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Cyclometalated Complexes of Ruthenium, Rhodium and Iridium as Catalysts for Transfer Hydrogenation of Ketones and Imines

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Abstract: A library of organometallic compounds derived from primary and secondary amines cyclometalated by ruthenium(II), rhodium(III) and iridium(III) was tested in the asymmetric transfer hydrogenation of a number of ketones and imines. All compounds displayed high catalytic activity for the reduction of ketones under mild conditions. The most enantioselective catalysts were based on secondary amines containing two asymmetric carbon atoms bound to the nitrogen atom. For the reduction of aryl alkyl ketones [Ar(C=O)R where R = CH_3 or CH_2R'] the cyclometalated ruthenium and rhodium derivatives of the (2*R*,5*R*)-2,5-diphenylpyrrolidine ligand displayed the best results with respect to activity and selectivity (*ee*s up to 97%). However, for the reduction of aryl *tert*-alkyl ketones [Ar(C=O)R″ in which R″ is a tertiary alkyl group] the best catalyst was a ruthenium compound derived from bis[(*R*)-1-phenylethyl]amine, allowing the reduction of isobutyrophenone and cyclohexyl phenyl ketone which were both reduced with high enantioselectivities (*ee*s up to 98%). This shows that the cyclometalated compounds have a high substrate specificity. In addition, acyclic and cyclic imines were reduced with good selectivities by both rhodium(III) and iridium(III) metalacycles built up with (2*R*,5*R*)-2,5-diphenylpyrrolidine.

Keywords: imines; iridium; ketones; rhodium; ruthenium; transfer hydrogenation

Introduction

Amongst the many catalytic applications of Ru(II) in organic synthesis (hydrogenation, oxidation, metathesis…),[1] hydrogen transfer has become very popular this last decade. It is indeed a very powerful tool in asymmetric synthesis, as it allows the formation of new stereocentres from a great variety of prochiral organic substrates on the way towards useful products for fine chemical industry.[2,3] This method has many advantages compared to alternative competing technologies: (i) the use of safe and low-cost reducing agents, (ii) an operational simplicity, and (iii) the reduction of safety constraints associated with the use of molecular hydrogen or stoichiometric amounts of metal hydrides.[2,4,5]

A large number of catalyst precursors has already been successfully tested for their ability to catalyse the hydrogen transfer reaction, leading to the reduction of ketones and imines. Most of these organometallic complexes were built up with chiral bidentate ligands such as diamines, amino acids or amino alcohols.[2,6] The prototype of such complexes was disclosed in the early 1990s by Noyori et al., who found that a Ru(II) half-sandwich complex ligated by chiral *N*-tosyl-1,2-diphenylethylenediamine was a very powerful catalyst precursor for the target reaction.[6b] Noyori et al. also proposed the concept of metal-ligand bifunctional catalysis after mechanistic studies.[7] They suggested that the substrate interacts with both a metal hydride unit and an acidic NH function of the ligand *via* a 6-membered ring transition state.

Organometallic compounds containing a metalacycle[8] as catalyst precursors in hydrogen transfer are still not very numerous.[9] However, a few groups have recently described promising catalytic results using N–C–N,[10] P–C–P,[10a,11] C–P,[12] and C–N–N[13] cycloruthenated or cycloiridiated[14] ligands.

Our contribution to this field was triggered by the discovery that cycloruthenated chiral benzylamines

are also attractive catalyst precursors for the reduction of acetophenone. They operate under mild conditions (room temperature), are robust (they can be used several times provided that more substrate is added) and allow the achievement of high TONs (up to 30,000 for reactions run at 80 °C) and high selectivities (up to 90%).[15] Mechanistic studies were performed on one of these systems: they indicated that the hydrogen transfer process proceeds *via* the formation of a substrate-catalyst complex between the Ru hydrides and the substrate, which is analogous to the 6-membered ring proposed by Noyori et al.[7] In the present paper, we present full data concerning the catalytic activities of a library of cyclometalated derivatives [M = Ru(II), Rh(III), Ir(III)] that all contain a metalacyclic unit, and we highlight their specific behaviours.

