Communications

A Versatile Catalyst for Reductive Amination by Transfer Hydrogenation**

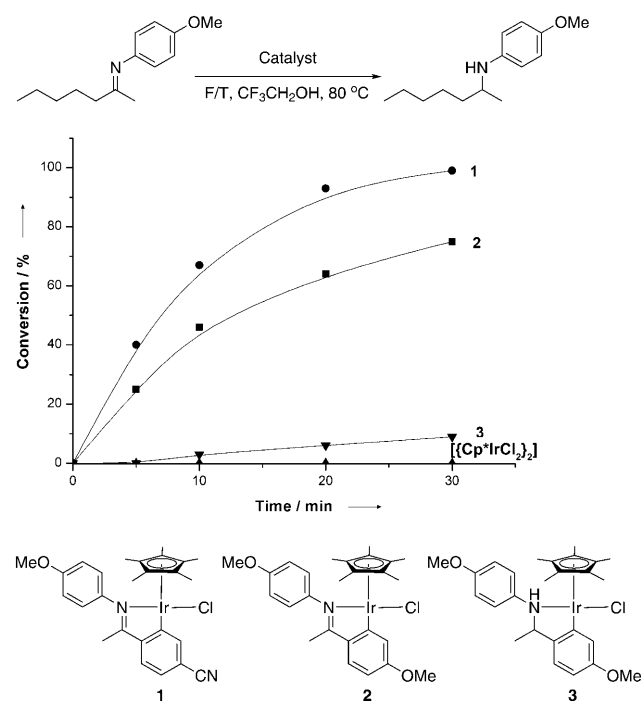*Chao Wang, Alan Pettman, John Bacsa, and Jianliang Xiao*

Reductive amination (RA), the coupling of ketones or aldehydes with amines in the presence of a reducing reagent, is one of the most studied and useful reactions in synthetic chemistry.[1] Applications of the reaction are widespread in the pharmaceutical, agrochemical, and chemical industries, materials science, and biotechnology.[1,2] In both academic research and commercial-scale preparations, RA is effected mainly with stoichiometric boron hydrides and heterogeneous hydrogenation.[2] Apart from generating copious waste, the use of boron hydrides is associated with other problems, such as the high toxicity of $NaBH_3CN$ and the inability to aminate aromatic ketones with $NaBH(OAc)_3$, two most widely used hydrides in RA.[1c,2a] RA by heterogeneous hydrogenation has long been practiced,[2b] but its application is limited by its relatively poor chemoselectivity, for example, reduction of C=O, C=C, and $-NO_2$ over C=N bonds.[1,2b] In the past decade or so, a small number of homogeneous catalysts and enzymes have been developed, allowing for enantioselective RA.[3–7] However, the substrate scope remains to be improved. Herein we disclose a class of air-stable cyclometalated imido Ir^{III} complexes that catalyze transfer hydrogenative RA with safe, inexpensive formate, providing high chemoselectivity and activity along with wide substrate scope.

Transfer hydrogenation has enjoyed a huge success in the reduction of ketones. However, its application in the reduction of imines, the key intermediate in RA, is less developed;[8,9] examples of transfer hydrogenative RA are even rarer.[7] In our effort to develop an asymmetric transfer hydrogenation system for RA, we initially examined reaction conditions for the transfer hydrogenation of a model imine prepared from acetophenone and *p*-anisidine, which was not reduced under asymmetric transfer hydrogenation conditions.[9] With a previously prepared [Cp*IrCl(Tsdpen-H)] catalyst [Cp* = pentamethylcyclopentadienyl; Tsdpen = (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine]

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(0.5 mol %),[10] 30% conversion to the corresponding amine in 13% *ee* was observed by using an azeotropic mixture of formic acid/triethylamine (F/T) in MeOH at 40°C in 3 h. Surprisingly, when the catalyst was prepared in situ by treating [{Cp*IrCl₂}₂] with Tsdpen, the conversion rose to 95%, but the resulting amine was racemic. Of yet further interest is that when [{Cp*IrCl₂}₂] (0.25 mol %) was used without any added ligand, the reaction proceeded to afford the same result as that obtained with the in situ catalyst.

