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Catalysis

Primary Amines by Transfer Hydrogenative Reductive Amination of Ketones by Using Cyclometalated Ir^{III} Catalysts

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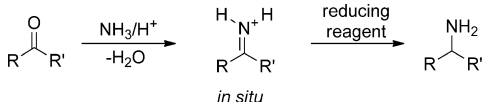
Abstract: Cyclometalated iridium complexes are found to be versatile catalysts for the direct reductive amination (DRA) of carbonyls to give primary amines under transfer-hydrogenation conditions with ammonium formate as both the nitrogen and hydrogen source. These complexes are easy to synthesise and their ligands can be easily tuned. The activity and chemoselectivity of the catalyst towards primary amines is excellent, with a substrate to catalyst ratio (S/C) of 1000 being feasible. Both aromatic and aliphatic primary amines were obtained in high yields. Moreover, a first example of homogeneously catalysed transfer-hydrogenative DRA has been realised for β-keto ethers, leading to the corresponding β-amino ethers. In addition, non-natural α-amino acids could also be obtained in excellent yields with this method.

Introduction

Primary amines are important motifs in organic compounds because of the presence of this functional group in numerous bioactive molecules and their widespread pharmaceutical applications. Hence, the efficient and economical production of primary amines is of high priority.[1] There are several methods with which these amines can be synthesised; typical examples include the reduction of nitriles, amides and nitro compounds,[2] alkylation of ammonia with organic halides[3] and hydroamination of alkenes.[4] However, one of the most desired and convenient ways of synthesising primary amines is by direct reductive amination (DRA),[5] in which a carbonyl group is condensed with an ammonia source and subsequently reduced in situ without the need of isolating the often unstable imine intermediate [Eq. (1)]. A well-known example is the classic Leuckart–Wallach reaction.[5i]



(1)

Reducing agents, such as pyridine borane, $NaBH_3CN$, and $NaBH(OAc)_3$ are commonly employed in the DRA process.[6] However, for successful, complete DRA, an excess amount of these boron reducing agents is often required. $NaBH_3CN$ is highly toxic and the final product is usually contaminated with cyanide. $NaBH(OAc)_3$ is poorly soluble in most commonly used organic solvents and pyridine borane, on the other hand, can be unsafe to use on industrial scales due to its propensity to violently decompose.[7] Heterogeneous catalysts have also been widely used in DRA;[8] however, poor chemoselectivity limits their performance. In this context, a homogeneously catalysed DRA would be of great interest. Indeed, a lot of effort has been made in developing homogeneous organocatalytic,[9] hydrogenative[10] and transfer hydrogenative[5f,11] catalytic systems for DRA in the past few years. However, they are mainly directed to the production of secondary and tertiary amines. In terms of primary amines, DRA reactions have been much less explored.

The first successful hydrogenative homogeneous metal-catalysed DRA with ammonia was reported by Beller and co-workers.[12] Although high selectivity was achieved towards primary amines, high temperatures and pressures were required (135 °C, 65 bar H_2). Most of the reported reactions were conducted with aromatic aldehydes and poor yields were obtained when aliphatic amines were used.[12] Kadyrov and co-workers also described the use of hydrogenative DRA with ammonia. However, the selectivity towards primary amine formation (vs. alcohol) and the yields obtained were relatively poor.[13] Subsequently, enantioselective DRA of β-keto amides and β-keto esters were also reported, albeit requiring high pressures of H_2.[14]

One way of overcoming these problems would be the transfer-hydrogenative DRA, by using a hydrogen source other than hydrogen gas. This is an operationally simple and versatile method for reduction, avoiding the need for high-pressure reactors that are typically required for hydrogenation.[7,15] The Leuckart–Wallach reaction uses formic acid as the reductant and no catalyst. However, it requires high temperatures and is poorly chemoselective. Despite the huge potential of catalytic DRA, only a few examples have been reported for the synthesis of primary amines by homogeneous metal-catalysed transfer hydrogenative DRA.[16] The first successful example of such a DRA with HCO_2NH_4 was reported by Kitamura and co-work-

