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Accelerated asymmetric transfer hydrogenation of aromatic ketones in water

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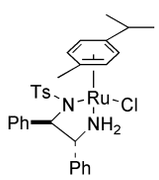
Asymmetric transfer hydrogenation of various simple aromatic ketones by the Ru-TsDPEN catalyst was shown to be feasible in aqueous HCOONa without calling for any catalyst modification, furnishing ee's of up to 95% and significantly faster rates than in the HCOOH–NEt_3 azeotrope.

Asymmetric transfer hydrogenation provides an attractive alternative to asymmetric hydrogenation, due to its operational simplicity and the easy availability of hydrogen sources of desired properties.[1] In 1995, Noyori, Ikariya, Hashiguchi and coworkers published a seminal paper, reporting the TsDPEN-coordinated (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) Ru(II) complex (Ru-TsDPEN) to be an excellent precatalyst for the asymmetric reduction of aromatic ketones.[2] The complex and related variants have since been applied to a wide range of prochiral ketones and imines.[3,4] 2-Propanol frequently serves as the hydrogen donor; but its involvement in a ketone : alcohol equilibrium deteriorates the enantioselectivity and prevents a complete conversion. In this regard, the HCOOH–NEt_3 azeotropic mixture provides a good replacement, as its reaction with a ketone would be irreversible. Indeed the azeotrope has allowed for complete reduction of substrates with high concentrations, furnishing high ee's under kinetic control.[3g] However, in terms of turnover frequency and number, there is still room for improvement. In a programme aimed at developing supported chiral diamines,[5] we observed that the asymmetric transfer hydrogenation of aromatic ketones with the Noyori catalyst could be accelerated by using water as solvent. Our preliminary results are herein described.



Ru-TsDPEN

In the context of using alternative solvents for green synthesis, water is certainly the most outstanding.[6] In line with this, a great number of aqueous phase catalytic reactions have been developed, although reduced catalytic activity and stereoselectivity have been recorded in most instances.[6,7] In the particular case of asymmetric transfer hydrogenation of ketones, only a few studies have been documented, however.[8] We recently reported that the polyethylene glycol-supported TsDPEN is highly effective in the Ru(II)-catalysed asymmetric reduction of unfunctionalised aromatic ketones by the HCOOH–NEt_3 azeotrope; but catalyst recycle appears to be possible only when water is present as cosolvent.[5a] In its absence, much reduced conversions and ee's were observed, indicating easy catalyst decomposition. This finding prompted us to examine the behaviour of the unmodified ruthenium catalyst in ketone reduction by HCOONa in water.

We initially used acetophenone as a model substrate for testing the feasibility of the reaction. The precatalyst was generated by reacting TsDPEN with $[RuCl_2(p\text{-cymene})]_2$ in water at 40 °C for 1 h.[9] Much to our surprise, following the addition of 5 equiv. HCOONa and acetophenone with a substrate/catalyst (S/C) ratio of 100, the ketone was fully converted into (*R*)-1-phenylethanol in 94% ee in 1 h reaction time. A comparison was thus made with the reaction run in the HCOOH–NEt_3 azeotrope.[10] The result was again unexpected; the 1 h conversion of acetophenone was less than 2%, with full conversion requiring more than 10 h. A few more, structurally-diverse ketone substrates were subsequently examined. As can be seen from Table 1, the reduction in water was considerably faster, delivering excellent ee's in all the cases. However, the enantioselectivities observed with the azeotrope were slightly higher.

Aiming to determine the potential applicability of the protocol in asymmetric synthesis, we then extended the reaction to a wider range of simple aromatic ketones. The reduction was carried out in water with no use of cosolvent. As is shown in Table 2, the Ru(II)-TsDPEN catalysed reduction by formate delivered high conversions for all the ketones investigated within a few hours. In most cases, the enantioselectivities were good to excellent. Thus, the *para*-substituted acetophenones all gave complete or nearly complete conversions with ee's of up to 95% in 2 h. There appeared to be no correlation between the electronic properties of the substitutes with the enantioselectivity, *e.g.* entries 3 *vs* 5. Of particular note is the reduction of *p*-methoxyacetophenone, achieving a >99% conversion and 95% ee. This is a problematic substrate in asymmetric transfer hydrogenation. With the HCOOH–NEt_3 mixture as both reductant and solvent, the Ru–TsDPEN catalyst under Noyori's conditions required about 60 h to complete the reduction (97% ee) at S/C = 200 and 28 °C.[3g] 2-Propanol as hydrogen source is less effective even in the presence of water: a water-soluble analogue of TsDPEN in combination with ruthenium delivered a conversion of 31% (91% ee) in 42 h at S/C = 100 and 22 °C in a 2-propanol–water mixture.[8f]