Results

Library of Catalyst Precursors

We have shown in preliminary form[15] that a few ruthenium complexes obtained *via* the cyclometalation reaction on primary or secondary amines were good catalyst precursors for the reduction of acetophenone in the presence of base and of 2-propanol as hydrogen source. We have now extended this study to a larger set of such compounds based on new chiral amines. Additionally, we have also prepared some of the related rhodium(III) and iridium(III) derivatives stabilised by a η^5-pentamethylcyclopentadienyl (Cp*) ligand. The choice of the cyclometalated ligands used in this library came from a preliminary study whereby a library of 30 *in situ*-made ruthenium derivatives was formed, following the cyclometalation procedure, with commercially available optically pure primary and secondary amines. The catalytic properties of these non-isolated complexes have been previously tested in the reduction of acetophenone in parallel using high-throughput screening.[15]

From this study chiral benzylamine derivatives emerged as the ligand class that induced the highest enantioselectivities. Consequently, we have focused on this structural motif to prepare the library of compounds of the present study that is depicted in Figure 1. The catalytic activities of compounds **1**, **4** and **6** in the reduction of prochiral ketones to alcohols have been published.[15] The library was now extended to the known compounds **2**, **5** and **7**–**13** whose syntheses and complete characterisations were described recently but for which we have not disclosed any catalytic properties as yet.[16,17]

We synthesised the new compound **3**, in order to check the influence of the steric hindrance at the

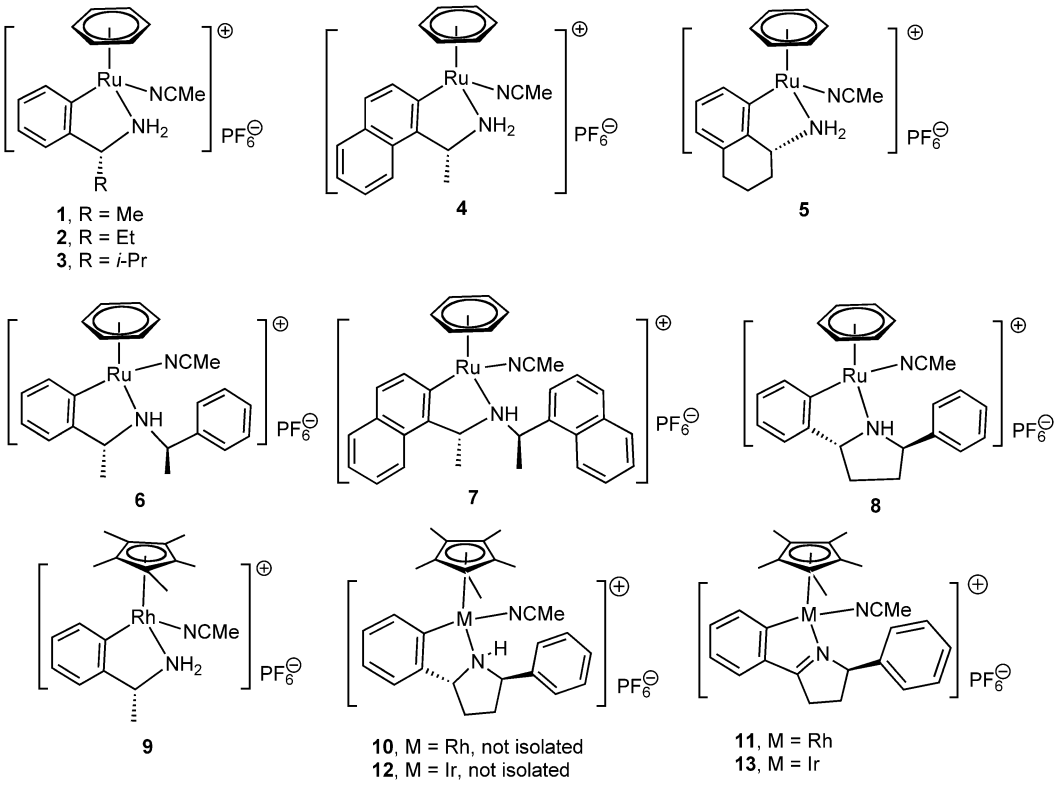

Figure 1. Library of cyclometalated compounds.

chiral centre on the enantioselectivity of the transfer hydrogenation. It is worth mentioning that the (*R*)-α-isopropylbenzylamine used for the synthesis of **3** was obtained from the corresponding (*S*)-alcohol (*ee* > 98%) that was synthesised by the enantioselective reduction of the commercially available isobutyrophenone, using compound **6** (see below). The synthesis of **3** was performed following a procedure similar to that used for **1** and **2**.[16a] The spectroscopic data of **3** are similar to those of **1** and **2**, i.e., in solution this compound exists as 2 diastereoisomers, which differ from one another by the configuration of the ruthenium atom.

