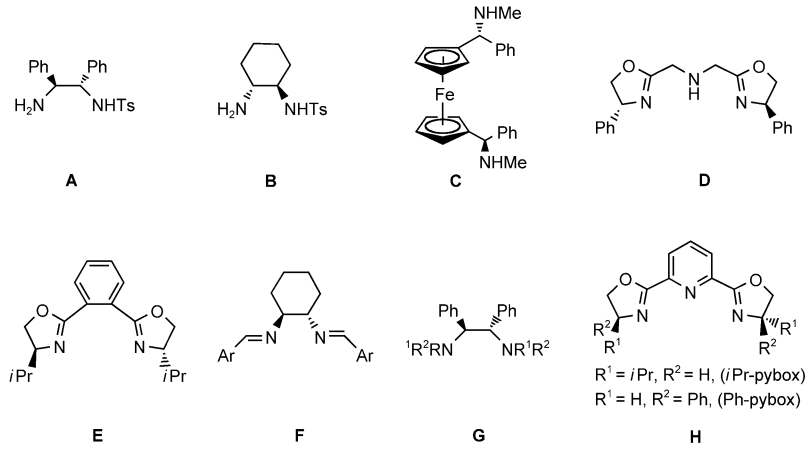


prompted us to study the catalytic activity of ruthenium(II) complexes with the ligands 2,6-bis(4′-R-oxazolin-2′-yl)pyridine (R-pybox) (R = *i*Pr, Ph) (**H**) which have shown remarkable efficiency in catalytic organic transformations involving asymmetric carbon–carbon bond formation, with high enantioselectivity.[14]

In this work we describe the stereoselective synthesis of ruthenium(II) phosphine or phosphite complexes containing the Ph-pybox ligand, namely *trans*-[$RuCl_2$(L)(κ^3-*N*,*N*,*N*-(*R*,*R*)-Ph-pybox)] {L = PPh_3 (**1a**), PPh_2Me (**2a**), $PPh_2(C_3H_5)$ (**3a**) (C_3H_5 = -CH_2-CH=CH_2), $PPh_2(C_4H_7)$ (**4a**) (C_4H_7 = -CH_2-C(CH_3)=CH_2), PMe_3 (**5a**), P*i*Pr_3 (**6a**), $P(OMe)_3$ (**7a**), $P(OPh)_3$ (**8a**)} and *cis*-[$RuCl_2$(L)(κ^3-*N*,*N*,*N*-(*R*,*R*)-Ph-pybox)] {L = PPh_3 (**1b**), P*i*Pr_3 (**6b**)}. These complexes are found to be active catalysts in asymmetric transfer hydrogenation of ketones, leading to the formation of *sec*-alcohols with high conversions and enantioselectivities, some of which are among those with the highest *ee* values reported to date.

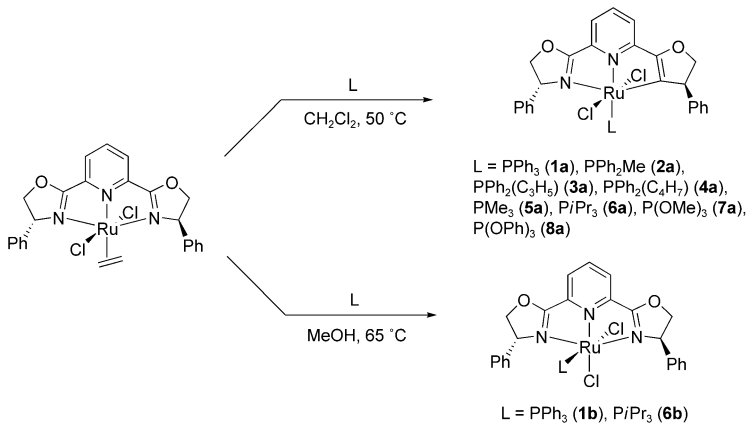
Abstract in Spanish: El tratamiento del complejo *trans*-[$RuCl_2(\eta^2$-$C_2H_4)$\{κ^3-*N*,*N*,*N*-(*R*,*R*)-Ph-pybox\}] [(*R*,*R*)-Ph-pybox = 2,6-bis\{4′-(*R*)-feniloxazolin-2′-il\}piridina] con fosfinas o fosfitos en diclorometano a 50 °C conduce a la formación de los nuevos complejos Ru^{II}-pybox: *trans*-[$RuCl_2$(L)\{κ^3-*N*,*N*,*N*-(*R*,*R*)-Ph-pybox\}] [L = PPh_3 (**1a**), PPh_2Me (**2a**), $PPh_2(C_3H_5)$ (**3a**), $PPh_2(C_4H_7)$ (**4a**), PMe_3 (**5a**), P*i*Pr_3 (**6a**), $P(OMe)_3$ (**7a**) y $P(OPh)_3$ (**8a**)]. Asimismo, la reacción de *trans*-[$RuCl_2(\eta^2$-$C_2H_4)$\{κ^3-*N*,*N*,*N*-(*R*,*R*)-Ph-pybox\}] con PPh_3 o P*i*Pr_3 en metanol a 65 °C genera los complejos *cis*-[$RuCl_2$(L)(κ^3-*N*,*N*,*N*-(*R*,*R*)-Ph-pybox] [L = PPh_3 (**1b**), P*i*Pr_3 (**6b**)]. No se ha observado isomerización *trans*–*cis* de los derivados **1a**–**8a**. Los complejos **1a**–**8a**, **1b**, **6b** junto con los análogos *trans*-[$RuCl_2$\{$P(OMe)_3$\}\{κ^3-*N*,*N*,*N*-(*S*,*S*)-*i*Pr-pybox\}] (**10a**) y los previamente descritos *trans*- y *cis*-[$RuCl_2(PPh_3)$\{κ^3-*N*,*N*,*N*-(*S*,*S*)-*i*Pr-pybox\}] (**9a** y **9b**, respectivamente) son catalizadores activos para la reacción de transferencia de hidrógeno de acetofenona en 2-propanol en presencia de NaOH (cetona/cat/NaOH = 500:1:6). Los derivados *cis*-Ph-pybox son los catalizadores más activos. En concreto, los complejos *cis* **1b** y **6b** conducen a conversiones casi cuantitativas en menos de 5 min con alta enantioselectividad (hasta 95 %). Otras cetonas aromáticas experimentan también reducción a los correspondientes alcoholes secundarios obteniéndose TOF muy altos y *ee* hasta 94 %. Una sutil combinación de las propiedades estéricas y/o electrónicas tanto de las fosfinas utilizadas como de las cetonas determinan los mejores resultados. La reducción de 3-bromoacetofenona por el catalizador **6b** transcurre con un alto TOF (27300 h^{-1}) y excelente *ee* (94 %). Se han reducido también alquil cetonas encontrándose altas y rápidas conversiones aunque con baja enantioselectividad.

