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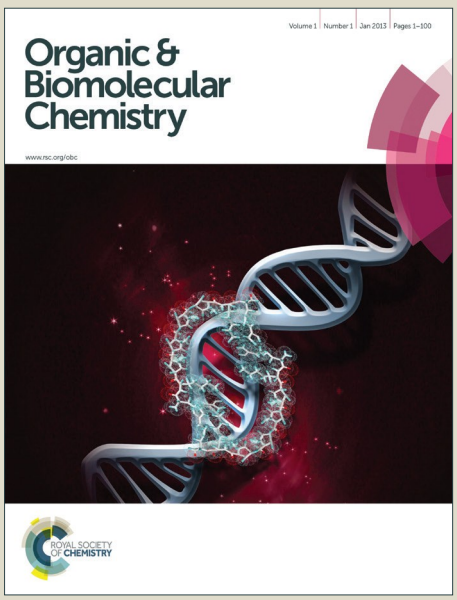

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ARTICLE

The kinetics and mechanism of the organo-iridium catalysed racemisation of amines

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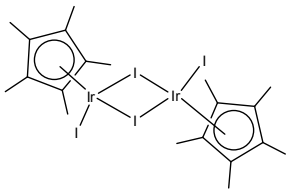
Abstract The dimeric iodo-iridium complex $[IrCp^*I_2]_2$ (Cp*=pentamethylcyclopentadiene) is an efficient catalyst for the racemisation of secondary and tertiary amines at ambient and higher temperatures with a low catalyst loading. The racemisation occurs with pseudo-first-order kinetics and the corresponding four rate constants were obtained by monitoring the time dependence of the concentrations of the (*R*) and (*S*) enantiomers starting with either pure (*R*) or (*S*) and show a first-order dependence on catalyst concentration. Low temperature ^{1}H NMR data is consistent with the formation of a 1:1 complex with the amine coordinated to the iridium and with both iodide anions still bound to the metal-ion, but at the higher temperatures used for kinetic studies binding is weak and so no saturation zero-order kinetics are observed. A cross-over experiment with isotopically labelled amines demonstrates the intermediate formation of an imine which can dissociate from the iridium complex. Replacing the iodides in the catalyst by other ligands or having an amide substituent in Cp* results in a much less effective catalysts for the racemisation of amines. The rate constants for a deuterated amine yield a significant primary kinetic isotope effect k_H/k_D = 3.24 indicating that hydride transfer is involved in the rate-limiting step.

Introduction

Enantiomerically pure chiral amines and alcohols are important building blocks for pharmaceutical and agrochemical products[1]. Even today, the most commonly used methods for their isolation are the classical resolution by crystallisation of diastereomeric salts[2] and enzymatic resolution[3]. The disadvantage of these resolution methods is their inefficiency, with, at best, only 50% of the desired enantiomer produced and the undesired one wasted. Catalysts that can racemise the unwanted enantiomer may enable dynamic kinetic resolution (DKR) using a suitable enzyme to yield 100% of the required enantiomer[4]. We have reported the use of the dimeric iodo-iridium complex $[IrCp^*I_2]_2$ (Cp*=pentamethylcyclopentadiene) **1** (SCRAM) as an efficient racemisation catalyst for the dynamic kinetic resolution of secondary amines in combination with immobilized lipases and a suitable acyl donor[5,6] and as epimerisation catalysts in diastereomeric crystallisation[7].

Although there are some catalysts for the direct synthesis of enantiomerically pure amines and alcohols[8], combining efficient and fast catalytic racemisation with an enantiomerically selective



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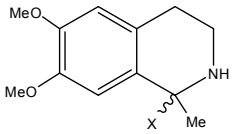

2a X=H
2b X=D

enzyme has many advantages. There are relatively few catalytic systems capable of racemising amines[9] and some of those involve extreme conditions, such as Raney nickel or cobalt or alkali metal hydroxides at high temperatures,[10] and Pd catalysts which generally require long reaction times[11]. Other systems have used electron-rich Shvö catalysts[12] and cationic half-sandwich ruthenium and iridium catalysts[13].

It would be useful to more fully understand our iridium-based catalytic system[5,6] to enable its optimisation and herein is reported kinetic and mechanistic studies to help achieve that goal.