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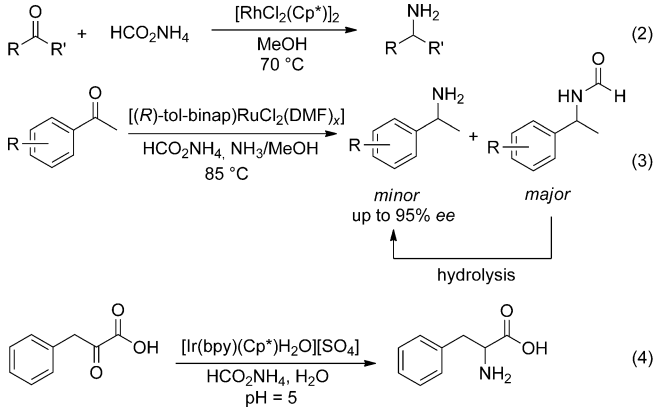
ers [Eq. (2)].[16a] The reaction conditions were milder than those used in the hydrogenative DRA and the catalyst was also effective in the DRA of α-keto acids. The substrate scope was, however, not satisfactory, and the selectivity towards primary amines was still an issue. Subsequently, Kadyrov and co-workers reported the enantioselective DRA with HCO_2NH_4 [Eq. (3)].[16b] The use of additional NH_3 was found to be crucial to enhance the enantioselectivity. High yields and enantioselectivities were only achieved in the case of aromatic ketones and inferior results were obtained when examples of aliphatic ketones were attempted. In addition, the selectivity towards primary amines was low, as *N*-formyl derivatives were obtained as the major products, which subsequently had to be hydrolysed. Ogo and co-workers reported a water-soluble catalyst that enabled DRA of α-keto acids under aqueous conditions [Eq. (4)].[16d] Optimal pH of 5 was critical for the selective synthesis of α-amino acids.



Although the few reports above have described the synthesis of primary amines by DRA, the results are still far from satisfactory. From the literature, we can highlight some major issues for both hydrogenative and transfer-hydrogenative DRA: 1) Substrate scope is limited, especially for ketones with additional functional groups, 2) selectivity towards primary amines is still a major challenge, 3) catalysts capable of the DRA of aliphatic ketones are highly desirable and 4) in terms of economy, a robust, versatile catalyst for the synthesis of primary amines by DRA is of high priority.[5a] Thus, developing a catalyst that overcomes these issues would be of great interest.

Recently, our group had developed a series of cyclometalated ketimine iridium complexes, iridicycles (Figure 1).[5f] Subsequently, we reported these catalysts for transfer-hydrogenation of carbonyls,[17] imines and DRA.[5f,18] These complexes are also highly effective in the hydrogenation of imino bonds and dehydrogenation of *N*-heterocycles.[19] Cyclometalated complexes based on rhodium, ruthenium and iridium have also been reported by other groups, and exploited in numerous reactions including oxidation of water.[20] Herein, we report the efficient synthesis of primary amines by transfer-hydrogenative DRA with these cyclometalated Ir^{III} complexes.[21]

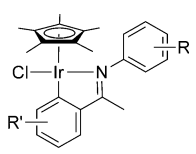


Figure 1. General structure of cyclometalated Ir^{III} complexes.

Results and Discussion

Aiming to find a robust catalyst for the DRA concerned, we first prepared a range of complexes **1a**–**k** (Figure 2), some of which had been reported recently.[18,19] In our study, 2-aceto-

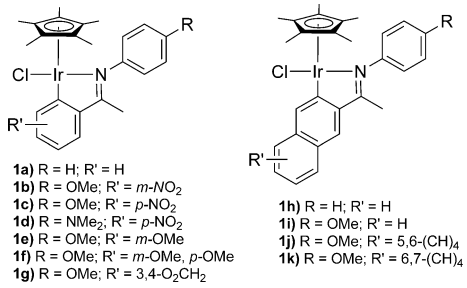
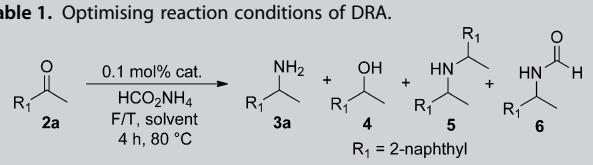


Figure 2. Cyclometalated Ir^{III} complexes examined in this study.

