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Fast Reductive Amination by Transfer Hydrogenation "on Water"

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Abstract: Reductive amination of various ketones and aldehydes by transfer hydrogenation under aqueous conditions has been developed, by using cyclometallated iridium complexes as catalysts and formate as hydrogen source. The pH value of the solution is shown to be critical for a high catalytic chemoselectivity and activity, with the best pH value being 4.8. In comparison with that in organic solvents, the reductive amination in an aqueous phase is faster, and the molar ratio of the substrate to the catalyst (S/C) can be set as high as 1×10^5, the highest S/C value ever reported in reductive amination reactions. The catalyst is easy to access and the reaction is operationally simple, allowing a wide range of ketones and aldehydes to react with various amines in high yields. The protocol provides a practical and environmental friendly new method for the synthesis of amine compounds.

Keywords: amination · amines · hydrogenation · iridium catalyst · water

Introduction

Amine moieties are widely found in natural products, agrochemicals and pharmaceuticals.[1] Development of methods for the efficient and economic production of amines has attracted great attention.[1,2] One of the best ways for producing amines is the reduction of imino C=N bonds,[1a,c,2n,q,s] which are most conveniently obtained from the condensation of carbonyl compounds with amines. However, imines are not always easy to synthesise and have limited stability. Reductive amination (RA) exploits imines in situ generated from carbonyl compounds and amines, alleviating the problematic imine isolation. Tremendous efforts have been devoted to the development of efficient RA reactions; however, the progress is far from satisfactory.[1b,c,2h,p,s–u] In most of the RA reactions developed, stoichiometric boron hydride reduction and heterogeneous hydrogenation dominate the scene.[1b,2t] Borane hydride reduction has been used in a number of industrial applications,[3] for example, synthesis of a CCR3 antagonist[4] and an antiangiogenic tyrosine kinase inhibitor.[5] However, the use of a stoichiometric amount of boron hydrides generates copious amounts of waste and is associated with other problems, such as toxicity issues with $NaBH_3CN$ and the inability to aminate aromatic ketones with $NaBH(OAc)_3$, two most widely used hydrides in RA.[2t,6] Although heterogeneous catalysts have found many applications in RA including industrial examples, they generally display poor chemoselectivity.[1b,7] Progress in developing homogeneous catalytic systems, including organometallic hydrogenative,[8] organocatalytic[9] and enzymatic[10] ones, has been made in recent years, even allowing for enantioselective RA in a few cases.[8a,c–e,h–k,9,10c] However, there is still much room for improvement in terms of substrate scope and catalytic activity.

Transfer hydrogenation, which usually uses organometallic catalysts and hydrogen sources other than hydrogen gas, is an operationally simple and versatile method for reduction and has been very successful in carbonyl reduction.[11] However, the development of transfer hydrogenation systems for the reduction of C=N bonds lags behind that for carbonyl groups.[12] Indeed, only a handful of examples of transfer hydrogenative RA have been reported.[13] Kitamura, Kadyrov, Wills, Ogo and Strotman and their co-workers reported RA using formate as hydrogen source, including asymmetric and aqueous versions.[13a–d,f] Carbtree and co-workers attempted RA of aldehydes with isopropanol as hydrogen source, by using an iridium carbene catalyst.[13e] Recently, we developed a versatile and efficient transfer hydrogenation system for RA, which exploits cyclometallated iridium complexes as catalysts and $HCOOH/Et_3N$ as hydrogen source in alcoholic solvents.[14]

In this paper, we disclose our findings that cyclometallated iridium complexes also catalyse RA with formate under aqueous conditions, when a suitable pH value is chosen [Eq. (1)]. It is shown that water not only serves as a green solvent, but also accelerates the RA reaction, affording better activity than in organic solvents.

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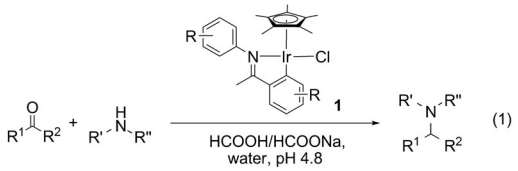
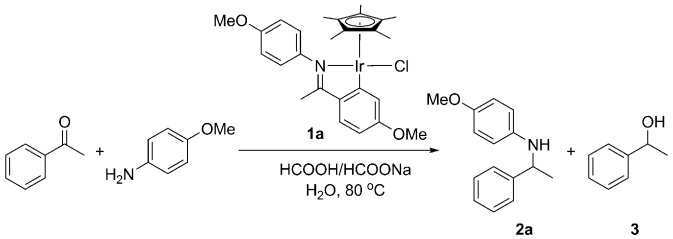


