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## The Kinetics and Mechanism of the Organo-Iridium-Catalysed Enantioselective Reduction of Imines

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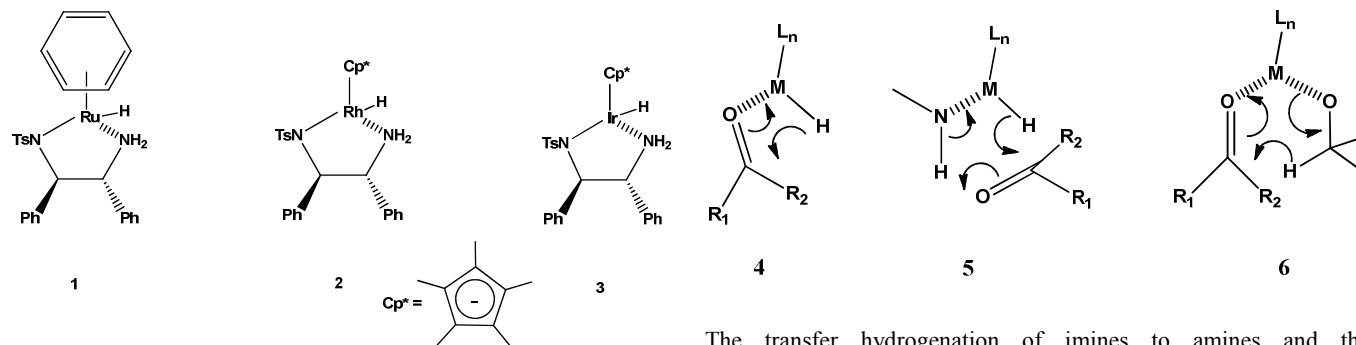
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The iridium complex of pentamethylcyclopentadiene and (*S,S*)-1,2-diphenyl-*N'*-tosylethane-1,2-diamine is an effective catalyst for the asymmetric transfer hydrogenation of imine substrates under acidic conditions. Using the Ir catalyst and a 5:2 ratio of formic acid: triethylamine as the hydride source for the asymmetric transfer hydrogenation of 1-methyl-3,4-dihydroisoquinoline and its 6,7-dimethoxy substituted derivative, in either acetonitrile or dichloromethane, shows unusual enantiomeric excess (ee) profiles for the product amines. The reactions initially give predominantly the (*R*) enantiomer of the chiral amine products with >90% ee but which then decreases significantly during the reaction. The decrease in ee is not due to racemisation of the product amine, but because the rate of formation of the (*R*)-enantiomer follows first-order kinetics whereas that for the (*S*)-enantiomer is zero-order. This difference in reaction order explains the change in selectivity as the reaction proceeds - the rate formation of the (*R*)-enantiomer decreases exponentially with time while that for the (*S*)-enantiomer remains constant. A reaction scheme is proposed which requires rate-limiting hydride transfer from the iridium hydride to the iminium ion for the first-order rate of formation of the (*R*)-enantiomer amine and rate-limiting dissociation of the product for the zero-order rate of formation of the (*S*)-enantiomer.

### Introduction

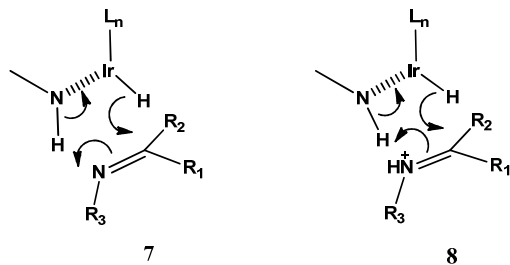
Chiral amines make up a significant fraction of the current portfolio of pharmaceuticals and agrochemicals<sup>1</sup>. Therefore there has been an extensive search for an enantioselective synthesis of these important constituents suitable for their large-scale manufacture. Due to economic and environmental pressures these processes need to be achieved with the minimum number of chemical steps, be energy and atom efficient, not produce toxic waste and, ideally, involve catalytic methods. Catalytic transfer hydrogenation (TH) is an attractive alternative to the direct reduction of substrates, avoiding the need for molecular hydrogen.<sup>2,3,4</sup> The first homogeneous catalytic systems appeared in the late 1960s and were based on iridium compounds<sup>5,6</sup> which were followed by the introduction of the versatile pentamethylcyclopentadienyl anion iridium and rhodium (Cp\*Ir and Cp\*Rh) catalyst precursors for these transformations<sup>7,8,9,10</sup> and their variants.<sup>11,12,13</sup>

Although the highly selective asymmetric reduction of alkenes and ketones has been accomplished using chiral rhodium and ruthenium catalysts,<sup>14</sup> the hydrogenation of imines using similar catalysts has proved much less successful.<sup>15</sup> Furthermore, most enantioselectivities obtained are moderate and require a high catalyst loading. Asymmetric transfer hydrogenation (ATH) commonly uses propan-2-ol or formic acid as the hydrogen donor, in conjunction with a chiral organometallic catalyst such as Noyori's ruthenium based complex<sup>16</sup> (**1**) and the iso-electronic rhodium (**2**) and iridium (**3**) CATHY catalysts<sup>17</sup>.