Results

Synthesis: Following the synthetic procedure we reported previously for the preparation of *i*Pr-pybox complexes *cis*- and *trans*-[$RuCl_2(PPh_3)$\{κ^3-*N*,*N*,*N*-(*S*,*S*)-*i*Pr-pybox\}] (**9a** and **9b**), [(*S*,*S*)-*i*Pr-pybox = 2,6-bis[4′-(*S*)-isopropyloxazolin-2′-yl]pyridine],[15] the related Ph-pybox derivatives *trans*-[$RuCl_2$(L)\{κ^3-*N*,*N*,*N*-(*R*,*R*)-Ph-pybox\}] (L = PPh_3 (**1a**), PPh_2Me (**2a**), $PPh_2(C_3H_5)$ (**3a**), $PPh_2(C_4H_7)$ (**4a**), PMe_3 (**5a**), P*i*Pr_3 (**6a**), $P(OMe)_3$ (**7a**) and $P(OPh)_3$ (**8a**)) have been obtained (Scheme 1).

Thus, stereoselective substitution of the ethylene ligand in *trans*-[$RuCl_2(\eta^2$-$C_2H_4)$\{κ^3-*N*,*N*,*N*-(*R*,*R*)-Ph-pybox\}][16] by phosphines or phosphites affords, after 3–4 h of heating at 50 °C in dichloromethane in a sealed tube, complexes **1a**–**8a** which are isolated as air-stable purple (phosphines) or dark pink (phosphites) solids (35–88 % yield). Complexes **1a**–**8a**, which are soluble in chlorinated solvents and 2-propanol, have been fully characterised by spectroscopic and analytical methods (see the Experimental Section for details). In particular, the $^{31}P\{^1H\}$ NMR spectra show a singlet resonance at δ = 0.1–40.6 (**1a**–**6a**) and δ = 123.4–146.0 (**7a** and **8a**). The stereochemistry is determined readily on the basis of the $^{13}C\{^1H\}$ NMR spectra, which exhibit the expected resonances in accordance with a C_2 symmetry showing one singlet resonance both for the two methylene groups and for the two *C*HPh groups in the oxazoline rings. These data compare well with those from the known analogous complex *trans*-[$RuCl_2(PPh_3)$\{κ^3-*N*,*N*,*N*-(*S*,*S*)-*i*Pr-pybox\}].[15]

Similarly, *cis* isomers **1b** and **6b** are obtained stereoselectively from *trans*-[$RuCl_2(\eta^2$-$C_2H_4)$\{κ^3-*N*,*N*,*N*-(*R*,*R*)-Ph-pybox\}] by the reaction with PR_3 (R = Ph, *i*Pr) in refluxing methanol (70–80 % yield) (Scheme 1). The $^{31}P\{^1H\}$ NMR spectra show a singlet resonance at δ = 39.0 (**1b**) and δ = 38.8 (**6b**). The $^{13}C\{^1H\}$ NMR spectra of **1b** and **6b** reveal loss of the C_2 symmetry, since two resonances appear for



Scheme 1. Synthesis of the complexes **1a**–**8a**, **1b** and **6b**.

each of the nonequivalent carbon nuclei of *C*HPh and CH_2 groups of the oxazoline rings (see the Experimental Section for further details). These data can be compared with those for *cis*-[$RuCl_2(PPh_3)\{\kappa^3$-*N*,*N*,*N*-(*S*,*S*)-*i*Pr-pybox}], for which the structure has been confirmed by X-ray crystallography.[15] All attempts to isolate other *cis*-Ph-pybox complexes have failed, leading instead either to the corresponding *trans* isomers (L = PMe_3, $P(OMe)_3$) or to an uncharacterised mixture of products (L = PPh_2Me, $PPh_2(C_3H_5)$, $P(OPh)_3$).

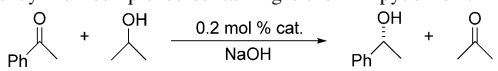
No *trans*–*cis* isomerisation of complexes **1a**–**8a** has been observed. This is in sharp contrast with the behaviour of the known analogous *i*Pr-pybox complex *trans*-[$RuCl_2(PPh_3)\{\kappa^3$-*N*,*N*,*N*-(*S*,*S*)-*i*Pr-pybox}] (**9a**), which isomerises rapidly in methanol at room temperature to generate the thermodynamically stable *cis* isomer **9b**.[15] Apparently, the steric interactions between the phosphines and the oxazoline substituents (phenyl vs isopropyl groups) govern the *cis* or *trans* preference. This is confirmed by the observed stability of the unsubstituted pybox complex *trans*-[$RuCl_2(PPh_3)(\kappa^3$-*N*,*N*,*N*-pybox)], which remains unchanged when heated in methanol for several hours.[15]

Catalytic transfer hydrogenation of ketones: Ruthenium(II) complexes have been widely applied as efficient catalysts in hydrogen transfer reactions between alcohols and ketones, so we have checked the catalytic activity of the complexes reported herein. Moreover, it was expected that the asymmetric induction of pybox ligands, in which the chiral centres on the oxazoline rings are located close to the metal, might lead to good enantioselectivities. In a typical experiment the ruthenium catalyst precursor (0.2 mol%) and NaOH were added to a solution of the ketone in *i*PrOH at 82 °C, the reactions being monitored by gas chromatography. Phenyl or isopropyl substituents in oxazoline rings of pybox ligands have been shown to be crucial in the catalytic enantioselectivities of ruthenium catalysts.[17] Therefore, we first explored, for comparative purposes, the catalytic activities of both *trans*- and *cis*-(*R*,*R*)-Ph-pybox with those of the corresponding (*S*,*S*)-*i*Pr-pybox derivatives **9a** and **9b** and the analogous *trans*-[$RuCl_2\{P(OMe)_3\}\{\kappa^3$-*N*,*N*,*N*-(*S*,*S*)-*i*Pr-pybox}] (**10a**).[18]

Table 1 summarises the conversion of acetophenone in 1-phenylethanol with Ph-pybox (**1a**, **1b** and **7a**) and *i*Pr-pybox complexes (**9a**, **9b** and **10a**) as catalysts. The most remarkable features are:

1) Although the *i*Pr-pybox complexes are active catalysts, Ph-pybox derivatives show much better efficiency and enantioselectivity (entries 1 vs 4, 2 vs 5 and 3 vs 6). All major secondary alcohols had the *S* configuration, except for complex **10a**.