The best Ru-containing catalysts were **6** and **8**, i.e., those obtained *via* the cyclometalation of bis[(*R*)-1-phenylethyl]amine and (2*R*,5*R*)-2,5-diphenylpyrrolidine by $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$. Consequently, we attempted the synthesis of the corresponding cyclometalated Rh(III) and Ir(III) compounds with these two ligands using the Rh and Ir dimers $[Cp^*MCl_2]_2$ as precursors. Full details about this chemistry have been published elsewhere.[17] Contrary to the Ru case,[16a] we found that the benzylamine ligands were easily dehydrogenated under the cyclometalation conditions once they were bound to the Rh(III) and Ir(III) centres, leading to cyclometalated imine derivatives. Thus, whereas bis[(*R*)-1-phenylethyl]amine led to intractable mixtures of products, (2*R*,5*R*)-2,5-diphenylpyrrolidine afforded a mixture of cyclometalated amine and imine, compounds **10**–**13**. Compounds **11** and **13** could be isolated pure, however **10** and **12** were always contamined by variable amounts of **11** and **13**, respectively.

Transfer Hydrogenation of Acetophenone

All organometallic compounds (**1**–**12**) derived from primary and secondary amines (Figure 1) were found to be good-to-excellent catalyst precursors for the reduction of acetophenone (substrate **A**, Figure 2) under mild conditions, as far as activity was concerned (see Table 1), with the noticeable exception of the iridium-containing catalyst (entry 14) that was significantly less active than the other compounds.

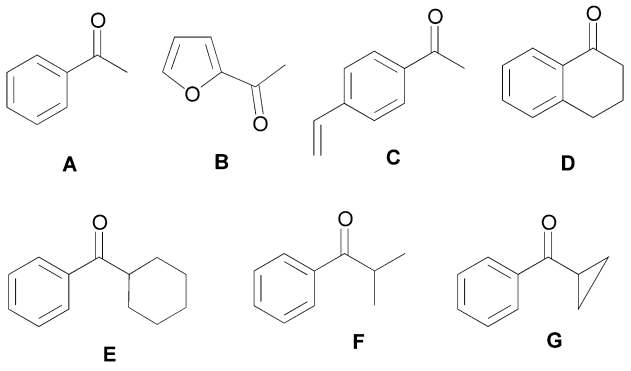

Figure 2. Library of ketone substrates.

Table 1. Asymmetric reduction of acetophenone, **A** with the library of catalyst precursors.[a]

Entry	Catalyst	Time	Yield [%][b]	*ee* [%][b]
1	**1**	40 min	95	39 (*S*)[c]
2	**2**	30 min	96	51 (*S*)
3	**3**	2 h	92	60 (*S*)
4	**4**	10 min	90	57 (*S*)[c]
5	**5**	2 h	93	54 (*S*)
6	**6**	30 min	96	76 (*S*)[c]
7	**7**	2 h	95	77 (*S*)
8	**8**	30 min	92	**88 (*S*)**
9[d]	**8**	3 h	95	**90 (*S*)**
10[e]	**8**	2 h	87	**90 (*S*)**
11[d]	**9**	2 h	90	34 (*S*)
12	**10**	1.5 h	96	**89 (*S*)**
13	**11**	2 h	5	–[f]
14	**12**	1 h	24	**89 (*S*)**
15	**13**	2 h	0	–
16[g]	**13**	30 h	64	**8 (*S*)**

[a] *Conditions:* ketone (10^{-1} M) in 10 mL of 2-propanol; [substrate]:[catalyst]:[*t*BuOK] = 100:1:5, 20 °C.
[b] Determined by chiral GC. The absolute configuration of the major enantiomer is given in parentheses.
[c] Published data.[15]
[d] Ketone (10^{-1} M) in 100 mL of 2-propanol.
[e] Reaction performed at 0 °C.
[f] **11** that was used was obtained with the racemic imine ligand.
[g] Reaction performed at 60 °C.

We independently prepared **11** and **13** directly from the imine ligand, and found that they were either poorly active (**11**, entry 13) or inactive (**13**, entry 15) at room temperature. A mediocre activity was observed for **13** at 60 °C in 2-propanol (entry 16), moreover the enantioselectivity was very poor (8%) at this temperature. As pointed out earlier, so far we were unable to obtain pure **10** and **12** as both of these compounds were contaminated by their corresponding cyclometalated imine, i.e., **11** and **13**, respectively.

However, these first results show that the activities and enantioselectivities observed in the transfer hydrogenation of acetophenone can reasonably be assigned to the cyclometalated pyrrolidine, i.e., **10** and **12** only. It is reasonable to assume that **11** and **13** are also inactive at room temperature with other more difficult substrates. Throughout this paper, we shall thus refer to the mixtures (**10**, **11**) and (**12**, **13**) as compounds **10** and **12**, respectively.