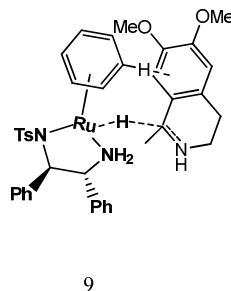


There are two mechanisms<sup>18</sup> commonly suggested for these metal-catalyzed transfer hydrogenation reactions: either a metal hydride is involved in the hydrogen transfer step (4) and (5) or the metal facilitates hydride transfer between the hydride donor and the substrate as in a Meerwein–Ponndorf–Verley type reduction (6). The most favoured pathways are those involving the metal-hydride which may occur by inner-sphere (4),<sup>18</sup> where the substrate is coordinated to the metal prior to hydride transfer, or outer-sphere (5) processes,<sup>19,20,21</sup> both of which assume full retention of all ancillary ligands. The inner sphere mechanism generates an alkoxide anion bound to the metal which requires protonation to release the product alcohol and hydride transfer to the metal to regenerate the catalyst. The commonly accepted mechanism for the Cp\*Ir-catalyzed asymmetric transfer hydrogenation of ketones is that involving a concerted process with the transfer of a metal hydride and a ligand proton occurring through a six-membered cyclic transition state i.e. outside the direct coordination sphere of the metal (5).<sup>22,23</sup> In the outer-sphere mechanism the metal-bound ligand, shown as NH in (5), is important in contributing to both proton and hydride transfer through its acidity. Relatively, if it is a better proton donor it will activate the carbonyl carbon towards nucleophilic attack but as a weaker Lewis base it will increase the positive charge density on the metal retarding hydride transfer. In some processes the proton transfer step to the carbonyl oxygen is facilitated by an external acid.<sup>18</sup> The picture presented in the inner sphere mechanism (4) formally requires an expansion of the coordinatively and electronically saturated metal and it has been suggested that prior ligand dissociation must occur<sup>24</sup> although some pathways are thought to involve the cooperative participation of two metal centres.<sup>25</sup> A recent study of a Cp\*Ir complex provided evidence for displacement of the Cp\* ligand which may be relevant to hydrogen transfer catalysis by providing the assumed required vacant coordination site.<sup>26</sup>

The transfer hydrogenation of imines to amines and the corresponding reverse reaction are expected to show significant differences to the ketone/alcohol reaction because of the differences in basicity, susceptibility to nucleophilic attack and their ability to bind to metal ions. There have been fewer investigations into the imine/amine reaction using organometallic catalysts, although kinetic and isotope labelling studies using a cyclopentadienone ruthenium catalyst<sup>27,28</sup> have attempted to differentiate an inner sphere mechanism, involving direct coordination of the substrate to the metal, and an outer sphere process in which the amine/imine nitrogen does not bind directly to the ruthenium. Distinguishing between stepwise and concerted hydride and proton transfer steps is also controversial<sup>29</sup>. It has been suggested<sup>30</sup> that the asymmetric transfer hydrogenation of imines with formic acid-triethylamine mixtures using Rh-chiral diamine catalysts involves the neutral imine as the reactive species, whereas prior imine protonation has been proposed because the isolated ruthenium hydride reacts faster with an imine substrate than a corresponding ketone due to the greater basicity of the imine.<sup>31,32,33</sup> Based on studies of the nucleophilic addition to imines in aqueous solution, it may be expected that the iminium would be the reactive species,<sup>34</sup> however recent iridium transfer hydrogenation catalysts have been developed by Crabtree<sup>35</sup> which are highly active under neutral and basic conditions. Finally, the concerted metal-ligand bifunctional mechanism<sup>22,23</sup> is presumably required when the neutral imine is the reactive species to prevent formation of the unstable nitrogen anion (7), but if the iminium species is involved then the necessity for protonation from a bound ligand is less likely and with no available nitrogen lone-pair proton transfer would have to occur through the  $\pi$ -bond (8).



The origin of enantioselection is also unclear with respect to the transfer hydrogenation of imines using Noyori / CATHy catalysts. Computational calculations<sup>36</sup> indicate that the control of stereochemistry in the transfer hydrogenation of aromatic ketones is due to a favourable  $\pi$ /CH interaction between a hydrogen atom on the  $\eta^6$ -arene ligand and the aromatic ring of the substrate (**9**). However, the transfer hydrogenation of aromatic imines leads to chiral amines with the opposite stereochemistry from that expected applying a similar rationale. Based on the effect of N-alkylation of the diamine ligand in the Ru complex (**1**) an ionic outer sphere mechanism for the asymmetric transfer hydrogenation of imines was proposed involving hydride transfer to the iminium ion whilst maintaining the  $\pi$ /CH interaction<sup>37</sup> (**9**).

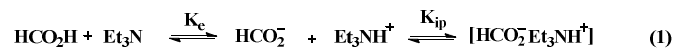


A detailed understanding of the mechanism of imine transfer hydrogenation would facilitate the design of more active and selective catalysts as well as optimisation of the process conditions minimising catalyst loading and deactivation. Herein we investigate the mechanism of the asymmetric transfer hydrogenation of imines using iridium CATHy catalysts (**3**).<sup>8</sup>

