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Rh^{III}- and Ir^{III}-Catalyzed Asymmetric Transfer Hydrogenation of Ketones in Water

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Abstract: Asymmetric transfer hydrogenation (ATH) of ketones by formate in neat water is shown to be viable with Rh-TsDPEN and Ir-TsDPEN catalysts, derived in situ from $[Cp^*MCl_2]_2$ (M = Rh, Ir) and TsDPEN. A variety of ketones were reduced, including non-functionalized aryl ketones, heteroaryl ketones, ketoesters, and unsaturated ketones. In comparison with Ir-TsDPEN and the related Ru^{II} catalyst, the Rh^{III} catalyst is most efficient in water, affording enantioselectivities of up to 99% *ee* at substrate/catalyst (S/C) ratios of 100–1000 even without working under an inert atmosphere. The aqueous phase reduction is shown to be highly pH-dependent; the optimum pH windows for TOF greater than 50 mol mol^{-1} h^{-1} for Rh- and Ir-TsDPEN are 5.5–10.0 and 6.5–8.5, respectively. Outside the pH window, the reduction becomes slow or stagnant depending on the pH. However, the enantioselectivities erode only under acidic conditions. At a higher S/C ratio, the aqueous ATH by Rh-TsDPEN is shown to be product- as well as by-product-inhibited; the product inhibition appears to stem at least partly from the reaction being reversible. The aqueous phase reduction is simple, efficient and environmentally benign, thus presenting a viable alternative for asymmetric reduction.

Keywords: asymmetric catalysis · hydrogenation · iridium · ketones · rhodium

Introduction

Catalysis in water is a field of increasing interest in modern chemistry, because of the substantial environmental and economical gains.[1] As a solvent for organic reactions, water bears a number of attractive physicochemical properties over traditional organic molecular solvents: it is non-flammable, non-explosive, non-toxic and non-carcinogenic. In addition, water is also one of the least expensive solvents. Not surprisingly, a great number of aqueous phase catalytic reactions have been documented. A disadvantage often associated with catalysis in water is the need for water soluble ligands/catalysts and the decrease in catalytic activity and/or stereoselectivity on going from organic solvents to water.[1] A surprising exception has recently arisen from the ATH of ketones and significantly,[2] a commercial aqueous phase ATH process has been launched.

ATH provides a powerful alternative to asymmetric hydrogenation for catalytic reduction because of its versatility and practical simplicity.[2–7] Among the various chiral catalysts reported, the most notable is the Ru-TsDPEN [TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine] complex developed by Noyori, Ikariya, Hashiguchi and co-workers.[8] The complex and related variants have since been applied to a wide range of prochiral ketones and imines.[2–4] However, with the most commonly used reductants and solvents, isopropanol and the azeotropic HCOOH/NEt_3 (molar ratio 5:2), reactions catalyzed by Ru-TsDPEN appear to be slow.[3] The work by Blacker,[3f] Blackmond,[4i] and Okano[5] shows that the reaction rates increase when the HCOOH/Et_3N ratio is lowered. We recently reported that the ATH of aromatic ketones with the Ru-(*R*,*R*)-TsDPEN catalyst[7a] or its polymer-supported analogue[7b] can be greatly accelerated by using water as solvent. Of further interest is that the ATH reaction is found to be pH-controlled, with higher pH favoring higher rates and enan-

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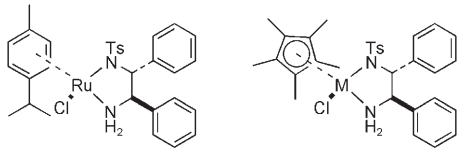
tioselectivities.[7c] We now disclose that the analogous, usually much less effective M-(*R*,*R*)-TsDPEN (M = Rh, Ir) catalysts[9] also displays remarkably enhanced activities and excellent enantioselectivities in the reduction of a wide range of ketones in neat water with no ligand modification, even in the open air with no need for inert gas protection throughout (Scheme 1).



Ru-TsDPEN M-TsDPEN
M = Rh, Ir

Scheme 1. Catalysts investigated in this study.

The Rh-TsDPEN and Ir-TsDPEN complexes,[9] mainly described by the groups of Tani,[9a] Blacker,[9c,d] Ikariya[9f] and Baker,[9b] have previously been shown to be highly effective in the reduction of α-chlorinated ketones and some imines;[9b,f] but they are less active than the isoelectronic Ru-TsDPEN in the reduction of other ketones. For instance, the reduction of acetophenone (acp) by Rh-TsDPEN in isopropanol (0.1 M) led to a 95% conversion and 84% *ee* at room temperature in 48 h with a S/C ratio of 100.[9a] The Ir-TsDPEN was less active still. In the HCOOH/NEt_3 azeotrope, these catalysts appear to be inactive. Replacing the TsDPEN ligand with some chiral 1,2-aminoalcohols yields much more active catalysts in isopropanol as shown by Blacker.[3f,9d] However, these catalysts tend to be less enantioselective than Ru-TsDPEN and, as with other catalysts using isopropanol as a reductant, their effect often depends on the use of a low concentration of substrate[2–4,9] unless the resulting products are removed in situ.[3f] Herein, we report that the M-TsDPEN catalyst (M = Rh, Ir) effects efficient ATH of ketones by formate in water, with the performance strongly depending on the solution pH.

Aqueous-phase transfer hydrogenation (TH) has been studied for more than two decades,[1e,2,10,11] with pioneering work being carried out by Joo,[12] Sasson[13] and Sinou.[14] In spite of the well-established aqueous-phase hydrogenation, TH in water had been less developed until a few years ago. Sasson and co-workers reported the aqueous-organic biphasic TH of C=C double bonds and carbonyl groups in the 1980s.[13] Up to 76% conversion was obtained for the aldehyde reduction with a [$RuCl_2(PPh_3)_3$] catalyst in 30 min; the reduction was less effective for ketones, however. The first example of TH of aldehydes catalyzed by transition metal in neat water was described by Joo and co-workers,[12] who reported the reduction of unsaturated aldehydes to the corresponding unsaturated alcohols by HCOONa with a water-soluble ruthenium–phosphine catalyst. Shortly after, Sinou et al. reported the TH and ATH of unsaturated carboxylic acids to saturated carboxylic acids by formates in water with rhodium catalysts bearing water-soluble phosphines.[14] In 1991, Bäckvall et al. reported that the TH reaction of ketones in biphasic system with a ruthenium catalyst, [$RuCl_2(PPh_3)_3$], the same catalyst used by Sasson, could be accelerated 10^3–10^4 times by adding a small amount of a base, NaOH.[15]

These aqueous TH reactions can be pH dependent as in the case of hydrogenation,[1e,16] and this has been demonstrated by Ogo, Watanabe and co-workers[17] in the achiral reduction of ketones and aldehydes by formate in water with water-soluble half-sandwich [$Ru(\eta^6\text{-}C_6Me_6)(bipy)(H_2O)]^{2+}$, [$Cp^*Ir(H_2O)_3]^{2+}$, and [$Cp^*Ir(bipy)(H_2O)]^{2+}$ complexes. A water-soluble molybdocene monohydride, [$Cp_2Mo(H)OTf$], was found to catalyze the TH of ketones and aldehydes in water, again with pH-controlled properties.[18] More recently, Süss-Fink and co-workers reported a series of water-soluble ruthenium–arene complexes containing 1,10-phenanthroline ligands;[19] these complexes can be used as catalyst for TH of ketones in aqueous solution using HCOOH as hydrogen source, with TONs up to 164 obtained.[19d] Very recently, we demonstrated that diamine ligands exert a remarkable accelerating effect on the iridium-catalyzed reduction of a wide range of aldehydes by HCOONa in neat water. The TOFs were up to $1.3\times10^5\,mol\,mol^{-1}\,h^{-1}$. The catalyst works for aromatic, α,β-unsaturated and aliphatic aldehydes and for those bearing functional groups such as halo, acetyl, alkenyl and nitro groups, and is highly chemoselective towards the formyl group.[7f]ATH in the presence of water with the Noyori–Ikariya-type Ru-TsDPEN catalysts was first reported by Williams, Blacker and co-workers;[6a,9c] the reaction was performed using a catalyst containing a modified, water-soluble TsDPEN ligand in isopropanol with water (up to 51%) being added. At about the same time, Chung et al.[6b,c] communicated the ATH of aromatic ketones by formate in neat water catalyzed by [$RuCl_2(p\text{-cymene})]_2$ and a (*S*)-proline amide ligand. Süss-Fink and co-workers[6n,19] have recently synthesized a series of water-soluble arene–ruthenium complexes containing a *trans*-1,2-diaminocyclohexane ligand, which were examined in the ATH of ketones in aqueous media with various degree of success.[19b] In parallel research, the groups of Deng and Tu developed water-soluble, amino-functionalized and supported TsDPEN ligands, which were shown to be effective for the ATH of various aromatic ketones in water in the presence of surfactants.[6d,e,h,l,o] More recently, Wills and co-workers synthesized a series of novel tethered catalysts for ATH of ketones for both organic (HCOOH/NEt_3) and aqueous-phase reduction of ketones; the Rh^{III} catalyst acts as an excellent catalyst for the reduction of a wide range of ketones, including aliphatic ones.[6j] A tetradentate PNNP ligand in combination with [$IrHCl_2(cod)]_2$ was shown to catalyze ATH of ketones in water by Gao and co-workers very recently.[6i,m] In 2004, we discovered that the unmodified Ru-TsDPEN catalyzes ATH of ketones in neat water with great rate acceleration.[7a] However, the application of M-TsDPEN (M = Rh, Ir) and related catalysts, without any ligand modification, to the aqueous-phase ATH reactions has rarely been attempted.[4s,7] Given these two catalysts

often show performance different from that of Ru^{II},[3f,j] it would be of both fundamental and practical significance to develop the aqueous-phase ATH chemistry of Rh^{III} and Ir^{III} catalysts.