For the rest of the ketones, the reduction again proceeded in general at significantly faster rates as compared with the same in the azeotrope, with good to excellent enantioselectivities. For instance, 1′-acetonaphthone was reduced to (*R*)-1-(1-naphthyl)ethanol in 98% conversion and 87% ee in 6 h. In the HCOOH–NEt_3 azeotrope with a similar catalyst, a conversion of only 71% was reached in 30 h at 50 °C.[5a] As with the reactions in the azeotrope, exceptions were observed with *o*-substituted acetophenones, which gave ee's as low as 20%. This decrease in enantioselectivity results most likely from disturbance of a chirality-determining diastereomeric transition state by the *o*-substituents, where CH–π interactions between cymene and the ketone aromatic ring have been revealed to be critical for ketone face selection (see Scheme 2 below).[11]

The HCOONa–water system can be readily applied to higher S/C ratios. Thus, as shown in Scheme 1, the reduction took pace smoothly at a S/C ratio of 1000 without compromising the ee's.

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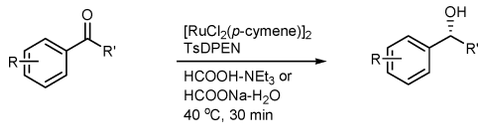
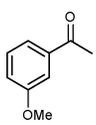
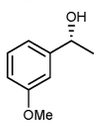
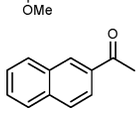
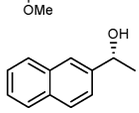
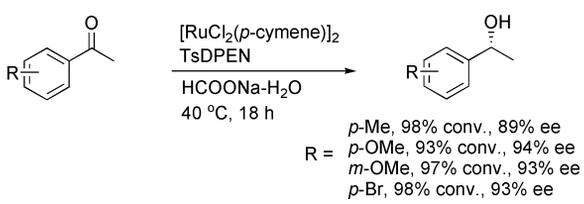
Table 1 Asymmetric transfer hydrogenation of ketones in HCOOH–NEt_3 *vs* HCOONa–H_2O[a]

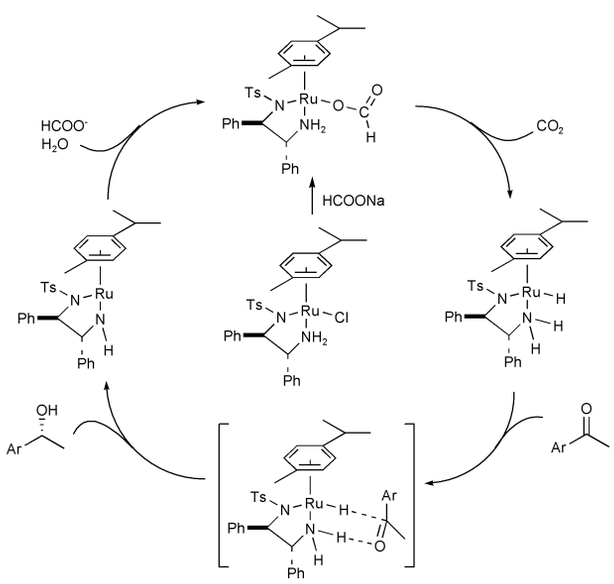


Ketone	Product	Solvent	Conv. (%)[b]	ee (%)[b]
		Azeotrope	1	>99
		Azeotrope[c]	98	97
		H_2O	76	95
		Azeotrope	4	>99
		H_2O	47	96
		Azeotrope	1	>99
		H_2O	33	98
		Azeotrope	3	>99
		H_2O	34	99

[a] The reactions were carried out in 2 ml of water or 1 ml of azeotrope with a S/C ratio of 100 at 40 °C for 30 min, unless otherwise indicated. For general procedures, see references 9 and 10. [b] Determined by GC equipped with a chiral column. The alcohol configuration was *R* and was determined by comparison of GC retention time or sign of optical rotation with literature data. [c] Reaction time: 12 h.