Results and Discussion

Cyclometallated iridium complexes are excellent catalysts for a range of reactions, including RA, almost all of which have been conducted in organic solvents.[15] It would be appealing to replace these solvents with water, because of the economical and environmental benefits water offers.[16] Water as solvent may also enable different activity and selectivity patterns from common organic solvents.[17] However, aqueous RA reactions are scarce in the literature. This is not unexpected, as water is generally thought to be adverse for RA reactions. The presence of water is expected to shift the equilibrium of a ketone or aldehyde with an imine to favour the former, particularly in the presence of an acid. In fact, drying agents are sometimes used to remove water generated from the imine formation step.[9] Previously, the groups of Ogo,[13d] Ajjou[8g] and Bhanage[8h] reported water-soluble catalysts for aqueous RA of aldehydes and aliphatic ketones. We were interested in learning if RA reactions could be carried out in a "on water" fashion, by using our water-insoluble cyclometallated iridium catalysts. We note that no aqueous RA of aromatic ketones has been reported thus far.

In our initial study of the aqueous RA, acetophenone and *p*-anisidine were chosen as model substrates, complex **1a** as precatalyst[14] and formate as hydrogen source (Figure 1). Imine formation from the ketone and amine and the subsequent imine reduction are known to benefit from acidic conditions.[8j,9,18] With this in mind, we first examined the effect of the pH value of the solution on the model reaction, by using HCOOH and HCOONa to adjust the pH values.[13d,17g,r,s,19] The reduction was carried out at 80 °C at a molar ratio of the substrate to the catalyst (S/C) of 1000:1. Indeed, both the catalytic activity and the selectivity were influenced dramatically by the pH of the solution (Figure 1). The reduction took place only at a certain pH region (ca. pH 1.5–6), with the best activity observed at approximately pH 3–4. However, both the desired amine product **2a** and the byproduct alcohol **3** were obtained. A bell-shaped conversion versus pH profile was observed for the formation of both **2a** and **3**, reminiscent of that commonly observed for imine formation.[20] Pleasingly, at pH 4.8, **2a** was observed as the sole product in 26% yield.

The observation of the bell-shaped relationship may be traced to some of the various equilibria in water, which are affected by the pH (Scheme 1). The Ir–H hydride is expected to form from decarboxylation of formate.[21] A lower pH enhances the concentration of protonated imines and hydrogen-bonded ketones, facilitating their reduction.[13d,17g,r,s,19]



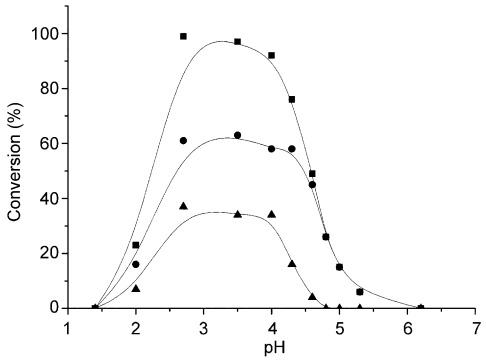
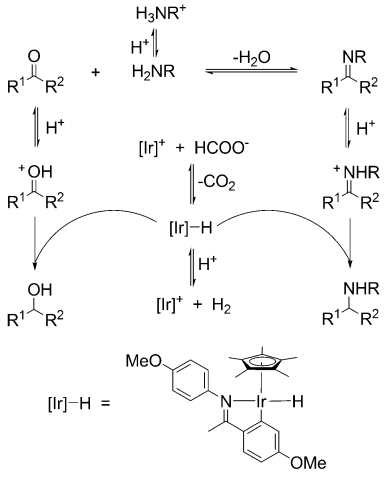


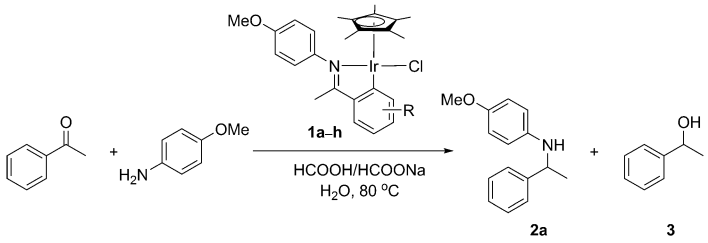
Figure 1. Effect of the pH value on the RA. Reaction conditions: acetophenone (2.5 mmol), *p*-anisidine (3 mmol), **1a** (0.0025 mmol), HCOOH/HCOONa solution (4 mL, 10 mol L^{-1}), 80 °C, 1 h. Conversion and yield were determined by ^{1}H NMR spectroscopy. ■ = total conversion, ● = yield of **2a**, ▲ = yield of **3**.