Results and Discussion

Comparison of aqueous ATH by Ru-, Rh- and Ir-TsDPEN catalysts: Having demonstrated the efficacy of Ru-TsDPEN in the aqueous reductions of aromatic ketones,[7a–c,e,g] we were interested in extending the chemistry to the isoelectronic Rh^{III} and Ir^{III} catalysts. We set out by investigating the ATH of acp with HCOONa in water. For comparison, the reactions in isopropanol, the azeotropic $HCOOH/NEt_3$ mixture, and an azeotrope/water mixture were also carried out. We also compared the catalytic performance of Rh- and Ir-TsDPEN with that of Ru-TsDPEN in these solvents for the reduction of acp. In each case, the precatalyst was generated in situ by reacting (*R*,*R*)-TsDPEN with $[RuCl_2(p\text{-cymene})]_2$ or $[Cp^*MCl_2]_2$ (M = Rh, Ir) in a solvent at 40 °C for 1 h. The ATH was initiated by introducing 1 mmol of substrate. Table 1 summarizes the results obtained. Remarkably, in the aqueous HCOONa system with Rh-TsDPEN as catalyst, the ketone was almost fully converted into (*R*)-1-phenylethanol in 97 % *ee* within half an hour (entry 1, Table 1). This compares favorably with the results observed with Ru-TsDPEN, which afforded a 95 % *ee* and required 1 h to deliver the same conversion. However, the iridium catalyst was less active and enantioselective, furnishing a 99 % conversion in 93 % *ee* within 3 h under the similar conditions (entry 1, Table 1). A comparison of the kinetic profiles of these three catalysts for the ATH of acp in aqueous HCOONa has also been made. As shown in Figure 1, the initial activity of the Rh-TsDPEN catalyst was much higher than those obtained with Ru- and Ir-TsDPEN catalyst. The Ir-TsDPEN catalyst was least active and the rate with the catalyst appears to show no dependence on the substrate concentration under the conditions used. The initial TOFs were 690, 220, 64 $mol\,mol^{-1}\,h^{-1}$ for Rh-, Ru- and Ir-TsDPEN, respectively. Recently, Deng and co-workers reported that the Rh-TsDPEN catalyst is also very efficient for the ATH of α-bromomethyl aryl ketones by HCOONa in water in the presence of a phase transfer catalyst.[4s]

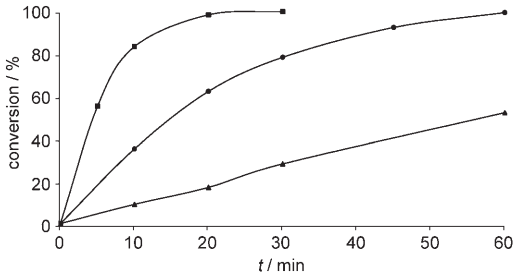


Figure 1. Comparison of the ATH of acp catalyzed by Rh-TsDPEN (■), Ru-TsDPEN (●) and Ir-TsDPEN (▲) in $HCOONa/H_2O$. Reactions were carried out at 40 °C, using 1 mmol of acp, 5 equiv HCOONa, and at a S/C ratio of 100 in 2 mL of water.

In sharp contrast to the excellent performance in aqueous HCOONa, the Rh- and Ir-TsDPEN catalysts were much less effective in the other reduction systems. Thus, in isopropanol the reaction afforded only a 45 % conversion (89 % *ee*) with Rh-TsDPEN and 48 % conversion (87 % *ee*) with Ir-TsDPEN at 40 °C in 24 h (entry 2, Table 1). In the $HCOOH/NEt_3$ azeotrope,[3j] there was little reduction with these two catalysts in 16 h, although with the ruthenium catalyst a 98 % conversion (97 % *ee*) was observed in 10 h under the same reaction conditions (entry 3, Table 1). Switching to a mixture of water and the azeotrope, somewhat improved conversion was noticed for the Rh^{III} and Ir^{III} catalysts; but neither the conversions nor the *ee* values can be compared with those obtained with HCOONa in water (entry 4, Table 1).

Table 1. Comparison of the asymmetric reduction of acp with M-TsDPEN under various conditions.[a]

Entry	Reductant/ Solvent	Ru-TsDPE			Rh-TsDPEN			Ir-TsDPEN		
		t [h]	Conv. [%][f]	*ee* [%][f]	*t* [h]	Conv. [%][f]	*ee* [%][f]	*t* [h]	Conv. [%][f]	*ee* [%][f]
1	HCOONa/ H_2O[b]	1	99	95	0.5	99	97	3	99	93
2	isopropanol[c]	24	81	89	24	45	89	24	48	87
3	azeotrope[d]	10	98	97	16	<1	–	16	no[g]	–
4	azeotrope/ H_2O[e]	16	98	97	24	18	64	24	39	83

[a] Reactions were carried out at 40 °C, using 1 mmol of acp and a S/C ratio of 100 in 2 mL of a solvent. [b] 5 equiv HCOONa. [c] 0.01 equiv KOH was added. [d] Azeotropic mixture of $HCOOH/NEt_3$ with a molar ratio of 5:2. [e] $V_{azeotrope} = V_{H_2O} = 1$ mL. [f] Determined by GC. The alcohol configuration was *R*. [g] No reaction was observed.

We and others have recently shown that the solution pH plays a critical role in affecting the rates and *ee* values in aqueous ATH with Ru-TsDPEN.[4n,s,6l,o,7c,9e,19] For the Rh- and Ir-TsDPEN, the same could be true and this would explain why the reaction is sluggish with $HCOOH/NEt_3$ in water. The initial pH values for the $HCOONa/H_2O$ and the azeotrope $(HCOOH/NEt_3)/H_2O$ systems indeed differed significantly, being 7 for the former and 3 for the latter. However, the pH of the reaction mixture is likely to change in the course of the reaction because of the decomposition of formate by the catalyst.[7c] To address these issues further and to find out the best pH window for practical ATH reac-

tions, we then investigated the effect of solution pH on the ATH of acp in water.

Effect of solution pH on the ATH by Rh- and Ir-TsDPEN in water: The Ru-TsDPEN-catalyzed ATH of acp by formate in water has been shown to vary with solution pH values; it barely took place below pH 4 and accelerated rapidly thereafter with the acceleration leveling off at pH >7, but the rate did not appear to decrease until about pH 9.[7c] To probe the effect of pH on the Rh- and Ir-TsDPEN-catalyzed ATH, we measured the initial TOFs at various initial pH values by adjusting the ratios of $HCOOH/NEt_3$ and HCOONa/NaOH. The $HCOOH/NEt_3$/water mixtures were used as both hydrogen source and solvent for reactions performed at pH < 7, while HCOONa/water was used for reactions at pH ≥7 with the pH being adjusted by varying the quantity of NaOH. The same results at pH < 7 were obtained when the pH was adjusted by using HCOONa/HCOOH instead of $HCOOH/NEt_3$.

As shown in Figure 2, the reduction of acp with Rh-TsDPEN and Ir-TsDPEN is indeed pH-dependent. In both cases, the reaction rates versus pH showed a volcano curve, with the highest rate being observed under neutral conditions, that is, at about pH 7.0–7.5. Deviating from pH 7 for Rh-TsDPEN and from pH 7.5 for Ir-TsDPEN resulted in rapid decrease in the reduction rates, and when the pH was varied by more than 2 units, the reaction slowed down by as much as two orders of magnitude. Clearly the pH window for optimum rates is narrow with both catalysts under the current conditions. This is somehow in contrast with the observation made with the Ru-TsDPEN and related catalysts,[7c,19] but is reminiscent of that observed with similar catalysts that contain a bipy ligand[17b] and with Ru-amino alcohol catalysts.[7g] Figure 2 also reveals that in order to obtain a TOF of higher than 50 mol mol^{-1} h^{-1}, the pH needs to be within 5.5–10.0 for Rh-TsDPEN and 6.5–8.5 for Ir-TsDPEN. These numbers should be of value for practical applications.