Table 1. Catalytic activity for transfer hydrogenation of acetophenone catalysed by Ru^{II} complexes containing either Ph-pybox or *i*Pr-pybox.[a]



	Catalyst	*t* [min]	Conversion [%][b]	*ee* [%][b]
		Ph-pybox complexes		
1	**1a**	30 (60)	78 (90)	82 (80)
2	**1b**	5	96	92
3	**7a**	5	96	61
		*i*Pr-pybox complexes		
4	**9a**	30 (120)	36 (56)	16 (16)
5	**9b**	30 (120)	29 (50)	5 (2)
6	**10a**	30	97	17

[a] Reactions were carried out at 82 °C using a 0.1 M acetophenone solution in 50 mL of 2-propanol (ketone/catalyst/NaOH 500:1:24). [b] Determined by GC analysis with a Supelco β-DEX 120 chiral capillary column. All the major secondary alcohols had the *S* configuration except for entry 6. Absolute configuration was determined by comparing optical rotations with literature values.

2) Very rapid conversions (almost quantitative in 5 min) are achieved at 82 °C with complexes *cis*-[$RuCl_2(PPh_3)(\kappa^3$-*N*,*N*,*N*-(*R*,*R*)-Ph-pybox)] (**1b**) and *trans*-[$RuCl_2\{P(OMe)_3\}(\kappa^3$-*N*,*N*,*N*-(*R*,*R*)-Ph-pybox)] (**7a**) (entries 2 and 3). The reactions become notably slower as the temperature decreases, with no enhancement of the enantioselectivity.
3) The efficiency and enantioselectivity of the catalyst seem to depend not only on the phosphine (L = PPh_3 (**1a**) vs L = $P(OMe)_3$ (**7a**); entry 1 vs 3) but also on the stereoisomer (entry 1 vs 2), *cis*-**1b** (L = PPh_3) giving rise to better conversion and *ee* value than the corresponding *trans*-**1a** (96% in 5 min vs 90% in 60 min; 92% vs 80% *ee*).

On the basis of these results, we next examined the optimisation of the reaction conditions using the Ph-pybox complexes as catalysts (Table 2). As a general feature, a strong dependence is observed on the NaOH/catalyst molar ratio, which should be not lower than approximately 6:1. Otherwise, the reaction becomes slower and less enantioselective (entry 1 vs 2, 3, 4).[19] On the other hand, when a higher molar ratio is used (up to approximately 24:1) a slightly

Table 2. Optimisation of reaction conditions for transfer hydrogenation of acetophenone catalysed by Ru^{II} complexes containing Ph-pybox.[a]

	Catalyst	Base [equiv][b]	t [min]	Conversion [%]	*ee* [%]
1[c]	**3a**	6:1	15	95	92
2	**3a**	5:1	15	96	87
3[c]	**3a**	5:1	30	96	90
4	**3a**	4:1	180	63	81
5	**3a**	24:1	30	97	84
6	**1b**	6:1	5	95	95
7	**1b**	24:1	5	96	92
8	**7a**	6:1	5	97	63
9	**7a**	24:1	5	96	61
10	**6b**	6:1	3	97	91
11[d]	**6b**	6:1	3(15)	64(95)	54(25)
12[e]	**6b**	6:1	3(15)	79(97)	86(75)

[a] Reactions were carried out at 82 °C using a 0.1 M acetophenone solution with 0.2 mol % catalyst in 50 mL of 2-propanol, except for entry 11. All the major secondary alcohols had the *S* configuration. [b] Equivalents of NaOH to catalyst. [c] Base was added 10 min before ketone. [d] A 1 M acetophenone solution in 5 mL of 2-propanol with 0.2 mol % catalyst was used. [e] Reaction in the presence of 2 equiv of $PiPr_3$.

Table 3. Transfer hydrogenation of acetophenone catalysed by Ph-pybox complexes under optimised conditions.[a]

	Catalyst	t [min]	TOF [h^{-1}][b]	Conversion [%]	*ee* [%]
1	**1b**	5	5700	95	95
2	**6b**	3	9700	97	91
3	**1a**	30	3480	95	90
4	**2a**	30	3840	97	94
5[c]	**3a**	30	2760	94	93
6[c]	**4a**	15	4320	95	90
7	**5a**	30	2580	98	6
8	**6a**	5	5760	96	90
9	**7a**	5	5820	97	63
10	**8a**	60	360	25	5

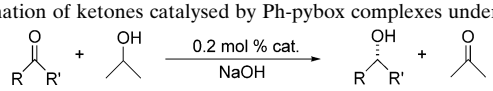
[a] Reactions were carried out at 82 °C with a 0.1 M acetophenone solution in 50 mL of 2-propanol (ketone/cat/NaOH = 500:1:6). All the major secondary alcohols had the *S* configuration. [b] TOF at t = 5 min, except for entry 2 (TOF at t = 3 min). [c] Base was added 10 min before ketone.

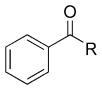
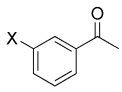
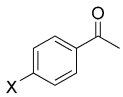
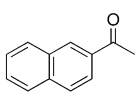
lower enantioselectivity (entry 6 vs 7; 8 vs 9) and/or a slower reactivity (entry 2 vs 5) are found. Intermediate molar ratios (for example, 10:1) were tested; a value of 6:1 gave the best performance, apparently indicating that a compromise should be reached in the amount of the stoichiometric excess of base. In a more concentrated solution (1 M vs 0.1 M ketone; entry 11), high losses of both the activity (64 % vs 97 % in 3 min) and enantioselectivity (54 % vs 91 %) occurred, along with a rapid erosion of the *ee* value over time.[20]

Preliminary experiments proved the influence of the coordinated phosphine in the activity of the catalyst (Table 1). To evaluate the influence of the electronic and/or steric properties of the phosphines we examined the catalytic activity of all *cis* and *trans* (*R*,*R*)-Ph-pybox complexes (**1b**, **6b** and **1a**–**8a**, respectively) for the reduction of acetophenone under the optimised reaction conditions (Table 3). Except for complex **8a** (L = $P(OPh)_3$, entry 10), the reactions were almost complete in a short time (3–30 min), demonstrating that the performances of the *cis* isomers **1b** and **6b**, with excellent enantioselectivities, were better than those of the corresponding *trans* isomers (entries 1 and 2). When *cis* isomers are used the conversion seems to be favoured for **6b** (L = $PiPr_3$) over **1b** (L = PPh_3), (97 % in 3 min vs 95 % in 5 min) whilst there is a slight decrease in the enantioselectivity (91 % vs 95 % *ee*) (entry 1 vs 2). For the *trans* isomers **1a**–**8a**, the steric properties of the phosphines seem to have the dominant influence on the efficiency and enantioselectivity; complex **6a** containing the bulkier phosphine $PiPr_3$ had the best performance (TOF = 5760 h^{-1}; *ee* 90 %) (entry 8). This is in contrast to the trend found in phosphite complexes, for which the bulkier ligand $P(OPh)_3$ is almost inactive (**8a** (L = $P(OPh)_3$, TOF = 360 h^{-1}, *ee* 5 %) vs **7a** (L = $P(OMe)_3$, TOF = 5820 h^{-1}, *ee* 63 %) (entry 10 vs 9).

