Fast Racemisation of Chiral Amines and Alcohols by Using Cationic Half-Sandwich Ruthena- and Iridacycle Catalysts


Abstract: The lipase-catalysed resolution of alcohols and amines yields only 50% of the desired enantiopure product. However, addition of a racemisation catalyst leads to 100% yield in what is called a dynamic kinetic resolution (DKR). There is a need for new racemisation catalysts that are fast and compatible with the conditions of the enzymatic reaction. We show that cationic half-sandwich ruthena- and iridacycle complexes are highly active and efficient in the racemisation of chiral alcohols and amines. Upon activation with base, these complexes are able to selectively racemise alcohols, whereas the non-activated complexes are selective catalysts for the racemisation of amines. We have applied the iridacycles in the DKR of racemic β-chloroalcohols to produce chiral epoxides in a biphasic system in good yields and high ee (ee = enantiomeric excess).

Keywords: alcohols · amines · iridium · metallacycles · racemisation

Introduction

Enantiomerically pure amines and alcohols are important building blocks for pharmaceutical and agrochemical products.[1] Although several catalytic methods exist for their preparation in an enantiopure form,[2] one of the most frequently used production methods involves the classical resolution by crystallisation of diastereomeric salts.[3] Enzymatic resolution is also frequently used.[4] The drawback of these resolution methods lies in the fact that only 50% of the desired enantiomer is produced; the other 50% of the non-desired enantiomer being mere waste. Designing catalysts that are capable of rapidly racemising the non-desired enantiomer and that are compatible with these enzymes enables a dynamic kinetic resolution (DKR) that can give a 100% yield of the desired enantiomer (Scheme 1).[5] Relatively few catalytic systems are available that can achieve this. The groups of Williams[6] and Bäckvall[7] developed the DKR of alcohols by using a combination of lipases and ruthenium catalysts. The latter used the dimeric Ru catalyst developed by Shvo.[8] These catalysts function through a dehydrogenation–hydrogenation sequence. DSM Pharmaceutical Products has further developed the Bäckvall system to allow industrial production of alcohols.[9]

Scheme 1. DKR of alcohols and amines.
The racemisation of amines is much more challenging. Raney cobalt, Raney nickel or alkali metal hydroxide have been used at high temperatures for the racemisation of amines.\textsuperscript{[10]} In addition, aldehydes or thiols have been used as catalysts at lower temperatures.\textsuperscript{[11]} The first DKR of amines was achieved by Reetz et al. who managed to acylate (rac)-$\alpha$-methylbenzylamine by using a combination of Pd/C and Candida antarctica lipase B (CALB, Novozym-435) in refluxing triethylamine.\textsuperscript{[12]} Although rather long reaction times were needed for complete conversion. Jacobs and de Vos used a basic support, such as BaSO$_4$, for the palladium catalyst, which increased the catalyst activity and allowed the racemisation to proceed under milder conditions. Thus, the time of the DKR reaction was reduced to three days.\textsuperscript{[13]} In addition, these authors found that application of a low pressure of dihydrogen suppressed the formation of secondary amines in the racemisation of primary amines. Palladium nanoparticles developed by Park et al. led to excellent yields and enantiomeric excess in the DKR of primary amines with a reaction time of three days.\textsuperscript{[14]} These nanoparticles could be recycled without any loss of activity for 10 consecutive runs. The Bäckvall group made several contributions to this area.\textsuperscript{[15]} They used the Shvo catalyst\textsuperscript{[15d]} and showed that better results were obtained when using an electron-rich variant thereof in the DKR of alcohols and amines.\textsuperscript{[15b,c]} Recently they reported the use of the transfer hydrogenation catalysts developed by Baratta for the racemisation of amines. No DKR could be achieved, though.\textsuperscript{[15a]} They applied this methodology in the synthesis of Norsetraline.

In general, the sensitivity of the metal catalyst for the enzyme seems to play an important role in the reactions since the dimeric iridium complex [Ir(Cp*)(I$_2$)]$_2$ (Cp* = pentamethylcyclopentadiene) was successfully used by Blacker as a fast racemisation catalyst for the dynamic kinetic resolution of 6,7-dimethoxy-1-methyl-tetrahydroisoquinoline in combination with immobilized Candida antarctica lipase, whereas palladium and ruthenium complexes showed much lower reactivity.\textsuperscript{[16]} The development of fast racemisation catalysts for alcohols and amines continues to be a major challenge. As we have developed the use of ruthenacycles as asymmetric transfer-hydrogenation catalysts, we were interested in studying these catalysts, and, in particular, the analogous iridacycles, as racemisation catalysts.\textsuperscript{[17]} The synthesis of iridacycles based on the reaction between [Ir(Cl$_2$)(Cp*)]$_2$ and benzylamines has been described by Davies\textsuperscript{[18]} and Pfeffer et al.\textsuperscript{[19]} Ikariya recently reported the use of iridacycles as alcohol oxidation catalysts.\textsuperscript{[20]}

