An Efficient Ir(III) Catalyst for the Asymmetric Transfer Hydrogenation of Ketones in Neat Water

Xiaohong Li,[a] John Blacker,[b] Ian Houson,[b] Xiaofeng Wu,[a] Jianliang Xiao*[a]

[a] Liverpool Centre for Materials and Catalysis, Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, UK
Fax +44(151)7943589; E-mail: j.xiao@liv.ac.uk

[b] NPIL Pharma, Leeds Road, Huddersfield, Yorkshire HD2 1GA, UK

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Abstract: The chiral M–CsDPEN [M = Ru, Rh, Ir; CsDPEN = (*R*,*R*,*R*)- or (*S*,*S*,*S*)-*N*-camphorsulfonyl-1,2-diphenylethylenediamine] catalysts have been shown to be efficient for the asymmetric transfer hydrogenation (ATH) of aryl ketones by formate in neat water. Of particular note is the Ir-(*R*,*R*,*R*)-CsDPEN catalyst, which catalyzes the ATH of a wide range of ketones and delivers almost full conversions within a few hours at a S/C ratio of 1000 at 40 °C in most cases, with enantioselectivities up to 98% ee.

Key words: asymmetric transfer hydrogenation, ketones, water, formate, camphor ligand

Catalysis in water is a field of increasing interest in modern chemistry, because of the substantial environmental and economical gains.[1] Among the many reactions using water as a solvent or cosolvent reported, asymmetric transfer hydrogenation (ATH) has recently attracted a great deal of attention[2,3] and significantly, a commercial aqueous-phase ATH process has been launched.[4] ATH provides a powerful alternative to asymmetric hydrogenation for the catalytic reduction of ketones and imines because of its combined versatility and practical simplicity.[2–6] Among the various chiral catalysts reported for the ATH reactions, the most notable is the Ru–TsDPEN [TsDPEN = (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine] complex developed by Noyori, Ikariya, Hashiguchi and co-workers.[7]

We recently reported that the ATH of aromatic ketones with the Ru–(*R*,*R*)-TsDPEN catalyst[3a] or its polymer-supported analogue Ru–PTsDPEN[3b] can be greatly accelerated by using water as solvent (Figure 1). More recently we demonstrated that ATH of ketones by Ru–TsDPEN in water is pH controlled, with higher pH favoring higher rates and enantioselectivities.[3c] Our ongoing research and that of Deng and co-workers also suggest that there exists similar chemistry for the ATH of ketones with Rh(III)- and Ir(III)–TsDPEN catalysts in water.[2g] Herein we report that a camphor-modified 1,2-diphenylethylenediamine ligand forms an excellent catalyst with iridium for the ATH of ketones in neat water.[8]

Camphorsulfonyl (Cs) has been used as a chiral auxiliary in a number of amine and amino alcohol ligands to promote reactions such as enantioselective addition of aldehydes, ketones and enones after coordination with a copper or titanium species.[9,10] Camphorsulfonyl chloride can also be used for the resolution of 2-diarylphosphino-2′-methoxy-1,1′-binaphthalene.[11] Additionally, chiral camphorsulfonamide units have been incorporated into hydrophobic ionic liquids and used as chiral auxiliaries in asymmetric addition to aldehydes.[12] Chiral camphor-derived ligands were also applied to the enantioselective borane reduction of prochiral ketones with up to 99% ee.[13]

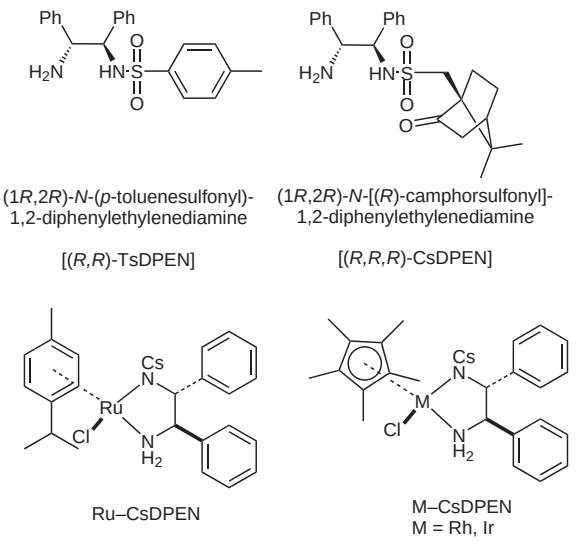

Figure 1

However, to the best of our knowledge, no reports on the application of Cs-containing ligands in the ATH of ketones in water have been published until now. Compared with TsDPEN, CsDPEN is both sterically and electronically different, and the carbonyl group introduces an additional functionality into the ligand, which could have a bearing on the reduction. Indeed, the M–CsDPEN catalyst has been found to behave differently from the M–TsDPEN and M–TsCYDN [TsCYDN = *N*-(*p*-toluenesulfonyl)-1,2-diaminocyclohexane] catalysts,[3] and of particular note is that Ir–CsDPEN efficiently catalyzes the ATH of a wide range of ketones in ee of up to 98% in neat water at a substrate/catalyst (S/C) ratio of 1000.