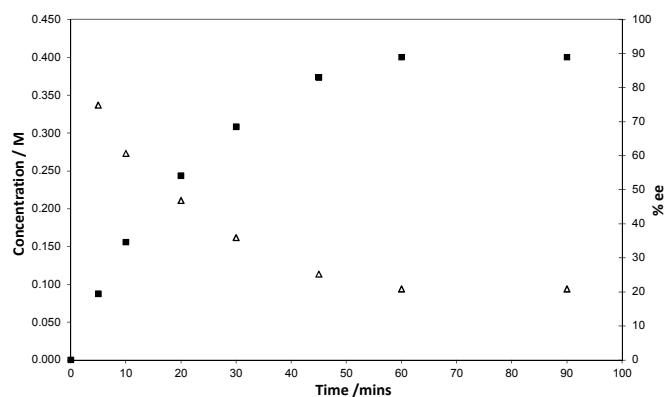
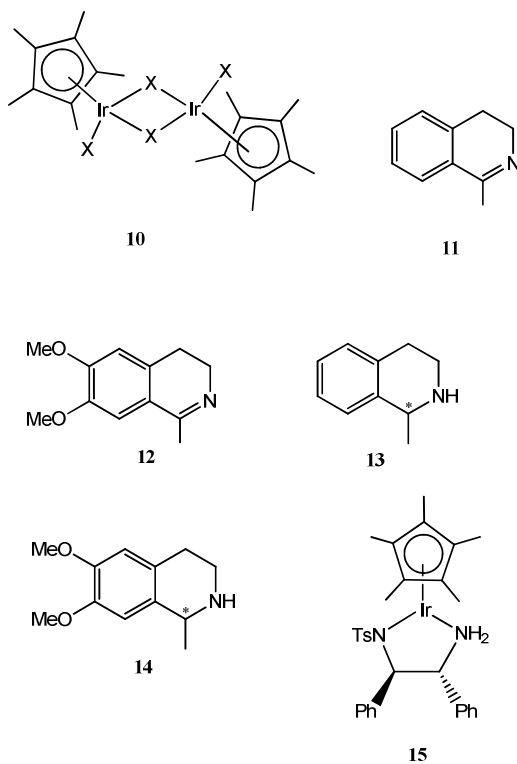
## Results and Discussion

The iridium based CATHy catalyst (**3**) is an effective catalyst for the transfer hydrogenation of imine substrates under acidic conditions.<sup>8,17</sup> It is usually formed *in-situ* through the reaction of the pentamethylcyclopentadienyl metal dimer ( $\text{IrCp}^*\text{Cl}_2$ ) (**10**, X = Cl)

and the ligand (*S,S*)-1,2-diphenyl-*N'*-tosylethane-1,2-diamine (TsDPEN). The synthesis of chiral 1,2,3,4-tetrahydroisoquinoline (**13**) derivatives is of interest because they often exhibit bioactivity with a potential use as drugs.<sup>38</sup> Using the Ir catalyst (**3**) for the asymmetric transfer hydrogenation of 1-methyl-3,4-dihydroisoquinoline (**11**) and its 6,7-dimethoxy substituted derivative (**12**), in either acetonitrile or dichloromethane, there are unusual enantiomeric excess (ee) profiles for the product amines (**13**) and (**14**), respectively. The reactions are carried out using a mixture of triethylamine and formic acid with the latter in excess in a ratio of 2:5. Under these conditions the reactant imine, triethylamine and the product amine are 100% protonated as shown by NMR studies (see ESI). The  $\text{p}K_a$  of formic acid in acetonitrile, which has not been reported, can be estimated to be 20.9 from the very good relationship of the acidities of other carboxylic acids between acetonitrile and water<sup>39</sup>. The  $\text{p}K_a$  of the conjugate acid of triethylamine in acetonitrile is 18.5, so at low concentrations the equilibrium constant for the acid-base equilibrium (**eq.1**) is expected to be  $4 \times 10^{-3}$ . However, the overall equilibrium constant *K* is influenced by ion-pairing in solvents of low dielectric constant so that  $K = K_e \times K_{ip}$  (**eq.1**) and as ion-pairing constants are typically of the order  $10^2$ - $10^3 \text{ M}^{-1}$ <sup>40</sup> and with the high concentrations of formic acid (2.4M), triethylamine (0.96M) and imine (0.4M) typically used, it is not surprising that under the experimental conditions used both bases are fully protonated. Furthermore, the solvent system is not just acetonitrile; it is a mixture of acetonitrile, *ca.* 10% formic acid and *ca.* 10% triethylamine so the solvent polarity is much higher than pure acetonitrile and the  $\text{p}K_a$  of formic acid will be lower than the value in pure acetonitrile. The reduction consumes one equivalent of formic acid but there is still an excess of formic acid at the end of the reaction.



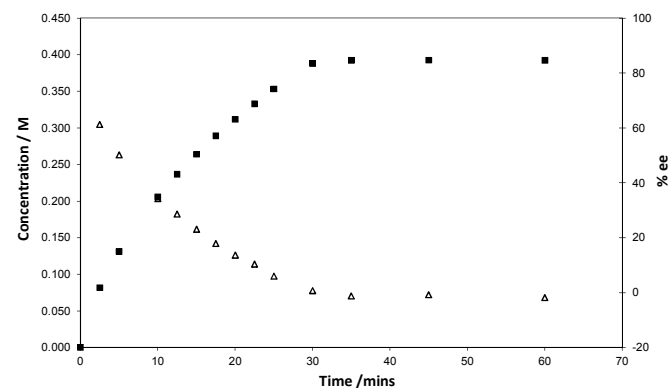
The reactions initially give predominantly the R enantiomer of the chiral amines (**13**) and (**14**) with > 90% ee which then decreases significantly during the reaction. For example, using the standard reaction conditions of 0.4 M imine (**11**), 0.5 mol% of catalyst (**3**), 6 equivalents of formic acid (2.4 M) triethylamine (0.96 M) (5:2 ratio formic acid : triethylamine, TEAF) at 20 °C in either acetonitrile or dichloromethane the ee drops from about 80% and 60% to 20% or zero, respectively (**Figs. 1 and 2**).