naphthone was chosen as a model substrate for the optimisation of reaction conditions. Our initial reduction experiments were carried out at an S/C ratio of 1000:1, by using 10 equivalents of HCO_2NH_4 and temperatures of 80 °C. The results are summarised in Table 1. Only 6% conversion was obtained when the reductive amination was carried out in the presence of the iridium dimer $[IrCl_2(Cp^*)]_2$ (Cp^* = 1,2,3,4,5-pentamethylcyclopentadienyl). Catalyst **1a**, bearing no substituents on the phenyl rings afforded 36% conversion with a high selectivity towards the primary amine **3a** (28% relative to the starting **2a**); however, the byproducts alcohol (**4a**), secondary amine (**5a**) and *N*-formyl (**6a**) were also observed in 5, 1 and 2% yields, respectively. These byproducts are common in metal-catalysed DRA reactions, although the later *N*-formyl derivative could be converted into the desired primary amine by one additional step of hydrolysis. Catalysts disfavouring the production of these byproducts, especially alcohol and secondary amine, would be highly beneficial. Catalyst **1b** and **1c**, with a *meta*- and *para*-NO_2 group (with respect to the imine) on the ligand did not improve the activity (Table 1, entries 3 and 4). When the R group was replaced with a more electron-donating $-NMe_2$ group, the activity decreased. Since the amino group might get protonated, we decided to continue with OMe as the R group (entry 5). Interestingly, catalyst **1e**, with an electron-rich OMe group at the *meta*-position significantly improved the catalytic activity, giving a 70% conversion in 4 h (entry 6). The result was slightly improved by introducing another methoxy group at the *para*-position also (entry 7). We further made the ligand more electron-rich and conjugated by introducing the 1,3-dioxol group on the phenyl ring. This led to a catalyst **1g** giving 98% conversion (Table 1, entry 8). These results were encouraging and led us to believe that conjugation may play an important role in the catalytic activity. We thus decided to replace the phenyl ring with other aromat-

Table 1. Optimising reaction conditions of DRA.



Entry[a]	Cat.	Solvent	Conv. [%][b]	**3a**[b]	**4**[b]	**5**[b]	**6**[b]
1	$[IrCl_2(Cp^*)]_2$	MeOH	6	–	1	–	5
2	**1a**	MeOH	36	28	5	1	2
3	**1b**	MeOH	9	5	1	1	2
4	**1c**	MeOH	38	35	–	1	2
5	**1d**	MeOH	12	7	3	1	1
6	**1e**	MeOH	70	64	2	2	2
7	**1f**	MeOH	86	79	2	2	3
8	**1g**	MeOH	98	90	3	2	3
9	**1h**	MeOH	42	34	4	1	3
10	**1i**	MeOH	99	94	1	2	2
11[c]	**1i**	MeOH	54	53	–	–	1
12[d]	**1i**	MeOH	82	65	9	3	5
13	**1j**	MeOH	93	84	1	2	6
14	**1k**	MeOH	65	53	4	3	5
15	**1i**	H_2O	99	1	98	–	–
16	**1i**	toluene	15	4	3	1	7
17	**1i**	DMF	18	3	–	2	13
18	**1i**	EtOAc	35	1	13	2	19
19	**1i**	TFE	96	81	4	3	8

[a] Reaction conditions: 2-acetonaphthone (0.5 mmol), HCO_2NH_4 (5 mmol), catalyst (5×10^{-4} mmol), HCO_2H/Et_3N (5:2) azeotrope (0.5 mL) and solvent (3 mL), stirred at 80 °C in a carousel tube for 4 h. [b] Determined by ^1H NMR spectroscopy (%). [c] In the absence of F/T azeoptrope. [d] Five equivalents of ammonium formate used.

ic rings, such as naphthyl and phenanthryl, which offer more extensive conjugation. To our delight, catalyst **1i**, which contains a naphthyl ring gave excellent results, with 99% conversion and a very high selectivity towards primary amines (entry 10).