Whilst the initial reduction is sluggish at both low and high pH values, further studies show that the kinetic profiles differ considerably under these conditions for both Rh- and Ir-TsDPEN. The reduction of acp with the rhodium catalyst is illustrated in Figure 3. As can be seen, the reduction is extremely slow when starting from pH 3, affording a conversion of less than 15% in 50 h (Figure 3a). Thereafter the reduction accelerated, reaching a full conversion in the subsequent about 20 h time. Significantly, the enantioselectivity varied as well, increasing from less than 10% at the beginning of the reaction to 85% when the reaction was complete, suggesting a competitive reaction pathway involving protonation of the diamine ligand in operation (see below).[7c]

At an initial pH 5, the reduction rate with Rh-TsDPEN became faster and the long induction period at pH 3 appears to have gone (Figure 3b). For example, over 40% conversion was observed in 4 h. In contrast, this level of conversion requires more than 40 h at pH 3 (Figure 3a). Furthermore,

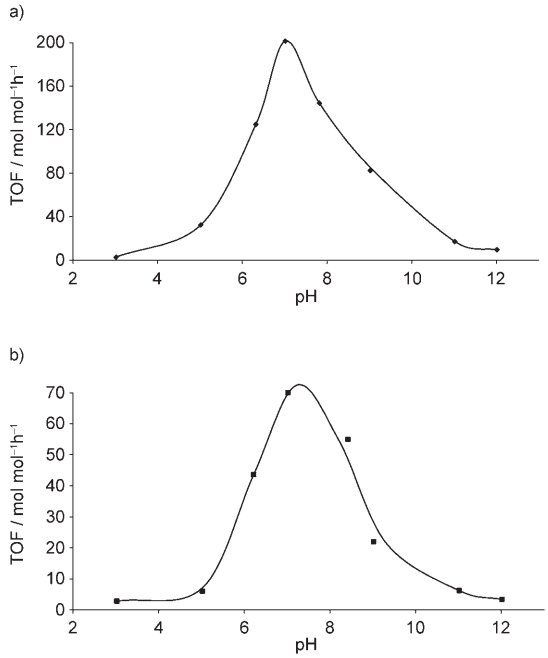


Figure 2. TOF–pH correlations for a) Rh-TsDPEN and b) Ir-TsDPEN catalyzed ATH of acp in water; the TOF was based on the conversion observed at 30 min reaction time. The reactions were carried out at 40 °C, using 1 mmol of acp and a S/C ratio of 100 in 2 mL of water.

the enantioselectivity was much higher and varied only slightly with time, at 84% *ee* in 1 h and 87% *ee* in 32 h, at which time the conversion had reached 97%.

In contrast, the reduction performed at nearly neutral conditions proceeds in much faster rate. Thus, the reduction with Rh-TsDPEN reached 95% conversion within 3 h at an initial pH 6, nearly 100% conversion within 0.5 h at a pH 7, and 95% conversion within 4.5 h at a pH 8, with the enantioselectivities at about 97% regardless of the initial pH. Figure 3c shows the conversion/*ee*%–time diagram for pH 7.

Interestingly, when the same reaction was performed at a higher initial pH 11, the Rh-TsDPEN catalyst gave a conversion of only 7% with 96% *ee* in 30 min, hence resulting in a low initial TOF that is comparable with that obtainable at about pH 4.5 (Figures 3d and 2a). However, the reaction accelerated thereafter, affording a 23% conversion within 60 min and a 95% conversion within 6 h, with enantioselectivity remaining approximately constant during the whole reaction (Figure 3d). This is in stark contrast to the reaction performed at low pH values where much prolonged reaction times are necessary for complete conversion. It is worthy noting that the onset of the acceleration coincided with a drop of the solution pH from 11 to about 9. This is true for both Rh- and Ir-TsDPEN catalysts, although in the case of the latter a longer time was required for the pH to drop by 2 units and so for the reduction to take off. One possible explanation for this is that a higher HO^- concentration results in a lower concentration of active catalyst and hence a lower reduction rate (see below). In line with this presumption, the reduction with Ir-TsDPEN was extremely low at a higher initial pH 12; but it accelerated after 22 h reaction

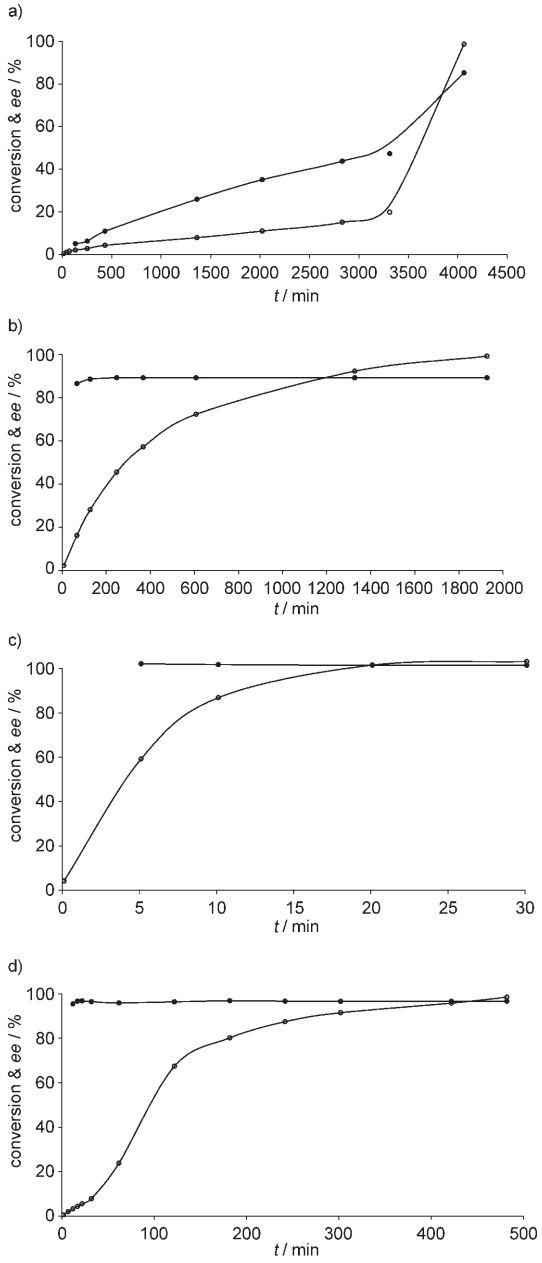


Figure 3. Conversion (○) and enantioselectivity (●) vs. time plots at different initial pH values for the ATH of acp with Rh-TsDPEN; a) pH 3; b) pH 5; c) pH 7; d) pH 11. See Figure 2 for conditions.

when the pH dropped from 12 to about 9 and completed after a prolonged time of 48 h. However, the reduction with Rh-TsDPEN at pH 12 was not complete under similar conditions and interestingly, this coincided with the solution pH remaining unchanged throughout this period of time.

The aforementioned pH drop is a result of formate decomposition. The resulting CO_2 is hydrated to form carbonic acid and then neutralized by HO^- to give HCO_3^-, or reacts with HO^- to give the same at pH >8. The hydrogencarbonate is further neutralized by HO^- at pH >10.[20] These reactions lead to decrease in the HO^- concentration and thus the pH of the solution. The formation of the carbonate in the reduction of acp by Rh-TsDPEN with sodium formate at a S/C ratio of 1000 was confirmed by adding $Ca(OH)_2$ to the aqueous phase after workup, which showed that 85% of formate had been converted into CO_3^{2-} or HCO_3^- during the ATH reaction.

Throughout the pH values of 3–12 examined, the Ir-TsDPEN catalyst behaved in a similar manner to the rhodium analogue, although it is generally less active and less enantioselective. As an example, Figure 4 shows the conversion/*ee*%–time diagram for Ir-TsDPEN at pH 7, comparing which with Figure 3c reveals the iridium catalysts to be less efficient.