**Fig.1** Change in concentration M (■) of product amine (14) during the transfer hydrogenation of 0.40M imine (12) in acetonitrile with catalyst ((S,S)-3) and the change in % enantiomeric excess (ee) (△) of product amine (14) as a function of time.

The enantioselectivity of the transfer hydrogenation is solvent dependent, with faster rates being favoured by dichloromethane but greater enantioselectivity in acetonitrile. In both solvents the enantiomeric excess decreases with increasing conversion, remaining constant after the reduction has reached completion. A possible explanation is that the product amine is racemised under the reaction conditions<sup>41</sup>. However, the enantiomeric excess of the amine formed during the transfer hydrogenation remains constant after the reduction is complete. Furthermore, under the standard

reaction conditions containing the (*R*) amine (14) in dichloromethane with



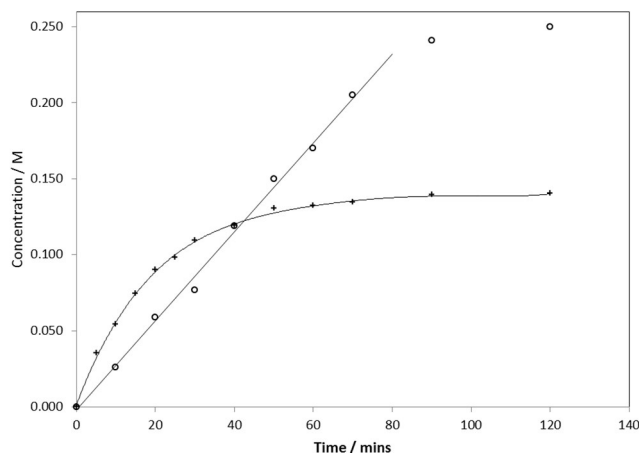
**Fig. 2** Change in concentration M (■) of product amine (14) during the transfer hydrogenation of 0.40M imine (12) in dichloromethane with catalyst ((S,S)-3) and the change in % enantiomeric excess (ee) (△) of product amine (14) as a function of time.

the catalyst (3) and 5:2 formic acid / triethylamine there is no racemisation after 12 hours. This lack of racemisation is not surprising as formate is a better hydride donor than the amine and the acidic nature of the medium means the amine is in its protonated form and unlikely to readily bind to the iridium catalyst. In dichloromethane the ee decreases to below zero, suggesting increased selectivity for the other enantiomer of the product amines (13) and (14) as the reaction progresses, rather than racemisation causing the decrease in ee. Finally, the large excess of formic acid and absence of a hydrogen acceptor indicates that the resting state of the catalyst is likely to be the 18-electron iridium hydride, (3), rather than the 16-electron species, (15), required for dehydrogenation.

The enantiomeric excess decreases at similar rates for various ratios of catalyst (3) to imine from 0.1 to 1.0 mol%. Analysis of the overall reaction profiles revealed that they do not obey first-order kinetics and appear to lie somewhere between zero and first-order. This is a consequence of the rate of formation of the (*R*)-enantiomer following first-order kinetics whereas that for the (*S*)-enantiomer is zero-order (Fig 3). This difference in reaction order explains the change in selectivity as the reaction proceeds - the rate formation of the (*R*)-enantiomer decreases exponentially with time while that for the (*S*)-enantiomer remains constant. As the reaction progresses the reaction becomes increasingly selective for the (*S*)-enantiomer which constitutes an ever increasing fraction of the total rate of the conversion of imines (11) or (12) to chiral amines (13) or (14), respectively, to the point where the rate of formation of the (*S*)-

enantiomer exceeds that of the (*R*)-enantiomer. For example, using 0.25 mol% of the iridium catalyst (**3**) the concentration of the (*S*)-enantiomer (**14**) exceeds that of the (*R*)-enantiomer after 30 mins (Fig.3).

Using the (*R,R*)-, rather than the (*S,S*)-, ligand TsDPEN to generate the iridium catalyst (**3**) inverts the kinetic profiles so that the reduction of the imine (**11**) in dichloromethane produces the (*R*)-(**13**) by zero-order kinetics and the (*S*)-enantiomer by a first-order process.

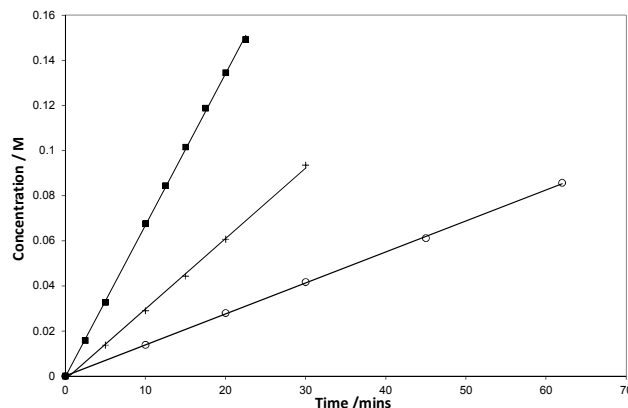


**Fig. 3** Rate profiles for the formation of the (*S*)(o) - and (*R*)(+) - enantiomers of (**14**) for the transfer hydrogenation of 0.40M (**12**) using 0.25 mol% of the iridium catalyst (**3**) in dichloromethane at 20°C