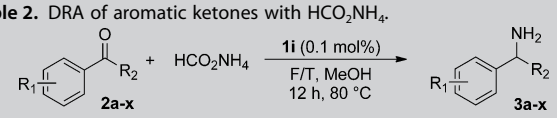
Addition of the formic acid–triethyl amine (F/T) azeotrope was found to promote the reaction. In its absence, the **1i**-catalysed reaction proceeded in only 54% conversion in 4 h (Table 1, entry 11). The F/T azeotrope increases the acidity of the reaction medium, and indeed it is known that the imine formation and its subsequent reduction benefits from the acidic conditions.[22] When the reaction was conducted with five equivalents of ammonium formate, the conversion decreased and formation of more byproducts was observed (entry 12). In contrast, the more conjugating catalysts **1j** and **1k**, bearing an anthracene and phenanthrene ring, respectively, gave lower conversions (entries 13 and 14). This is at least partly due to their low solubility in the reaction medium. It was confirmed that the reaction did not proceed in the absence of a catalyst.

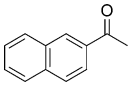
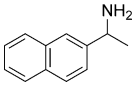
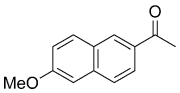
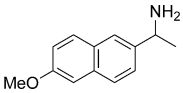
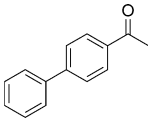
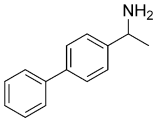
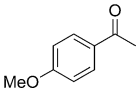
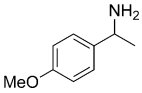
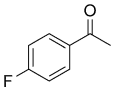
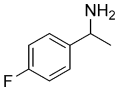
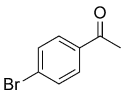
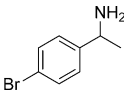
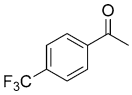
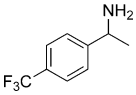
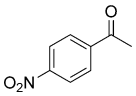
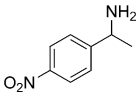
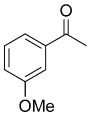
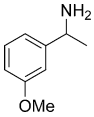
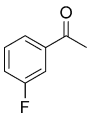
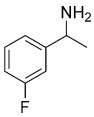
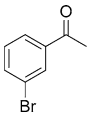
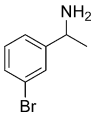
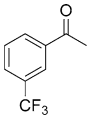
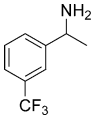
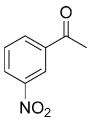
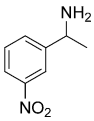
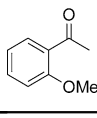
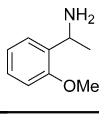
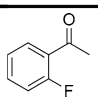
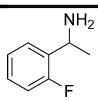
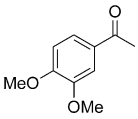
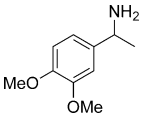
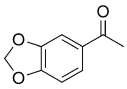
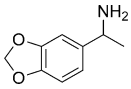
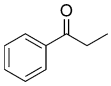
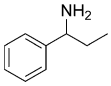
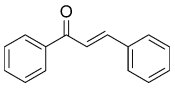
Next, we investigated the reaction in various solvents. MeOH was found to be the best medium, giving high selectivity towards the primary amine relative to other solvents (Table 1, entries 16–19). Interestingly, when the reaction was conducted in water, the reduction of ketone dominated, with the alcohol product observed in 98% ratio (entry 15). We have recently shown that aqueous media of lower pH favour the ketone reduction over the imine formation.[17,18]

The substrate scope was examined with catalyst **1i** under the optimised conditions (0.1 mol% **1i**, 80 °C in MeOH). The results of DRA of aromatic ketones are summarised in Table 2. All the phenyl derivatives, regardless of the nature of the substituents and their positions, gave excellent yields (Table 2, entries 3–16). The naphthyl derivatives also reacted well giving high yields (entries 1 and 2). Disubstituted aromatic ketones and those with increasing chain length at the α-position did not affect the yields of the product (entries 17–19). When an α,β-unsaturated ketone was subjected to the DRA under the present conditions, reduction of the carbon double bond was observed as well (entry 20). This suggests that when a double bond is present next to a carbonyl, 1,4-reduction pathway is favoured over 1,2-reduction, and it is not surprising, as 1,4-reduction is frequently observed in transfer hydrogenation.[23] The cyclic substrates, 1-indanone and 1-tetralone, both gave their corresponding amines in excellent yields (entries 21 and 22). In contrast to the α,β-unsaturated ketone, when 2-acetylbenzofuran was used, the double bond was retained, with 1-(benzofuran-2-yl)ethanamine obtained in 91% yield (entry 23), a result that reflects the aromaticity of the substrate. A thiophene ring was also tolerated well, affording 1-(2,5-dimethylthiophen-3-yl)ethanamine in an excellent yield (entry 24). It was found that a prolonged reaction time increases the concentration of *N*-formyl derivatives in these reactions. In fact, reaction times of 4–12 h were sufficient for the completion of the DRA.