Various aryl-substituted ketones have also been reduced to the corresponding *sec* alcohols. Table 4 (entries 1–10) shows the best results in terms of TOF and *ee* values for each substrate (additional tables collecting complete data, including catalysts **1a**, **1b**, **3a**, **6a**, **6b** and **7a**, are available as Supporting Information).[21] Confirming the catalytic activity observed for the reduction of acetophenone, complex **6b** also shows the best activities and enantioselectivities for most of the substrates (TOF and *ee* values in the range 2820–27 300 h^{-1} and 86–94 %, respectively) (entries 3, 5, 7, 8

Table 4. Transfer hydrogenation of ketones catalysed by Ph-pybox complexes under optimised conditions.[a]



	Ketone		Catalyst	t [min]	Conversion [%]	TOF [h^{-1}][b]	*ee* [%]	Configuration
1		R = Me[c]	**1b**	5	95	5700	95	*S*
2		R = Me[c]	**6b**	3	97	9700[d]	91	*S*
3		R = Et	**6b**	5	97	5820	92	*S*
4		X = MeO	**7a**	15	99	3490	76	*S*
5		X = Br	**6b**	1(60)	32(65)	2820	86(80)	*S*
6[e]		X = MeO	**3a**	15	97	4320	91	*S*
7		X = Br	**6b**	1(3)	91(>99)	27300[f]	94(93)	*S*
8		X = MeO	**6b**	5	83	4980	89	*S*
9[e]		X = Br	**3a**	120	97	600	70	*S*
10			**6b**	5	97	5820	92	*S*
11		R = Et	**6b**	10	>99	5700	11	*R*
12		R = Et	**7a**	10	>99	5820	11	*S*
13		R = *i*Pr	**7a**	10	99	4440	31	*S*

[a] Reactions were carried out at 82 °C using a 0.1 M ketone solution in 50 mL of 2-propanol (ketone/catalyst/NaOH 500:1:24). [b] TOF at t = 5 min. [c] Ketone/catalyst/NaOH 500:1:6. [d] TOF at t = 3 min. [e] Base was added 10 min before ketone. [f] TOF at t = 1 min.

and 10). However, *trans* isomers are the most active for the reduction of 2-methoxyacetophenone (**7a**; entry 4), 3-methoxyacetophenone (**3a**; entry 6) and 4-bromoacetophenone (**3a**; entry 9) (TOF and *ee* values in the range 600–4320 h^{-1} and 70–91 %, respectively).

Alkyl ketones are also reduced rapidly and quantitatively in approximately 10 min (entries 11, 12 and 13), but low enantioselectivities are achieved.

Discussion

We report here a series of six-coordinate *cis*- and *trans*-dichlororuthenium(II) complexes containing the chiral terdentate ligands 2,6-bis(4′-R-oxazolin-2′-yl)pyridine (R = Ph, *i*Pr). Starting from the readily accessible precursor *trans*-[$RuCl_2(\eta^2\text{-}C_2H_4)\{\kappa^3\text{-}N,N,N\text{-}(R,R)\text{-Ph-pybox}\}$], complexes *trans*-**1a**–**8a**, *cis*-**1b** and **6b**, along with the previously reported *trans*- and *cis*-[$RuCl_2(PPh_3)\{\kappa^3\text{-}N,N,N\text{-}(S,S)\text{-}i\text{Pr-pybox}\}$][15] (**9a** and **9b**, respectively) and the analogous (*S*,*S*)-*i*Pr-pybox complex *trans*-[$RuCl_2\{P(OMe)_3\}\{\kappa^3\text{-}N,N,N\text{-}(S,S)\text{-}i\text{Pr-pybox}\}$],[18] (**10a**) are prepared stereoselectively in good yield. These derivatives belong to the series of chloride ruthenium(II) complexes which fulfil the requirement to be precursors of active species in the catalytic hydrogenation of ketones by hydrogen transfer from *i*PrOH/base. It is well established that the hydrogen transfer occurs through the formation of ruthenium hydride intermediates and that the role of the base is the generation of the hydride species from the chloride derivatives.[22] An active 16-electron species is also required mechanistically, to provide the vacant site that enables attachment of the ketone (hydridic route).[22] We have not performed a mechanistic study, but the basic solution used in the catalytic processes most probably leads to the formation of the hydride intermediate required: that is, extraction of one chloride ligand and generation of the metal–hydride bond (by β-elimination of isopropoxide), in addition to ketone coordination through dissociation of the other chloride ligand. Figure 1 shows the putative four-membered cyclic transition state which should govern the coordination of the ketone (**A** or **B**) and the kinetically controlled formation of the major diastereoisomer responsible for the enantioselectivity.

This proposal is consistent with:

1) the observed loss in the catalytic activity (from 97 to 79 %) and the fast erosion of the *ee* value (from 91 to 86 and 75 % after 15 min) in the presence of free phosphine (Table 2; entry 10 vs 12), which indicates unequivocally the interference of the phosphine with the ketone by occupying the vacant site;[23]

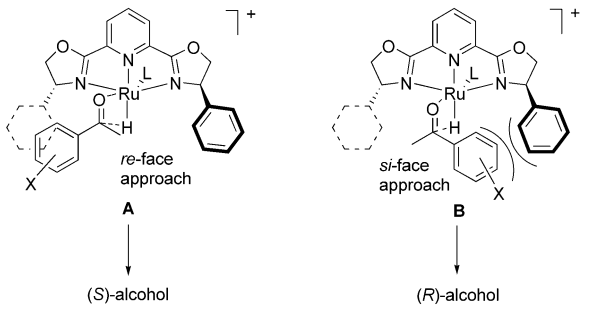


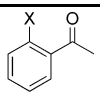
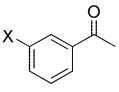
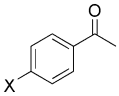
Figure 1. Transition structures of asymmetric transfer hydrogenation of aromatic ketones.

2) the higher activity of the *cis* than the *trans* precursors from which the active species (**A**) are directly accessible;
3) the absolute configurations of the *sec*-alcohols (*S*) resulting from the selective enantiofacial binding ability of the metal fragment which enables the approach of the aryl ketones to the coordination site through the less hindered enantioface. This leads to an optimisation of the chiral pocket by reducing the steric interactions between the aryl groups of the oxazoline ring and the ketones.

It is apparent that the *cis* complexes **1b** (L = PPh_3) and **6b** (L = P*i*Pr_3) also containing the bulkier phosphines show the best performances in the reductions of acetophenone (Table 3), for which the highest activity and enantioselectivity are achieved. However, as shown in Table 4 for substituted aryl ketones, the overall catalytic performance seems to be the result of a subtle combination of the steric and/or electronic properties of both the phosphines and the ketones. Although conversion and *ee* values are affected in each catalyst by the substituent and its position with respect to the ketone group, a general trend in terms of steric and/or electronic effects cannot be deduced.

