

A remarkably effective catalyst for the asymmetric transfer hydrogenation of aromatic ketones in water and air

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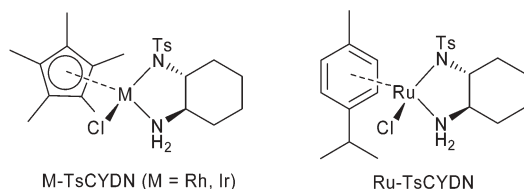
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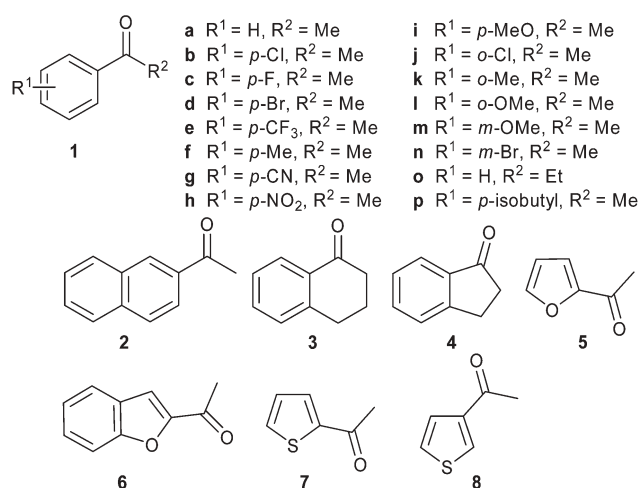
A Rh(III) complex generated *in situ* from [Cp*RhCl₂]₂ and (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-cyclohexanediamine (TsCYDN) serves as a remarkably effective, robust catalyst for the asymmetric transfer hydrogenation of aromatic ketones by HCOONa in water in air, affording alcohols in up to 99% ee.

Enantioselective reduction of prochiral ketones leading to optically pure secondary alcohols is a subject of considerable interest from both an academic and industrial perspective because of the significance of these intermediates for the manufacture of pharmaceuticals and advanced materials. During the last decade, remarkable efforts have been devoted to the development of this method by using organometallic complexes as catalysts.¹ Noyori and co-workers first reported on the use of monotosylated diamines and 1,2-aminoalcohols as ligands for ruthenium-catalyzed asymmetric transfer hydrogenation (ATH) of aromatic ketones in 2-propanol or the azeotropic formic acid–triethylamine mixture.^{2–4} This significant discovery led to the development of a series of new chiral ligands by a number of research groups.^{5–8} In terms of rates and turnover numbers, there is still room for improvement, however. Additionally, as with most organometallic complexes, these catalysts necessitate conditions devoid of air and water, thus rendering practical applications cumbersome. We now report that the Rh-TsCYDN catalyst alongside M-TsCYDN (M = Ru, Ir) displays superb activities and excellent enantioselectivities in the reduction of ketones in water, with no need for organic solvents or inert gas protection throughout the entire operation.




We recently reported that the ATH of aromatic ketones with the Noyori–Ikariya Ru-(*R,R*)-TsDPEN [TsDPEN = (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine] catalyst can be considerably accelerated by using water as solvent.^{9,10} We have now found that significantly faster reduction is delivered when the Rh-TsCYDN catalyst is adopted in neat water with formate as

reductant. The M-TsCYDN and related catalysts were first described by the groups of Tani,^{6c} Knochel¹¹ and Ikariya¹² for the same reactions under anaerobic conditions in organic media; but the reactions tend to be slow (*vide infra*).^{6c,11–13} We started with the ATH of acetophenone by HCOONa using M-TsCYDN as catalyst in water. The precatalyst was generated by simply reacting the (*R,R*)-TsCYDN ligand with [RuCl₂(*p*-cymene)]₂, [Cp*RhCl₂]₂ and [Cp*IrCl₂]₂ respectively in undegassed water (2 mL) at 40 °C for 1 h in the open air with no use of a base. The resulting suspensions were used for the ATH without purification, and the ATH was initiated by introducing HCOONa (5.0 mmol) and acetophenone (1.0 mmol) and carried out without any inert gas protection. Much to our delight, with Rh-TsCYDN, the acetophenone was almost fully converted into (*R*)-1-phenylethanol in 95% ee in 15 min. The Ir-TsCYDN was less active, furnishing a 99% conversion and 93% ee in 1 h, while the Ru-TsCYDN required 2 h for the same reduction to give an 85% ee (Table 1). In contrast, as shown in Table 1, the ATH of acetophenone in 2-propanol with Rh-TsCYDN and Ir-TsCYDN and in HCOOH–Et₃N with Ru-TsCYDN necessitated much longer reaction times.^{11a,12} In the same azeotrope for the same reaction, an analogous chiral ‘roofed’ *cis*-diamine in combination with ruthenium was recently reported to give a 53% conversion (86% ee) in 67 h at 25 °C.^{11b}



Encouraged by the results obtained with Rh-(*R,R*)-TsCYDN, we then extended this system to a wide range of substituted acetophenones **1**, the related ketones **2–4**, and the heteroaryl ketones **5–8**. As before the reaction was carried out in neat water without using any co-solvent in the open air and without any degassing throughout. The Rh-(*R,R*)-TsCYDN catalyzed ATH

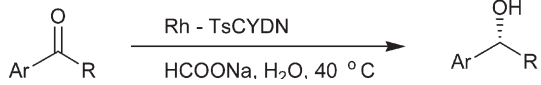
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Table 1 Comparison of the ATH of acetophenone with M-TsCYDN under different conditions