## Results and Discussion

We started by investigating the behaviour of half-sandwich metallacycles in the racemisation of (S)-1-phenylethanol (S1) and (R)-2-chloro-1-phenylethanol (S2). Cycloruthenated complexes of the type [Ru($\eta^5$-C$_5$H$_5$)(C-N)(CH$_3$CN)]- (PF$_6$)$_2$, in which C-N is a chiral primary or secondary amine attached to the metallated aromatic ring through an alkyl group, have been shown to be very effective for the asymmetric transfer hydrogenation of aromatic ketones.\textsuperscript{[17]} We therefore decided to prepare an analogous complex, but with an achiral amine, and to test its activity for the racemisation of both alcohols (Scheme 2). Complex 1 was obtained analytically pure according to the transformation shown in Scheme 2.

![Scheme 2. Synthesis of ruthenacycle complex 1.](image)

It is noteworthy that, due to the presence of stereogenic centres on the Ru and N atoms, 1 consists of two pairs of enantiomers $R_R$S$_N$/S$_R$R$_N$ and $R_R$R$_N$/S$_R$S$_N$, which show well-separated signals in their $^1$H- and $^{13}$C NMR spectra and are found in a diastereomeric ratio of 56:44 ($de = 12\%$; $de =$ diastereomeric excess) in CD$_3$CN (Scheme 3). Considering the sterically less-constrained structure of the $R_R$R$_N$/S$_R$S$_N$ pair (the NMe group is further away from the CH$_3$CN ligand than in the other pair) it is most probably the major one. These diastereomers rapidly interconvert in solution.\textsuperscript{[21]}

The catalytic activity of 1 was examined in the racemisation of (S)-S1 and (R)-S2 in the presence of KOtBu as an activator (Scheme 4). Complex 1 gave very poor results in di-
This indicated that catalyst deactivation in the racemisation attempts of (R)-S2 was due to the formation of small amounts of 2-chloroacetophenone, the dehydrogenation product of S2, which reacted with the active species. A similar behaviour had already been observed in the transfer hydrogenation of functionalised β-keto-esters catalysed by (β-amino-alcohol)(arene)ruthenium(II) complexes.[22]

The active species I', generated by the action of KOtBu on I, has been identified by 1H NMR spectroscopy in CD3CN (see the Experimental Section) as a neutral cyclometallated ruthenium hydride complex in which the NH proton is NMR silent, presumably due to rapid exchange with CD3CN under basic conditions (Scheme 6). Like I, complex I' displays two sets of signals in its 1H NMR spectrum, which indicates the presence of two diastereomers. The diastereoisomers are found in an approximate ratio of 1:1, and the ruthenium hydride signals are detected at δ = −7.13 and −7.85 ppm. The chemical shifts corresponding to the η1-benzene units and the aryl protons are strongly shielded in comparison to those of the cationic species I, which is characteristic of a neutral cycloruthenated complex.[23] Presumably, deprotonation of I leads to the formation of the neutral complex, which reacts with iso-propanol to form I'.

2-Chloroacetophenone reacts almost instantaneously with I' (or with I in the presence of KOtBu) to give the inhibited species. Unfortunately, the latter could not be isolated due to decomposition during the workup. The 1H NMR spectroscopic analysis of a crude reaction mixture points at the formation of a new cycloruthenated species that is present in solution in only one diastereomeric form. However, the exact structure remains unclear.

We next focused on the synthesis of electron-rich half-sandwich iridacycle complexes, as these complexes were expected to have a higher stability toward air and moisture compared to ruthenacycles. A first set of cationic iridacycles 2–4 (Scheme 7) was synthesized from [Ir(Cp*)(Cl2)]2 and two equivalents of benzylamine, N-methylbenzylamine or N,N-dimethylbenzylamine, respectively, in the presence of sodium hydroxide and potassium hexafluorophosphate in acetonitrile at 45°C for 16 h (Scheme 5). After filtration of the reaction mixture through alumina, the complexes 2–4 were obtained as yellowish powders in high yields (up to 92%).

Contrary to ruthenacycle I (Scheme 3), the two pairs of enantiomers R,S/S,R and R,S/R,S were not observed by 1H NMR spectroscopy at RT for iridacycle 3.
which might be due to the faster inversion of configuration at the iridium centre.

This hypothesis was confirmed by studying the behaviour of 3 by using variable-temperature $^1$H NMR spectroscopy in CD$_3$CN (Figure 1a,b). The N-methyl and Cp* moieties give very broad signals at 20°C. At 0°C, the two diastereoisomeric N-methyl groups are clearly observed as are the two Cp*-methyl moieties (Figure 1a and b, respectively). This effect was more pronounced at −10 and −20°C. The coalescence temperature of the Cp*-methyl signals is 3°C.