Compounds **2** and **3** differ from **1** by the size of the substituent at the benzylic position. The substitution of a methyl by an ethyl and then by an isopropyl group each time enhanced the enantioselectivity by *ca*. 10% with no significant modification of the activity (entries 1–3). However the *ee*s obtained with all

catalysts, based on primary amines remained modest (entries 1–5, maximum = 60% for entry 3), though it was somewhat higher than that of the other compounds obtained with primary amines (entries 1–5). The same trend was observed for the rhodium compound **9** which displayed an even lower selectivity than that of **1** (entry 11). It was thus confirmed here that the best catalysts were those obtained with secondary amines, especially the derivatives of the pyrrolidine ligand. This is true for both the ruthenium (**8**) and the rhodium (**10**) compounds.

Good enantioselectivity was also obtained with catalyst **8** at higher substrate-to-catalyst ratio (entry 9, S/C = 100) but no significant improvement was observed upon lowering the temperature (entry 10).

We also checked that a base must be present. No reaction took place after 48 h in the absence of base. There is however no influence of the nature of the base (*t*-BuOK or KOH), nor of its concentration (varying the base:catalyst ratios from 1.5 to 10) on activity or selectivity.

Substrate Scope of the Best Catalysts

The catalyst precursors that showed the best performance in the reduction of acetophenone, i.e., **6**, **8**, **10** and **12**, were further tested on a set of prochiral ketones (Figure 2). The results under various reaction conditions (reaction time, temperature and concentration) are described in Table 2.

Acetylfuran (**B**) was best reduced by the catalysts **8** and **10**, whereas **6** was less selective and **12** less active. The rhodacycle **10** was the most active catalyst of the library for the reduction of **B**. Indeed, when the concentration of the ketone was 0.1 M and the experiment was run at room temperature, the reaction was complete after 15 min and the *ee* dropped fast from 82% to 57% after 6 h. This last result is consistent with the high activity of **10** which also catalyses the reverse reaction, thus leading to an erosion of *ee*; **10** catalysed this reverse reaction at a much higher rate than the other cyclometalated complexes. Thus, the best results were obtained by lowering the temperature, the reaction time and the concentration of the substrate (entry 7). With both ruthenacycle **8** and rho-

Table 2. Reduction of the substrates **B–G** with catalysts **6**, **8**, **10** and **12**.[a]

Entry	Substrate	Catalyst	Temperature	Time [h]	Substrate concentration (M)	Yield [%][b]	*ee* [%][b]
1	B	**6**	r.t.	0.75	10^{-1}	95	86[c]
2	**B**	**8**	r.t.	1.5	10^{-1}	82	87[c]
3	**B**	**8**	0 °C	6	10^{-1}	**86**	**92**
4	**B**	**8**	r.t.	7	10^{-2}	74	89
5	**B**	**8**	0 °C	7	10^{-2}	97	90
6	**B**	**10**	r.t.	2	10^{-2}	94	89
7	**B**	**10**	0 °C	0.75	10^{-2}	**98**	**92**
8	**B**	**12**	r.t.	3	10^{-1}	37	89
9	**C**	**6**	r.t.	0.75	10^{-1}	94	79
10	**C**	**6**	r.t.	2	10^{-2}	75	82
11	**C**	**6**	0 °C	4	10^{-2}	88	87[c]
12	**C**	**8**	r.t.	0.5	10^{-1}	90	86[c]
13	**C**	**10**	0 °C	3	10^{-2}	**81**	**93**
14	**C**	**12**	r.t.	6	10^{-1}	91	85
15	**D**	**8**	r.t.	0.5	10^{-1}	57	**96**[c]
16	**D**	**10**	r.t.	0.5	10^{-1}	56	91
17	**D**	**12**	r.t.	7	10^{-1}	39	**96**
18	**E**	**6**	r.t.	1.5	10^{-1}	**97**	**98**[c]
19	**E**	**8**	r.t.	1.5	10^{-1}	74	48[c]
20	**E**	**10**	r.t.	1.5	10^{-1}	88	85
21	**E**	**12**	r.t.	1.5	10^{-1}	58	81
22	**F**	**6**	r.t.	1.5	10^{-1}	**97**	**98**[c]
23	**F**	**8**	r.t.	1.5	10^{-1}	95	48[c]
24	**F**	**10**	r.t.	1.5	10^{-1}	75	75
25	**F**	**12**	r.t.	3.5	10^{-1}	38	74
26	**G**	**6**	r.t.	4	10^{-1}	32	89[c]
27	**G**	**8**	r.t.	4	10^{-1}	18	45[c]
28	**G**	**10**	r.t.	4	10^{-1}	32	36

[a] *Conditions:* solvent = 2-propanol; [substrate]:[catalyst]:[*t*-BuOK] = 100:1:5.
[b] Determined by chiral GC.
[c] Published data.[15c]

dacycle **10**, running the reaction at 0 °C led to an increase of the enantioselectivity but also, more surprisingly, to a slight increase in the activity (see entries 4, 5 and 6, 7, respectively).