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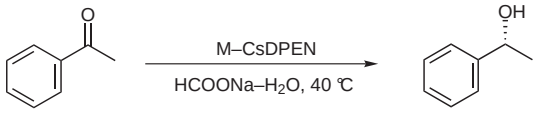
Table 1 ATH of Acetophenone with M–(*R*,*R*,*R*)-CsDPEN in Water[a]



Entry	S/C	Rh			Ru			Ir		
		Time (h)	Conversion (%)[b]	ee (%)[b]	Time (h)	Conversion (%)[b]	ee (%)[b]	Time (h)	Conversion (%)[b]	ee (%)[b]
1	100	0.7	99	99	2	99	97	0.7	98	97
2[c]	100	0.7	97	98	2	99	96	0.7	99	96
3	1000	20	89	99	20	95	96	2.5	97	98

[a] Conditions: 40 °C, 1.0 mmol of acetophenone, 5 equiv HCOONa, S/C = 100, in 2 mL of H_2O, or 10 mmol of ketone, 5 equiv HCOONa, S/C = 1000, in 8 mL of H_2O.
[b] Determined by GC. The alcohol configuration was *R*.
[c] Using (*S*,*S*,*S*)-CsDPEN as ligand. The configuration of the product was *S*.

Our initial investigation focused on determining which M–CsDPEN catalyst would offer the best performance. The precatalysts were generated in situ by reacting CsDPEN with $[RuCl_2(p\text{-cymene})]_2$ or $[Cp^*MCl_2]_2$ (M = Rh, Ir) in water at 40 °C for one hour. The ATH was initiated by introducing the substrate at a S/C ratio of 100. Table 1 summarizes the results obtained with the Ru-, Rh- and Ir–CsDPEN complexes. The reactions were nearly complete within 40 minutes with Rh- and Ir–(*R*,*R*,*R*)-CsDPEN, whereas two hours were necessary with Ru–(*R*,*R*,*R*)-CsDPEN (entry 1, Table 1). The M–(*S*,*S*,*S*)-CsDPEN complexes showed similar catalytic performance expected for the opposite product configuration (entry 2, Table 1), indicating that the sense of the enantioselective reduction is determined by the chelating amino part of the ligand. When increasing the S/C ratio, the difference between the complexes became significant. At a S/C ratio of 1000, the Ir–CsDPEN is the most effective catalyst for the ATH of acetophenone; the reaction nearly finished within 2.5 hours, whilst with the other two catalysts the reaction was not completed even after a prolonged reaction time of 20 hours. However, the enantioselectivities with all three catalysts were not decreased in comparison with those obtained at a S/C ratio of 100.

We also compared the kinetic profiles of the Rh-, Ru- and Ir–CsDPEN-catalyzed ATH of acetophenone at a S/C ratio of 1000. As shown in Figure 2, the Ir–CsDPEN was more active than the other two complexes; the Ru–CsDPEN showed the lowest initial activity. Although the reduction with both the rhodium and ruthenium catalysts was fast initially, it became sluggish at ca. 80% conversion, suggesting possible product inhibition.[14] This observation is somewhat in contrast with that made with M–TsDPEN or TsCYDN. The Ir–TsCYDN catalyst is known to be less active than its rhodium analogue,[3d] and our ongoing study suggests that of the three M–TsDPEN catalysts (M = Ru, Rh, Ir), the iridium appears to be least active.