Iridacycle complexes 2–4 were studied in the catalytic racemisation of (S)-phenylethanol (S1) and (R)-2-chloro-1-phenylethanol (S2). We soon observed a key role for the N-substituent on the ligand in complexes 2–4. First investigations were done by using 5 mol% of 4 at 70°C in toluene. As observed with the ruthenacycles, complex 4 was not able to racemise chiral alcohols without activation with base (Table 2, entries 1–2). Activation with 1.2 equivalents of potassium-tert-butoxide led to a highly efficient catalyst for the racemisation of S1 since 34% ee was obtained in 24 h at 70°C in toluene (entry 3). Acetophenone (15%) was also observed by GC analysis. Under the same reaction conditions, 29% ee was obtained in the racemisation of (S)-S2 with complete selectivity since no corresponding ketone was found (entry 4). Lowering the temperature to RT had the expected effect on the rate of racemisation of (S)-S1 (83% ee, entry 5). Surprisingly, the rate of racemisation of (R)-S2 was higher at RT compared to 70°C. Indeed, after 24 h, S2 was obtained quantitatively in 8% ee (entry 6). Complexes 2 and 3 were then tested at RT in the racemisation of (S)-S1 and (R)-S2. Complex 2 was inactive in the presence of (S)-S1, but was able to racemise (S)-S2 almost to completion (100 and 3% ee, respectively, entries 9–10). Mono-N-methyl-substituted iridacycle 3 was the most efficient catalyst since complete racemisation of both (S)-S1 and (R)-S2 was observed after 24 h at RT (3 and 0% ee, respectively, entries 7–8).

Subsequently, we studied the kinetics of the racemisation of chiral α-aryl and alkyl alcohols S1–S8 by using the optimised reaction conditions (5 mol% of catalyst 3, 6 mol% of potassium-tert-butoxide). Reaction with 1.2 equivalents of potassium-tert-butoxide led to a highly efficient catalyst for the racemisation of S1 since 34% ee was obtained in 24 h at 70°C in toluene (entry 3). Acetophenone (15%) was also observed by GC analysis. Under the same reaction conditions, 29% ee was obtained in the racemisation of (S)-S2 with complete selectivity since no corresponding ketone was found (entry 4). Lowering the temperature to RT had the expected effect on the rate of racemisation of (S)-S1 (83% ee, entry 5). Surprisingly, the rate of racemisation of (R)-S2 was higher at RT compared to 70°C. Indeed, after 24 h, S2 was obtained quantitatively in 8% ee (entry 6). Complexes 2 and 3 were then tested at RT in the racemisation of (S)-S1 and (R)-S2. Complex 2 was inactive in the presence of (S)-S1, but was able to racemise (S)-S2 almost to completion (100 and 3% ee, respectively, entries 9–10). Mono-N-methyl-substituted iridacycle 3 was the most efficient catalyst since complete racemisation of both (S)-S1 and (R)-S2 was observed after 24 h at RT (3 and 0% ee, respectively, entries 7–8).
KOrBu, PhMe, RT; Table 3). With S1, 50% and complete racemisation was achieved in 1 and 7 h, respectively (Table 3, entry 1). A tremendous increase of reaction rate was observed with S2 since complete racemisation was achieved within 5 min at RT (entry 2). Similar high rates have only recently been reported by Bäckvall and co-workers for this substrate.[24] Decreasing the catalyst loading to 1 mol% allowed complete racemisation to be reached in 3 h with a half-life time of racemisation of 20 min (entry 3). The catalyst was still active after 16 h. Indeed, when a new batch of (R)-S2 was added only 6% ee was observed 2 h after the addition (entry 4). Furthermore, complete racemisation of (R)-S2 was obtained in 1 h in a mixture of toluene/water as the solvent (entry 5), which showed the high tolerance of 3 to aqueous media.

Table 3. Racemisation of alcohols with iridacycle 3 at room temperature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>(t_{1/2}(\text{min}))</th>
<th>(t_{\text{compl.}}(\text{min}))</th>
<th>Ketone [%]</th>
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<tr>
<td>1</td>
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<td>60</td>
<td>420</td>
<td>6</td>
</tr>
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<td>–</td>
<td>5</td>
<td>–</td>
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<td>3(1)</td>
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<td>20</td>
<td>180</td>
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<tr>
<td>4(1)</td>
<td>S2</td>
<td>–</td>
<td>1080</td>
<td>–</td>
</tr>
<tr>
<td>5(1)</td>
<td>S2</td>
<td>–</td>
<td>60</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>S3</td>
<td>20</td>
<td>240</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>S4</td>
<td>120</td>
<td>720</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>S5</td>
<td>17</td>
<td>200</td>
<td>8</td>
</tr>
<tr>
<td>9(2)</td>
<td>S6</td>
<td>360</td>
<td>1440</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>S7</td>
<td>150</td>
<td>960</td>
<td>7</td>
</tr>
<tr>
<td>11</td>
<td>S8</td>
<td>240</td>
<td>1440</td>
<td>12</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.75 mmol of enantiomerically pure substrate (ee > 99%), 5 mol% of 3, 6 mol% KOrBu, 2.4 mL of PhMe. [b] With 1 mol% of 3. [c] After 16 h, 0.2 mmol of (S)-S2 was added and the reaction mixture was stirred for an additional 2 h, 6% ee after 18 h. [d] Reaction achieved in a mixture of PhMe/H2O 1:1. [e] 10% ee after 24 h.