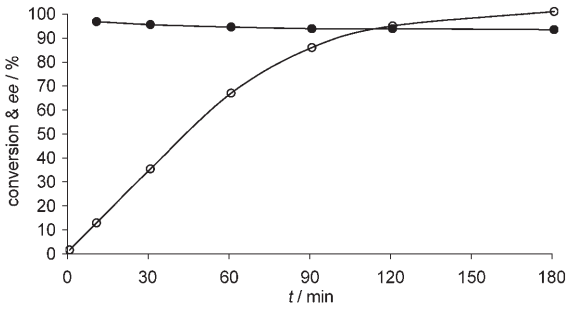
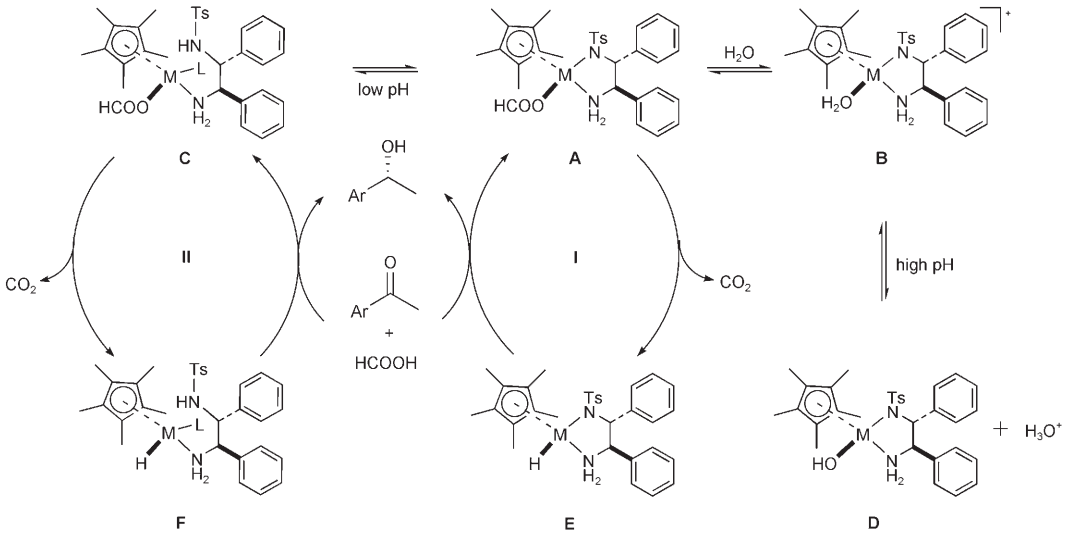


Figure 4. Conversion (○) and enantioselectivity (●) vs. time plot at the initial pH value of 7 for the ATH of acp with Ir-TsDPEN. See Figure 2 for conditions.

Proposed mechanisms: The observations made at the various pH values could be accounted for by the mechanism suggested in Scheme 2. The formato complex **A**, formed from the corresponding chloride precatalyst, is likely to be in equilibrium with the aqua complex **B**.[19,21] At around the neutral conditions, the reduction proceeds via the catalytic cycle **I**, in which the ketone is reduced by the hydride **E** via Noyori's concerted mechanism.[22,23] When the solution is made acidic, protonation of the TsDPEN ligand takes place, giving rise to the ring-opened formato species **C**. This opens up the possibility of cycle **II**, which is expected to be less efficient in terms of both TOF and enantioselectivity, as a highly organized six-membered pericyclic transition state would be more difficult to form with the hydride **F** than **E**. We have recently provided evidence that supports the possible involvement of the cycle **II** at low pH.[7c] This cycle is in competition with the cycle **I** under acidic conditions. The more acidic the solution, the more likely will the cycle **II** become; this leads to slower and less enantioselective reduction. There also exists a possibility of the hydrides **E** and **F** being protonated to form M-(H_2) or H_2 under acidic conditions, reducing the reduction rate by the hydrides.[17c,24]

When the solution becomes basic, a new scenario emerges. The aqua species **B** can be deprotonated to form a hydroxo species **D** under basic conditions. The pK_a of closely related Rh^{III} and Ir^{III} complexes are about 8 {$[RhCp^*(bipy)(H_2O)]^{2+}$, 8.2; $[IrCp^*(bipy)(H_2O)]^{2+}$, 7.5};[25] **B** may be expected to display a somewhat higher value. The equilibrium between **B** and **D** should becomes in favor of the latter when the solution pH increases, and at the pH of about 11, **D** is presumably the dominated metal species in solution.



Scheme 2. Proposed catalytic cycles for ATH in water at different pH values.

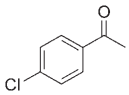
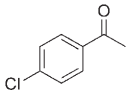
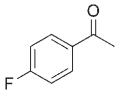
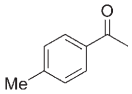
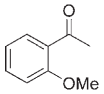
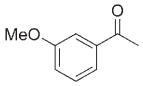
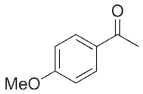
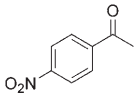
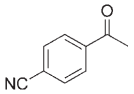
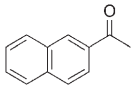
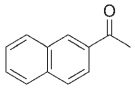
The low concentration in **A** thus explains the low initial TOFs shown in Figure 2. Unlike the reaction at the low pH 3, however, the reduction at pH 9–11 has no negative impact on the enantioselectivity. This is because species **D** is not involved in the catalytic cycle and serves only as a reservoir of the active species **A**. Further support for the pH-dependent equilibrium involving **A** and **D** comes from the observation made with the reduction at pH 11, which accelerated only after the pH dropped to about 9 as aforementioned. This drop in pH leads to an increase in the concentration of **A** and consequently the reduction rate. In addition, compound **A** contains an acidic NH_2 group (the NH_2 group is estimated to have a pK_a 14 in [$RuCl_2$(dpen)(binap)][26]),[22,23] and so its concentration could also decrease as a result of NH_2 deprotonation at high pH values.

ATH of ketones around neutral conditions: To broaden the scope of the aqueous rhodium and iridium catalysis, we then extended the ATH to a range of non-functionalized aromatic ketones. Based on the studies presented above, we chose the aqueous HCOONa as the reduction system, which is approximately pH neutral under the conditions employed. No organic cosolvent was added. As shown in Table 2, the Rh- and Ir-TsDPEN catalyst delivered high conversions for most of the ketones in a short reaction time and in most cases the enantioselectivities were good to excellent, with *ee* values reaching up to 99%. Exceptions were encountered for aryl ketones bearing strongly electron-donating groups. This is evident by comparing entries 3, 6, 11, and 12 with 7 and 10; the 4′-Me and 4′-OMe substituted acetophenones were much less active. The reaction rates appear to correlate with the LUMOs of the ketones, with lower values giving rise to faster reactions. For example, of the three MeO-substituted acetophenones, 3′-methoxyacetophenone, which has the lowest LUMO, displayed the highest rate, suggesting that the slow rates for the other two could result from a weaker bonding interaction between the M–H hydride and the carbonyl carbon at the six-membered pericyclic transition state.[22,23,27] Steric and potential chelating effects might have also contributed in the case of 2-substituted ketones (entries 5 and 8, Table 2). In line with the observation made with acp, the rhodium catalyst is generally more active and more enantioselective than the iridium analogue (entries 1–7, 9–14, 16, Table 2). Thus, the reduction of 2′-acetonaphthone with Rh-TsDPEN led to a 97% conversion and 96% *ee* within 45 min; with Ir-TsDPEN a complete conversion and a lower *ee* of 80% were obtained in 3 h (entry 13, Table 2).

It is noteworthy that, in comparison with the reactions performed in isopropanol, the HCOOH/NEt_3 azeotrope, or the azeotrope/water mixture, the reduction by HCOONa with Rh-TsDPEN and Ir-TsDPEN in water is much faster and more enantioselective. For example, the reduction of 1-tetralone with Rh-TsDPEN in isopropanol furnished a 79% conversion and 97% *ee* in 48 h at room temperature (S/C = 100),[9f] and the reduction of 2′-acetonaphthone in an isopropanol/water mixture led to a 81% conversion and 82% *ee* in 64 h with a water-soluble analogue of Rh-TsDPEN; the corresponding iridium catalyst was even less effective.[9d] Of further interest is that the Rh^{III}-catalyzed reactions require neither pre-degassing of the solvent nor protecting by inert gas throughout the entire operation (entries 2, 4, and 14, Table 2).

The protocol works particularly well for some heteroaryl ketones, as shown by the examples in Table 3. Thus, for instance, the reduction of 2-acetylfuran with Rh-TsDPEN was complete within 5 min, yielding (*R*)-1-(2-furyl) ethanol in 99% *ee*. Excellent *ee* values were obtained with the same catalyst for the other ketones except 3-acetylpyridine; these represent one of the best enantioselectivities registered for these ketones.[3g] As in the case of aryl ketones, the corresponding iridium catalyst was less efficient, and there again appears to be a correlation between the rates and the LUMOs of the acetylpyridines.[27]

Table 2. ATH of ketones by HCOONa with Rh- and Ir-TsDPEN in water.[a]

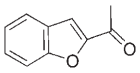
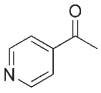
Entry	Ketone	Rh-TsDPEN			Ir-TsDPEN		
		t [h]	Conv [%][b]	*ee* [%][b]	t [h]	Conv [%][b]	*ee* [%][b]
1		0.5	99	97	3.5	99	93
2		0.5[c]	99	97	12	95	92
3		0.4	>99	94	3	>99	82
4		0.4[c]	>99	94	4	99	84
5		1	97	71	5	98	47
6		0.5	98	95	4	97	89
7		6	98	93	15	96	88
8		24	66	81	20	90	71
9		0.5	97	98	8	97	90
10		20	90	97	24	97	91
11		0.5	98	88	2	98	73
12		0.17	98	91	0.5	98	84
13		0.75	97	96	3	100	80
14		0.75[c]	98	96	10	99	80
15		9	91	97	9	98	95
16		3	96	99	9	96	97

[a] Conditions: 40 °C, 1 mmol of ketone, 3–8 equiv HCOONa, S/C = 100, in 2 mL of water. [b] Determined by GC. The alcohol configuration was *R*. [c] Reactions were performed without nitrogen protection throughout.