Results and Discussion

The dimeric iodo-iridium complex $[IrCp^*I_2]_2$ (Cp*=pentamethylcyclopentadiene) **1** is an efficient catalyst for the

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racemisation of secondary and tertiary amines at ambient and higher temperatures with a low catalyst loading. For example, the racemisation of both *(R)* and *(S)*-*6*,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline **2a** are quantitatively complete within 2hrs. in dichloromethane at 40°C using 0.5 mol% catalyst **1**. The racemisation of 0.50 M amine **2a** in dichloromethane with $2.5x10^{-3}$ M catalyst **1** at 40°C occurs with pseudo-first-order kinetics and the corresponding four rate constants were obtained by monitoring the concentrations of the (*R*) and (*S*) enantiomers starting with either pure (*R*) or (*S*) **2a** (**Figure 1**). As the reaction proceeds to equilibrium, the observed rate constants k_{obs} are twice those of the forward ones k_f (**Eqn. 1,** with the equilibrium constant K = 1.0 for racemisation). All four rate constants were identical within experimental error and k_{obs}= 5.82±0.29 x 10^{-4} s^{-1}. These rate constants show a first-order dependence on catalyst concentration, giving a second-order rate constant k_{cat} = 0.931±0.056 $M^{-1}s^{-1}$, based on the dimer concentration.

$$k_{obs} = k_f + k_r = k_f (1 + 1/K) \qquad \textbf{Eqn. 1}$$

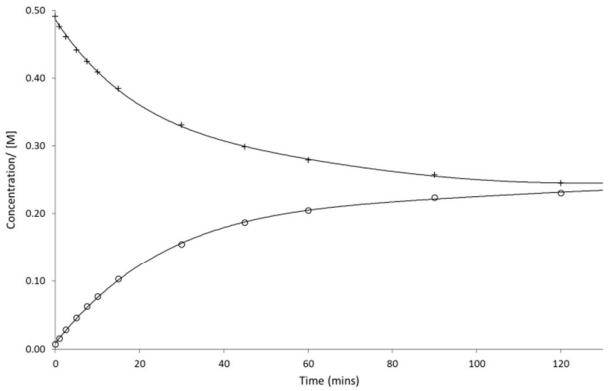
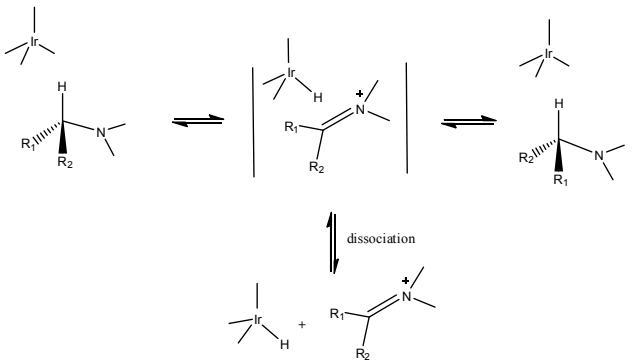


Figure 1 The reaction rate profile for the racemisation of 0.50 M *(S)*-*6*,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline **2a** at 40°C in dichloromethane catalysed by $6.25x10^{-4}$ M iodo-iridium complex $[IrCp^*I_2]_2$ **1** (+ decrease in *S*-enantiomer, o increase in *R*-enantiomer)

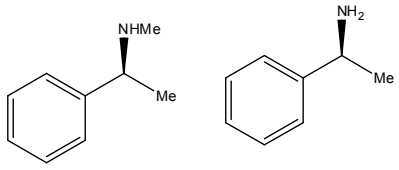
The iridium-catalysed racemisation of chiral amines presumably requires hydride transfer to the metal-ion, generation of an imine intermediate followed by hydride transfer back to the imine on its opposite face (**Scheme 1**). Tertiary amines must form an iminium-ion intermediate, whereas those formed from primary and secondary ones may also deprotonate to form the neutral imine. If the intermediate can escape from the complex before hydride-transfer then other reactions may occur. The rates of racemisation and dissociation of the imine intermediate and product amine are presumably dependent on the effective positive charge on the metal-ion, which, in turn, controls its ability to act as a Lewis acid and to donate/accept a hydride ion. A simple way to modify this effective charge and hence change catalytic activity is to change or add substituents to the ligands attached to the metal and investigate the effect of different solvents. The aim of this work is to explore these factors and investigate its impact on catalytic activity through a determination of the reaction mechanism.