was observed with S2 since complete racemisation was achieved within 5 min at RT (entry 2). Similar high rates have only recently been reported by Bäckvall and co-workers for this substrate.[24] Decreasing the catalyst loading to 1 mol% allowed complete racemisation to be reached in 3 h with a half-life time of racemisation of 20 min (entry 3). The catalyst was still active after 16 h. Indeed, when a new batch of (R)-S2 was added only 6% ee was observed 2 h after the addition (entry 4). Furthermore, complete racemisation of (R)-S2 was obtained in 1 h in a mixture of toluene/water as the solvent (entry 5), which showed the high tolerance of 3 to aqueous media.

Compared to substrate (S)-S1, the presence of an electron-withdrawing group at the para position of (S)-1-(4-fluorophenyl)ethanol (S3) strongly decreased the time of complete racemisation to 4h, with a half-time of racemisation of 20 min (Table 3, entry 6). Compared to S1, a longer reaction time was needed to perform the complete racemisation of (S)-1-phenylbutanol (S4) possessing a longer alkyl chain (entry 7). Racemic 1-(2-naphthyl)ethanol (S5) was obtained from (S)-S5 in 200 min with a \(t_{1/2}\) of racemisation of 17 min (entry 8). The rate of racemisation decreased with a more rigid substrate structure, such as (R)-1-indanol (S6), since complete racemisation was obtained after 24 h (entry 9). Iridacycles also showed activity in the catalytic racemisation of aliphatic alcohols. However lower reactivity was observed in the racemisation of (S)-2-butanol (S7) and (R)-2-hexanol (S8) with a \(t_{1/2}\) of racemisation of 150 and 240 min and complete racemisation in 16 and 24 h, respectively (entries 10–11). In all cases, when using \(\alpha\)-methyl-substituted alcohols, the formation of the corresponding ketone was observed, showing that the rate-determining step is the reduction of the ketone to the corresponding racemic alcohol. This is also corroborated by the faster racemisation of S2. The reduction rate is enhanced by the presence of electron-withdrawing groups. Based on these results, we suggest that the substrate dissociates from the metal centre after dehydrogenation. This was also shown by adding one equivalent of 2-bromoacetophenone to (S)-S1 in the presence of 5 mol% of 3 and 5.2 mol% of base in toluene (Scheme 8). Only acetophenone and the corresponding racemic bromoalcohol were detected quantitatively by GC analysis.

The tolerance of half-sandwich iridacycle 3 towards aqueous media and its high efficiency in the racemisation of (R)-2-chloro-1-phenylethanol (S2) at RT led us to combine this racemisation reaction with an enzymatic kinetic resolution process. Janssen et al. found that haloalcohol dehalogenase Hhec is very efficient in the resolution of \(\beta\)-chloaloalcohols to afford enantiopure epoxides.[25] By using the double mutant Hhec C153S W249F and catalytic amounts of the activated iridacycle 3, enantioenriched epoxides were obtained by dynamic kinetic resolution of racemic substituted 2-chloro-1-phenylethanol in a one-pot reaction in high yields and with excellent enantioselectivities (up to 90 and 98% ee, respectively; Scheme 9).[26] Unfortunately, only enzymatic
resolution and no racemisation was observed when using aliphatic β-chloroalcohols.

Thus, iridacycle complexes 1–3 have shown their efficiency in the catalytic racemisation of chiral alcohols. In addition, they can be combined with aqueous enzymes for a dynamic kinetic resolution.

**Amine racemisation:** We also investigated the behaviour of these complexes in the catalytic racemisation of chiral amines, such as the complexes in the catalytic racemisation of chiralamines, such as (S)-α-methylbenzylamine (S9) and (S)-N,α-dimethylbenzylamine (S10), as model substrates in toluene (0.25 mol) at 100°C when using 2 mol% of iridacycle (Scheme 10). In contrast to the corresponding reaction with alcohols, no racemisation was observed after activating 1–3 with potassium-tert-butoxide.

![Scheme 10. Racemisation of α-methylbenzylamine derivatives.](image)

Without activation, preliminary tests with (S)-α-methylbenzylamine (S9) showed that only slow racemisation of this substrate was observed and mainly formation of side products was detected. The side products are formed by the condensation reaction of the imine intermediate with the substrate to form dimers. This result shows that, in the case of substrate S9, the rate-determining step in the catalytic cycle is the reduction of the imine to the racemic amine.