There are several possible explanations for the differences in the kinetic profiles for the formation of the two enantiomers using the (*S,S*)-TsDPEN ligand:

- The formation of the (*S*)-enantiomer involves tight binding of the imine to a single catalytic species, or slow dissociation of the product (*S*) amine from the catalyst, giving rise to saturation and zero-order kinetics; whereas the (*R*)-enantiomer is produced from weaker catalyst binding so exhibiting below saturation, first-order, kinetics.
- There are different rate limiting steps for the formation of each enantiomer such that the formation of the (*S*)-enantiomer is independent of the concentration of the imine.
- There are two distinct species of the iridium catalyst each responsible for the separate formation of each enantiomer. The two catalytic processes have different rate limiting steps or equilibria such that the rate of formation of the (*S*)-enantiomer is independent of the concentration of imine.

The zero-order rate of formation of the (*S*)-enantiomer changes proportionally with catalyst concentration (Fig.4) to give a first-order rate constant of  $5.12 \times 10^{-2} \text{ s}^{-1}$ . The rate of formation of the (*R*) enantiomer also shows a first-order dependence on the catalyst concentration giving an overall second order rate constant of  $0.875 \text{ M}^{-1} \text{ s}^{-1}$ .



**Fig. 4** Reaction profile for the formation of (*S*)-(**14**) at different catalyst loadings of the iridium catalyst (**3**) (0.50 mol% (■), 0.25 mol% (+) and 0.125 mol% (o)) in the transfer hydrogenation of 0.4M (**12**) using 6 M equiv. TEAF in dichloromethane at 20°C.

The catalytic rate constants for the transfer hydrogenation of imines (**11**) or (**12**) to chiral amines (**13**) or (**14**), respectively, catalysed by the iridium complex **3** in acetonitrile and dichloromethane are given in Table 1. The dimethoxy imine (**12**) is at least 10-fold more basic than the unsubstituted imine (**11**)<sup>32</sup> and yet there is less than a two-fold difference in reactivity for the formation of both enantiomers (Table 1).

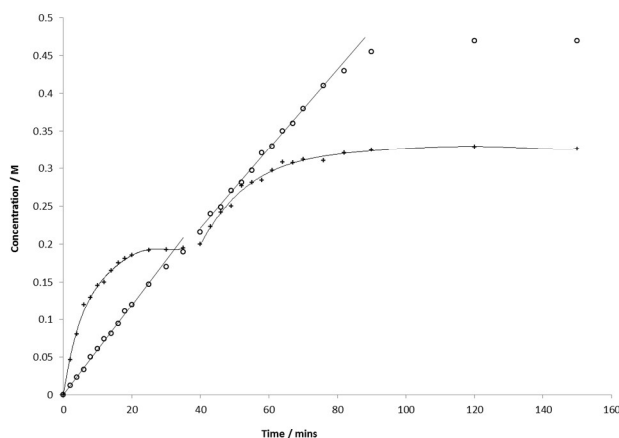
**Table 1** The first and second order catalytic rate constants for the reduction of imines **11** and **12** catalysed by the iridium complex **3** in acetonitrile and dichloromethane (DCM) at 20°C.

Rate constant	Unsubstituted imine ( <b>11</b> )		Dimethoxy imine ( <b>12</b> )	
	acetonitrile	DCM	acetonitrile	DCM
$k(S)/s^{-1}$	$2.01 \times 10^{-2}$	$7.27 \times 10^{-2}$	$9.80 \times 10^{-3}$	$5.12 \times 10^{-2}$
$k(R)/M^{-1}s^{-1}$	0.595	1.40	0.481	0.875

The enantioselectivity of the reaction system is dependent on the concentration of imine, being (*R*)-selective at high concentrations



and (*S*)-selective at low concentrations. Starting with the standard reaction conditions the transfer hydrogenation of (**12**) in dichloromethane was followed by a second aliquot addition of 0.4 M imine (**12**) and 2 M equivalents of formic acid after the reduction of the first aliquot had reached completion (Fig. 5). There is a change in the rate of decrease in enantioselectivity as the second aliquot of imine is added as expected if the reaction becomes more (*R*)-selective on the addition of imine. The rate of formation of amine during the reduction of the second aliquot of amine is approximately half of that for the reduction of the first aliquot: the first-order rate of formation of the (*R*)-enantiomer is approximately halved during the reduction of the second aliquot whereas the zero-order rate of formation of the (*S*)-enantiomer is slightly decreased as expected

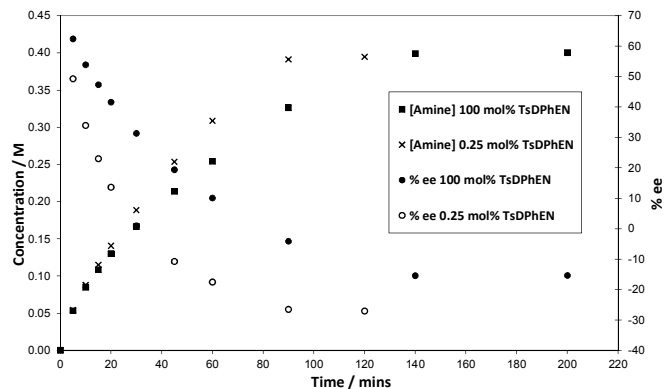


**Fig. 5** Formation of (*R*)- (+) and (*S*)- (o) enantiomers of amine (**14**) during the transfer hydrogenation of 0.40M (**12**) using 0.5 mol% of the iridium catalyst (**3**) and 6 equiv. TEAF in dichloromethane at 20°C with the addition of the 0.40 M (**12**) and 2 equiv. formic acid after 35 minutes.

from the 10% dilution for the second phase. The major difference between the two reaction phases is the presence of 0.4 M product amine (**14**).