Table 5 shows the influence of the substituent and its position in the aryl group on the catalytic activity of complex **6b**. Whereas 2- and 4-bromoacetophenone are reduced with moderate conversions and/or *ee* values (entries 2 and 6), excellent values are achieved for 3-bromoacetophenone (entry 4). No equivalent influence on conversion and *ee* is

Table 5. Transfer hydrogenation of aryl-substituted ketones catalysed by complex **6b** under optimised conditions.[a]

	Ketone		*t* [min]	Conversion [%]	TOF [h^{-1}][b]	*ee* [%]
1		X = MeO	120	94	2100	47
2		X = Br	60	65	2820	80
3		X = MeO	5	97	5820	82
4		X = Br	1(3)	91 (>99)	27300[b]	94 (93)
5		X = MeO	5	83	4980	89
6		X = Br	60	69	1260	54

[a] Reactions were carried out at 82 °C using a 0.1 M ketone solution in 50 mL of 2-propanol (ketone/catalyst/NaOH = 500:1:24). All the major secondary alcohol products had the *S*-configuration. [b] TOF at *t* = 5 min. [c] TOF at *t* = 1 min.

found for derivatives containing the electron-releasing methoxy group. Thus, the highest conversion is again found for the 3-substituted ketone (entry 3), but a better *ee* is achieved for the 4-substituted one (entry 5). The 2-methoxy ketone (entry 1) produces a moderate performance. Therefore, the optimisation of the chiral pocket apparently requires an appropriate phosphine with specific steric and electronic properties for each substrate.

Nevertheless, as far as we know, *cis* complexes **1b** and **6b** are among the best catalysts reported to date for asymmetric transfer hydrogenation of ketones, with efficiencies and selectivities comparable to those of the Noyori catalysts.[6] The highest TOF (27300 h^{-1}) and excellent *ee* (94%) found for the reduction of 3-bromoacetophenone by catalyst **6b** are noteworthy. Although reductions with highly efficient asymmetric ruthenium(II) catalysts containing the chiral ligand [(4*S*)-2-(S_p)-2-diphenylphosphinoferrocenyl]-4-isopropyloxazoline have also been described, they proceed with a slower rate and in addition a larger quantity of catalyst is required (0.5 mol%).[24]

Conclusion

This work reports a new type of highly efficient catalysts for transfer hydrogenation of aryl ketones. The presence of the phenyl substituent in the oxazoline ring of the tridentate chiral ligand pybox is important for attainment of high catalytic activity and enantioselectivity, which indeed are among the best reported to date for the asymmetric reduction of ketones. Providing that the pybox chiral ligands are commercially available[25] and the ruthenium(II) complexes are air-stable and exhibit good thermal stability, wide practical utility in transfer hydrogenation of ketones may be predicted.

Experimental Section

General: The manipulations were performed under an atmosphere of dry nitrogen using vacuum-line and standard Schlenk techniques. All reagents were obtained from commercial suppliers and used without further purification. Solvents were dried by standard methods and distilled under nitrogen before use. [$RuCl_2(\eta^2\text{-}C_2H_4)\{\kappa^3\text{-}N,N,N\text{-}(R,R)\text{-Ph-pybox}\}$] and $PPh_2(C_3H_5)$ were prepared by the methods reported in the literature. Infrared spectra were recorded on a Perkin-Elmer 1720-XFT spectrometer. The conductivities were measured at room temperature, in acetone (ca. 10^{-4} M) solutions, with a Jenway PCM3 conductimeter. The C, H and N analyses were carried out with a Perkin-Elmer 240-B microanalyser. NMR spectra were recorded on a Bruker DPX-300 instrument at 300 MHz (^{1}H), 121.5 MHz (^{31}P) or 75.4 MHz (^{13}C) using $SiMe_4$ or 85% H_3PO_4 as standards. DEPT experiments have been carried out for all the complexes.

Synthesis of *trans* complexes 1a, 4a, 6a and 8a: A solution of *trans*-[$RuCl_2(\eta^2\text{-}C_2H_4)\{\kappa^3\text{-}N,N,N\text{-}(R,R)\text{-Ph-pybox}\}$] (0.150 g, 0.263 mmol) and an excess of the phosphine or phosphite (1.315 mmol) in dichloromethane (15 mL) was heated at 50°C in a sealed tube for 4 h. The solvent was then concentrated to about 3 mL and the residue transferred to a silica gel chromatography column. Elution with a mixture of dichloromethane/methanol (50:1) gave a purple band (for **1a**, **4a** and **6a**) or a dark pink band (for **8a**) from which the corresponding complex was isolated by solvent removal.

*Complex **1a***: Yield 53% (0.075 g); elemental analysis (%): calcd for $C_{41}H_{34}Cl_2N_3O_2PRu\cdot 0.5\,CH_2Cl_2$: C 58.91, H 4.17, N 4.97; found: C 59.27, H 4.34, N 5.35; $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 40.56 (s); ^{1}H NMR ($CDCl_3$): δ = 4.43 and 4.74 (m, 2H each, CH_2), 4.89 (t, 2H, J(H,H) = 8.4 Hz, C*H*Ph), 6.72–7.42 (m, 25H, Ph), 7.92 (s, 3H, C_5H_3N); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 69.85 (s, *C*HPh), 80.39 (s, CH_2), 124.12, 127.54, 128.32–128.91, 134.54, 134.67, 139.50 (s, Ph, and CH of C_5H_3N), 137.14 (d, J(C,P) = 37.6 Hz, *i*PPh_3), 149.56 (s, $C_{2,6}$ of C_5H_3N), 168.24 (s, C=N).

*Complex **4a***: Yield 73% (0.100 g); elemental analysis (%): calcd for $C_{39}H_{36}Cl_2N_3O_2PRu$: C 59.93, H 4.64, N 5.38; found: C 59.11, H 4.14, N 5.19; $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 38.16 (s); ^{1}H NMR ($CDCl_3$): δ = 0.82 (s, 3H, Me), 2.06 and 2.82 (m, 1H each, PCH_2), 3.88 and 4.11 (s, 1H each, C(Me)=C*H*$_2$), 4.36 (m, 2H, C*H*Ph), 4.81–4.93 (m, 4H, OCH_2), 6.56–7.30 (m, 20H, Ph), 7.75 (m, 3H, C_5H_3N); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 24.60 (s, Me), 35.55 (d, J(C,P) = 17.3 Hz, PCH_2), 69.38 (s, *C*HPh), 78.91 (s, OCH_2), 114.09 (d, ^3J(C,P) = 6.2 Hz, C(Me)=*C*H$_2$), 123.55, 126.51–140.54 (s, Ph, C(Me)=CH_2, and CH of C_5H_3N), 148.70 (s, $C_{2,6}$ of C_5H_3N), 167.20 (s, C=N).