Scheme 1. Reactions that are possible under aqueous conditions and are affected by the pH value of the solution (H^+ refers to H_3O^+). For the isolation and structure of the hydride, see reference [25].

However, when the solution becomes too acidic, imine formation will be inhibited and the hydride protonated, leading to slower RA. Under basic conditions, imine formation and reduction will both be inhibited. Offering no metal–ligand bifunctional ability,[11c,j,22] complex **1** catalyses imine reduction most likely through the ionic mechanism, that is, direct hydride transfer to the C=N bond.[11g,18c,23] Hence, certain acidic conditions will facilitate the hydrogenation of imines by way of their protonation. The pH value of 4.8 may be a critical point, where the imine is protonated whereas the

Table 1. Optimising reaction conditions of the RA.



Entry[a]	Catalyst	R	t [min]	Conv.[b] [%]	**2a**[b] [%]	**3**[b] [%]
1	**1a**	*p*-OMe	90	76	73	3
2	**1b**	*p*-Cl	90	32	32	0
3	**1c**	*p*-Br	90	30	30	0
4	**1d**	*p*-CF_3	90	9	9	0
5	**1e**	*p*-CN	90	17	17	0
6	**1f**	*p*-NO_2	90	61	60	1
7	**1g**	4,5-$(CH)_4$	90	87	82	5
8[c]	**1g**	4,5-$(CH)_4$	120	99	96 (95)	3

[a] Reaction conditions: acetophenone (2.5 mmol), *p*-anisidine (3 mmol), catalyst (0.0025 mmol), HCOOH/HCOONa solution (pH 4.8, 4 mL), 80 °C, solution bubbled with argon for 15 min in a sealed tube. [b] Determined by ^{1}H NMR spectroscopy. [c] Acetophenone (2.5 mmol) and *p*-anisidine (5 mmol). Number in brackets refers to the yield of the isolated product.

ketone is in its free form, explaining why the reduction of the imine is the main reaction at this condition.

Knowing the best pH value for the RA, we set out to further optimise the reaction by screening various cyclometallated iridium catalysts. The results are summarised in Table 1. Catalyst **1a** afforded 76% conversion in 1.5 h at S/C = 1000, with a **2a**/**3** ratio of > 24. The *para*-Cl and *para*-Br substituents on the ligand effected lower conversions than **1a**, although the chemoselectivities were excellent (Table 1, entries 2 and 3). Interestingly, although the electron-deficient substituents *para*-CF_3 and *para*-CN gave quite low conversions (Table 1, entries 4 and 5), the catalyst with the *para*-NO_2 group demonstrated good activity and selectivity (Table 1, entry 6). The most active catalyst is that derived from **1g**, which contains a naphthyl group, affording 87% conversion with a **2a**/**3** ratio of 16. The structure of **1g** was confirmed by X-ray diffraction (Figure 2).

Further studies showed that the reduction with catalyst **1g** was very fast before reaching approximately 80% conversion under the conditions given in Table 1 (Figure 3). A turnover frequency (TOF) of 1.1×10^3 h was observed in the first 30 min. Thereafter (at ≈60 min), the reaction became sluggish, however, and this was accompanied with more significant hydrogenation of acetophenone to give alcohol **3** (Figure 3). Bearing this in mind, we increased the ratio of *p*-anisidine to acetophenone. This led to 99% conversion in 2 h and a higher **2a**/**3** ratio of 32 (Table 1, entry 8). Under this condition, the amine **2a** was isolated in an excellent yield of 95%.

The rate of the RA reaction in the aqueous solution of pH 4.8 was faster than in our previously reported alcohol system.[14] We compared the rate of reduction under aqueous conditions with that in MeOH and DMF (the volume of the organic solvent was determined such that when it is replaced with the same volume of water the resulting aqueous solution would display pH 4.8). As is shown in Figure 4, the initial rate under aqueous condition is about six times of that in MeOH and DMF. More strikingly, the reaction in the organic media became sluggish, showing little progress after the first 30 min.