Scheme 1

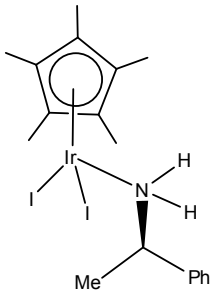
(i) Complex formation

It was assumed that racemisation required initial complex formation between the iridium dimer **1** and the amine substrate, although the absence of saturation zero-order kinetics and the observation of first-order ones suggest that this binding is not strong under the reaction conditions. However, at -40°C, the addition of the (*S*)-secondary amine **3** and the primary amine (*S*)-α-methylbenzylamine **4** to a solution of the iridium dimer **1** in deuterated chloroform showed the presence of complexes as evidenced by ^{1}H NMR**.** An equimolar mixture of **4** and **1** showed that all of the amine added formed a



3 **4**

complex with the iridium. Both NH protons were still present indicating that HI is not liberated at this low temperature, which also suggests that both iodide anions are still bound to the iridium **6**. However, the two NH_2 hydrogens in the complex are non-equivalent, shifting downfield from δ =1.62ppm in the free base to an apparent triplet (J = 10.4 Hz) at δ = 4.01ppm and a doublet (J = 10.3 Hz) at δ = 4.22ppm. The α-CH shifts downfield from δ = 4.15ppm in the free base to an unresolved multiplet at δ = 4.38ppm in the complex, whereas the α-methyl shifts from δ = 1.41 to 1.56ppm (d, J = 6.8 Hz). The cyclopentadienyl methyl groups shift slightly up-field from δ = 1.85 to 1.83ppm. All of which is consistent with the formation of a 1 : 1 complex with the amine coordinated to the iridium and with both iodide anions still bound to the metal-ion. After adding further amine **4**, the excess remains uncomplexed and no 2 : 1 complex is formed. It is probable that the iridium-amine complex has the structure **5** which has no overall charge and in which the formal Ir^{3+} is a four-coordinate eighteen electron species.



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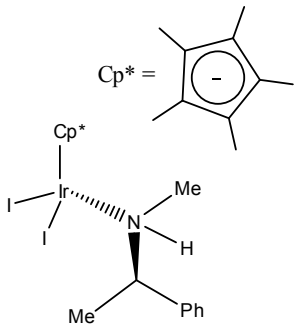

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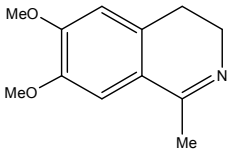
An equimolar mixture of the secondary amine **3** with **1** in deuterated chloroform at -40 °C shows ~78% of the amine uncomplexed, indicating that the binding constant is lower than with the primary amine **4**. The *N*-methyl group of **3** presumably hinders complexation with the iridium. Increasing the concentration of amine **3** increases the amount of the complex formed, from which an equilibrium constant of 0.33 M^{-1} can be calculated. The Cp* methyl protons are virtually unchanged in the new complex from δ = 1.853 to 1.852ppm, whereas the amine α-CH shifts downfield from δ = 3.66 to 4.31ppm in the complex, the α-CH_3 moves from δ = 1.38 to 1.45ppm and the *N*-methyl changes from δ = 2.31 to 2.70ppm and from a singlet to a doublet (J = 6.3 Hz). The structure **6** is suggested for the complex and, although under the normal racemisation conditions there is at least a fifty-fold excess of secondary amine, the higher temperature of 80°C means that it is probable that only a small fraction of the catalyst is converted to the iridium-amine complex. Consequently, the iridium catalyst does not become saturated and the kinetic profiles are not zero-order in substrate amine concentration. The difference in binding constants of primary and secondary amines may explain the differences between their rates of racemisation which is discussed later.

There is no direct evidence that the expected imine intermediates, such as **7**, form stable complexes with the iridium dimer **1** even at the lower temperature of -40°C.



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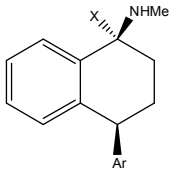
(ii) Intermediate imine formation