The chemoselectivity of our catalysts was tested in the reduction of the 4-vinylacetophenone **C**. We found that the ketone function was reduced selectively with all catalysts, whilst the vinylic group remained intact. The enantioselectivity of **6** and **10** towards the reduction of **C** could be significantly improved by lowering the temperature, and by lowering the concentration of the substrate resulting in 87% and 93% *ee*, respectively (entry 11 and 13).

High *ee*s were obtained in the reduction of substrate **D** using **8**, **10** or **12** as catalysts (entries 15–17). However, the activity of these complexes was mediocre. Only very short reaction times (entries 15 and 16) could be used for **8** and **10** as longer reaction times induced significant losses in enantioselectivities with no improvements in the yield of the reaction. The iridium derivative **12** was here again rather sluggish (entry 17). Note that **6** was neither active nor selective for the reduction of this substrate.

An unexpected result was obtained as we found that **6** was very efficient for the reduction of the substrates that bear a tertiary carbon atom α to the ketone function in **E** and **F**. It was both very active and selective leading to 98% *ee*s (entries 18 and 22); **8** was rather inefficient in this instance (<50% *ee*, entries 19 and 23), **10** was a reasonably good catalyst. However, the cyclopropyl ketone **G** defied this trend; whereas with catalyst **6** a good *ee* was obtained, its reduction was slow with **6**, **8** and **10**.

Reduction of Imines by Transfer Hydrogenation

Among the methods available to generate optically active amines, asymmetric hydrogen transfer on imines is of high fundamental and economic importance. However, it has been much less explored until recently.[18] In the early 1990s, Bäckvall's group reported the first hydride transfer on imine using $[RuCl_2(PPh_3)_3]$, K_2CO_3 and 2-propanol as the hydride source.[19] Noyori then reported the first asymmetric example of transfer hydrogenation on a few imine substrates, which occurred with excellent yields and enantioselectivities.[20] Rhodium complexes related to Noyori's catalyst were also successfully used for this reaction.[21] Some other examples of transfer hydrogenation of imines have been reported during the latest years,[22] including an interesting application in a key step of a total enantioselective synthesis.[23] We then decided to test our cyclometalated compounds in the enantioselective reduction of prochiral imines, and, to this end, we selected a small set of substrates depicted in Figure 3.

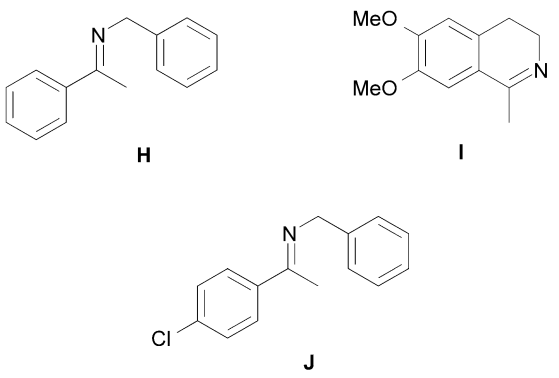

Figure 3. Library of imines.

The reaction conditions were optimised using substrates **H** and **I**, with catalyst **6**. The best source of hydrogen proved to be a 1:1 mixture of formic acid and triethylamine from which traces of water had to be strictly excluded in order to avoid the hydrolysis of the imine function, prior to its reduction. To achieve this, a 5:2 $HCOOH/NEt_3$ mixture was azeotropically distilled and dry NEt_3 was added. A co-solvent had to be used in order to solubilise the substrate and dichloromethane was found to be the best choice. The complexes **1–7** and **9** were tested under the optimised reaction conditions, but none of them gave satisfyingly enantioselectivities and they were not used further. Indeed the catalysts derived from primary amines led to amines with *ee*s inferior to 20%, whereas **6** and **7** led to mediocre results (*ee*s < 40%). Additionally, a fast erosion of *ee* was observed when using these catalysts.

On the other hand, better results were obtained with catalysts **8**, **10** and **12** for the reduction of the substrates **H** - **J** (Table 3).

The iridium compound **12** displayed good activity for all 3 substrates with *ee*s ranging from 57 to 77%.

Table 3. Reduction of the imines **H–J** with catalysts **8**, **10** and **12**.[a]

Entry	Substrate	Catalyst	Yield [%][b]	*ee* [%][c]
1	**H**	**8**	52	60
2	**H**	**10**	70	**91**
3	**H**	**12**	90	76
4	**I**	**8**	11	71
5	**I**	**10**	95	14
6	**I**	**12**	100	**77**
7	**J**	**8**	21	60
8	**J**	**10**	42	34
9	**J**	**12**	64	57

[a] *Conditions:* imine (0.016 M) in 2.5 mL of CH_2Cl_2, HCO_2H/Et_3N (1/1 molar) (0.5 mL), the ratio [substrate]:[catalyst] = 100:1, 20 °C. Time = 19 h.
[b] Determined by ^1H NMR.
[c] Determined by chiral HPLC.