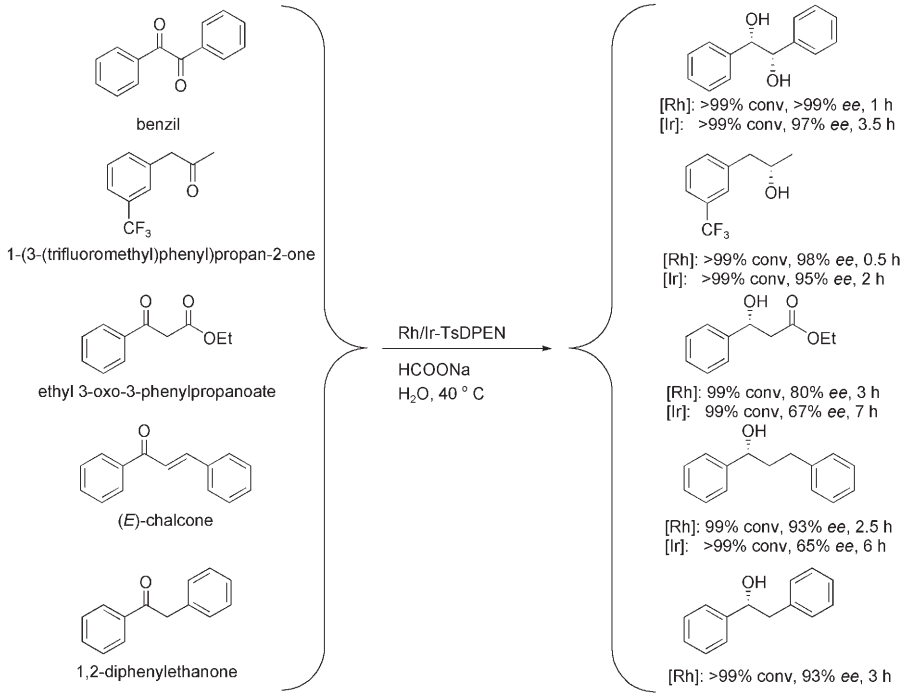
alyzed by Rh-TsDPEN, both the conversion and enantioselectivity reached more than 99% within 1 h, while for the same reaction catalyzed by Ir-TsDPEN, it took a longer time, 3.5 h, to obtain comparable results. The same phenomenon was also observed in the ATH of other ketones, such as 1-(3-(trifluoromethyl)phenyl)propan-2-one, ethyl 3-oxo-3-phenylpropante, (*E*)-chalcone, and 1,2-diphenylethanone. In all cases, good to excellent *ee* values and about 99% conversions were obtained with Rh-TsDPEN within a short reaction time. However, the Ir-TsDPEN was less effective in the case of the ATH of 1,2-diphenylethanone, only affording a conversion of 22% with 90% *ee* within 3 h. It should be emphasized that both the C=C double bond and the carbonyl group of (*E*)-chalcone were reduced with either Rh- or Ir-TsDPEN. GC monitoring showed that the C=C double bond was first reduced. In fact when the reduction with Rh-TsDPEN was terminated after 1 h reaction, the saturated ketone was isolated in 35% yield (63% total conversion). The ease of C=C bond saturation results probably from polarization of the double bond by the electron-withdrawing carbonyl group, facilitating the hydride addition at the 3-position. However, it has been rare to reduce both the carbonyl group and C=C bond under ATH conditions.[28] Additionally, it is also unusual that a β-ketoester (ethyl 3-oxo-3-phenylpropanoate) could be transfer-hydrogenated to the secondary alcohol with Rh- or Ir-TsDPEN catalyst. These results indicate that the aqueous ATH catalyzed by M-TsDPEN using sodium formate can be applied to a broad spectrum of substrates.

The aqueous phase catalysis with M-TsDPEN was also applied to other synthetically valuable ketones. Some of the reactions are shown in Scheme 3. For the ATH of benzil cat-

Table 3. ATH of heteroaryl ketones by HCOONa with M-TsDPEN (M = Rh, Ir) in H_2O.[a]

Ketone	Rh-TsDPEN			Ir-TsDPEN		
	t [h]	Conv. [%][b]	*ee* [%][b]	t [h]	Conv. [%][b]	*ee* [%][b]
	0.08	>99	99	1.5	>99	96
	0.25	>99	95	1.5	99	90
	1.5	92	99	16	98	93
	0.5	99	98	1.5	>99	60
	24	98	98	20	100	87
	16	99	78	16	99	56

[a] See Table 2 for conditions. [b] By GC. *R* alcohols obtained.



Scheme 3. ATH of ketones of more diversity in water.

ATH at higher S/C ratios: In the ATH of ketones with Rh-TsDPEN in HCOONa/H_2O, a higher S/C ratio is also feasible. Table 4 shows the results obtained for some ketones which were reduced with Rh-TsDPEN at a higher S/C ratio of 1000. The reduction finishes in general in a few hours with no decrease in *ee* values in comparison with the reaction at a S/C of 100. An example of particular note is the reduction of 2-acetylfuran, which completed in 1 h with 99% *ee* in the open air with no degassing or nitrogen protection during the entire reaction (entry 11, Table 4).

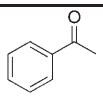
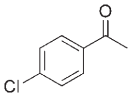
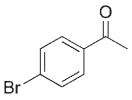
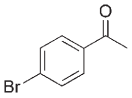
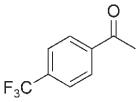
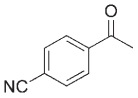
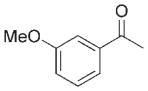
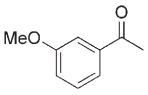
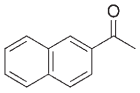
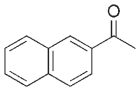
The reduction of 4′-bromoacetophenone, 3′-methoxylacetophenone and 2′-acetonaphthone is, however, sluggish (entries 3, 7 and 9, Table 4). For these substrates, the reaction is fast at the beginning but decelerates significantly with time. Of further note is that the enantioselectivities of the products decrease with time as well. For instance, the conversion of 3′-methoxyacetophenone increased from 17% at 3 h to 22% at 22 h reaction time accompanied with a change in *ee* from 90% to 86%. Figure 5 illustrates the variation of conversion/*ee* with time for the reduction of 2′-acetonaphthone. However, these substrates can be readily reduced with excellent *ee* values by a simple switch of ligand, that is using Rh-TsCYDN [TsCYDN = *N*-(*p*-toluenesulfonyl)-1,2-diaminocyclohexane] instead of Rh-TsDPEN (entries 4, 8 and 10, Table 4).[7d]

Factors affecting reaction rates

Effect of substrate concentration: The sluggish reaction rate at a high S/C ratio could be due to high substrate concentrations. The ATH reaction was therefore examined at the concentrations of acp ranging from 0.25 to 5.0 M.[29] At initial [acp] < 1 M, the initial reaction rate increased with the initial concentration of acp (Figure 6). However, at initial [acp] > 1 M, the initial reaction rate indeed decreased proportionally with increasing initial acp concentration.

This seems to suggest a substrate inhibition effect. However, it does not explain the results above (Figure 5), as the initial rates were high and the concentration of ketone was low (0.5 M). The substrate inhibition shown in Figure 6 probably results from phase separation. With more acp added, diffusion may become a problem and reduction at the oil/water interface will be less likely. The latter could give rise to high rates according to a recent study by Marcus.[30] A substrate inhibition effect has been reported recently by

Table 4. ATH of ketones by HCOONa with Rh-TsDPEN at a S/C ratio of 1000 in water.[a]

Entry	Ketone	t [h]	Conv. [%][b]	ee [%][b]
1[c]		3	87	97
2		3	98	94
3[d]		4	64	95
4		2[g]	>99	92
5		1.5	99	94
6		4.5	98	92
7[e]		3	17	90
8		2[g]	98	93
9[f]		1	26	97
10		3[g]	99	97
11		1	99	99

[a] Conditions: 40 °C, 5 mmol of ketone, 5–8 equiv HCOONa, S/C = 1000, in 10 mL of water. [b] Determined by GC; the alcohol configuration was *R*. [c] The conversion was 70% with 97% *ee* in 30 min. [d] The conversion was 66% with 95% *ee* in 22 h. [e] The conversion was 22% with 86% *ee* in 22 h. [f] The conversion was 39% with 95% *ee* in 18 h. [g] The reactions were carried out with Rh-TsCYDN under the same conditions.[7d]

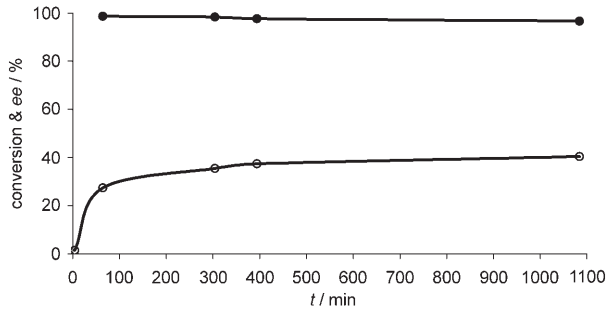


Figure 5. Conversion (○) and enantioselectivity (●) vs. time plot for the ATH of 2′-acetonaphthone with Rh-TsDPEN. See Table 4 for conditions.