It is a reasonable proposal that the racemisation of amines involves hydride transfer from the amine to the iridium catalyst and consequent intermediate formation of an imine and iridium hydride complex (**Scheme 1**). It is therefore important to know whether the imine dissociates from the iridium prior to its reduction and, if so, can it be readily trapped? The racemisation of two different amines together enables a classical cross-over experiment to be conducted. Epimerisation at C1 of (1*S*,4*S*, **8a**) the anti-depressant *cis*-sertraline[14] (Ar = 3,4-dichlorophenyl) forms *trans*-**8** and causes a decrease in the diastereoisomeric excess (de). The secondary amine 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro-isoquinoline **2a** shows a higher reactivity with the iridium catalyst **1** with k_{cat} = 4.90 $M^{-1}s^{-1}$ at 80°C in toluene compared with *cis* sertraline **8a** k_{cat} = 0.351 $M^{-1}s^{-1}$. This >10-fold difference in reactivity ensures that using 1-deuterated isoquinoline **2b** the steady-state concentration of the deuterated catalyst is the major species present during catalytic turnover. Using 0.25M concentrations of each of the amines, deuterated **2b** and **8a,** in toluene at 80°C and 1.0x10^{-3}M iridium catalyst **1**, reaction samples were analysed by GCMS and the proportion of isotopically labelled isoquinoline **2a** and **2b** and the *cis* and *trans* diastereomers of **8a** and **8b** determined. The deuterium content of each amine changes with time (**Figure 2**).



8a X=H
8b X=D

The rate of deuterium-incorporation into *cis*-sertraline **8a** is similar to the rate of formation of the *trans* isomer and the rate of deuterium loss from the isoquinoline **2b** is much slower than its rate of racemisation but similar to its incorporation into *cis*-sertraline. The second-order rate constants at 80°C are k_{cat} = 1.18x10^{-1} $M^{-1}s^{-1}$ and k_{cat} = 1.35 x10^{-1} $M^{-1}s^{-1}$ for deuterium incorporation into *cis*-sertraline **8a** and its loss from **2b**, respectively.

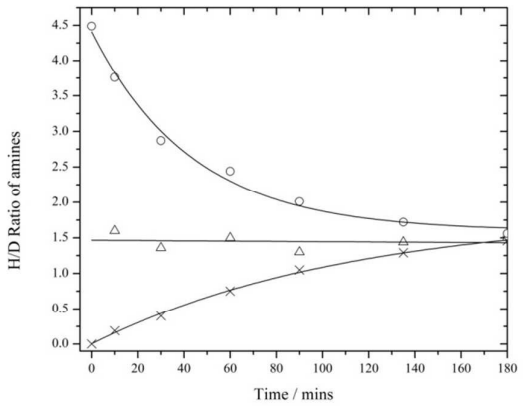
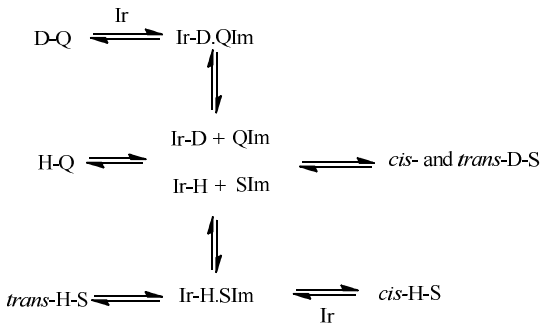


Figure 2 Reaction rate profile of the ratio of protonated to deuterated amine for the racemisation of *cis*- sertraline **8a** in the presence of deuterated **2b** using the iridium catalyst **1** in toluene at 80°C (x ratio of **2a/2b**, o ratio of **8a/8b**, △ ratio of H/D *trans*-**8**).

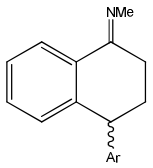
If amine dehydrogenation and imine hydrogenation take place within the coordination sphere or solvent cage of the iridium complex then there would be no deuterium exchange between the two amines **8** and **2b** whereas if the imine intermediate dissociates prior to reduction then isotopic scrambling would occur and the deuterium

content become distributed in both amines (**Scheme 2** where Ir-H and Ir-D are the H and D hydrides of the catalyst **1**, D-Q is the deuterated isoquinoline **2b** and QIm its corresponding imine **7** and *cis*- and *trans*- H-S and D-S are the isomeric and isotopically labelled sertraline **8a** and SIm its associated imine). The ratio of protonated to deuterated *trans*-**8** is constant throughout the reaction profile and the rate of racemisation of *cis*- to *trans*-**8** is similar to the rate of deuterium incorporation into *cis*-sertraline, both of which indicate that almost complete dissociation of the imine-iridium hydride complex occurs during turn-over. Furthermore there



Scheme 2

are small amounts of the imines **7** (7%) and **9** (<5%) formed, presumably due to loss of hydrogen from the iridium hydride catalyst.