We have been puzzled by the results observed using **10**. For substrate **H**, it is the most enantioselective catalyst (*ee* = 91%, entry 3) whereas with substrate **I** and the even more related substrate **J**, it is the worst one. We have no rational explanation so far for this result, except it is another illustration that in asymmetric catalysis, there is no such a thing as a "universal catalyst".

Discussion

The cyclometalated amines of the library display good-to-excellent activities in the transfer hydrogenation of ketones and imines (conversion >90% under standard conditions for at least one of the substrates tested). The only ones that showed good-to-excellent enantioselectivities (*ee* up to 98%) are those based on secondary chiral amines. However, no catalyst in our library appears to be consistently better than all the others for the small selection of prochiral substrates tested. As usually in enantioselective catalysis, each substrate requires a specific catalyst.

The moderate enantioselectivities of cyclometalated primary amines are in line with the mechanistic studies performed recently:[24] the main conclusion that was drawn from these studies was that ruthenacycles based on chiral primary benzylamines are unable to induce very high enantioselectivities, because of the formation of a diastereomeric mixture of Ru hydride intermediates leading to catalysts that display competitive rates but opposite enantioselectivities.

At this stage of our study, we can conclude that **8** and **10** are the best of our catalysts for the reduction of ketones having a methyl or an alkyl group connected *via* a *secondary* carbon to the C=O unit, and that **6** is the best catalyst for the reduction of those ketones that bear an alkyl group connected *via* a *tertiary* carbon atom to the carbonyl unit. Although the iridium complex **12** is a mediocre catalyst for the reduction of ketones, it is rather efficient for the reduction of imines.

The performances of our best catalysts for the reduction of ketones (**6**, **8** and **10**) are in line with those of other compounds described recently. For instance, Noyori's catalyst[25] was known to be a sluggish and moreover non-selective catalyst for the reduction of **E** or **F**. Morris et al.[26] got significantly improved results using a so-called 'reverse-tethered' catalyst derived from Noyori's catalyst by linking its amino group to the (η^6-arene)Ru unit, obtaining thus excellent *ee*s for the reduction of the substrates **E** and **F** (94% and 95%, respectively). These latter figures were, however, slightly lower those reached with the catalyst **6** (98% in both cases).

The efficiencies of our ruthenium catalysts **6**, **7** and **8** derived from the metalation of secondary amines

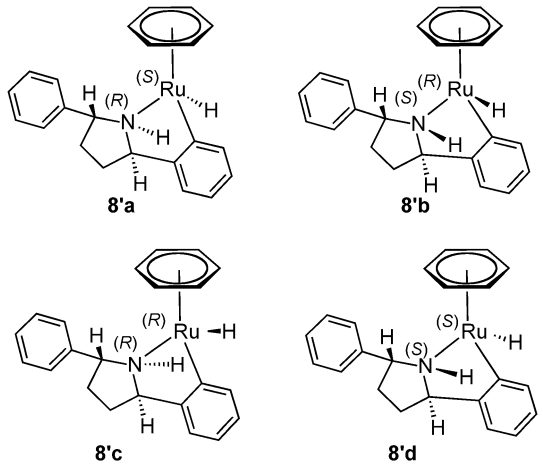

Figure 4. The likely catalytically active species **8′a** and **8′b** derived from **8**, and the inactive ones **8′c** and **8′d**.

are to be re-examined in light of the mechanism of the reaction that was recently studied in detail.[24] It was shown that the true intermediate is likely to be a ruthenium hydride that interacts with the ketone *via* both a Ru–H and an NH unit according to Noyori's outer sphere mechanism.[7] Assuming that the stereochemistry of the hydrides follows that of the acetonitrile complexes **6** or **8** that we recently established *via* ^{1}H NMR and X-ray diffraction studies,[16] likely representations of the catalysts might well be related to those depicted in Figure 4 (for **8** only). In diastereoisomers **8′a** and **8′b** the Ru–H and N–H vectors are *cis*, therefore they display the correct geometry for the formation of the 6-membered transition state with the incoming substrate. On the other hand **8′c** and **8′d** display antiparallel N–H and Ru–H bonds, and the mechanism above can obviously not take place.