*Complex **6a***: Yield 80% (0.148 g); elemental analysis (%): calcd for $C_{32}H_{40}Cl_2N_3O_2PRu$: C 54.78, H 5.75, N 5.99; found: C 53.97, H 5.46, N 5.83; $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 34.14 (s); ^{1}H NMR ($CDCl_3$): δ = 0.74 (br, 7H) and 1.20 (br, 11H) (Me), 2.19 (br, 3H, C*H*Me$_2$), 4.51 (m, 2H, C*H*Ph), 5.00–5.18 (m, 4H, CH_2), 7.14–7.33 (m, 10H, Ph), 7.87 (s, 3H, C_5H_3N); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 16.55 and 18.58 (br, Me), 27.65 (br, *C*HMe$_2$), 69.83 (s, *C*HPh), 78.65 (s, CH_2), 124.26, 126.90, 127.65, 128.01, 128.61, 128.76 and 132.54 (s, Ph, and CH of C_5H_3N), 139.31 (s, C_{ipso} of Ph), 149.03 (s, $C_{2,6}$ of C_5H_3N), 168.32 (s, C=N).

*Complex **8a***: Yield 35% (0.078 g); elemental analysis (%): calcd for $C_{41}H_{34}Cl_2N_3O_5PRu$: C 57.82, H 4.02, N 4.93; found: C 57.39, H 4.43, N 4.99; $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 123.41 (s); ^{1}H NMR ($CDCl_3$): δ = 4.47 (t, J(H,H) = 7.4 Hz, 2H, C*H*Ph), 5.07 and 5.18 (m, 2H each, CH_2), 6.58–7.11 (m, 25H, Ph), 7.92 (d, 2H, J(H,H) = 6.5 Hz, $H_{3,5}$ of C_5H_3N), 8.02 (t, 1H, J(H,H) = 7.1 Hz, H_4 of C_5H_3N); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 70.10 (s, *C*HPh), 79.33 (s, CH_2), 121.40, 121.45, 123.05, 123.60, 127.10, 127.44, 128.30, 128.36, 136.83 and 138.98 (s, Ph, and CH of C_5H_3N), 147.92 (s, $C_{2,6}$ of C_5H_3N), 152.39 (d, ^2J(C,P) = 14.6 Hz, C_{ipso} of Ph of $P(OPh)_3$), 166.26 (s, C=N).

Synthesis of *trans* complexes 2a, 3a, 5a and 7a: A solution of *trans*-[$RuCl_2(\eta^2\text{-}C_2H_4)\{\kappa^3\text{-}N,N,N\text{-}(R,R)\text{-Ph-pybox}\}$] (0.150 g, 0.263 mmol) and a small excess of phosphine or phosphite (0.316 mmol) in dichloromethane (15 mL) was heated at 50°C in a sealed tube for 4 h. The residue was then concentrated to ca. 3 mL and a mixture (50 mL) of pentane/diethyl ether (2:1) was added, yielding a purple (for **2a**, **3a** and **5a**) or a dark pink solid (for **7a**) which was washed with pentane (3×30 mL) and vacuum-dried.

*Complex **2a***: Yield 73% (0.142 g); elemental analysis (%): calcd for $C_{36}H_{32}Cl_2N_3O_2PRu$: C 58.30, H 4.35, N 5.67; found: C 58.09, H 4.22, N 5.62; $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 17.46 (s); ^{1}H NMR ($CDCl_3$): δ = 1.36 (d, 3H, ^2J(H,P) = 5.6 Hz, Me), 4.45 (m, 2H), 4.72 (m, 2H) and 4.98 (m, 2H) (CH_2 and C*H*Ph), 6.74–7.43 (m, 20H, Ph), 7.90 (s, 3H, C_5H_3N); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 14.45 (d, J(C,P) = 28.0 Hz, Me), 69.14 (s, *C*HPh), 79.39 (s, CH_2), 123.41, 126.80–133.37 and 138.68 (s, Ph, and CH of C_5H_3N), 135.99 (d, J(C,P) = 36.7 Hz, C_{ipso} of Ph of PPh_2Me), 141.39 (d, J(C,P) = 33.2 Hz, C_{ipso} of Ph of PPh_2Me), 148.87 (s, $C_{2,6}$ of C_5H_3N), 167.33 (s, C=N).

*Complex **3a***: Yield 88% (0.179 g); elemental analysis (%): calcd for $C_{38}H_{34}Cl_2N_3O_2PRu$: C 59.46, H 4.46, N 5.47; found: C 58.54, H 4.94, N 5.55; $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 33.93 (s); ^{1}H NMR ($CDCl_3$): δ = 1.93 and 2.97 (m, 1H each, PCH_2), 4.27–4.43 (m, 4H) and 4.81–4.95 (m, 4H) (OCH_2, C*H*Ph and CH=C*H*$_2$), 6.63 (m, 1H, C*H*=CH_2), 6.84 (m, 3H), 6.98–7.25 (m, 17H), 7.72 (m, 1H) and 7.87 (m, 2H) (Ph and C_5H_3N); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 33.06 (d, J(C,P) = 21.0 Hz, PCH_2), 69.30 (s, *C*HPh), 78.91 (s, OCH_2), 116.74 (d, ^3J(C,P) = 7.6 Hz, CH=*C*H$_2$), 123.53, 126.74–129.00, 132.56, 133.39, 133.50, 133.60, 136.84 and 138.80 (s, Ph, *C*H=CH_2, and CH of C_5H_3N), 148.69 (s, $C_{2,6}$ of C_5H_3N), 167.21 (s, C=N).

*Complex **5a***: Yield 65% (0.105 g); elemental analysis (%): calcd for $C_{26}H_{28}Cl_2N_3O_2PRu$: C 50.57, H 4.57, N 6.81; found: C 49.61, H 4.88, N 6.65; $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 0.08 (s); ^{1}H NMR ($CDCl_3$): δ = 1.02 (d, ^2J(H,P) = 8.6 Hz, Me), 4.52 (m, 2H) and 5.16 (m, 4H) (CH_2 and C*H*Ph), 7.24–7.34 (m, 10H, Ph), 7.92 (m, 3H, C_5H_3N); $^{13}C\{^1H\}$ NMR

($CDCl_3$): δ = 16.89 (d, J(C,P) = 25.7 Hz, Me), 69.90 (s, *C*HPh), 78.69 (s, CH_2), 123.46 (s, $C_{3,5}$ of C_5H_3N), 127.33, 128.04, 128.65 (s, Ph), 132.01 (s, C_4 of C_5H_3N), 139.26 (s, C_{ipso} of Ph), 148.21 (s, $C_{2,6}$ of C_5H_3N), 167.47 (s, C=N).