Iridacycles 2–4 showed good reactivity with (S)-α-methyl-N-methylbenzylamine (S10) since a decrease of enantiomeric excess down to 10% ee was obtained in toluene at 100°C when using 2 mol% of catalyst after 16 h. Moreover, no side products were observed. Kinetic studies showed that catalysts 2 and 4 have the same activity after 3 h \((t_{1/2\text{rac}}) = 200 \text{ min})\), but catalyst 2 is more active than 4 after 8 h (15 and 26% ee, respectively; Figure 2). A different behaviour was observed with iridacycle 3 synthesised from N-methylbenzylamine: the racemisation rate is higher than with catalysts 2 and 4 (41% ee after 1 h). After the initial fast racemisation, catalyst 3 seems to be deactivated after 2 h since only a decrease of less than 13% ee was detected in the next 6 h (34% ee after 2 h and 21% ee after 8 h).

The use of more polar solvents, such as chlorobenzene, allowed an increase of the reaction rate (Figure 3). This effect might be due to the enhanced solubility of these complexes in this solvent. Complete racemisation of (S)-α-methyl-N-methylbenzylamine (S10) was obtained with catalysts 3 and 4 in 8 h, \((t_{1/2\text{rac}}) = 30 \text{ and } 90 \text{ min}, \text{respectively})\). Although catalyst 3 seems to be deactivated after 2 h, the effect is less prominent than in toluene. No improvement was observed with catalyst 2 since the time of half-racemisation was about 180 min as in toluene and complete racemisation was obtained after 16 h.

![Figure 2. Enantiomeric excess versus time in the racemisation of S10 (0.75 mmol, 0.25 mol) with 2 mol% of [Ir] at 100°C in toluene.](image)

![Figure 3. Enantiomeric excess versus time in the racemisation of S10 (0.75 mmol, 0.25 mol) with 2 mol% of [Ir] at 100°C in chlorobenzene.](image)
bility of \( \text{3} \) in CDCl\(_3\). It was found that complex \( \text{3} \) slowly oxidized to imine-complex \( \text{5} \). Moreover, iridacycle \( \text{5} \) synthesized from \([\text{Ir(Cp}^*\text{)(Cl}_2)]\) and \(N\)-benzylidinemethylamine showed lower reactivity relative to complex \( \text{3} \) since only 55\% \( ee \) was obtained in 16 h in the racemisation of \( \text{S10} \).

The presence of a secondary amine moiety in the ligand, as in \( \text{3} \), seems to be important in terms of reactivity during the racemisation reaction since \( \text{3} \) is initially the most active. To counter the oxidation of the ligand, iridacycles \( \text{6} \) and \( \text{7} \) were synthesized with ligands containing an \( \text{sp}^2 \) carbon centre at the benzylic position and a secondary amine, such as phenylimidazoline and phenylimidazole. To compare with \( \text{6} \) and \( \text{7} \), iridacycle \( \text{8} \) possessing a 2-phenyloxazoline ligand was also synthesized (Figure 4). These complexes were obtained analytically pure in excellent yields (up to 95\%) and show a high stability towards air and moisture.

Iridacycle \( \text{8} \) is able to racemize (S)-\( \text{S10} \) but no enhancement of reactivity was observed (26\% \( ee \) after 16 h at 100\°C when using 2 mol\% of catalyst in toluene). On the contrary, both catalysts \( \text{6} \) and \( \text{7} \) showed very high activities in the racemisation of \( \text{S10} \) with 2 mol\% of iridacycle at 100\°C. Complete racemisation was obtained in chlorobenzene within 40 and 180 min with \( \text{6} \) and \( \text{7} \), respectively, with a remarkably short time of half-racemisation of 4 min and less than 20 min, respectively (Figure 5). As expected, no deactivation of the catalysts was observed. By using the same conditions, the reaction was scaled-up to 2 g of enantiopure substrate racemisation is complete in 3 h with a time of half-racemisation of 20 min. At 80\°C the time of half-racemisation is about 45 min with a complete racemisation in 6 h. Decreasing the temperature to 60\°C reduces the rate of the reaction (\( t_{1/2(60\text{C})}=45\text{ min} \) complete racemisation in 16 h) but only a low turnover was observed at 40\°C since a loss of enantiomeric excess of less than 10\% was observed after 4 h. In chlorobenzene at 100\°C, the rate of the reaction increases relative to toluene since complete racemisation was obtained in 40 min (\( t_{1/2(40\text{C})}=4 \text{ min} \); Table 1). At 80\°C, the rate of the reaction is slightly higher than in toluene.

![Figure 4. ORTEP style plot of cationic iridacycle 8.](image)

**Figure 4.** ORTEP style plot of cationic iridacycle 8. Thermal ellipsoids are drawn at the 50\% probability level and hydrogen atoms are omitted for clarity.