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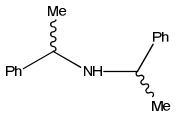

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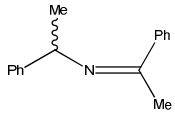

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The reaction of 1.0 M (*S*)-α-methylbenzylamine **4** in toluene at 80°C with 1.0 x 10^{-2}M catalyst **1** gives, after 24 hrs., mainly the diastereoisomers of the secondary amine dimer **10** with a small amount (<10%) of the enantiomers of the corresponding imine **11**, identified by GCMS and independent synthesis, but with no racemisation of **4**. This is also consistent with the intermediate imine dissociating from the complex (**Scheme 1**) and then reacting with the amine starting material followed by loss of ammonia to give **11** and its subsequent reduction to give **10**. The fact that no racemisation of **4** is observed indicates that its reaction with the imine intermediate is considerably faster than the hydrogenation of the imine by the iridium hydride.

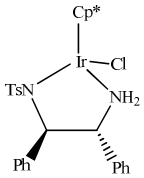
(iii) Effect of variables

The rates of hydride transfer to and from the iridium catalyst, those of association and dissociation of the amine reactant/product to and from the iridium catalyst and also those of dissociation and re-association of the imine and iridium hydride intermediates are presumably dependent on the effective positive charge on the metal-ion (**Scheme 1**). This effective charge and hence changes in catalytic activity can be modified by solvent and the nature of the ligands attached to the metal.

The rates of racemisation of (+/-) *cis*-sertraline **8a** are remarkably constant in a variety of solvents, for toluene, mesitylene, cumene, 1,4-dioxane and t-butyl acetate k_{cat} = 0.33±0.02 $M^{-1}s^{-1}$ at 80°C. However, in polar solvents such as DMF and DMSO the catalyst **1** is inactive towards racemisation.

Replacing the iodides in the organo-iridium catalyst **1** by chloride or bromide give iridium complexes which are much less effective in catalysing the racemisation of amines under the conditions in which the corresponding iodo-complex **1** is active. For example, the chloro-derivative is more than 3-orders of magnitude less effective in catalysing the racemisation of (*S*)-**2a**, as well as producing more impurities. This contrasts with the insignificant difference between chloride, bromide and iodide as anionic ligands in the cyclopentadienylruthenium catalysed racemisation of alcohols[15]. Replacing the halo-ligands by the diamine as in **12** also completely reduces the racemisation activity.

Substituting an electron-withdrawing group in the cyclopentadiene complex such as with the amide **13a**[16] also reduces the catalytic activity. For example, the rates of racemisation of *(R)* and *(S)-6*,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline **2a** in dichloromethane at 40°C occurs with pseudo-first-order kinetics dependent on the catalyst concentration and the corresponding second-order rate constant k_{cat} = 0.134 $M^{-1}s^{-1}$, based on the dimer concentration. This corresponds to just a 7-fold reduction in catalytic activity despite the decreased electron density in the cyclopentadiene anion ligand due to the presumed charge transfer to the amide substituent. In toluene as solvent and at at 40°C the second-order catalytic rate constant for the racemisation of **2a** by the iridium catalyst with the amide substituted cyclopentadiene ligand **13a** is k_{cat} = 1.37x10^{-2} $M^{-1}s^{-1}$ showing catalytic activity is 10-fold slower than in dichloromethane. The amide substituent in **13a** presumably increases the positive charge density on the iridium relative to that in **1**, although the structural changes in the solid as determined by x-ray crystallography are small.



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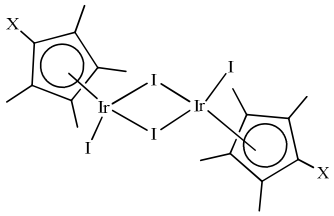


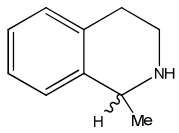
13a = $CONMe_2$
13b = CF_3

The analogous trifluoromethyl derivative **13b** was not as well characterised but it also was less effective as a catalyst for racemisation, showing about half the reactivity of the parent complex **1**.

As for varying the substrate, primary amines undergo dimerisation faster than racemisation as described earlier but tertiary amines are racemised by **1**, although at a slower rate than an analogous

secondary amine. For example, the racemisation of the tertiary amine (*S*)-*N,N*-dimethyl-α-methylbenzylamine in toluene at 90°C with catalyst **1** shows k_{cat} = 1.70x10^{-3} M^{-1}s^{-1} which is 10-fold less than that for the analogous secondary amine **4** at 80°C. In the case of tertiary amines the intermediate iminium ion formed by hydride transfer to the iridium cannot deprotonate which may affect its rate of dissociation from the complex.