It is possible that the amine product (**14**) acts as a ligand for the iridium species. However, adding 0.2 M (*R*)- or (*S*)-, or racemic (**14**) at the start of the reaction just prior to the addition of TEAF reduced the overall rate of reduction, the zero-order rate of formation of the (*S*)-enantiomer, and the exponential rate of formation of (*R*)-(**14**) by less than half. This small effect of added amine product could be just a general base effect rather than specific interaction with the iridium, so the transfer hydrogenation was repeated with the addition of 0.2 M triethylamine to the standard conditions of 6 equivalents of formic acid (2.4 M) and triethylamine (0.96 M) which resulted in the

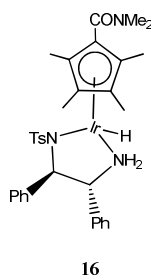
similar, relatively small, changes seen with added amine product (**14**). Finally, the catalytic reduction was carried out with excess (0.4 M) of the ligand (*S,S*)-1,2-diphenyl-*N'*-tosylethane-1,2-diamine (TsDPEN) with ( $5 \times 10^{-4}$  M) iridium dimer [ $\text{IrCp}^*\text{Cl}_2$ ]<sub>2</sub> (**10**) which shows the usual profile of being more selective for the (*R*)-enantiomer, and the decrease in the enantiomeric excess similar to that of the standard reaction (Fig. 6). The effect of additional ligand is similar to that of other added amines and indicates that there is no unreacted iridium dimer (**3**) present in the standard reaction conditions and that the catalytic species contains a single molecule of (*S,S*)-TsDPEN which does not dissociate during catalytic turnover. The enantiomeric excess is greater with excess ligand throughout the reaction and the overall profile is much closer to first-order as the excess of ligand favours the formation of the (*R*)-enantiomer compared with the standard conditions. The observed



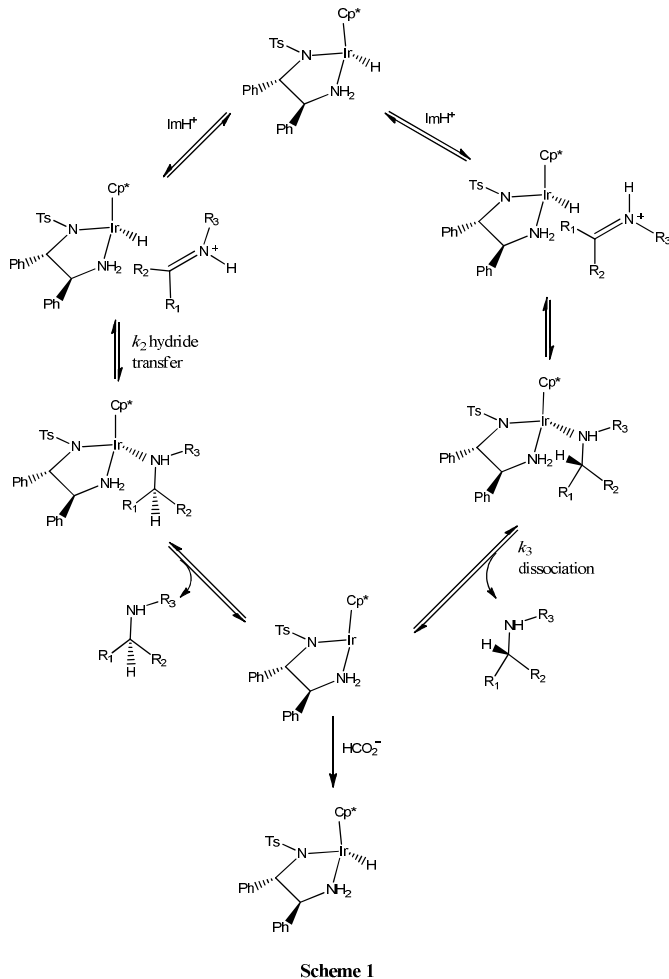
**Fig. 6** The change in amine (**14**) concentration and % ee with 0.25mol% TsDPEN (x) and (o) respectively and with 100mol% TsDPEN (■) and (●) respectively for the reduction of 0.4M (**12**) using 1.0 mM of the iridium catalyst (**3**) and 6 equiv. TEAF in dichloromethane at 20°C with the addition of 1.0 mM and 0.4 M (*S,S*)-TsDPEN.

zero-order rate of formation of (*S*)-(**14**) with excess ligand is nearly halved compared with 0.25 mol% (*S,S*)-TsDPEN, whereas the first-order rate constant for the formation of (*R*)-**12** is slightly greater than with a catalytic amount of ligand. There are two steps during catalytic reduction and turnover which require hydride transfer – reduction of the iridium species (**15**) by formate to regenerate the catalyst (**3**) and hydride transfer from the catalyst (**3**) to the iminium ion. The first-order rate of formation of the (*R*)-enantiomer shows a small but significant deuterium kinetic isotope effect (KIE) ( $k_{\text{H}}/k_{\text{D}} = 1.55$ ) using deuterated formic acid ( $\text{DCO}_2\text{H}$ ), whereas the zero-order rate of formation of the (*S*)-enantiomer shows no KIE ( $k_{\text{H}}/k_{\text{D}} = 1.00$ ).