Interestingly, we noted that the reaction under the aqueous condition was heterogeneous or biphasic, whereas that in the organic solvents was homogeneous (Figure 5). Thus,

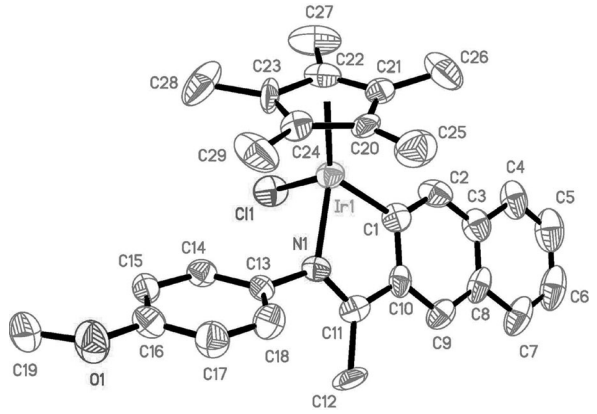


Figure 2. X-Ray diffraction structure of catalyst **1g**. Selected distances [Å] and angles [°]: Ir1–N1 2.080(7), Ir1–C1 2.005(9), Ir1–Cl1 2.410(2); Ir1-N1-C11 119.2(6), Ir1-C1-C10 117.6(6), N1-Ir1-C1 76.7(3).

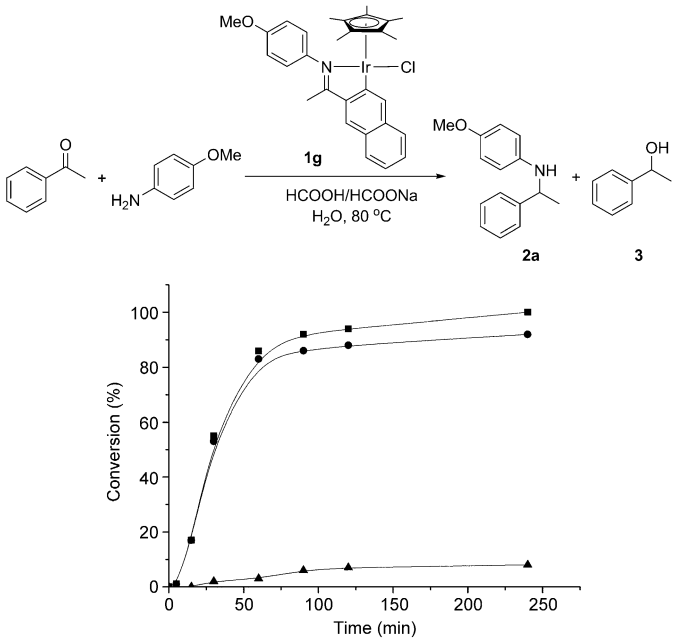


Figure 3. Reaction profile of the RA with catalyst **1g**. Conditions: acetophenone (2.5 mmol), *p*-anisidine (3 mmol), catalyst (0.0025 mmol), HCOOH/HCOONa solution (pH 4.8, 4 mL), 80 °C. ■ = conversion of the ketone, ● = yield of **2a**, ▲ = yield of **3**, determined by ^{1}H NMR spectroscopy.

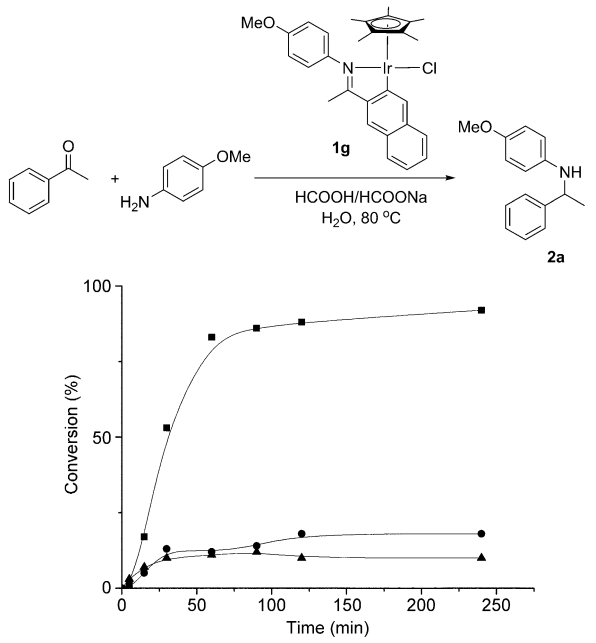


Figure 4. Comparison of the effect of water, MeOH and DMF on the RA. Reaction conditions: acetophenone (5 mmol), *p*-anisidine (6 mmol), **1g** (0.005 mmol), 80 °C. ■ = aqueous HCOOH/HCOONa solution (pH 4.8, 8 mL); ● = MeOH (1 mL), Et_3N/HCOOH (v/v 2:1, 7 mL); ▲ = DMF (1 mL), Et_3N/HCOOH (v/v 2:1, 7 mL). Conversions were determined by ^1H NMR spectroscopy.