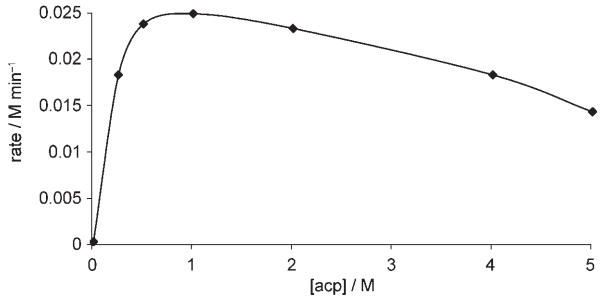


Figure 6. Initial reaction rate vs. initial substrate concentration plot for ATH of acp with Rh-TsDPEN in water. Conditions: Rh-TsDPEN (0.01 mmol, prepared in situ), acp (0.5–10 mmol), HCOONa (5 mmol) in H_2O (2 mL) at 40 °C.

Noyori for the asymmetric hydrogenation of acp catalyzed with [Ru(OTf)(*p*-cymene)(TsDPEN)] (OTf = $CF_3SO_3^-$) under slightly acidic conditions.[31] This substrate inhibition effect could partly result from a C–H activation reaction between ketone and reactive catalytic intermediate as proposed by Ikariya.[32]

Effect of product inhibition: Another possible explanation for the stagnant reduction with Rh-TsDPEN at high S/C ratio is product inhibition. To shed light on this proposition, we first carried out the ATH of 2′-acetonaphthone with Rh-TsDPEN in aqueous HCOONa, under exactly the same conditions as those employed in Table 4, except that 2.4 mmol of the product, (*R*)-1-(naphthalene-2-yl)ethanol (97% *ee*), was introduced together with the ketone at the beginning. Surprisingly, GC analysis showed that there was no increase in the alcohol content in the mixture after a long reaction time of 48 h, showing that 2′-acetonaphthone is not reduced at all under such conditions, and this is likely to be a result of product inhibition.

The ATH of an easy-to-reduce acetophenone in the presence of the same alcohol was also examined. As shown in Table 5, when 4′-trifluoromethylacetophenone was mixed with 1-(naphthalene-2-yl)ethanol in a molar ration of 2:1 (with a total S/C ratio of 1500), the reduction of the ketone **M** practically stopped at a conversion of about 86%. In the absence of the alcohol additive **N**, the reduction reached 99% conversion in 1.5 h. Interestingly, about 10% of **N** was converted into the corresponding ketone in 6 h. These results show that the aqueous phase ATH with Rh-TsDPEN can be inhibited by the product, and the reduction is reversible.

To gain further evidence to the suggestion that the reaction is reversible, deuterated (*R*)-1-(naphthalene-2-yl)ethanol was introduced into the reduction of acp under otherwise the same conditions as those for Table 5. The reaction led to a 60% conversion of acp with 96% *ee* in 15 h, and at the same time, 9% of the deuterated (*R*)-1-(naphthalene-2-yl)ethanol was de-deuterated to give 2′-acetonaphthone [Eq. (1)]. Analysis of the MS spectrum shows that (*R*)-1-phenylethanol contains about 2% deuterium, which accounts for about 67% of the deuterium released from the

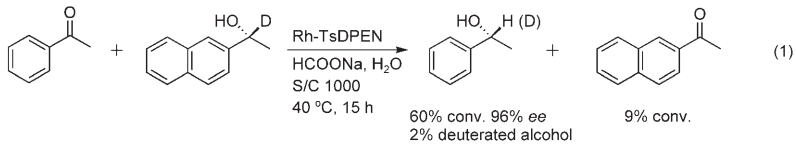
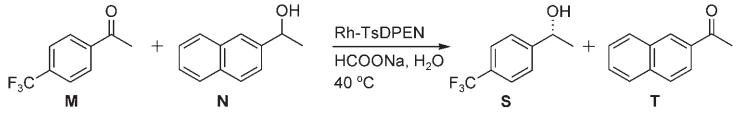


Table 5. ATH of 4-CF_3-acetophenone with Rh-TsDPEN by HCOONa in water in the presence of an alcohol additive.[a]



Entry	t [min]	**M** to **S** Conv [%][b]		*ee* [%][b]		**N** to **T** Conv [%][b,c]
		Without **N**	With **N**	Without **N**	With **N**	
1	5	10	9	96	95	no[d]
2	10	20	11	96	95	0.2
3	20	42	23	95	94	1.2
4	30	62	43	95	93	3.5
5	45	90	63	94	94	3.3
6	90	99	85	94	93	3.4
7	240	–	86	–	93	9

[a] Conditions: 40 °C, 10.0 mmol of 4′-CF_3-acetophenone, 5.0 mmol of 1-(naphthalene-2-yl)ethanol when **N** present, 5 equiv HCOONa, S/C = 1000, in 10 mL of water. [b] Determined by GC; The alcohol configuration was *R*. [c] Relative to (*R*)-1-(naphthalene-2-yl)ethanol. [d] Not detected.

de-deuteration, showing that the ATH reaction is indeed reversible. The reverse reaction is likely to be brought about by a 16-electron rhodium species (possibly the amide species derived from **E**, Scheme 2), which results in the formation of 2′-acetonaphthone and a deuteride analogue of **E**. The latter reduces acp affording the deuterated alcohol.

Effect of byproduct: Apart from the alcohol product, the ATH reaction produces hydrogencarbonate and carbonate. They could compete with formate for coordination to Rh^{III}. In order to test this, we performed the ATH of acp in the presence of sodium carbonate. Figure 7 compares the kinetic profile of the reduction with that in the absence of the salt. Clearly, the carbonate byproduct exerts a significant inhibition effect on the ATH rate.

The inhibition of carbonate is also seen in the ATH of 4′-trifluoromethylacetophenone. As shown in Figure 8, the reaction afforded a 95% conversion with 95% *ee* in 1 h and finished in 1.5 h without Na_2CO_3 being added; however, the same reaction gave only a 61% conversion in 1.5 h and 78% conversion in 4 h in the presence of the carbonate salt. Similar observations were also made when using $NaHCO_3$ as additive, showing that the byproducts of ATH in water also contribute to the slowing down of rates at higher S/C ratios.

Taken together, these results establish that there exists product and byproduct inhibition in the aqueous ATH by Rh-TsDPEN catalysis and this inhibition becomes particularly significant at higher S/C ratios for ketones that appears to display lower reduction potentials.[33] As indicated, the inhibiting effect of the carbonate and hydrogencarbonate byproduct could probably be traced to their competition with formate for coordination to Rh^{III}. The alcohols derived from these ketones should be easier to oxidize, and indeed the reactions involving these ketones and alcohols are reversible. Thus, the observed product inhibition can be at least partly ascribed to the reverse reaction of alcohol with the active rhodium species. The reversibility of ketone reduction in isopropanol is well known[3,34] and product inhibition by potentially chelating alcohols has been suggested to explain some sluggish ATH reactions.[35] Considering the transition state for ketone reduction may involve the Rh–H-based HOMO interacting with the LUMO of the carbonyl group,[22] a more electron-rich rhodium center could be expected to facilitate the hydride transfer from Rh^{III} to a carbonyl carbon that is attached to an electron-rich aryl group and by the same argument, to inhibit the process of hydride transfer from the corresponding alcohol to Rh^{III}. This may offer an explanation for the re-

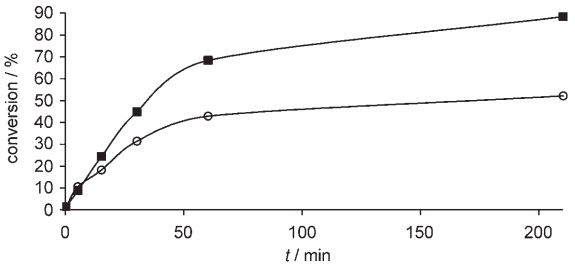


Figure 7. Comparison of ATH of acp with Rh-TsDPEN in water [no Na_2CO_3 added (■), Na_2CO_3 added after 5 min reaction (○)]. The reactions were carried out at 40 °C in 8 mL H_2O, S/C = 1000, 5 mmol ketone, 25 mmol HCOONa, and 15 mmol Na_2CO_3 when added.