The interactions of the imine reactant and amine product with the iridium-ion and the rates of hydride transfer are expected to be dependent on the effective positive charge on the metal-ion. A simple way to modify this effective charge and hence change catalytic activity is with a substituent in the cyclopentadienyl residue such as the amide (**16**)<sup>42</sup>. The electron-withdrawing amide substituent in **16** presumably decreases the electron density in the cyclopentadiene anion ring, making the iridium-ion relatively more positive compared with that in the unsubstituted catalyst **3**. Using the (*S,S*)-ligand TsDPEN, the ATH of the imine **12** with the substituted catalyst **16** in dichloromethane at 20°C is much slower than that with the unsubstituted Cp\* (**3**). However, the rate of formation of the (*R*)-product amine **14** still follows first-order kinetics whereas that for the (*S*)-enantiomer is zero-order as seen for the catalyst **3**. Both catalytic constants for (*R*)- and (*S*)-enantiomer formation using **16** are about 130-fold less than the analogous ones using catalyst **3** (**Table 1**);  $k(R)$  being  $6.46 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$  and  $k(S) = 4.17 \times 10^{-4} \text{ s}^{-1}$ .



All of the above observations can be used to deduce a reaction mechanism. To generate both enantiomeric amine products from a single catalytic species requires hydride transfer to occur with different orientations of the iminium ion with respect to the catalyst (**Scheme 1**). It has been suggested that the orientation of the iminium ion to the catalyst is controlled by its H-bonding to either the metal-bound  $\text{-NH}_2$ <sup>43</sup> (even though there is no available electron pair) or the sulfonyl oxygens<sup>44</sup> of the diamine ligand. Such a scheme requires rate-limiting hydride transfer from the iridium hydride to the iminium ion for the first-order rate of formation of the (*R*)-enantiomer amine ( $k_2$  in **Scheme 1**) and rate-limiting dissociation of the product for the zero-order rate of formation of the (*S*)-enantiomer ( $k_3$  in **Scheme 1**).

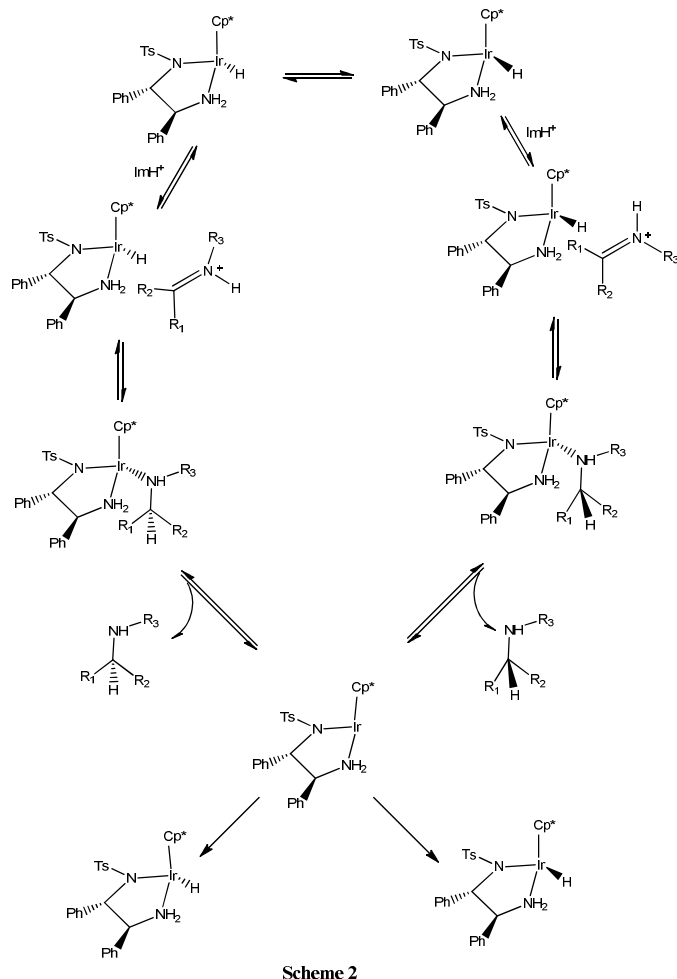


These different rate-limiting steps are compatible with the observed different kinetic orders and the KIE for formation of the two enantiomers. The slower zero-order rate of catalytic ATH observed for formation of the *S*-enantiomer by the amide substituted iridium derivative (**16**) would also be explained by the slower rate of dissociation of the amine product ( $k_3$  in **Scheme 1**) due to the greater positive charge on the metal-ion. For the first-order formation of the *R*-amine, this additional positive charge density on the iridium would decrease the rate of hydride transfer ( $k_2$  in **Scheme 1**).

If the ATH occurs with two catalytic species being present then the observations could be explained with two diastereomeric species of the iridium hydride each having different catalytic activities (**Scheme 2**). In this case the zero-order rate of formation of the (*S*)-enantiomer is unlikely to occur with rate-limiting formation of the catalyst by hydride transfer from formate ion because of the lack of a KIE, but again could involve rate-limiting dissociation of the product (*S*)-amine. The first-order rate of formation of the (*R*)-enantiomer



amine could involve rate-limiting hydride transfer from the iridium hydride to the iminium ion. At present it is not possible to distinguish between these two schemes.