<table>
<thead>
<tr>
<th>Entry(^{[a]})</th>
<th>Solvent</th>
<th>( T ) [( ^\circ \text{C} )]</th>
<th>( t_{1/2(\text{rac})} ) [min]</th>
<th>( t_{\text{compl(\text{rac})}} ) [min]</th>
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<td>1(^{[b]})</td>
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<td>–</td>
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<tr>
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<td>PhMe</td>
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<td>7</td>
<td>PhCl</td>
<td>100</td>
<td>4</td>
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\(^{[a]}\) Reaction conditions: 0.25 mmol of substrate, 2 mol\% of [Ir], 1 mL of PhMe. \(^{[b]}\) 63\% \( ee \) observed after 16 h. \(^{[c]}\) 68\% \( ee \) observed after 16 h.
It is expected that the reactivity of the catalytic system decreases with the temperature, but it is still efficient at 60°C ($t_{1/2(100)} = 90$ min). As in toluene, only slow racemisation is obtained at 40°C (less than 12% in 4 h). However, iridacycle 6 has been shown to be very efficient in racemising (S)-α-methyl-N-methylbenzylamine since racemic product S10 was obtained in 40 min at 100°C in chlorobenzene.

To demonstrate the robustness of catalyst 6 in the racemisation of (S)-S10, we added new batches of enantiopure S10 every 40 min (Figure 6). By starting from a reaction mixture of 0.25 mmol of S10 in chlorobenzene ([S10] = 0.25 M) in the presence of 2 mol% of 6 at 100°C, complete racemisation was obtained after 40 min. At this time, 0.25 mmol of (S)-S10 was added to the reaction, increasing the concentration of the reaction mixture to [S10] = 0.5 M and the substrate/catalyst ratio to 100. Just after addition, the ee was 50%, as expected. After 2 min, the ee of the product already dropped to 42%, which shows the high activity of the catalyst under these conditions. Almost complete racemisation was obtained after 80 min (1.5% ee). A new batch of (S)-S10 was added at 80 min ([S10] = 0.75 M, s/c = 150) and a sample analysed 2 min after the addition gave 44% ee for S10. At 120 min, the rate of racemisation slowed down since the ee of S10 was 11%. Final addition of (S)-S10 ([S10] = 1 M, s/c = 200) highly influenced the catalytic system in terms of reactivity. At 2 min, after addition, only 48% ee was observed and 18% ee after 160 min. Complete racemisation was obtained after 6 h.

We reinvestigated the racemisation of primary amine (S)-α-methylbenzylamine (S9) by using 2 mol% of iridacycle 6 in toluene at 100°C. The decrease of enantioselectivity was found to be low and corresponds to the formation of side products. A way to overcome the formation of byproducts might be the addition of dihydrogen during the reaction. However, the hydrogen pressure must not be too high otherwise it could inhibit the dehydrogenation step during the catalysis. A significant improvement was indeed achieved. Upon using a hydrogen atmosphere of 1 atm in toluene at 100°C with 2 mol% of 6 for 16 h ee values down to 34% were reached, but the selectivity of the reaction was still low (36%).

To extend the scope of the reaction, we investigated the catalytic racemisation of a series of chiral amines including primary, secondary and tertiary amines by using 2 mol% of 6 as the catalyst in toluene (Table 5).

With primary amine (S)-S9, only dimer formation was observed (Table 5, entry 1).[27] Racemisation of (S)-α-methyl-N-methylbenzylamine (S10) was fast in toluene at 100°C with 2 mol% of 6 ($t_{1/2(100)} = 15$ min, entry 3). Using chlorobenzene instead of toluene, $t_{1/2(100)}$ was decreased to 4 min and complete racemisation was obtained after 40 min (entry 4). (S)-N-benzyl-α-methylbenzylamine (S11) showed the highest reactivity since complete racemisation was obtained after 15 min ($t_{1/2(<5)} < 5$ min, entry 5). Quinoline was also investigated as a substrate. Complete racemisation of (S)-2-methyl-1,2,3,4-tetrahydroquinoline (S12) was obtained overnight (entry 6).[28] Further studies on the racemisation of cyclic benzylid primary amines, such as (S)-1-aminoindane (S13) and (S)-1,2,3,4-tetrahydro-1-naphthylamine (S14), gave good results with complete racemisation in 6 and 10 h, respectively ($t_{1/2(<30)} = 120$ min, entry 7; $t_{1/2(<30)} < 90$ min, entry 8). In these cases, major formation of dimers was also observed. Finally, iridacycle 6 was able to racemise tertiary amine (S)-α,N,N-trimethylbenzylamine (S15) overnight (entry 9).

Iridacycles are very efficient in the catalytic racemisation of chiral secondary and tertiary amines. However, dimer formation was observed during the racemisation of primary amines. This suggests that the imine resulting from the dehy-
dregnation of the chiral amine does not stay coordinated to the iridium centre and that the rate-determining step might be the hydrogenation of the imine derivative.

Conclusion

We have synthesized and characterized a small library of half-sandwich cationic ruthenua- and iridacycle complexes and studied their behaviour in the catalytic racemisation of chiral amines and alcohols. We found that readily synthesized electron-rich iridacycles and studied their behaviour in the catalytic racemisation of chiral amines and alcohols. We found that readily synthesized electron-rich iridacycles and studied their behaviour in the catalytic racemisation of chiral amines and alcohols. We found that readily synthesized electron-rich iridacycles and studied their behaviour in the catalytic racemisation of chiral amines and alcohols. We found that readily synthesized electron-rich iridacycles and studied their behaviour in the catalytic racemisation of chiral amines and alcohols.