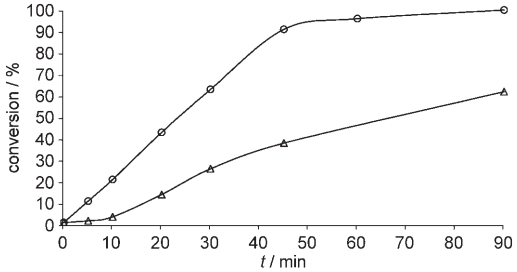


Figure 8. Comparison of ATH of 4-CF_3-acp with Rh-TsDPEN in water [without initial addition of Na_2CO_3 (○), with initial addition of Na_2CO_3 (3 equiv, △)]. For reaction conditions, see Figure 7.

markable activity observed with Rh-TsCYDN (Table 4); TsCYDN is expected to be more electron-rich than TsDPEN.[7d]

Conclusion

The results presented in this paper show that the M-TsDPEN (M = Rh, Ir) complexes are excellent catalysts for the aqueous ATH of a wide range of ketones including non-functionalized aromatic ketones, heteroaryl ketones, ketone esters and unsaturated ketones, affording enantioselectivities of up to 99% *ee*. In most cases, the Rh-TsDPEN catalyst is more effective than Ir-TsDPEN; the initial TOFs in the ATH of acp at a S/C ratio of 100 were 690, 220 and 64 mol mol^{-1} h^{-1} for Rh-, Ru- and Ir-TsDPEN, respectively. The rhodium catalysis is viable in air at a high S/C ratio as well, circumventing the need for nitrogen protection. Thus, 2-acetylfuran was reduced in 99% *ee* at S/C = 1000 in 1 h in the open air during the entire operation. However, product and byproduct inhibition is observed for some substrates that are difficult to reduce, and this is likely to result from the competitive reverse reaction of alcohols and the coordination to rhodium by carbonates.

As with the aqueous ATH by Ru-TsDPEN,[7c] both the Rh- and Ir-TsDPEN catalyzed ATH by formate in water are pH-dependent, with the optimum pH windows for TOF greater than 50 mol mol^{-1} h^{-1} being 5.5–10.0 and 6.5–8.5 for Rh-TsDPEN and Ir-TsDPEN, respectively. When the ATH was performed at either a lower (<4) or a higher (>11) initial pH, the initial rates were slow. However, low enantioselectivities, which varied with solution pH, were observed only at low pH values, suggesting that the reduction mechanism varies with pH.

ATH reactions have gone through a period of significant development in the past few years.[2–9] The aqueous phase ATH developed by us and other groups offers another easy entry to practical production of chiral secondary alcohols.[2,6,7] It requires no modification of the ligands/catalysts, no organic cosolvent, no surfactants to increase substrate solubility, and often no inert gas protection. Importantly, it can give fast reaction rates alongside excellent enantioselectivities and thus has substantial environmental as well as economical gains to offer.

Experimental Section

General: $[Cp^*RhCl_2]_2$, $[Cp^*IrCl_2]_2$, and ketones were obtained from Aldrich, Fluka or Lancaster and were used as received. The products of the ATH were analyzed by a Varian CP-3380 GC equipped with a Chrompack Chirasil-Dex CB column (25 m × 0.25 mm, 80 psi helium carrier gas, 60 psi hydrogen gas and 250 °C injector temperature) or by a GILSON UV/VIS-151 HPLC equipped with a Chiral OD, OD-H or OB-H column (2-propanol/hexane, ambient temperature, 254 nm detection). When necessary, the products were isolated by flash chromatography (silica gel, hexane/ethyl acetate 8:1).

The precatalyst was prepared from $[Cp^*RhCl_2]_2$ or $[Cp^*IrCl_2]_2$ and 1.2 equiv (*R,R*)-TsDPEN in water. After stirring at 40 °C for 1 h, the suspension was directly used for the following reduction reactions. The pH was measured by a Microprocessor pH Meter with H1 1311 probe (HANNA Instruments).

Typical procedure for acp reduction: After preparing the precatalyst, HCOONa (340 mg, 5.0 mmol) and acp (120 mg, 1.0 mmol, S/C = 100) were added to the solution. Following quickly degassing three times, the solution was allowed to react at 40 °C for a certain period of time. After cooling to room temperature, the organic phase was extracted with Et_2O (3 × 2 mL) and passed through a short silica gel column before being subjected to GC analysis. For isolation, the mixture was then dried over Na_2SO_4, concentrated, and purified by silica gel column to give the product (*R*)-1-phenylethanol.[7b,36]

The reduction with the rhodium catalyst can be performed in the air during the entire operation including catalyst preparation (using distilled water without degassing); little change in conversions and *ee* values was observed.

The ATH of acp with Rh-TsDPEN can also be performed at a S/C of 1000 in air: The procedure was the same as before except that acp (0.6 g, 5 mmol), HCOONa (1.7 g, 25 mmol), and H_2O (10 mL) were used. The reduction led to 87% conversion and 97% *ee* at 40 °C in 3 h.

The ATH of other ketones with M-TsDPEN was carried out using the same standard procedure as for acp and the products were routinely analyzed by comparing their GC/HPLC and NMR (^1H and ^{13}C) data with the literature, and by polarimetry, MS and elemental analysis when necessary. The stereochemistry of products was assigned by comparing the GC/HPLC retention time or the $[\alpha]_D$ values with the literature data.

Analytic data of sample products: While all the products under question have previously been reported in the literature,[7b,36–45] the analytic details of some sample products and related procedures are given below.

(*R*)-1-Phenylethanol:[7b,36] $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol) or $[Cp^*IrCl_2]_2$ (4.0 mg, 0.005 mmol), (*R,R*)-TsDPEN (4.4 mg, 0.012 mmol) and acp (120 mg, 1.0 mmol). Results: 40 °C, 30 min, 99% conversion and 97% *ee* with Rh-TsDPEN, and 40 °C, 3.5 h, 99% conversion and 93% *ee* with Ir-TsDPEN. GC (120 °C column temperature): 6.27 min (*R*); 6.90 min (*S*). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.49 (d, *J* = 6.5 Hz, 3H), 1.83 (br s, 1H), 4.88 (q, *J* = 6.5 Hz, 1H), 7.24–7.28 (m, 2H), 7.32–7.38 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 25.5, 70.8, 125.8, 127.8, 128.9, 146.2 ppm; MS CI: *m/z* (%): 140 (29) $[M+NH_4^+]$, 122 (100) $[M^+]$; elemental analysis calcd (%) for $C_8H_{10}O$ (122.16): C 78.65, H 8.25; found: C 78.47, H 8.35.

(*R*)-1-(Benzofuran-2-yl)ethanol:[37a,38,39] $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol) or $[Cp^*IrCl_2]_2$ (4.0 mg, 0.005 mmol), (*R,R*)-TsDPEN (4.4 mg, 0.012 mmol) and 1-(benzofuran-2-yl)ethanone (160 mg, 1.0 mmol). Results: 40 °C, 15 min, >99% conversion in 95% *ee* with Rh-TsDPEN and 40 °C, 1.5 h, 99% conversion in 90% *ee* with Ir-TsDPEN. HPLC (2-propanol/hexane 5:95, 0.5 mL min^{-1} flow rate): 16.80 min (*R*); 31.43 min (*S*). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.63 (d, *J* = 6.5 Hz, 3H), 2.17 (br s, 1H), 5.02 (m, 1H), 6.61 (s, 1H), 7.20 (ddd, *J* = 7.5, 7.3, 1.1 Hz, 1H), 7.26 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 7.45 (m, 1H), 7.53 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 21.8, 64.6, 102.2, 111.6, 121.4, 123.2, 124.6, 128.5, 155.2, 160.6 ppm; MS CI: *m/z* (%): 162 (8) $[M^+]$, 145 (100); elemental analysis calcd (%) for $C_{10}H_{10}O_2$ (162.19): C 74.06, H 6.21; found: C 73.80, H 6.16.

(*R*)-1-(4′-Nitrophenyl)ethanol:[37,40] $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol) or $[Cp^*IrCl_2]_2$ (4.0 mg, 0.005 mmol), (*R,R*)-TsDPEN (4.4 mg, 0.012 mmol) and 4′-nitroacetophenone (165 mg, 1.0 mmol). Results: 40 °C, 30 min, 98% conversion in 88% *ee* with Rh-TsDPEN and 40 °C, 2 h, 98% conversion in 73% *ee* with Ir-TsDPEN. GC (175 °C column temperature): 8.56 min (*R*); 9.36 min (*S*). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.52 (d, *J* = 6.5 Hz, 3H), 2.10 (br s, 1H), 5.03 (q, *J* = 6.5 Hz, 1H), 7.55 (m, 2H), 8.21 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 25.9, 69.9, 124.2, 126.5, 147.6, 153.4 ppm; elemental analysis calcd (%) for $C_8H_9NO_3$ (167.16): C 57.48, H 5.43, N 8.38, found: C 57.30, H 5.50, N 8.44.