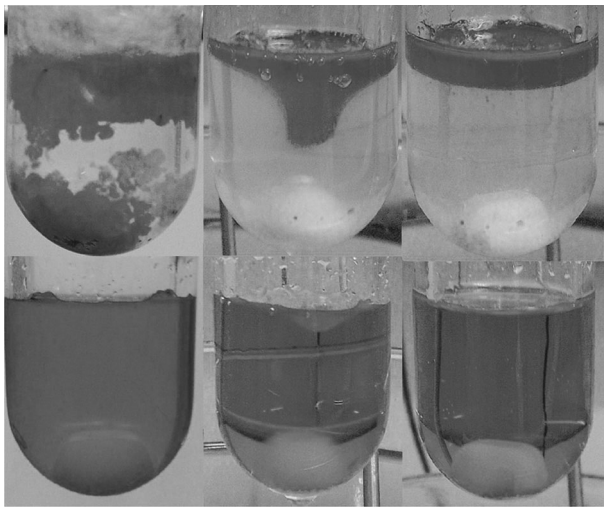


Figure 5. Photos of the RA of acetophenone with *p*-anisidine in water and organic solvent under the conditions given in Figure 4. Top) Reaction in aqueous HCOOH/HCOONa solution. Bottom) Reaction in MeOH. From left to right: before reaction, during reaction and after reaction.

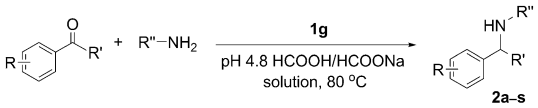
the faster rate associated with the aqueous conditions may stem from an increased concentration of substrates as a result of the reaction happening "on water".[16e,17f,l] Alternatively, water molecules may participate in the transition states of the rate-determining step.[17r,24]

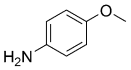
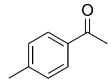
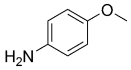
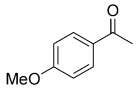
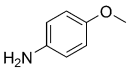
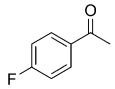
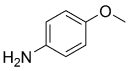
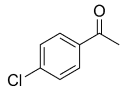
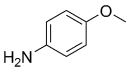
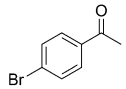
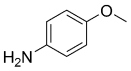
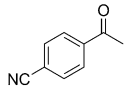
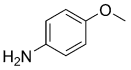
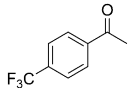
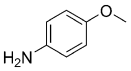
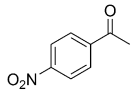
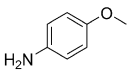
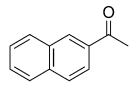
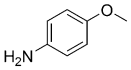
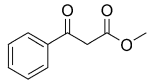
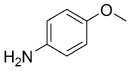
The substrate scope of the aqueous HCOOH/HCOONa system with catalyst **1g** was firstly examined in the reactions of aromatic ketones with various amines. The results are summarised in Table 2. Aromatic ketones with electron-withdrawing or electron-donating substituents all react well with *p*-anisidine, affording excellent yields in 2 h at S/C of 1000 (Table 2, entries 1–10). The electronic effects of these substituents on the RA are not obvious for these substrates under the conditions employed. A β-ketoester also reacted, allowing direct access to amino acids; but it needed lower pH (pH 4.2) and showed lower activity (Table 2, entry 11). The RA is more significantly affected by the amine partners, however. For aromatic amines, relatively lower yields were obtained for substituents other than *p*-OMe (Table 2, entries 12–16). The *p*-Cl- and *p*-Br-substituted anilines were particularly less reactive, requiring longer time or higher catalyst loading to reach acceptable yields. This appears to suggest that the RA is rate limited by the step of the imine formation. Benzyl amine reacted quite well with acetophenone to afford 87% yield at S/C of 2000 in 4 h. However, aliphatic amines provided lower yields, although they are good substrates when using MeOH as solvent (Table 2, entry 18).[14] A chiral amino acid ester could also act as amine source, providing excellent diastereoselectivity, albeit with low yield (Table 2, entry 19).