Compared with the dimethoxy amine **2a**, the unsubstituted analogue, (*S*)-1-methyl-1,2,3,4-tetrahydroisoquinoline **14**, undergoes a 4-fold slower rate of racemisation with catalyst **1** in toluene at 60°C, k_{cat} = 1.37x10^{-1} M^{-1}s^{-1}.



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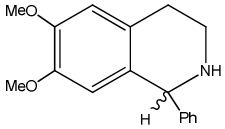

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Substituting the 1-methyl for 1-phenyl in the secondary amine (*R*)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline **15** causes more than a 100-fold lower reactivity with respect to racemisation with catalyst **1** in toluene at 80°C and the reaction also occurs with significant amounts of imine and *iso*quinoline formation. The second-order rate constant k_{cat} = 1.74x10^{-2} M^{-1}s^{-1} is presumably a consequence of a steric effect and a more resonance stabilised imine/iminium ion.

A summary of the catalytic rate constants for the racemisation of amines by the iridium catalyst **1** is given in Table **2**.

Table 2 Second order rate constants k_{cat} for the racemisation of amines catalysed by the iridium complex **1** in toluene at 80°C

Amine	k_{cat} / M^{-1}s^{-1}
(*S*)-N-methyl-α-methylbenzylamine **3**	2.16 x 10^{-2}
(*S*)-N-benzyl-α-methylbenzylamine **4**	4.27 x 10^{-3}
6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline **2**	4.90
cis-sertraline **8a**	3.50 x 10^{-1}
(*S*)-N,N-dimethyl-α-methylbenzylamine[a]	1.70x10^{-3}
(*S*)-1-methyl-1,2,3,4-tetrahydroisoquinoline[b] **14**	1.37x10^{-1}
(*R*)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline **15**	1.74x10^{-2}

[a] at 90°C; [b] at 60°C

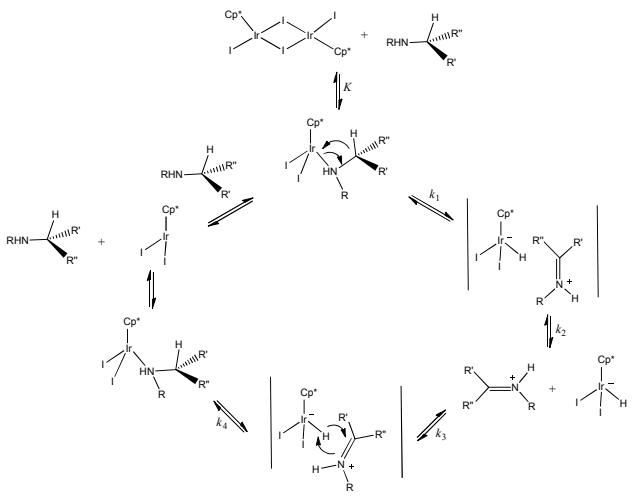
(iv) Kinetic isotope effect and the reaction mechanism

The (*S*)- and (*R*)- enantiomers of 1-deuterated 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline **2b** were synthesised in order to determine any kinetic isotope effect. The racemisation of 0.25M (*S*)- and (*R*)- **9** in dichloromethane with 6.25x10^{-4} M catalyst **1** at 40°C yielded four pseudo-first-order rate constants corresponding to the decrease in the concentrations of (*S*)-**2b** and (*R*)-**2b** and increase in the concentrations of (*R*)-**2b** and (*S*)-**2b**, respectively. All four rate constants were identical within experimental error to give k_{obs}= 1.80±0.06 x 10^{-4} s^{-1} and with a first-order dependence on catalyst concentration, the second-order rate constant k_{cat} = 0.287 M^{-1}s^{-1}. based on the dimer concentration. Comparing these rate constants with those for the analogous 1-^{1}H derivative **2a** yields a primary kinetic isotope effect k_H/k_D = 3.24 (Table 3) indicating that hydride transfer is involved in the rate-limiting step[17]. The rate of racemisation of *(S)*- 1- deutero-**2a** catalysed by the amide substituted cyclopentadiene iridium complex **13a** in dichloromethane at 40°C yields a second-order rate constant k_{cat} = 2.08 x 10^{-2} M^{-1}s^{-1}, giving a primary kinetic isotope effect k_H/k_D = 6.44.