These observations prompted us to ponder what the real catalytic species might be. One possibility is a cyclometalated iridium complex with the substrate ketimine acting as ligand through C–H activation.[11,12] This hypothesis was quickly supported by the fact that by simply stirring [{Cp*IrCl₂}₂] and the imine substrate in MeOH at 40°C for 1 h, the iridium dimer was converted into a cyclometalated imido complex in greater than 99% conversion.[13]

Encouraged by the results above, we then explored cyclometalated Ir^{III} complexes of aromatic ketimines for the reduction of an aliphatic ketimine, which itself is difficult to undergo cyclometalation and indeed showed no activity in the [{Cp*IrCl₂}₂]-catalyzed reduction (Figure 1). Dramatic accel-

Figure 1. Reduction of aliphatic ketimine (above) with cyclometalated iridium complexes and [{Cp*IrCl₂}₂]. Reactions were carried out on a 1 mmol scale at S/C = 4000 with 1 mL F/T in 3 mL CF₃CH₂OH. **1** (●), **2** (■), **3** (▼), and [{Cp*IrCl₂}₂] (▲).

eration in the reaction rate was observed by using cyclo-metalated iridium complexes. As is shown in Figure 1, at a substrate/catalyst (S/C) ratio of 4000, complex **1** afforded greater than 99% conversion in 30 min in trifluoroethanol, providing an initial turnover frequency (TOF) of 1.9×10^4 h^{-1}, the highest TOF value ever reported for transfer hydrogenation of imines.[7] The more electron-rich catalyst **2** displayed somewhat lower activity. In sharp contrast, complex **3**, derived from the saturated amine, showed much lower activity (Figure 1).[12a,b] The crystal structure of **1** was confirmed by X-ray diffraction; details are given in the Supporting Information. Various mono- and bidentate amine and phosphine ligands, for example, PPh₃, 1,3-bis(diphenylphosphino)propane (dppp), 2,2′-bis(diphenylphosphino)-1,1′-binathphtyl (binap), dpen, and Tsdpen, were also tested; however, they all failed to provide more than 10% conversion at S/C = 1000 in 15 min.

Subsequent examination of various imine substrates demonstrated that complex **1** is indeed both highly active and very versatile (Table 1). At an S/C ratio of 1000, both aromatic and aliphatic ketone-derived imines were reduced quickly, with the latter being reduced in 0.5–2 h (Table 1, entries 1–3). Aromatic ketimines tend to be less reactive; but full conversion was still reached in 5 h (Table 1, entries 4–7). The amine part of the imines can be either aromatic or aliphatic. Aldimines are particularly active under the conditions developed. Thus, even at S/C = 10000, the amine shown was isolated in 65% yield in 2 h (Table 1, entry 8).

RA was then investigated, initially using 2-heptanone and *p*-anisidine as substrates. A quick screening revealed that complex **2** was, somewhat surprisingly, more active than complex **1** in the cheaper solvent MeOH; the former showed conversion of 85% for the ketone while the latter showed 42% at S/C = 1000 in 20 min. The chemoselectivity is excellent in both cases; ketone reduction was scarcely detectable by ¹H NMR spectroscopy.

Using catalyst **2**, various aliphatic ketones were first reductively aminated in MeOH at S/C = 1000. As shown in Table 2, aliphatic ketones, including those that are α-branched, all reacted well with *p*-anisidine (Table 2, entries 1–6). In the case of 2-heptanone, a higher S/C ratio of 10000 was examined, affording the amine in 73% yield of the isolated product in 12 h (Table 2, entry 1). Benzylic, aliphatic, electron-deficient, and various secondary amines are also viable substrates, albeit requiring a higher catalyst loading or longer reaction time in some cases (Table 2, entries 7–13). To our delight, isolated and conjugated carbon–carbon double bonds are well tolerated (Table 2, entries 14, 15, and 20). Cyclic ketones are very reactive (Table 2, entries 16 and 17). However, β-ketoesters are less so, entailing an S/C ratio of 200 to give a satisfactory yield in 24 h (Table 2, entries 18 and 19); enamines were detected in the crude products. α,β-Unsaturated aldehyde was also reductively aminated with retention of the carbon–carbon double bond (Table 2, entry 20). Amino alcohols and amino acids are both suitable amine sources (Table 2, entries 21 and 22). Interestingly, amino acids coupled with D-glucose at either high or body temperature, and the product, which precipitated out of the reaction medium, could be readily isolated by simple

Table 1: Reduction of imines with complex **1**.

Entry[a]	Product	Time [h]	Yield [%][b]
1		0.5	97
2		2	94
3		2	91
4		5	93
5		5	92
6		5	97
7		5	95
8		0.5	96/65[c]

[a] Reaction conditions: imine (0.5 mmol), **1** (0.5 µmol), F/T (0.5 mL), CF₃CH₂OH (3 mL), 80 °C. [b] Yield of isolated product. [c] S/C = 10000 at 1 mmol scale for 2 h.

filtration, albeit with some product loss (Table 2, entries 23 and 24). This type of RA reaction may find applications in drug synthesis as well as biotechnology.[2]

Aromatic ketones were targeted next. These are less active substrates and indeed show low activity in RA with boron hydrides.[1c] Imine formation seems to be turnover limiting, as water scavengers or strong Lewis acids are usually employed to promote the condensation of an amine with a carbonyl substrate.[4b,g,5] Although the acidic environment in our system is expected to accelerate this first step of RA, aromatic ketones were still less reactive than their aliphatic counterparts. Hence, a lower S/C ratio of 200 was used. The results are presented in Table 3. Substituents on different positions of the aromatic ring of the ketones appear to have little influence on the yield (Table 3, entries 1–3). Both electron-withdrawing and -donating groups on the ring are tolerated (Table 3, entries 4–6), and there is no reduction of

Table 2: RA of aliphatic ketones and aldehydes with amines.