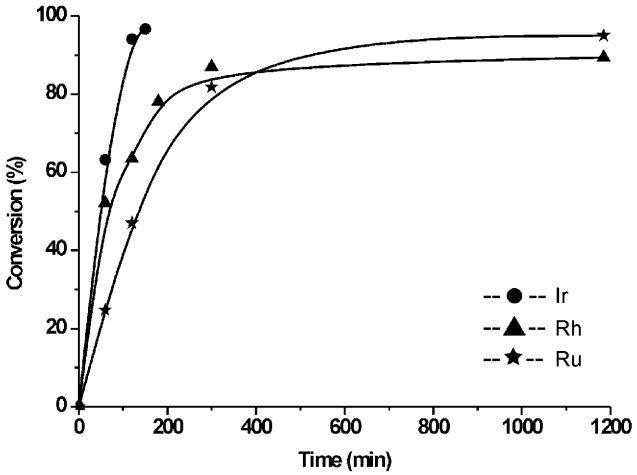
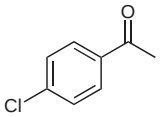
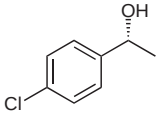
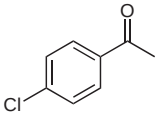
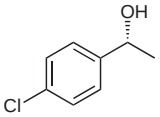
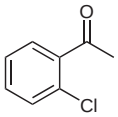
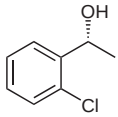
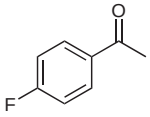
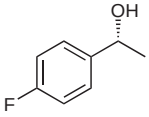
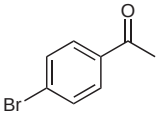
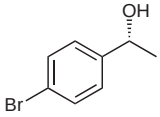
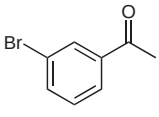
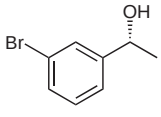
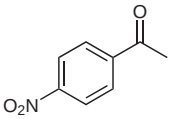
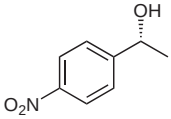
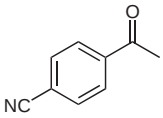
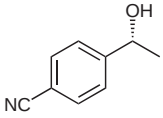
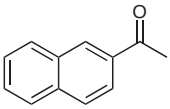
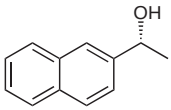
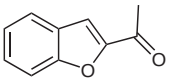
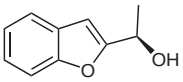


Figure 2 Comparison of the ATH of acetophenone catalyzed by Rh-, Ru- and Ir–CsDPEN in water at a S/C ratio of 1000. For reaction conditions, see Table 1.

Consequently, we extended the Ir–(*R*,*R*,*R*)-CsDPEN catalyst to a wide range of ketones under the same conditions at a S/C ratio of 1000. Table 2 and Table 3 show the results obtained. For the aryl ketones without electron-donating substituents, the Ir–CsDPEN delivered full conversions within a few hours, affording excellent enantioselectivities (Table 2). It is notable that the ATH of 1-(benzofuran-2-yl)ethanone nearly finished within 45 minutes, furnishing a 94% ee (entry 10, Table 2). Steric effects may also play a role. Compared with the ATH of 4′-chloroacetophenone (96% ee, entry 1, Table 2), a lower enantioselectivity (88% ee, entry 3, Table 2) was obtained for the ATH of 2′-chloroacetophenone. These reactions were performed under nitrogen. However, they could also be run in the air. Thus, there was no significant decrease in conversion and enantioselectivity in the ATH of 4′-chloroacetophenone without nitrogen protection throughout the reaction (entry 2, Table 2).

Table 2 ATH of Aryl Ketones without Electron-Donating Substituents by Ir–(*R*,*R*,*R*)-CsDPEN in Water[a]

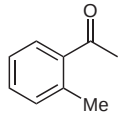
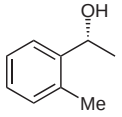
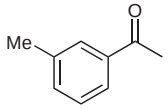
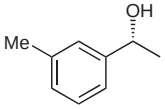
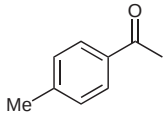
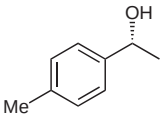
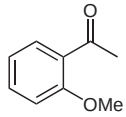
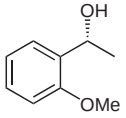
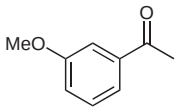
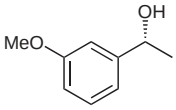
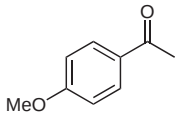
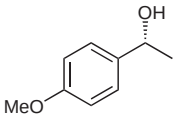
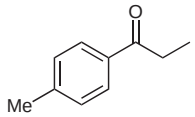
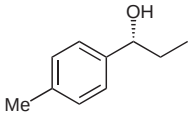
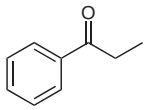
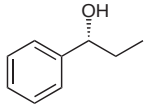
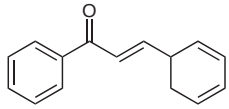
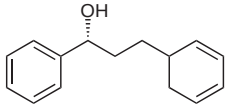
Entry	Ketone	Alcohol	Time (h)	Conversion (%)[b]	ee (%)[b]
1			2	99	96
2			2	>99	95[c]
3			3	98	88
4			3.1	99	96
5			1.8	97	95
6			2	>99	93
7			2	99	93
8			2	99	94
9			4	>99	97
10			0.75	>99	94

[a] See Table 1 for conditions for reduction at a S/C ratio of 1000.
[b] Determined by GC or HPLC. The alcohol configuration was *R*.
[c] The reaction was performed without nitrogen protection throughout.