Catalyst	Solvent	<i>t</i> /h	% Con	% ee
Ru-TsCYDN	formate ^a	2	99	85
	iPrOH ^b	—	—	—
	azeotrope ^c	24	99	94
Rh-TsCYDN	formate ^a	0.25	> 99	95
	iPrOH ^b	12	85	97
	azeotrope ^c	—	—	—
Ir-TsCYDN	formate ^a	1	99	93
	iPrOH ^b	12	36	96
	azeotrope ^c	—	—	—

^a Reaction was carried out at 40 °C, using 1 mmol of ketone, 5 equiv. HCOONa, and a S/C ratio of 100 in 2 mL of water, with conversion and ee determined by GC. ^b 30 °C reaction temperature, 0.1 M ketone in 2-propanol with 200/1 S/C ratio, reference 12. ^c azeotrope = azeotropic HCOOH–NEt₃ mixture, 30 °C and 100/1 S/C ratio, reference 11a.

with sodium formate in water delivered almost completed conversions for most ketones within 1 h, as is shown in Table 2.¹⁴ In most cases the enantioselectivities were good to excellent. For instance, the reduction of 4-methoxyacetophenone led to a 99% conversion in 93% ee at 40 °C in 30 min in water (entry 8, Table 2). In comparison, the reaction performed in 2-propanol using the same catalyst at 30 °C gave a 22% conversion (> 99% ee) in 24 h with a S/C ratio of 200/1,¹² and a similar

Table 2 ATH of ketones with Rh-TsCYDN by HCOONa in H₂O in air^a


Entry	Ketone	<i>t</i> /min	% Con ^b	% ee ^b
1	1b	10	> 99	94
2	1c	20	> 99	94
3	1d	15	99	91
4	1e	10	> 99	91
5	1f	30	> 99	92
6	1g	25	98	90
7	1h	45	98	87
8	1i	30	99	93
9	1j	20	> 99	77
10	1k	60	98	80
11	1l	60	98	79
12	1m	30	97	93
13	1n	15	> 99	89
14	1o	60	97	92
15	2	45	99	95
16	3	30	94	97
17	4	20	98	95
18	5	5	99	99
19	6	10	99	96
20	7	15	98	94
21	8	45	99	99

^a Reactions were carried out at 40 °C, using 1 mmol of ketone, 5 mmol HCOONa and a S/C ratio of 100 in 2 mL of water.

^b Determined by GC. The alcohol configuration was *R*.

cis-diamine catalyst gave a 91% conversion (92% ee) in 24 h at 25 °C in HCOOH/Et₃N at a S/C ratio of 200/1.^{11b} The ATH of 4'-chloroacetophenone and 4'-fluoroacetophenone catalyzed by Rh-(*R,R*)-TsCYDN in water gave > 99% conversions in 94% ee in a short reaction time of 10–20 min (entries 1 and 2, Table 2). 1-Tetralone and 1-indanone were reduced with Rh-(*R,R*)-TsCYDN in water to give up to 98% conversion and 97% ee in half a hour (entries 16 and 17, Table 2); switching to 2-propanol the reduction resulted in a 43–53% conversion with 95–97% ee in 24 h (30 °C, 200/1 S/C ratios), however.¹² The heterocyclic ketones were also reduced in general at fast rates with good to excellent enantioselectivities by HCOONa with Rh-(*R,R*)-TsCYDN in water (entries 18–21, Table 2). The most notable is the reduction of 2-acetylfuran, which afforded a > 99% conversion and 99% ee in 5 min (entry 18, Table 2).

As with reactions catalysed by related Ru-TsDPEN catalysts,⁹ acetophenones bearing electron donating substituents tend to give slower reactions, *e.g.* entries 1 and 4 *vs.* 5 and 8, and *o*-substitution eroded significantly the enantioselectivities (entries 9–11, Table 2). Considering that the reduction of the carbonyl C=O bond by the Ru(II)-H hydride intermediate resembles somewhat a nucleophilic addition reaction,¹⁵ this is not surprising. However, the very electron-withdrawing –CN and –NO₂ substituents did not lead to faster reduction.

This aerobic catalysis by Rh-TsCYDN in water also applies to higher S/C ratios.^{1a,3b,c,5} Table 3 gives a few examples. As can be seen, the reduction of 2-acetylfuran furnished a 98% conversion in 1.5 h with 99% ee at S/C = 1000 in the open air, with the initial turnover frequency (TOF) reaching 3500 mol mol^{–1} h^{–1}. This represents one of the best results in terms of rates and ee's reported for ketones of this type. Even the totally water-insoluble 4'-isobutylacetophenone could be readily reduced with a 94% ee at S/C = 1000 (entry 3, Table 3). The reduction could be performed at a higher temperature of 65 °C with a faster rate but a decreased ee (**1c**, entry 2, Table 3).

In conclusion, our results show that the Rh-TsCYDN complex is an excellent ATH catalyst for use in water. It delivers fast rates, high enantioselectivities and high turnover numbers, and requires neither organic solvents nor inert gas protection,^{3b,c} or substrate solubility in water. The aqueous phase catalysis thus provides an attractive alternative for conducting asymmetric transfer hydrogenation in a less costly, simpler and “greener” manner.

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Table 3 Aerobic ATH of ketones with Rh-TsCYDN in H₂O at a S/C ratio of 1000^a

Entry	Ketone	<i>t</i> /h	% Con ^b	% ee ^b	TOF ^c
1	1c	2.5	> 99	93	2200
2	1c	0.75 ^d	98	89	4100
3	1p	3.5	> 99	94	1100
4	5	1.5	98	99	3500

^a Reactions were carried out at 40 °C, using 10 mmol of ketone, 50 mmol HCOONa and a S/C ratio of 1000 in 10 mL of water.

^b Determined by GC. ^c Based on 5-min conversions; in mol mol^{–1} h^{–1}. ^d The reaction was carried out at 65 °C.

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