Entry[a]	Ketones/ aldehydes	Amines	Time [h]	Yield [%][b]
1	(aliphatic ketone)	H_2N–C$_6$H$_4$–OMe	1	98/73[c]
2	(benzodioxole ketone)	H_2N–C$_6$H$_4$–OMe	1	98
3	(isopropyl methyl ketone)	H_2N–C$_6$H$_4$–OMe	5	95
4	(branched ketone)	H_2N–C$_6$H$_4$–OMe	5	91[d]
5	(cyclopropyl methyl ketone)	H_2N–C$_6$H$_4$–OMe	5	92
6	(cyclohexyl methyl ketone)	H_2N–C$_6$H$_4$–OMe	5	96
7	(aliphatic ketone)	(benzylamine) NH_2	5	90
8	(benzodioxole ketone)	H_2N–C$_4$H$_9$	5	94
9[e]	(benzodioxole ketone)	H_2N–C$_6$H$_4$–Br	12	98
10	(benzodioxole ketone)	(pyrrolidine)	5	96
11	(benzodioxole ketone)	(N-methylbenzylamine)	5	83
12[e]	(benzodioxole ketone)	(N-methylbutylamine)	12	86
13[e]	(benzodioxole ketone)	(N-methylaniline)	12	95
14	(hex-5-en-2-one)	H_2N–C$_6$H$_4$–OMe	1	96
15	(methylheptenone)	H_2N–C$_6$H$_4$–OMe	1	97
16	(cyclohexanone)	H_2N–C$_6$H$_4$–OMe	1	99
17	(2-methylcyclohexanone)	H_2N–C$_6$H$_4$–OMe	1	99 (>16:1)[g]
18[f]	(methyl 2-oxocyclopentanecarboxylate, OMe)	H_2N–C$_6$H$_4$–OMe	24	80 (>99:1)[h]
19[f]	(β-ketoester, OMe)	H_2N–C$_6$H$_4$–OMe	24	71
20	(cinnamaldehyde)	H_2N–C$_6$H$_4$–OMe	1	90

Table 2: (Continued)

Entry[a]	Ketones/ aldehydes	Amines	Time [h]	Yield [%][b]
21	(benzaldehyde)	(diphenyl amino alcohol) HO, NH_2	1	93
22	(benzaldehyde)	(phenylalanine) NH_2, CO_2H	2	77/80[i]
23	(mannose sugar)	(phenylalanine) NH_2, CO_2H	5	65/63[i]
24	(mannose sugar)	(tryptophan) NH_2, CO_2H, HN-indole	5	73/70[i]

[a] Reaction conditions: ketone/aldehyde (0.5 mmol), amine (0.6 mmol), **2** (0.5 μmol), F/T (0.5 mL), MeOH (3 mL), 80 °C. [b] Yield of isolated product. [c] S/C = 10000 at 1 mmol scale for 12 h. [d] d.r. = 1.1:1. [e] S/C = 200 for 12 h. [f] S/C = 200 for 24 h. [g] *trans/cis* ratio. [h] *cis/trans* ratio. [i] The second number refers to the yield of isolated product at 37 °C for 12 h.

-CN and -NO$_2$ groups, which is a common problem faced in heterogeneous hydrogenation (Table 3, entries 4 and 5).[1,2b] Aromatic, benzylic, and aliphatic primary amines and cyclic secondary amines all served as good amine sources (Table 3, entries 8–11). However, an example of an electron-deficient amine proved less reactive, and some ketone reduction was noted (Table 3, entry 7). Acylic secondary amines are also less reactive, with less than 50% conversion observed in the amination of acetophenone under the standard conditions. Tetralone reacted well with both aromatic and benzylic amines (Table 3, entries 12 and 13). Both α- and β-ketoesters could be used to afford good yields (Table 3, entries 14 and 15). However, an unreacted enamine was again detected in the case of the β-ketoester. Although excellent diastereoseletivities were obtained with chiral amines, the yields were relatively low, possibly because of steric effects (Table 3, entries 16 and 17).
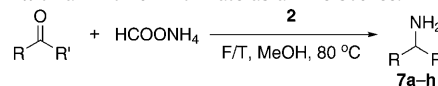
The use of ammonia as the amine source to generate primary amines without deprotection is highly desirable. To our delight, both ammonium formate and ammonia in MeOH could be used as viable amine sources. Table 4 shows examples obtained with ammonium formate. Aromatic ketones, including an α-branched one, worked very well, affording full conversions at S/C = 200 in 5–24 h (Table 4, entries 1–5). Reminiscent of the observations above, aliphatic ketones are more reactive. For example, Table 4, entry 6 shows full conversion with the more favorable S/C ratio of 1000 in 5 h. α- and β-Ketoesters again reacted well, thus allowing direct access to amino acids (Table 4, entries 7 and 8).