Complex ***7a***: Yield 72% (0.085 g); elemental analysis (%): calcd for $C_{26}H_{28}Cl_2N_3O_5PRu$: C 46.93, H 4.24, N 6.31; found: C 46.91, H 4.40, N 6.12; $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 146.05 (s); ^1H NMR ($CDCl_3$): δ = 3.12 (d, 9H, ^3J(H,P) = 10.2 Hz, Me), 4.55 (m, 2H, C*H*Ph), 5.17 (m, 4H, CH_2), 7.25–7.31 (m, 10H, Ph), 7.90 (m, 3H, C_5H_3N); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 51.39 (d, ^2J(C,P) = 5.6 Hz, Me), 70.39 (s, *C*HPh), 79.24 (s, CH_2), 123.08 (s, $C_{3,5}$ of C_5H_3N), 127.42, 127.74, 128.39 (s, CH of Ph), 135.83 (s, C_4 of C_5H_3N), 139.45 (s, C_{ipso} of Ph), 148.17 (s, $C_{2,6}$ of C_5H_3N), 166.32 (s, C=N).

Synthesis of *cis* complexes 1b and 6b: A solution of *trans*-[$RuCl_2(\eta^2$-$C_2H_4)\{\kappa^3$-*N,N,N*-(*R,R*)-Ph-pybox}] (0.150 g, 0.263 mmol) and an excess of phosphine (0.789 mmol) in methanol (15 mL) was heated at 65°C for 5 h. The solvent was then concentrated to ca. 3 mL and the residue transferred to a silica gel chromatography column. Elution with a mixture of dichloromethane/methanol (50:1) gave a red band from which the corresponding complex was isolated by solvent removal.

Complex ***1b***: Yield 70% (0.295 g); elemental analysis (%): calcd for $C_{41}H_{34}Cl_2N_3O_5PRu{\cdot}0.5\,CH_2Cl_2$: C 58.91, H 4.17, N 4.97; found: C 59.27, H 4.34, N 5.35; $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 39.03 (s); ^1H NMR ($CDCl_3$): δ = 4.30–4.63 (m, 4H, CH_2), 5.03 and 5.50 (m, 1H each, C*H*Ph), 6.91–7.64 (m, 28H, Ph and C_5H_3N); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 67.90, 68.30, 78.18, 81.13 (s, CH_2 and *C*HPh), 124.44, 124.54, 127.62–128.91, 130.88, 131.92, 132.06, 132.35, 132.48, 133.03, 136.62, 139.04 (s, Ph, and CH of C_5H_3N), 151.79, 152.15 (s, $C_{2,6}$ of C_5H_3N), 167.70, 169.44 (s, C=N).

Complex ***6b***: Yield 81% (0.148 g); elemental analysis (%): calcd for $C_{41}H_{34}Cl_2N_3O_5PRu{\cdot}0.5\,CH_2Cl_2$: C 52.46, H 5.55, N 5.65; found: C 53.12, H 5.89, N 5.74; $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 38.83 (s); ^1H NMR ($CDCl_3$): δ = 0.69–0.76 (br, 6H) and 1.06–1.40 (br, 12H) (Me), 1.90 (m, 1H) and 2.12 (m, 2H) (C*H*Me_2), 4.48 (m, 1H), 4.97 (m, 1H), 5.19 (m, 3H) and 5.42 (m, 1H) (CH_2 and C*H*Ph), 7.22–7.29 (m, 7H) and 7.56–7.70 (m, 6H) (Ph and C_5H_3N); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 19.04 and 20.17 (s, Me), 28.30 (d, J(C,P) = 19.7 Hz, P*C*H), 67.49 and 69.75 (s, *C*HPh), 78.46 and 79.63 (s, CH_2), 124.90 and 125.11 (s, $C_{3,5}$ of C_5H_3N), 128.03–129.63 (s, Ph, and C_4 of C_5H_3N), 137.18 and 139.11 (s, C_{ipso} of Ph), 154.51 and 155.28 (s, $C_{2,6}$ of C_5H_3N), 168.65 and 169.37 (s, C=N).

General procedure for hydrogen transfer reactions: The ketone (5 mmol) and the catalyst (0.01 mmol) were placed in a three-bottomed Schlenck flask under a dry nitrogen atmosphere and 2-propanol (50 mL) was added. The solution was heated at 82°C and the corresponding amount of base from a 0.080 M solution in 2-propanol was added after 15 min (unless otherwise specified). The reaction was monitored by gas chromatography. The corresponding alcohol and acetone were the only products detected in all cases.

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[1] a) A. Togni, L. M. Venanzi, *Angew. Chem.* **1994**, *106*, 517–547; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 497–526; b) F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159–2231.

[2] For recent reviews on the chemistry of complexes containing phosphorus–nitrogen ligands, see: a) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336–345; b) M. Gómez, G. Muller, M. Rocamora, *Coord. Chem. Rev.* **1999**, *193–195*, 769–835; c) P. Espinet, K. Soulantica, *Coord. Chem. Rev.* **1999**, *193–195*, 499–556; d) P. Braunstein, F. Naud, *Angew. Chem.* **2001**, *113*, 702–722; *Angew. Chem. Int. Ed.* **2001**, *40*, 680–699.

[3] a) G. Zassinovich, G. Mestroni, S. Gladiali, *Chem. Rev.* **1992**, *92*, 1051–1069; b) S. Gladiali, G. Mestroni in *Transition Metal for Organic Synthesis, Vol. 2* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**, p. 97.

[4] a) A. Pfaltz, *Acta Chem. Scand. Ser. B* **1996**, *50*, 189–194; b) B. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422; c) D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835–875; d) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron* **1998**, *54*, 1–45.

[5] For recent reviews see: a) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97–102; b) M. J. Palmer, M. Wills, *Tetrahedron: Asymmetry* **1999**, *10*, 2045–2061; c) R. Noyori, M. Yamakawa, S. Hashiguchi, *J. Org. Chem.* **2001**, *66*, 7931–7944; d) K. Everaere, A. Mortreux, J.-F. Carpentier, *Adv. Synth. Catal.* **2003**, *345*, 67–77; e) D. Carmona, M. P. Lamata, L. A. Oro, *Eur. J. Inorg. Chem.* **2002**, 2239–2251.

[6] a) S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563; b) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522; c) K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739; d) K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem.* **1997**, *109*, 297–300; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285–288; e) K. Püntener, L. Schwink, P. Knochel, *Tetrahedron Lett.* **1996**, *37*, 8165–8168; f) water-soluble ruthenium(II) catalysts containing (*S*)-proline amide ligands have also given excellent performances: H. Y. Rhyoo, H.-J. Park, Y. K. Chung, *Chem. Commun.* **2001**, 2064–2065.

[7] a) K. Murata, T. Ikariya, R. Noyori, *J. Org. Chem.* **1999**, *64*, 2186–2187; b) K. Mashima, T. Abe, K. Tani, *Chem. Lett.* **1998**, 1199–1200; c) K. Mashima, T. Abe, K. Tani, *Chem. Lett.* **1998**, 1201–1202.