Table 3 Observed pseudo-first-order rate constants k_{obs} and second order catalytic rate constants k_{cat} for the isomerisation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline **2a** and its 1-deuterated analogue **2b** catalysed by 0.5 mol % iridium complex **1** in dichloromethane at 40°C

2a (1-H)	2b (1-D)	2a (1-H)	2b (1-D)	KIE
k_{obs} / s^{-1}	k_{obs} / s^{-1}	k_{cat} / M^{-1}s^{-1}	k_{cat} / M^{-1}s^{-1}	k_H/k_D
5.82 x 10^{-4}	1.80 x 10^{-4}	0.931	0.287	3.24

A reaction mechanism compatible with this data involves dissociation of the catalytic dimer in the presence of reactant amine to form a complex with no overall charge in which the formal Ir^{3+} is four-coordinate and an eighteen electron species and with an equilibrium constant *K* (**Scheme 3).** Hydride transfer from the amine to iridium (step k_1) generates a formally negatively charged iridium complex that is still four-coordinate and an eighteen electron species, but in an ion-pair with the positively charged iminum-ion. These two ions may dissociate (step k_2) before, or at a rate competitive with, hydride transfer back to the iminium ion (step k_4) to generate the enantiomeric amine either after conformational rotation of the iminium-ion or its re-association (step k_3). The primary kinetic isotope effect indicates that hydride transfer is the rate-limiting step. As the reaction profile is symmetrical for this reversible equilibrium process, the free-energies of the transition states for hydride transfer from amine to iridium and from iridium hydride to iminium ion are the same.



Scheme3

Conclusions

The dimeric iodo-iridium complex $[IrCp^*I_2]_2$ **1** is an efficient catalyst for the racemisation of secondary amines at ambient and higher temperatures with a low catalyst loading. With low concentrations of catalyst, the racemisation occurs with pseudo-first-order kinetics. The corresponding pseudo-first-order rate constants were identical within experimental error obtained by measuring the time dependence of the concentrations of the (*R*) and (*S*) enantiomers starting with either pure (*R*) or (*S*) and all show a first-order dependence on catalyst concentration yielding second-order rate constants. Low temperature ^{1}H NMR data is consistent with the formation of a 1:1 complex with the amine coordinated to the iridium and with both iodide anions still bound to the metal-ion. However, at the higher temperatures used for the kinetic studies binding is weaker and therefore saturation zero-order kinetics are not observed. A cross-over experiment with isotopically labelled amines demonstrates the intermediate formation of an imine which can dissociate from the iridium complex. Replacing the iodides in the catalyst by other ligands or having an amide substituent in Cp* results in a much less effective catalysts for the racemisation of amines. The rate constants for a deuterated amine yield a significant primary kinetic isotope effect k_H/k_D = 3.24 indicating that hydride transfer is involved in the rate-limiting step.

Experimental

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline: *N*-(3, 4-dimethoxyphenethyl) acetamide (20g, 0.09 mol) was suspended in *o*-xylene (200ml), cooled in an ice bath, to which was added dropwise $POCl_3$ (41.75ml, 0.445 mol) followed by heating to reflux for 3 hrs. After cooling, the mixture was poured into ice water, basified to pH 11, extracted with ethyl acetate, washed with water and dried, to afford 6,7-dimethoxy-1-methyl-3,4-dihydro*iso*quinoline as a yellow solid (15.8g, 85.8%). ^{1}H-NMR (500MHz, $CDCl_3$) δppm 2.36 (3H, *s*, CH_3), 2.65 (2H, *t*, CH_2), 3.64 (2H, *dd*, CH-N), 3.91 (6H, *d*, OCH_3), 6.69 (1H, s, ArH), 6.99 (1H, *s*, ArH). ^{13}C-NMR (500MHz, CDCl3) δppm 23.1 (CH_3), 25.4(CH_2), 46.72(CH_2N), 55.9(OCH_3), 108.7(CH), 109.93(CH), 122.17(qC), 130.8(qC), 147.1(qC), 150.5(qC), 163.2(qC). MS ($M+H^+$) = 206.1188. Mpt.108°C