These RA reactions probably proceed via an ionic pathway, in which an Ir—H hydride is transferred to a protonated imine without coordination of the C=N moiety to the metal. The Noyori metal–ligand bifunctional mechanism is less likely.[14] We detected no reduction of the imino

Table 3: RA of aromatic ketones with amines.
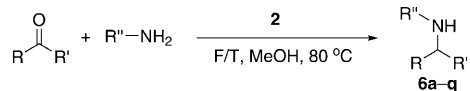
Entry[a]	Ketones	Amines	Yield [%][b]
1	acetophenone	H₂N–C₆H₄–OMe	92
2	MeO-substituted acetophenone	H₂N–C₆H₄–OMe	90
3	OMe-substituted acetophenone	H₂N–C₆H₄–OMe	87
4	NC-substituted acetophenone	H₂N–C₆H₄–OMe	95
5	O₂N-substituted acetophenone	H₂N–C₆H₄–OMe	90
6	MeO-substituted acetophenone	H₂N–C₆H₄–OMe	88
7	acetophenone	H₂N–C₆H₄–Br	71
8	acetophenone	benzylamine (C₆H₅CH₂NH₂)	90
9	OMe-substituted acetophenone	benzylamine	89
10	acetophenone	H₂N–butyl	91
11	acetophenone	pyrrolidine (NH)	92
12	1-tetralone	H₂N–C₆H₄–OMe	88
13	1-tetralone	benzylamine	80
14	methyl benzoylformate	H₂N–C₆H₄–OMe	81
15	ethyl benzoylacetate	H₂N–C₆H₄–OMe	75
16	2-acetylnaphthalene	(R)-α-methylbenzylamine	65 (>20:1)[c]
17	1-tetralone	(R)-α-methylbenzylamine	73 (>99:1)[c]

[a] Reaction conditions: ketone (0.5 mmol), amine (0.6 mmol), **2** (2.5 μmol), F/T (0.5 mL), MeOH (3 mL), 80 °C, 12 h. [b] Yield of isolated product. [c] The d.r. value is given in parentheses.

Table 4: RA with ammonium formate as amine source.

Entry[a]	Ketones	Time [h]	Yield [%][b]
1	acetophenone	5	85
2	isobutyrophenone	24	83
3	MeO-substituted acetophenone	12	88
4	1-tetralone	12	80
5	2-acetylnaphthalene	12	90
6[c]	methylenedioxyphenyl ketone	5	95
7	methyl benzoylformate (OMe)	5	93
8	methyl benzoylacetate (OMe)	12	90

[a] Reaction conditions: ketone (0.5 mmol), HCOONH₄ (5 mmol), **2** (2.5 μmol), F/T (0.5 mL), MeOH (3 mL), 80 °C. [b] Yield of isolated product. [c] S/C = 1000.

bond in **1** when **1** (15 mg) was subjected to heating (80 °C) in the presence of F/T (0.5 mL) in CF₃CH₂OH (0.5 mL) for 15 min, and as mentioned above, **3** is much less active (Figure 1).

In conclusion, cyclometalated iridium complexes have been identified as versatile catalysts, allowing the efficient RA of a wide variety of carbonyl compounds with a diverse range of amines and safe, inexpensive formate. We believe this is the first catalytic system that rivals boron hydrides in chemoselectivity, activity, and substrate scope. Further advantages include the modular nature of ligands and easy preparation of catalysts. Chiral versions of these catalysts are being developed in our laboratory.

Experimental Section

Typical procedure for RA: A carousel reaction tube was charged with a magnetic stir bar and *p*-anisidine (0.6 mmol). The tube was degassed and recharged with nitrogen three times. 2-Heptanone (0.5 mmol) was then introduced with syringe, followed by 1 mL of a solution of catalyst **2** in MeOH (5×10^{-4} mol L^{-1}). To the mixture was injected another 2 mL of distilled MeOH and finally 0.5 mL of HCOOH/Et₃N azeotrope. The resulting mixture was stirred at 80 °C for 1 h. The reaction mixture was cooled to room temperature, quenched with

Communications

water, basified with aqueous KOH, extracted with ethyl acetate, and purified by flash chromatography (hexane/ethyl acetate 10:1).

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