Scheme 1 Asymmetric transfer hydrogenation of ketones at S/C = 1000.



Scheme 2 A possible pathway for the reduction of ketones by formate in water.

It is not yet clear to us why the Ru-TsDPEN-catalysed asymmetric transfer hydrogenation is faster in water than in the HCOOH–NEt_3 mixture. However, the following observations may shed some light on the question. The ketones of this study are not soluble in water and when water is the solvent, the catalyst is partitioned in the substrate and aqueous phases, being more soluble in the former. Hence, the reaction in water may have taken place in the substrate. Fig. 1 compares the

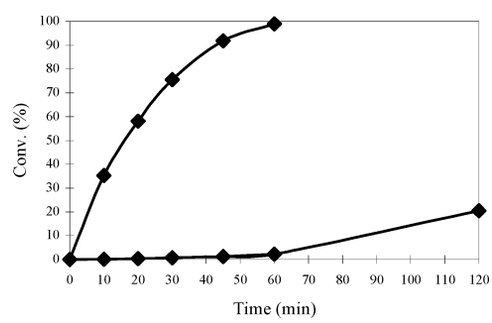


Fig. 1 Conversion–time diagram for the reduction of acetophenone by Ru-TsDPEN in HCOONa-H_2O (■) and HCOOH–Et_3N (◆). The reaction was carried out in 2 ml of water or 1 ml of azeotrope with a S/C ratio of 100 at 40 °C. For more detailed conditions, see references 9 and 10.

kinetic profiles of reduction of acetophenone by the Ru-TsDPEN catalyst of this study in water and in HCOOH–NEt_3, showing the reaction in the azeotrope to be markedly slower (98% conversion in 12 h reaction time) and associated with an induction period. The difference in rates may partly stem from a difference in ketone concentration in the two systems, particularly if the reduction in water occurs in the substrate phase. The induction period observed could be associated with the catalyst preparation. The precatalyst used for the azeotrope was prepared by reacting TsDPEN with $[RuCl_2(p\text{-cymene})]_2$ in CH_2Cl_2 while that for water was made by stirring the two species in water.[10] However, the precatalyst prepared in water led to even a longer induction period when the azeotrope, instead of the formate, was introduced as hydrogen source, affording a conversion of 93% in 10 h. Clearly, the source of hydrogen plays an important role here, with the active catalyst generated instantly when HCOONa is employed in water.

The role of the formate is further revealed by altering its concentration and using deuterated reagents in the hydrogenation of acetophenone. The reaction rate decreased with reduction in the formate concentration, with the initial rate decreasing by *ca.* half when the quantity of HCOONa was lowered from 5 (2.5 M in water) to 2 equivalents. Replacing $HCOO^-$ with $DCOO^-$ resulted in a primary isotope effect of k_H/k_D = 3.2 (with 99% deuterium incorporated at the OH-

Table 2 Asymmetric transfer hydrogenation of ketones with Ru–TsDPEN in H_2O–HCOONa[a]