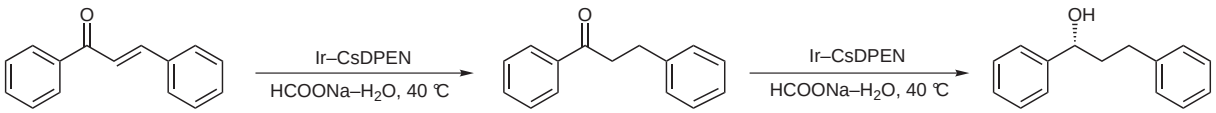
In contrast, the reactions went slower in most cases for the ATH of ketones with electron-donating or α-substituents. Thus, for the 2′- and 4′-methyl or methoxy-substituted acetophenones, the ATH reactions necessitated a longer time to deliver nearly full conversions (Table 3). The ATH of 4′-methylpropiophenone afforded a 78% conversion even after a prolonged reaction time of 50 hours (entry 7, Table 3). (*E*)-Chalcone was reduced in 25 hours, affording the fully saturated 1,3-diphenylpropan-1-ol with 92% ee (entry 9, Table 3). GC monitoring shows that the C=C bond was first saturated followed by the carbonyl (Equation 1). This is probably a result of polarization of the C=C bond by the carbonyl group, facilitating the hydride addition at the 3-position.[15]

The slower reduction of the relatively electron-rich ketones is to some degree related to the LUMOs of these substrates, with lower values giving rise to faster reactions. For example, of the three methoxy-substituted acetophenones, the 3′-methoxy variant, which has the lowest LUMO, displayed the highest rate, suggesting that the slow rates with the other two could result from a weaker

Table 3 ATH of Aryl Ketones with Electron-Donating or α-Substituents by Ir–(*R*,*R*,*R*)-CsDPEN in Water[a]

Entry	Ketone	Alcohol	Time (h)	Conversion (%)[b]	ee (%)[b]
1			29	84	93
2			4.5	98	97
3			8.5	94	92
4			21	99	85
5			3	>99	98
6			22	94	97
7			50	78	86
8			9.5	98	97
9			25	>99[c]	92

[a] See Table 1 for conditions at S/C = 1000.
[b] Determined by GC. The alcohol configuration was *R*.
[c] The product contained 2% of the saturated ketone.



Equation 1

bonding interaction between the Ir–H hydrogen and the carbonyl carbon at a possible six-membered pericyclic transition state.[16]

An interesting question arose as to whether the carbonyl group of the ligand was reduced during the reaction. Replacing CsDPEN with the hydroxylated analogue, obtained from reduction of the camphor C=O bond using $NaBH_4$, yielded a slightly lowered reaction rate with no change in ee in the ATH of acetophenone at a S/C ratio of 1000. But analysis of the catalyst residue by NMR and IR after the ATH reaction with Ir-CsDPEN showed that the carbonyl group remained intact, suggesting that the carbonyl is not reduced during the catalysis. Reduced camphor ligands have been reported to be more efficient than their parents in some catalytic reactions, however.[9c,9e,12]

In summary, the camphor-modified 1,2-diphenylethylenediamine, CsDPEN, is an efficient ligand for ATH of aryl ketones in neat water. The Ir–CsDPEN catalyst is shown to be particularly effective for the aqueous phase reduction. It catalyzes the ATH of a wide range of aryl ketones, furnishing high conversions at a S/C ratio of 1000 in a few hours for a number of substrates with ee of up to 98% in water with no organic solvent. The reduction appears to be more effective towards ketones without electron-donating substituents on the aryl rings.

Preparation of the Precatalyst

The M–CsDPEN catalyst was prepared from $[RuCl_2(p\text{-cymene})]_2$ (3.1 mg, 0.005 mmol), $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol), or $[Cp^*IrCl_2]_2$ (4.0 mg, 0.005 mmol), and (*R*,*R*)-CsDPEN (5.1 mg, 0.012 mmol) in H_2O (8 mL). After stirring at 40 °C for 1 h, the suspension was used for the following reduction.

Typical Procedure for Acetophenone Reduction

After preparing the precatalyst, HCOONa (3.40 g, 50.0 mmol) and acetophenone (1.20 g, 10 mmol) were added to the solution. Following quick degassing (3 ×), the solution was allowed to react at 40 °C for a certain period of time. After cooling to r.t., the organic phase was extracted with Et_2O (3 × 2 mL) and passed through a short silica gel column before being subjected to GC [Varian CP-3380 equipped with a Chrompack Chirasil-Dex CB column (25 m × 0.25 mm)] or HPLC (GILSON UV/VIS-151 equipped with a chiral OB-H column) analysis.

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

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