The reactions of aliphatic ketones with various amines were investigated next. 4-Phenylbutan-2-one was chosen as a model substrate to react with different amines initially. Aliphatic ketones generally showed higher activity than aromatic ketones. An S/C of 2000 can be employed for most of the substrates. As can be seen in Table 3, aromatic amines reacted quite well with 4-phenylbutan-2-one, apart from *p*-Br- and the electron-withdrawing *p*-CF_3-substituted aniline (Table 3, entries 1–7). Benzylamine was also a good substrate for 4-phenylbutan-2-one (Table 3, entry 8). However, aliphatic amines, particularly the sterically more demanding ones, were again poorer substrates (Table 3, entries 9–11). A slightly higher pH of 5.0 was used for cyclohexylamine (Table 3, entry 11). Likewise, secondary amines displayed lower activity, probably again due to their steric hindrance. Thus, only 64% yield were obtained for methylphenylamine at S/C of 200 for 24 h (Table 3, entry 12). The methyl ester of phenylalanine reacted much faster with 4-phenylbutan-2-one than with acetophenone, affording 95% yield at S/C of 2000 in 3 h, with a d.r. of 79:21 (Table 3, entry 13). An α,β-unsaturated ketone reacted with *p*-anisidine to give a fully reduced product in good yield (Table 3, entry 14). Water-insoluble long-chain or cyclic ketones all reacted with *p*-anisidine, furnishing good to excellent yields at S/C of 2000 in 2 h (Table 3, entries 16–18).

Despite its water solubility, acetone was also a viable substrate for the water-insoluble *p*-anisidine (Table 3, entry 15). However, little reaction took place when the ketone and amine were both water soluble, for example, acetone with *n*-butylamine. These results show the importance of phase separation in the RA studied, supporting the "on water" nature of the catalysis.

Table 2. RA of aromatic ketones with different amines.



Entry[a]	Ketone	Amine	S/C	t [h]	Yield [%][b]
1			1000	2	95
2			1000	2	98
3			1000	2	95
4			1000	2	94
5			1000	2	98
6			1000	2	98
7			1000	2	98
8			1000	2	96
9			1000	2	93
10			1000	2	92
11[c]			200	12	71
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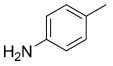
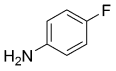
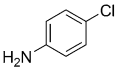
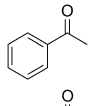
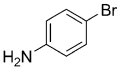
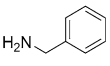
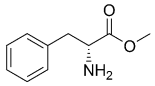
13			1000	2	91
14			1000	2	93
15			1000	10	77
16			200	24	59
17			2000	4	87
18			200	64	82

Table 2. (Continued)

Entry[a]	Ketone	Amine	S/C	t [h]	Yield [%][b]
19			500	24	44 (>99:1)[d]

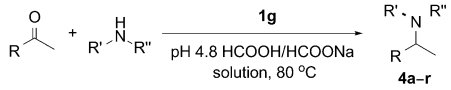
[a] Reaction conditions: ketone (2.5 mmol), amine (5 mmol), **1g**, HCOOH/HCOONa solution (pH 4.8, 4 mL), 80 °C. [b] Yield of the isolated product. [c] pH 4.2. [d] The diastereomeric ratio (d.r.) is given in brackets.