It is interesting to note that the major isomers of **6** and **8** (respectively, 69% and 76%), having an acetonitrile ligand instead of a hydride ligand, present antiparallel Ru–NCMe and NH bonds. Assuming that replacing acetonitrile with a hydride will not dramatically affect the ratio of isomers, this would mean that the active catalysts are the minor isomers, and hence the activity of our catalysts could roughly be twice as high as that measured.

As the configuration of the alcohol is mainly *S*, the most active species should be that having the R_N,S_M configuration as this one should lead specifically to the *S* enantiomer of the alcohol.[24] The S_N, R_M isomer leading to the *R* product is thus much less efficient or much less abundant on the basis of molecular models (a strong steric interaction between the non-metalated phenyl unit and the benzene ring is apparent).

The mechanism of the transfer hydrogenation with the RhCp* and IrCp* derivatives of the cyclometalated amines is not known. However, based on literature data,[27] it is very likely that an outer sphere mecha-

nism analogous to the one depicted for the Ru compound is operative as well. No crystal structure of the pyrrolidine complexes **10** and **12** could be obtained yet because of the existence of the mixture of compounds observed during the synthesis of these complexes. However, the ^{1}H NMR spectra revealed that both precatalysts **10** and **12** exist as one diastereomer only (with a R_M, R_N configuration). This isomer is the one having the NCMe and the NH antiparallel to each other. It is here again rather likely that the active catalysts are also very minor ones.

Conclusions

We have synthesised a library of chiral metalacycles [M = Ru(II), Rh(III) and Ir(III)] which were tested as enantioselective transfer hydrogenation catalysts on a set of different substrates using first high-throughput screening as preliminary experiments, and then Schlenk tube techniques. We observed good activities for most of the tested substrates and high-to-very-high enantioselectivities for some of them, the most selective ones being those compounds derived from cyclometalation of secondary amines. As often in asymmetric catalysis, we observed a high specificity of a given catalyst for a type of substrate with no easy way to predict a matching catalyst-substrate couple. The use of metals such as Rh or Ir enabled a diversification of the substrate field, with promising results for imines. This family of cyclometalated catalysts has the advantage of being easy to synthesise in one step from chiral commercial ligands. They can be used *in situ* and display good robustness, which are two qualities required for routine applications.

Experimental Section

Experiments were carried out under an argon atmosphere using a vacuum line. Diethyl ether and pentane were distilled over sodium and benzophenone, dichloromethane and acetonitrile over calcium hydride, and methanol over magnesium under argon immediately before use. Column chromatography was carried out on Merck aluminium oxide 90 standardised. (*R*)-1-Phenyl-2-methylpropylamine was synthesised following a published procedure for the amination of alcohols, the optically active alcohol used being that obtained through the reduction of substrate **F** by catalyst **6**, see entry 22, Table 2.[28] All substrates for the reduction of ketones and imines were commercially available or prepared according to published procedures. NMR spectra were obtained at room temperature on a Bruker AC-300 spectrometer and referenced to $SiMe_4$. ^{1}H NMR spectra were recorded at 300.13 MHz and $^{13}C\{^1H\}$ NMR spectra (broadband decoupled) at 75.48 MHz. The NMR assignments were supported by 2D spectra. Multiplicity: s = singulet, d = doublet, m = multiplet, br = broad signal. ES-mass spectra were recorded on a Bruker Daltonics MicroTOF spectrometer. Elemental analyses were carried out at the Service Central d′Analyse du CNRS, Vernaison.

Typical Procedure for the Catalytic Transfer Hydrogenation of Ketones in Schlenk Tubes

The catalyst (10 μmol) was dissolved in 2-propanol (10 mL) under argon, and the ketone (1 mmol) was added, followed by *t*-BuOK (5.6 mg, 50 μmol); the mixture was stirred at room temperature. The reaction was periodically monitored by GC on an HP 5890 Series II chromatograph; samples were filtered over silica gel using Et_2O as eluent. The conversions and *ee* values were determined by GC using a chiral capillary column (Chiraldex β-PM, 50 m × 0.25 mm).

Typical Procedure for the Catalytic Transfer Hydrogenation of Imines

To a stirred solution of the imine substrate (1 mmol) and the catalyst precursor (5 μmol) in CH_2Cl_2 (2 mL), was added a freshly prepared solution of HCO_2H/Et_3N (1/1 molar, 0.5 mL). After stirring under argon at room temperature for 24 h, an aliquot was diluted with Na_2CO_3 solution and extracted twice with EtOAc. The extracts were washed with brine, dried over $MgSO_4$, and evaporated under vacuum. An aliquot in hexane/2-propanol (90:10) was analysed using a chiral HPLC column (Chiralcel OD 250 × 4.6 mm).