(*R*)-1-(2′-Naphthtyl)ethanol:[7b,36] $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol) or $[Cp^*IrCl_2]_2$ (4.0 mg, 0.005 mmol), (*R,R*)-TsDPEN (4.4 mg, 0.012 mmol)

and 2-acetonaphthone (170 mg, 1.0 mmol). Results: 40 °C, 45 min, 97% conversion in 96% *ee* with Rh-TsDPEN and 40 °C, 3 h, 100% conversion in 80% *ee* with Ir-TsDPEN. GC (165 °C column temperature): 10.20 min (*R*); 10.58 min (*S*). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.59$ (d, $J = 6.5$ Hz, 3H), 1.98 (brs, 1H), 5.07 (q, $J = 6.5$ Hz, 1 H), 7.25–7.52 ppm (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): $\delta = 25.6$, 71.0, 124.2, 126.2, 126.6, 128.1, 128.4, 128.7, 133.3, 133.7, 143.6 ppm; MS CI: *m/z* (%): 172 (35) [M^+], 155 (100); elemental analysis calcd (%) for $C_{12}H_{12}O$ (172.22): C 83.69, H 7.02; found: C 83.63, H 7.06.

(2*S*)-1-(3′-Trifluoromethylphenyl)propan-2-ol:[41] $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol) or $[Cp^*IrCl_2]_2$ (4.0 mg, 0.005 mmol), (*R,R*)-TsDPEN (4.4 mg, 0.012 mmol) and 3′-(trifluoromethyl)phenylacetone (202 mg, 1.0 mmol). Results: 40 °C, 30 min, >99% conversion and 98% *ee* with Rh-TsDPEN and 40 °C, 2 h, >99% conversion and 95% *ee* with Ir-TsDPEN. $[\alpha]_D^{25}$ +24.5° ($c = 1.1$ in ethanol) with Rh-TsDPEN, and $[\alpha]_D^{25}$ = +23.6° ($c = 1.4$ in ethanol) with Ir-TsDPEN {lit. $[\alpha]_D$ = +24.9° ($c = 1.0$ in ethanol)[41]}; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.26$ (d, $J = 6.0$ Hz, 3H), 1.53 (brs, 1H), 2.77 (dd, $J = 14.0$, 8.0 Hz, 1H), 2.84 (dd, $J = 14.0$, 4.8 Hz, 1H), 4.05 (m, 1H), 7.39–7.51 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): $\delta = 23.4$, 45.8, 69.1, 124.6 (q, $^1J_{C,F} = 270.0$ Hz), 123.7 (q, $^3J_{C,F} = 4.0$ Hz), 126.5 (q, $^3J_{C,F} = 4.0$ Hz), 129.3, 131.2 (q, $^2J_{C,F} = 32.0$ Hz), 133.2, 140.0 ppm; MS CI: *m/z* (%): 222 (100) [M+NH_4^+]; elemental analysis calcd (%) for $C_{10}H_{11}F_3O$ (204.19): C 58.82, H 5.43; found: C 59.22, H 5.54.

(*S,S*)-1,2-Diphenylethanediol:[42] $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol) or $[Cp^*IrCl_2]_2$ (4.0 mg, 0.005 mmol), (*R,R*)-TsDPEN (4.4 mg, 0.012 mmol) and benzil (210 mg, 1.0 mmol). Results: 40 °C, 1 h, >99% conversion in >99% *ee* with Rh-TsDPEN and 40 °C, 3.5 h, >99% conversion in 97% *ee* with Ir-TsDPEN. $[\alpha]_D^{25}$ = −94.9° ($c = 1.08$ in ethanol) with Rh-TsDPEN and $[\alpha]_D^{25}$ = −92.8° ($c = 1.26$ in ethanol) with Ir-TsDPEN {lit. $[\alpha]_D$ −95.2° ($c = 1.28$ in ethanol)[42]}; m.p. 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 2.90$ (brs, 2H), 4.71 (s, 2H), 7.10–7.14 (m, 4H), 7.21–7.32 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 79.5, 127.3, 128.3, 128.5, 140.2 ppm; MS CI *m/z* (%): 232 (100) [M+NH_4^+], 214 (36) [M^+], 197 (16); elemental analysis calcd (%) for $C_{14}H_{14}O_2$ (214.26): C 78.48, H 6.59; found: C 78.27, H 6.61.

(*R*)-1,2-Diphenylethan-1-ol:[37,43] $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol) or $[Cp^*IrCl_2]_2$ (4.0 mg, 0.005 mmol), (*R,R*)-TsDPEN (4.4 mg, 0.012 mmol) and deoxybenzoin (196 mg, 1.0 mmol). Results: 40 °C, 3 h, >99% conversion in 93% *ee* with Rh-TsDPEN and 40 °C, 72 h, 56% conversion in 96% *ee* with Ir-TsDPEN. HPLC (2-propanol/hexane 5:95; 1.0 mL min^{-1} flow rate): 12.23 min (*R*); 15.13 min (*S*). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.96$ (brs, 1H), 2.99 (dd, $J = 14.0$, 8.0 Hz, 1H), 3.05 (dd, J = 14.0, 5.2 Hz, 1H), 4.90 (dd, $J = 8.0$, 4.8 Hz, 1H), 7.19–7.38 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): $\delta = 47.0$, 76.2, 126.8, 127.5, 128.5, 129.3, 129.4, 130.4, 138.9, 144.7 ppm; MS CI: *m/z* (%): 198 (100) [M^+], 181 (32); elemental analysis calcd (%) for $C_{14}H_{14}O$ (198.26): C 84.81, H 7.12; found: C 84.70, H 7.18.

(*R*)-Ethyl 3-hydroxy-3-phenylpropanoate:[44] $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol) or $[Cp^*IrCl_2]_2$ (4.0 mg, 0.005 mmol), (*R,R*)-TsDPEN (4.4 mg, 0.012 mmol) and ethyl 3-oxo-3-phenylpropanoate (192 mg, 1.0 mmol). Results: 40 °C, 3 h, 99% conversion in 80% *ee* with Rh-TsDPEN and 40 °C, 7 h, 99% conversion in 67% *ee* with Ir-TsDPEN. HPLC (2-propanol/hexane 10:90; 0.5 mL min^{-1} flow rate): 19.82 min (*R*); 22.60 min (*S*). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.27$ (t, $J = 7.1$ Hz, 3H), 2.71 (dd, $J = 16.4$, 4.1 Hz, 1H), 2.77 (dd, $J = 16.4$, 8.9 Hz, 1H), 3.33 (brs, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 5.14 (dd, $J = 8.8$, 4.0 Hz, 1H), 7.26–7.39 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): $\delta = 14.5$, 43.7, 61.3, 70.7, 126.1, 127.8, 128.2, 129.0, 142.8, 172.9 ppm; MS CI: *m/z* (%): 194 (100) [M^+], 177 (47); elemental analysis calcd (%) for $C_{11}H_{14}O_3$ (194.22): C 68.02, H 7.27; found: C 67.66, H 7.33.

(*R*)-1,3-Diphenylpropan-1-ol:[37a,45] $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol) or $[Cp^*IrCl_2]_2$ (4.0 mg, 0.005 mmol), (*R,R*)-TsDPEN (4.4 mg, 0.012 mmol) and (*E*)-chalcone (208 mg, 1.0 mmol). Results: 40 °C, 2.5 h, 99% conversion in 93% *ee* with Rh-TsDPEN and 40 °C, 6 h, >99% conversion in 65% *ee* with Ir-TsDPEN. HPLC (2-propanol/hexane 5:95; 1.0 mL min^{-1} flow rate): 16.60 min (*S*); 22.89 min (*R*). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.86$ (brs, 1H), 1.99–2.08 (m, 1H), 2.09–2.19 (m, 1H), 2.63–2.79 (m, 2H), 4.69 (dd, $J = 7.9$, 5.4 Hz, 1H), 7.19–7.21 (m, 2H), 7.26–7.32 (m, 3H), 7.35–7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 32.9, 41.3, 74.8, 126.7, 128.5, 129.3, 129.4, 142.7, 145.4 ppm; MS CI: *m/z* (%): 212 (100) [M^+], 194 (13); elemental analysis calcd (%) for $C_{15}H_{16}O$ (212.19): C 84.87, H 7.60; found: C 84.66, H 7.58.

1,3-Diphenylpropan-1-one:[28] $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol) or $[Cp^*IrCl_2]_2$ (4.0 mg, 0.005 mmol), (*R,R*)-TsDPEN (4.4 mg, 0.012 mmol) and (*E*)-chalcone (208 mg, 1.0 mmol). Results: 40 °C, 1 h, 35% yield with Rh-TsDPEN. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 3.07$ (t, $J = 8.0$ Hz, 2H), 3.30 (t, $J = 8.0$ Hz, 2H), 7.18–7.32 (m, 5H), 7.43–7.47 (m, 2H), 7.53–7.94 (m, 1H), 7.95 ppm (d, $J = 2.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): $\delta = 30.6$, 40.8, 126.5, 128.4, 128.8, 128.9, 129.0, 133.4, 137.3, 141.7, 199.6 ppm; MS CI: *m/z* (%): 228 (100) [M+NH_4^+], 211 (42) [M^++H]; elemental analysis calcd (%) for $C_{15}H_{14}O$ (210.27): C 85.68, H 6.71; found: C 85.48, H 6.74.

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