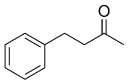
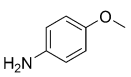
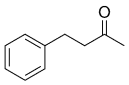
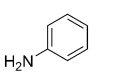
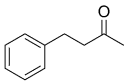
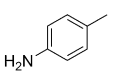
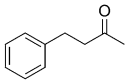
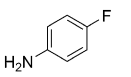
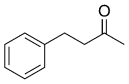
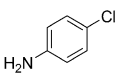
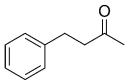
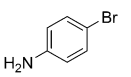
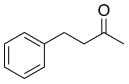
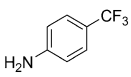
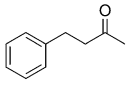
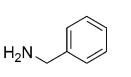
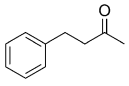
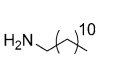
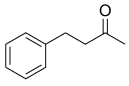
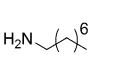
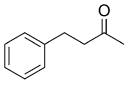
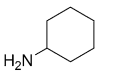
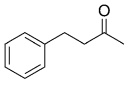
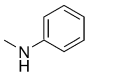
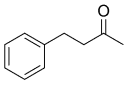
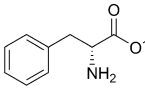
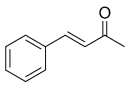
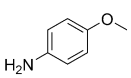
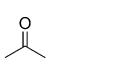
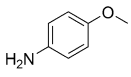
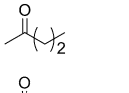
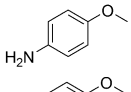
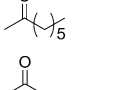
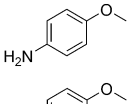
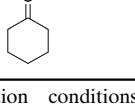
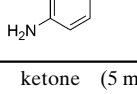
We also explored the RA of another type of carbonyl group, that is, aldehydes. Aldehydes were more reactive than ketones in general (Table 4). Over 90% yield were obtained for most of the aromatic aldehydes with different substituents reacting with *p*-anisidine at S/C of 2000 in 2 h (Table 4, entries 1–9). The only exception was found for *para*-chlorobenzaldehyde, which gave a lower yield of 79% (Table 4, entry 5). Switching to other aromatic amines with varying substituents showed that they reacted smoothly with benzaldehyde affording high yields (Table 4, entries 10–14). Aliphatic amines generally showed better activity in reactions with aldehydes than with ketones (Table 4, entries 16–18). Thus, a high yield of 97% was achieved for *n*-octylamine at S/C of 2000 in 2 h (Table 4, entry 16). In particular, the lower steric hindrance of the aldehydes compared with the ketones renders their reaction with secondary amines much easier (Table 4, entries 19). Similarly, *N*-methylbenzylamine reacted with benzaldehyde to afford an excellent yield of 98% (Table 4, entry 20). The methyl ester of phenylalanine is also a good amine donor (Table 4, entry 19).

In the RA of aldehydes, a slow background reaction was observed for the reaction of benzaldehyde with *p*-anisidine. As shown by the conversion–time profiles in Figure 6, the RA does happen in the absence of **1g**; but it is much slower than the RA catalysed with 0.05 mol% **1g**.

To explore the potential application of the catalytic iridium system in the practical synthesis of amines, we studied the RA of benzaldehyde with *p*-anisidine at higher S/C ratios. A pH value of 4.6 was used for these reactions to ensure the quantity of the hydrogen source to be sufficient. The results are shown in Table 5. As can be seen, at S/C = 1×10^4, where 25 mmol of aldehyde were used, the RA afforded a conversion of 91% within 10 h, with the amine isolated in 76% yield (Table 5, entry 1). At higher S/C ratios of 2×10^4 and 5×10^4 corresponding to a scale of 50 and 125 mmol of aldehyde, respectively, the reaction also worked quite well, affording yields of 91 and 88% in 16 and 36 h, respectively (Table 5, entries 2 and 3). Impressively, the reaction still proceeded well at still higher S/C of 1×10^5 (250 mmol scale), the highest S/C ratios ever reported for RA reactions (Table 5, entry 4).[8a]

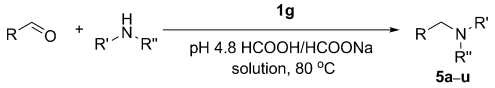
Table 3. RA of aliphatic ketones with different amines.

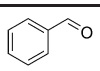
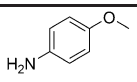


Entry[a]	Ketone	Amine	S/C	t [h]	Yield [%][b]
1			2000	2	98
2			2000	2	99
3			2000	2	98
4			2000	2	98
5			2000	2	99
6			1000	2	96
7			2000	2	79
8			2000	2	97
9			2000	2	54
10			1000	6	85
11[c]			200	48	52
12[c]			200	24	64
13			2000	3	95 (=79:21)[d]
14			1000	4	93
15			1000	2	98
16			2000	2	88
17			2000	2	98
18			2000	2	95

[a] Reaction conditions: ketone (5 mmol), amine (10 mmol), **1g**, HCOOH/HCOONa solution (pH 4.8, 8 mL), 80 °C. [b] Yield of the isolated product. [c] pH 5.0. [d] The d.r. value is given in brackets.

Table 4. RA of various aldehydes with different amines.