Typical Procedure for High-Throughput Catalytic Transfer Hydrogenation

The experiment was performed in a liquid handling robot (Zinner Lizzy), placed in a glove box. Stock solutions of catalysts (1.12 mM), substrates (60 mM), and *t*-BuOK (5.6 mM) were prepared in 2-propanol under argon. A few drops of CH_2Cl_2 were used to dissolve entirely the catalyst. Aliquots of 1 mL of each stock solution were mixed in wells placed on a microplate. 1 mL 2-propanol was added in each well and the solutions were placed on an orbital shaker and vortexed at room temperature for 2 h. Aliquots (0.5 mL) were put in GC vials and mixed with 0.1 mL of glacial acetic acid (10% in 2-propanol) to stop the reaction. Samples were diluted in EtOAc (1 mL) and submitted to GC analysis. The conversions and *ee* values were determined by GC using a chiral capillary column (Chrompack CP-Sil 5CB, 25 m × 0.25 mm).

Synthesis of {(η^6-C_6H_6)Ru[C_6H_4-2-(*R*)-CH(*i*Pr)NH_2]-($NCCH_3$)}(PF_6) (3)

To a suspension of $[Ru(\eta^6\text{-}C_6H_6)Cl_2]_2$ (0.298 g, 0.6 mmol), NaOH (0.048 g, 1.2 mmol) and KPF_6 (0.442 g, 2.4 mmol) in CH_3CN (15 mL) was added (*R*)-1-phenyl-2-methylpropylamine (0.021 g, 0.6 mmol) and the mixture was stirred at 20 °C under argon during 72 h. The resulting green suspension was filtered over celite, concentrated under vacuum and filtered over standardised Al_2O_3 (12 × 3 cm) using CH_3CN as eluent. A light green fraction was collected, concentrated under vacuum and vigorously stirred with 20 mL of hexane during 2 h, in order to extract the residual free amine. The CH_3CN layer was evaporated under vacuum. The residue was then redissolved in a minimum amount of

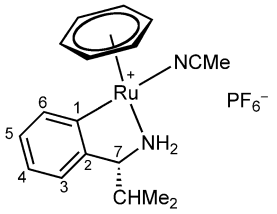

Figure 5. Numbering scheme for compound **3**.

CH_2Cl_2 and a yellow solid precipitated upon addition of *n*-pentane; yield: 150 mg (52%). ^{1}H NMR (see Figure 5 for numbering system; <300 MHz, CD_3CN): major diastereoisomer (56%), δ=7.79 (d, 1H, H-6, $^3J_{H,H}$=7.1 Hz), 7.05–6.85 (m, 2H, H-4+H-5), 6.81 (m, 1H, H-3), 5.57 (s, 6H, η^6-C_6H_6), 5.18 (br, 1H, NH), 3.76 (m, 1H, H-7), 2.87 (br, 1H, NH), 2.37 (m, 1H, C*H*Me$_2$), 1.14 (d, 3H, Me, $^3J_{H,H}$=7.0 Hz), 0.64 (d, 3H, Me, $^3J_{H,H}$=6.9 Hz); minor diastereoisomer (44%), δ=7.88 (d, 1H, H-6, $^3J_{H,H}$=7.4 Hz), 7.05–6.85 (m, 3H, H-3+H-4+H-5), 5.61 (s, 6H, η^6-C_6H_6), 4.40 (br, 1H, NH), 4.11 (br, 1H, NH), 3.62 (m, 1H, H-7), 1.72 (m, 1H, C*H*Me$_2$), 0.97 (d, 3H, Me, $^3J_{H,H}$=6.8 Hz), 0.87 (d, 3H, Me, $^3J_{H,H}$=6.8 Hz); ^{13}C{^{1}H} NMR (75 MHz, CD_3CN): major isomer, δ=165.7 (C-1), 150.0 (C-2), 140.3 (C-6), 127.3 (C-5), 124.3 (C-4), 124.0 (C-3), 87.8 (η^6-C_6H_6), 70.0 (C-7), 32.7 (*C*HMe$_2$), 20.0 (Me), 17.6 (Me); minor isomer, δ=167.6 (C-1), 148.2 (C-2), 140.3 (C-6), 127.5 (C-5), 124.5 (C-4), 123.7 (C-3), 87.8 (η^6-C_6H_6), 72.0 (C-7), 31.2 (*C*HMe$_2$), 20.1 (Me), 14.5 (Me); anal. calcd. for $C_{18}H_{23}N_2PF_6Ru{\cdot}2.5\,CH_2Cl_2$ (725.5): C 33.93, H 3.89, N 3.86; found : C 34.20, H 3.82, N 4.18; ES-MS : *m/z* (%)=369.09 (4) $[M]^+$, 328.10 (100) $[M-CH_3CN]^+$.

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