[8] a) I. Ojima in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**; b) I. Ojima, *Catalytic Asymmetric Synthesis*, 2nd ed., VCH, Weinheim, **2000**; c) S. E. Denmark, E. N. Jacobsen (Eds.), *Acc. Chem. Res.* **2000**, *33*(6), special issue on *Catalytic Asymmetric Synthesis*.

[9] L. Schwink, T. Ireland, K. Püntener, P. Knochel, *Tetrahedron: Asymmetry* **1998**, *9*, 1143–1163.

[10] a) Y. Jiang, Q. Jiang, X. Zhang, *J. Am. Chem. Soc.* **1998**, *120*, 3817–3818; b) M. Gómez, S. Jansat, G. Muller, M. C. Bonnet, J. A. J. Breuzard, M. Lemaire, *J. Organomet. Chem.* **2002**, *659*, 186–195.

[11] P. Krasik, H. Alper, *Tetrahedron* **1994**, *50*, 4347–4354.

[12] a) F. Touchard, P. Gamez, F. Fache, M. Lemaire, *Tetrahedron Lett.* **1997**, *38*, 2275–2278; b) F. Touchard, F. Fache, M. Lemaire, *Tetrahedron: Asymmetry* **1997**, *8*, 3319–3326.

[13] A series of ruthenium complexes containing tridentate N,P,N ligands have also been found to be active in asymmetric transfer hydrogenation: a) Q. Jiang, D. Van Plew, S. Murtuza, X. Zhang, *Tetrahedron Lett.* **1996**, *37*, 797–800; b) Y. Jiang, Q. Jiang, G. Zhu, X. Zhang, *Tetrahedron Lett.* **1997**, *38*, 215–218; c) Y. Jiang, Q. Jiang, G. Zhu, X. Zhang, *Tetrahedron Lett.* **1997**, *38*, 6565–6568.

[14] For a review see ref. [4d]; for recent catalytic applications of pybox complexes, see: a) K. Nomura, S. Warit, Y. Imanishi, *Macromolecules* **1999**, *32*, 4732–4734; b) D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell, R. J. Staples, *J. Am. Chem. Soc.* **1999**, *121*, 669–685; c) D. A. Evans, C. S. Burgey, M. C. Kozlowski, S. W. Tregay, *J. Am. Chem. Soc.* **1999**, *121*, 686–699; d) D. A. Evans, D. M. Barnes, J. S. Johnson, T. Lectka, P. von Matt, S. J. Miller, J. A. Murry, R. D. Norcross, E. A. Shaughnessy, K. R. Campos, *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594; e) S. E. Schaus, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 1001–1004; f) T. P. Yoon, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 2911–2912; g) D. A. Evans, Z. K. Sweeney, T. Rovis, J. S. Tedrow, *J. Am. Chem. Soc.* **2001**, *123*, 12095–12096; h) S. Iwasa, F. Takezawa, Y. Tuchiya, H. Nishiyama, *Chem. Commun.* **2001**, 59–60; i) C.-X. Zhao, M. O. Duffey, S. J. Taylor, J. P. Morken, *Org. Lett.* **2001**, *3*, 1829–1831; j) M. A. Esteruelas, A. M. López, L. Méndez, M. Oliván, E. Oñate, *New J. Chem.* **2002**, *26*, 1542–1544; k) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638–5639; l) H. Suga, K. Inoue, S. Inoue, A. Kakehi, *J. Am. Chem. Soc.* **2002**, *124*, 14836–14837; m) S. Iwasa, S. Tsushima, T. Shimada, H. Nishiyama, *Tetrahedron* **2002**, *58*, 227–232; n) S. Iwasa, H. Maeda, K. Nishiyama, S. Tsushima, Y. Tsukamoto, H. Nishiyama, *Tetrahedron* **2002**, *58*, 8281–8287; o) S. Iwasa, S. Tsushima, K. Nishiyama, Y. Tsuchiya, F. Takezawa, H. Nishiyama, *Tetrahedron: Asymmetry* **2003**, *14*, 855–865.

[15] V. Cadierno, M. P. Gamasa, J. Gimeno, L. Iglesias, S. García-Granda, *Inorg. Chem.* **1999**, *38*, 2874–2879.
[16] H. Nishiyama, Y. Itoh, H. Matsumoto, S.-B. Park, K. Itoh, *J. Am. Chem. Soc.* **1994**, *116*, 2223–2224.
[17] See, for instance: a) H. Nishiyama, Y. Itoh, Y. Sugawara, H. Matsumoto, K. Aoki, K. Itoh, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247–1262: in the asymmetric cyclopropanation of olefins with diazoacetates catalysed by the [$RuCl_2(C_2H_4)$(R-pybox)] complexes, *i*Pr-pybox complex has been found to be much more active and selective than the Ph-pybox analogues; according to ref. [14k]: copper(I)-Ph-pybox complexes are more active and enantioselective catalysts in the addition of terminal alkynes to imines than the corresponding *i*Pr-pybox analogues.
[18] Complex **10a** has been prepared by heating a mixture of [$RuCl_2(\eta^2$-$C_2H_4)\{\kappa^3$-*N*,*N*,*N*-(*S*,*S*)-*i*Pr-pybox$\}$] and an excess of $P(OMe)_3$ at 40 °C in dichloromethane for 1 h (35% yield) (unpublished results from this laboratory).
[19] For complexes containing the allyl-substituted phosphines an improvement in performance has been obtained by adding the base 10 min before the ketone (entry 3 vs 2). This fact may be explained by assuming an isomerisation of the allyl group in the presence of base, which may occur before the chloride abstraction from the metal. Therefore, the active species probably contain diphenyl(2-methylvinyl)phosphine.
[20] Pathways that favour the reverse reaction leading to loss of *ee* cannot be discarded either.
[21] We have found that a base/catalyst of ca. 24:1 leads to better conversions for these substrates, in contrast to the ratio (ca. 6:1) found for acetophenone.
[22] For a short review and mechanistic studies see: a) J.-E. Bäckvall, *J. Organomet. Chem.* **2002**, *652*, 105–111; b) O. Pàmies, J.-E. Bäckvall, *Chem. Eur. J.* **2001**, *7*, 5052–5058.
[23] The dissociation of the coordinated phosphine or phosphite has to be discarded; otherwise, no influence on *ee* values would be observed.
[24] Y. Nishibayashi, I. Takei, S. Uemura, M. Hidai, *Organometallics* **1999**, *18*, 2291–2293.
[25] From Aldrich 2003–2004: (*R*,*R*)-Ph-pybox (49606-5); (*S*,*S*)-Ph-pybox (49607-3). From TCI 2003: (*R*,*R*)-Ph-pybox (B2219); (*S*,*S*)-Ph-pybox (B2220).

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