Experimental Section

General: Starting materials were purchased from Acros, Sigma-Aldrich, Strem, Merck or Alfa Aesar, and were used as received unless stated otherwise. All solvents were reagent grade and, if necessary, dried and dis-tilled prior to use. Toluene and diethylether were distilled over Na/ benzophenone. Column chromatography was performed on silica gel (Aldrich 60, 230–400 mesh) or neutral activated aluminium oxide (Merck aluminium oxide 90 neutral activated). TLC was performed on silica gel 60/Kieselgel 60F254 or neutral aluminium oxide 60 F254. 1H and 13C NMR spectra were recorded on a Varian VXR300 (299.79 MHz for 1H, 75.48 MHz for 13C) or a Varian AMX400 (399.93 MHz for 1H, 100.6 MHz for 13C) spectrometer. Chemical shifts are reported in δ values (ppm) relative to the solvent peak (CDCl3, δ = 7.26 (1H), 77.0 ppm (13C)). The following abbreviations are used to indicate multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Mass spectra (HRMS) were performed on a Jeol JMS-600H. GCMS spectra were recorded on a Hewlett Packard HP6890 equipped with a HP1 column and an HP 5973 Mass Selective Detector. GC analytical were performed on a Shimadzu GC-17A or a Hewlett Packard HP6890 chromatograph equipped with the columns indicated for each compound separately. HPLC analysis was performed on a Shimadzu HPLC system equipped with two LC-10AD VP solvent delivery systems, a DGU-14A degasser, a SIL-10AD VP auto injector, an SPD-M10A VP diode array detector, a CTO-10A VP column oven and an SCL-10A VP system controller by using the columns indicated for each compound separately. Elemental analyses were carried out on a EuroVector Euro EA elemental analyser.

Synthesis and characterization of the cationic ruthenacycle complex: The procedure described by Pfeffer et al. was used.[9] A suspension of [Ru(C5Me5)2Cl] (200 mg, 0.4 mmol), N-methylbenzylamine (72 µL, 0.56 mmol), NaOH (32 mg, 0.8 mmol) and KPF6 (294 mg, 1.6 mmol) in CH3CN (6 mL) was stirred at RT for 3 d. The resulting dark-yellow susp-ension was filtered over Al2O3 by using CH3CN as the eluent. A yellow fraction was collected and concentrated under vacuum to 1–2 mL. Addition of Et2O (4 mL) gave a yellow solid that was washed with Et2O (3 × 2 mL) and pentane (3 × 2 mL). Yield: 200 mg, 0.30 mmol, 74%.

[Ru(q-C5H4)(CH2NMe)(CH2)(NCMe)](PF6) (1): 1H NMR analysis revealed the presence of two pairs of enantiomers Rg/Sp/SP/Rg and Rg/Rg/SP/Sp in a 56:44 ratio in CD2CN. Enantiomers Rg/Sp/SP/Rg: 1H NMR (400 MHz, CD2CN, 298 K): δ = 7.2 (d, 2JH,r = 17.6 Hz, 1H; CHr), 7.04–6.90 (m, 3H; CH3), 5.57 (s, 6H; CH2), 4.04 (m, 1H; NH), 3.94 (d, 2JH,r = 13.6, 2JH,s = 4.4 Hz, 1H; CHCl), 3.61 (dd, 2JH,r = 13.6, 2JH,s = 5.0 Hz, 1H; CHN), 3.06 (d, 2JH,r = 6.0 Hz, 3H; NCH3), 2.55 ppm (s; CH2CN); 13C NMR (100.6 MHz, CD2CN, 298 K): 166.4, 147.6, 140.9, 124.2, 122.0 (CH2, 118.3 (CH3), 87.9 (CH2), 47.3 (NCH3), 1.3 ppm (CH2CN), enantiomer Rg/Rg/SP/Sp; 1H NMR (400 MHz, CD2CN, 298 K): δ = 7.86 (d, 2JH,r = 17.6 Hz, 1H; CHr), 7.04–6.90 (m, 3H; CH3), 5.61 (s, 6H; CH2), 4.04 (m, 1H; NH), 3.77 (d, 2JH,r = 14.0, 2JH,s = 5.6 Hz, 1H; CHCl), 3.37 (dd, 2JH,r = 14.0, 2JH,s = 9.0 Hz, 1H; CHN), 2.84 (d, 2JH,r = 6.0 Hz, 3H; NCH3), 2.15 ppm (s; CH2CN); 13C NMR (100.6 MHz, CD2CN, 298 K): δ = 139.9, 127.1, 124.5, 122.4 (CH2), 118.3 (CH3), 88.3 (CH2), 63.2 (CH3), 45.7 (NCH3), 1.3 ppm (CH2CN); elemental analysis calcd (%) for C16H19F6N2PRu: C 39.59, H 3.74, N 5.71.