Entry[a]	Aldehyde	Amine	S/C	t [h]	Yield [%][b]
1			2000	2	98
2			2000	2	98
3			2000	2	95
4			2000	2	97
5			2000	2	79
6			2000	2	92
7			2000	2	97
8			2000	2	96
9			2000	4	97
10			2000	5	97
11			2000	2	94
12			2000	2	98
13			2000	2	99
14			1000	2	95
15			2000	2	96
16			2000	2	97
17			1000	4	83
18			1000	4	93
19			1000	5	72
20			1000	2	98
21			500	2	99

[a] Reaction conditions: aldehydes (5 mmol), amine (10 mmol), **1g**, HCOOH/HCOONa solution (pH 4.8, 8 mL), 80 °C. [b] Yield of the isolated product.

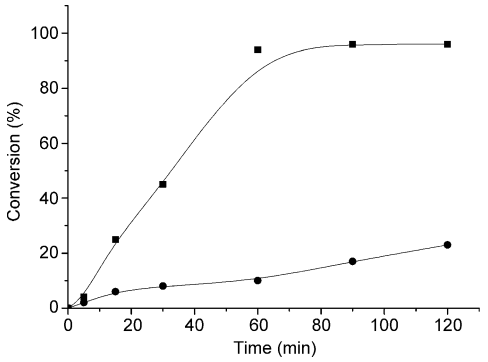
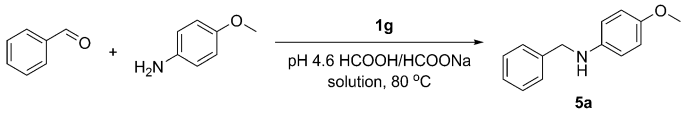


Figure 6. Comparison of catalysed RA with the background RA. Reaction conditions: benzaldehyde (5 mmol), *p*-anisidine (6 mmol), **1g** (0.0025 mmol), 80 °C. ■ = catalysed reaction, ● = background reaction without catalyst.

Table 5. RA at high S/C ratios.



Entry[a]	S/C	*t* [h]	Yield [%][b]
1	10000	10	91 (76)[c]
2	20000	16	91
3	50000	36	88
4	100000	48	95

[a] Reaction conditions: aldehydes (1 equiv; see the text for the amount used), amine (2 equiv), **1g**, HCOOH/HCOONa solution, 80 °C. [b] Determined by ^{1}H NMR spectroscopy by using 1,3,5-trimethoxybenzene as internal standard. [c] Number in brackets refers to the yield of the isolated product.

Conclusion

The reductive amination of various ketones and aldehydes with a range of amines has been realised with iridium-catalysed transfer hydrogenation in water, by using economic and less toxic formic acid as hydrogen source. The pH of the solution is shown to play an important role in regulating the activity and chemoselectivity of the RA, with certain acidic conditions necessary for optimal RA. The reaction proceeds in a heterogeneous manner, providing another example of transition-metal-catalysed "on water" reactions, is faster than that in organic solvents, where the reaction is homogeneous, and allows for unprecedentedly high S/C ratios. Thus, the cyclometallated iridium complex **1g**, which catalysed "on water" RA, offers an efficient, green and practical new method for accessing amines.

Experimental Section

General procedure for the preparation of the cyclometallated complexes:[15b,25] [{Cp*IrCl$_2$}$_2$] (Cp* = 1,2,3,4,5-pentamethylcyclopentadiene) (1 equiv), an imine ligand (2.2 equiv) and NaOAc (10 equiv) were placed into a Schlenk tube. The tube was then degassed and recharged with argon three times. Dichloromethane was then added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite and dried over $MgSO_4$. Following removal of the solvent under vacuum, the resulting solid was washed with diethyl ether/hexane. Single crystals suitable for X-ray analysis were obtained by diffusion of hexane into a solution of dichloromethane. The imine ligands were prepared according to the literature.[12e]

Typical procedure for the RA: A reaction tube was charged with a magnetic stir bar and *p*-anisidine (5 mmol). Acetophenone (2.5 mmol) was then introduced with a syringe, followed by catalyst **1g** (0.0025 mmol). To the mixture was injected a water solution of HCOOH/HCOONa (4 mL, pH 4.8), prepared from HCOOH (88%, 0.4 mL), HCOONa·2H$_2$O (2.45 g) and water (3.6 mL). The resulting mixture was bubbled with argon for 15 min and stirred at 80 °C for 2 h. After cooling to room temperature, the solution was adjusted to pH 2–3 with HCl (4 M), stirred for 10 min and then basified with aqueous NaOH solution (6 M) to pH 9–10. The resulting solution was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. After removing the solvent in vacuum, the product was purified by flash column chromatography (petroleum ether (m.p. = 60–90 °C)/ethyl acetate 30:1).

Acknowledgements

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