Entry	Ketone	Alcohol	Time (h)	Conv. (%)[b]	Ee (%)[b]
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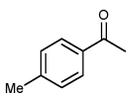
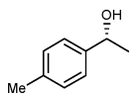
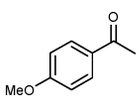
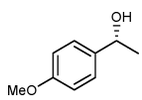
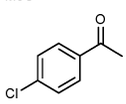
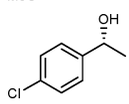
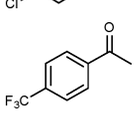
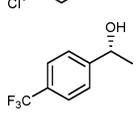
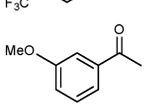
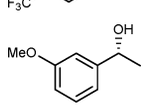
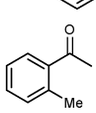
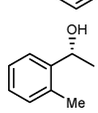
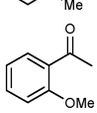
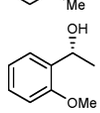
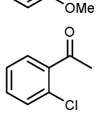
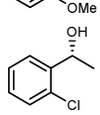
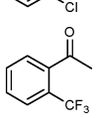
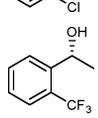
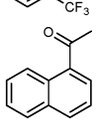
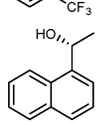
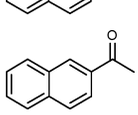
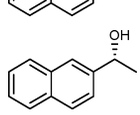
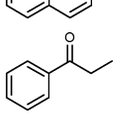
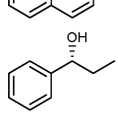
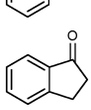
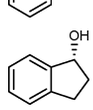
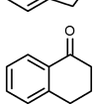
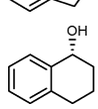
2			2	98	90
3			2	>99	95
4			2	>99	91
5			2	99	94
6			2	98	94
7			6	>99	80
8			2	96	72
9			2	>99	89
10			6	100	20
11			6	98	87
12			3	95	95
13			2	>99	86
14			2	93	95
15			3	97	94

[a] The reactions were performed at 40 °C, using 1 mmol of ketone, 5 equiv. HCOONa, and a S/C ratio of 100 in 2 ml of water. [b] Determined by GC equipped with a chiral column. The alcohol configuration was *R*.

bound carbon); but switching from H_2O to D_2O led to a much less significant difference ($k_H/k_D = 1.5$). If the reduction proceeds *via* a mechanism similar to the one in 2-propanol,[11,12] these observations would be consistent with the C–H cleavage from the formato complex being rate limiting (Scheme 2).[13] However, Fig. 1 shows that the rate is also dependent of the concentration of ketone. Thus there exists a possibility that the turnover could be controlled by hydrogen transfer to ketone with a late transition state. Very recently, Ikariya has shown that the 16-electron amide complex reacts with HCOOH to give the formato species, which undergoes decarboxylation leading to the ruthenium hydride, with both reactions occurring readily at subzero temperatures in THF.[14] In our case, interpretation of the mechanism is further complicated by the biphasic nature of the reaction and clearly, more remains to be done in order to clarify the mechanism and the role of water.

In summary, this work demonstrates that the Ru-TsDPEN complex is an excellent precatalyst for the asymmetric transfer hydrogenation of various aromatic ketones by HCOONa in water. In comparison with the previously established

conditions, the current protocol affords faster rates and only slightly decreased enantioselectivities, showing that water is not only green but can also benefit a catalytic reaction in terms of activity, selectivity and productivity.

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Notes and references

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9 General procedure: a suspension of $[RuCl_2(p\text{-cymene})]_2$ (3 mg, 0.005 mmol) and TsDPEN [(*R*,*R*), 5 mg, 0.012 mmol] in H_2O (2 ml) was degassed three times and stirred at 40 °C for 1 h. HCOONa (340 mg, 5.0 mmol) and a ketone (1.0 mmol) were then introduced. The mixture was degassed three times and stirred at 40 °C for a certain period of time. After cooling to room temperature, the organic compounds were extracted with Et_2O (6 ml). The conversion and enantioselectivity were determined by GC analysis (Chrompack Chirasil-Dex CB (25 m × 0.25 mm) column).

10 General procedure: the catalyst was prepared by reacting $[RuCl_2(p\text{-cymene})]_2$ (3 mg, 0.005 mmol) and TsDPEN [(*R*,*R*), 5 mg, 0.012 mmol] in CH_2Cl_2 (2 ml) at room temperature for 30 min. After removal of CH_2Cl_2 under reduced pressure, a mixture of a ketone (1.0 mmol) and the HCOOH–Et_3N (5 : 2) azeotrope (1.0 ml) were introduced. Following degassing three times, the mixture was stirred at 40 °C for a certain period of time. The solvent was then removed at room temperature and Et_2O (6 ml) added to extract the product. This procedure is not entirely the same as that of Noyori.[3g]

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