Synthesis and characterization of cationic iridacycle complexes: The procedure described by Pfeffer et al. for analogous compounds was used.[10] In a typical experiment, a 50 mL Schlenk tube was thoroughly flame-dried and put under an atmosphere of nitrogen, after which the following compounds were added, respectively, in acetonitrile (5 mL): [Ir(Cp*)(CH2NMe)-C6H4] (1), [Ir(C5Me5)(CH2NMe)-C6H4] (2), [Ir(C5Me5)(CH2NMe)-C6H4] (3). The solution was stirred at 45ºC for 16 to 50 h. The mixture was then cooled down to RT, washed with hexane and filtered over neutral aluminium oxide (eluents: MeCN). The resulting solution was concentrated in vacuo. Subsequent stripping with dry Et2O yielded the desired iridacycle complex.

[Ir(q-C5H4)(CH2-2,NHMe)(CH2)(NCMe)](PF6) (2): Complex 2 was obtained as a brown-solid racemate (216 mg, 78% yield) by using benzylamine (43 mg). 1H NMR (400.0 MHz, CD2CN, 298 K): δ = 7.40 (d, 2JH,r = 1.4, 7.1 Hz, 1H; Ph-H), 7.12 (d, 2JH,r = 7.6 Hz, 1H; Ph-H), 6.98 (td, 2JH,r = 1.3, 7.2 Hz, 2H; Ph-H), 4.35 (s, 2H; NH2), 4.24 (m, 1H; CH3), 3.86 (m, 1H; CH3), 2.39 (s, 3H; NCCCH3), 1.75 ppm (s, 15H; CH2; CH2); 13C NMR (100.6 MHz, CD2CN, 298 K): δ = 150.2, 149.1, 135.9, 127.4, 123.1, 121.3 (CH3), 89.6, 56.1, 9.1 ppm (CH2CN); HRMS (EI+): m/z: calcd. for C16H19N4+: 434,1460 (~CH2CNPF6•); found: 434,1441; elemental analysis calcd (%) for C16H19N4PF6: C 59.9, H 3.57, N 5.79; found: C 59.9, H 3.57, N 5.79.

[Ir(q-C5Me5)(CH2-2,NHMe)(CH2)(NCMe)](PF6) (3): Complex 3 was obtained as a yellow powder (233 mg, 0.37 mmol, 92%) by using N-methylbenzylamine (49 mg). 1H NMR (400.0 MHz, CD2CN, 298 K): δ = 7.36 (d, 2JH,r = 6.9 Hz, 1H; Ph-H), 7.07 (d, 2JH,r = 6.9 Hz, 1H; Ph-H), 7.00 (t, 2JH,r = 7.2 Hz, 1H; Ph-H), 6.92 (d, 2JH,r = 7.0 Hz, 1H; Ph-Ph), 4.40 (s, 1H; NH), 4.17 (s, 1H; CH3), 3.68 (s, 1H; CH3), 3.11 (s, 3H; NCH3), 2.38 (s, 3H; NCCCH3), 1.68 ppm (s, 15H; CH2; CH2); 13C NMR (100.6 MHz, CD2CN, 298 K): δ = 150.2, 146.5, 135.2, 134.4, 127.4, 123.6, 121.0, 119.1 (CH3CN), 89.8, 67.2, 44.7, 9.0 ppm (CH2CN); HRMS (EI+): m/z: calcd. for C16H19N4PF6*: 448,1616 (~CH2CNPF6•); found: 448,1617; elemen-
tional analysis (calcd) (%) for C₂₀H₂₈F₆N₂PIr: C 37.91, H 4.45, N 4.42; found: C 38.84, H 4.54, N 3.99.

\[ \text{[IrC₄(C₂H₆)₂(CH₂=CHCH₂CN)(NCCCH₃)]PF₆} \] (4): Complex 4 was obtained as a yellow powder (227 mg, 0.36 mmol, 91%) by using \( \text{C}_2\text{H}_5\text{CN} \) and KOTBu (1.3 mg, 12 mol%) were dissolved in freshly distilled toluene (3 mL) after which the mixture was stirred for 15 min at RT. The resulting solution was slowly transferred by syringe into another Schlenk tube containing water (3 mL) and a chiral alcohol (200 mg). Care was taken not to disturb the suspension, since this resulted in deactivation of the catalyst. The reaction was monitored by periodically taking 1 mL aliquots from the mixture, filtering them over silica gel (eluent: EtO\(_2\)O) and analysing the resulting samples by chiral GC. Chirasil-Dex CB column (25 m×0.25 mm×0.25 μm), gas vector: helium, flow = 1 mL min\(^{-1}\); injector: 250°C; program: 100°C for 3 min, 120°C (15°C min\(^{-1}\)) for 15 min, 140°C (15°C min\(^{-1}\)) for 15 min, 100°C (15°C min\(^{-1}\)) for 15 min, 100°C for 15 min, 100°C for 15 min, 100°C for 15 min, 100°C for 15 min, 100°C for 15 min, 100°C for 15 min.

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