6,7-dimethoxy-(R and S) 1H/D-1-methyl-1,2,3,4-tetrahydro-isoquinoline: To a preformed ruthenium catalyst ($[RuCyCl_2]_2$, 0.01221g, 0.02 mol) and 1,2-diphenyl-*N*-tosylethane-1,2-diamine TsDPEN ((*R, R) or (S, S)* 0.0146g, 0.04 mol) in acetonitrile was added 6, 7-dimethoxy-1-methyl-3, 4-dihydro*iso*quinoline (1.026g, 5 mmol) and stirred for 5 minutes. An azeotropic mixture of formic acid or deuterated DCO_2H (5mmol) and triethylamine (2 mmol) (2.6g) was then added at 28°C and stirred for 2 hrs. Dichloromethane (20ml) was added, washed with 2M NaOH, water, dried to afford the crude amines as brown oils. The amines were converted to their salts with methanolic HCl and then recrystallised from ethanol/hexane and finally the free bases formed by treatment with NaOH and extraction with dichloromethane to give pure samples of *(R)* and *(S)*-*6*,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro*iso*quinoline and their 1-deuterated analogues. -(*R and S*)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydro*iso*quinoline, (*R*) 0.90g, 87%; (*S*) 0.87g, 84%; ^{1}H-NMR (500MHz, $CDCl_3$) δppm 1.44 (3H, *d*, CH_3, JHz 6.7), 1.90 (1H, br, NH), 2.64; 2.67 (1H, dt, CH_2, JHz 16.1, 4.7 Hz), 2.78; 2.81 (1H, ddd, CH_2, JHz 16.1, 8.7, 5.5 Hz), 2.99, 3.02 (1H, ddd, CH_2, JHz 12.6, 8.7, 4.7 Hz), 3.23; 3.26 (1H, dt, CH_2, JHz 12.6, 5.1 Hz), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.03 (1H, q, JHz 6.6 Hz), 6.57 (1H, s, ArH), 6.63 (1H, s, ArH) ^{13}C-NMR (500MHz, CDCl3) δppm 22.8 (CH_3), 29.5 (CH_2), 41.8 (CH_2), 51.2 (CH), 55.9 (OCH_3), 56.0 (OCH_3) 109.3 (CH), 111.9 (CH), 126.8 (qC), 132.4 (qC), 147.4 (qC), 147.4 (qC). MS [ESI]: m/z 208 $[M+H]^+$. Mp 51.5 °C

(*R and S*) *6*,7-dimethoxy-1-deutero-1-methyl-1,2,3,4-tetrahydro*iso*quinoline (*R*) 0.95 g, 92 % and (*S*) 0.92g, 89%. ^{1}H-NMR (500MHz, CDCl3) δppm 1.40 (2H, *t*, CH_3, JHz 8.9Hz), 1.80 (1H,br, NH), 2.63; 2.67 (1H, dt, CH_2, JHz 16.1, 4.9 Hz), 2.77; 2.80 (1H, ddd, CH_2, JHz 16.0, 8.5, 5.4 Hz), 2.98, 3.01 (1H, ddd, CH_2, JHz 12.8, 8.7, 4.8 Hz), 3.23; 3.26 (1H, dt, CH_2, JHz 12.7, 5.2 Hz), 3.85 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.57 (1H, s, ArH), 6.62 (1H, s, ArH). ^{13}C-NMR (500MHz, CDCl3) δppm 22.2 (CH_2D, m), 29.6 (CH_2), 41.8 (CH_2), 50.5 (CD, m), 55.9 (OCH_3), 56.0 (OCH_3), 109.3 (CH), 112.0 (CH), 126.9 (qC), 132.5 (qC), 147.3 (qC), 147.4 (qC). Mpt =52.8°C. Some deuteration of the 1-methyl group occurred suggesting that there may be some coordination of the enamine to the ruthenium catalyst as well as the iminium ion.

Enantioselectivities were determined by gas chromatography using an Agilent 7890 GC system with FID detection. The system was fitted with a Restek Rt-bDEXsm (30m x 0.25mm x 0.25µm) column and analysis was carried out at 180°C isothermal for 45 mins using 12 psi helium as carrier gas (0.564 ml/min) the retention times of the (*R*)-amine, (*S*)-amine and imine were 31.4, 30.0 and 32.7 mins., respectively.

The synthesis and characterisation of the dimeric iodo-iridium complex $[IrCp^*I_2]_2$ **1.**has been previously reported.[6]

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