## Conclusions

The iridium complex of pentamethylcyclopentadiene and (*S,S*)-1,2-diphenyl-*N'*-tosylethane-1,2-diamine is an effective catalyst for the asymmetric transfer hydrogenation of imine substrates under acidic conditions. Using the Ir catalyst for the asymmetric transfer hydrogenation of 1-methyl-3,4-dihydroisoquinoline and its 6,7-dimethoxy substituted derivative, in either acetonitrile or dichloromethane, shows unusual enantiomeric excess (ee) profiles for the product amines. The reactions initially give predominantly the (*R*) enantiomer of the chiral amine products with > 80% ee but which then decreases significantly during the reaction. The

decrease in ee is not due to racemisation of the product amine, but because the rate of formation of the (*R*)-enantiomer follows first-order kinetics whereas that for the (*S*)-enantiomer is zero-order. This difference in reaction order explains the change in selectivity as the reaction proceeds - the rate formation of the (*R*)-enantiomer decreases exponentially with time while that for the (*S*)-enantiomer remains constant.

## Experimental

**Reaction Procedures.** Unless stated otherwise, the reactions were followed using 0.4 M imine (**12**), *x* mol% pentamethylcyclopentadienyl metal dimer ( $\text{IrCp}^*\text{Cl}_2$ ) (**10**, X = Cl); 2*x* mol% of the ligand (*R,R*) or (*S,S*)-1,2-diphenyl-*N'*-tosylethane-1,2-diamine (TsDPEN); 6 and 2.4 mole equivalents of formic acid and triethylamine, respectively (5:2 ratio formic acid : triethylamine, TEAF) in either acetonitrile or dichloromethane at 20°C. For example, pentamethylcyclopentadienyliridium (III) chloride dimer, **10** (X= Cl), (11.7 mg, 0.0147 mmol), (*S,S*)-TsDPEN (10.8 mg, 0.0294 mmol) and 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, **12**, (1.204 g, 5.873 mmol) were dissolved in acetonitrile (11.7 ml) at 20 °C. The reaction solution was agitated using a magnetic stirrer and sparged at 50 ml/min with acetonitrile saturated nitrogen, passed through this solvent prior to entering the reaction flask, for 30 mins. TEAF (3.048g, 35.24 mmol formic acid) was then added in one aliquot and the reaction then sampled at regular intervals for GC analysis by quenching ~200  $\mu\text{l}$  into 2.5 M sodium hydroxide (2.0 ml) / dichloromethane (2.0 ml), isolating and drying the organic layer using sodium sulfate.

**Analytical.** The following methods were used for the analysis of all transfer hydrogenation reactions using **12** as the substrate: GC column - HP Crosslinked 5% Ph Me siloxane (25 m x 0.32 mm x 0.52  $\mu\text{m}$ ); oven temp. 150 °C for 7 mins., then ramped at 10°C/min to 300°C and held for 5 mins.; inlet pressure 12.0 psi. 6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, **12**, retention time 12.4 mins., 6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline, **14**, retention time 12.7 mins. Capillary electrophoresis (for ee): Beckman Coulter P/ACE MDQ; bare fused silica capillary column (31 cm x 50  $\mu\text{m}$ , effective length = 21 cm); voltage -15.0 kV; eluent pH 2.5 triethylammonium phosphate buffer containing 2.0% w/v highly sulfated  $\gamma$ -cyclodextrin; detector wavelength 200 nm. **12** retention time 3.48 mins., retention times: (*R*)- **14** 4.93 mins., (*S*)-**14**

7.13 mins. G. C. (for ee): samples were derivatised using trifluoroacetic anhydride prior to injection; Varian Chirasil -Dex-CB column (25 m, 250  $\mu\text{m}$ , 0.25  $\mu\text{m}$ ); oven temp. 165°C isothermal for 60 mins., inlet pressure 10.0 psi., retention times: (*R*)-**14** = 41.6 mins., (*S*)-**14** = 42.5 mins.

*Attempted racemisation of (R)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline*. **12**, Pentamethylcyclopentadienyliridium (III) chloride dimer, **10**, (1.9 mg,  $2.385 \times 10^{-3}$  mmol) and (*R*)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, **14**, (100 mg, 0.487 mmol) were dissolved in dichloromethane (1.95 ml) to give an orange solution that was agitated using a magnetic stirrer. Samples were taken after 2 and 12 h and analysed by GC by adding one drop to a GC vial containing dichloromethane by chiral capillary electrophoresis by adding 200  $\mu\text{l}$  of the reaction solution to 10 ml ultra-pure water. A similar experiment was conducted in the presence of a solution of TEAF, in which pentamethylcyclopentadienyliridium (III) chloride dimer, **10**, (1.9 mg,  $2.385 \times 10^{-3}$  mmol), (*S,S*)-TsDPEN (1.8 mg,  $4.9 \times 10^{-3}$  mmol), (*R*)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, **14**, (100 mg, 0.4873 mmol) and a pre-prepared TEAF solution in dichloromethane (1.95 ml,  $1.225 \times 10^{-2}$  mmol  $\text{HCO}_2\text{H}$ ) resulting in an orange solution that was agitated using a magnetic stirrer. Samples were taken after 2 and 12 h and analysed as above. Finally, the experiments were repeated using (*R*)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, **14**, Iridium CATHy catalyst, **3** and 6 mol. eq. formic acid.

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#### Notes and references

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