Reactions of aliphatic ketones with HCO_2NH_4 are summarised in Table 3. As can be seen, 4-phenylbutan-2-one and its variant 4-(3,4-methylenedioxy)phenyl-2-butanone both were converted to their corresponding amines in excellent yields (Table 3, entries 1 and 2). Cyclohexanamine and 1-cyclohexylethanamine were also obtained in good yields (entries 3 and 4). Interestingly, a bulkier substrate, cyclododecanone, was also aminated in a high yield without any predicament (entry 5). Long-chain aliphatic substrates worked well, furnishing good yields regardless of the position of the carbonyl unit (entries 6 and 7). Still interestingly, 6-methylhept-5-en-2-one gave its corresponding amine in a very good yield, leaving its C=C double bond intact. This shows the selectivity of the catalyst towards C=N bond reduction over a C=C bond. Indeed, the reduction of C=C double bond is only observed when it is present at a position α to the C=O group. 3,3-Dimethyl-1,5-dioxaspiro-[5.5]undecan-9-one, a useful monoprotected form of the dione, was selectively aminated in excellent yield without the hydrolysis of its 1,3-dioxane being observed (entry 9). Thus, the catalytic system offers a simple and efficient way of obtaining aminocyclohexanones, which are useful intermediates, especially for the synthesis of Pramipexole, a dopamine agonist of the non-ergoline class used for the treatment of signs and symptoms of idiopathic Parkinson's disease.[24] 2-Aminotetralin, another key precursor, was also obtained in a very good yield from its corresponding β-tetralone (entry 10). 2-Aminotetralins are used in the synthesis of many therapeutic agents and have also been known to possess other pharmacological activities, including dopamine receptor activity.[25]

Table 2. DRA of aromatic ketones with HCO_2NH_4.



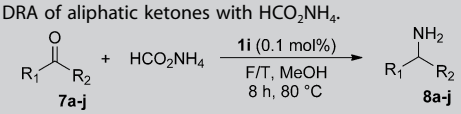
Entry[a]	Ketones	Amines		Yield [%][b]
1			**3a**	93
2			**3b**	94
3			**3c**	84
4			**3d**	91
5			**3e**	88
6			**3f**	89
7			**3g**	91
8			**3h**	85
9			**3i**	90
10			**3j**	89
11			**3k**	90
12			**3l**	87
13			**3m**	82
14			**3n**	88
15			**3o**	84
16			**3p**	86
17			**3q**	90
18			**3r**	92
19			**3s**	88
20			**3t**	82
21			**3u**	90
22			**3v**	87
23			**3w**	91
24			**3x**	92

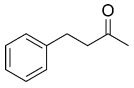
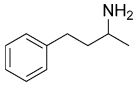
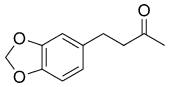
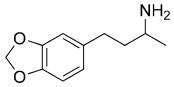
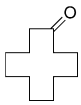
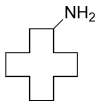
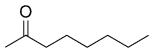
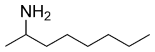
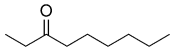
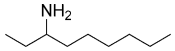
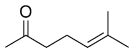
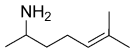
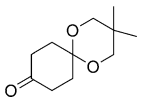
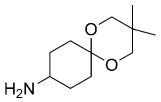
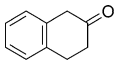
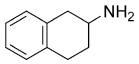
[a] Reaction conditions: ketone (0.5 mmol), HCO_2NH_4 (5 mmol), catalyst (5×10^{-4} mmol), HCO_2H/Et_3N (5:2) azeotrope (0.5 mL) and MeOH (3 mL), stirred at 80 °C in a carousel tube for 12 h. [b] Yield of isolated product.

Next, we expanded the substrate scope to β-keto ethers. The product β-amino ethers, generated from the DRA, are of biological interest as the analogues are effective sodium channel blockers.[26] To the best of our knowledge, the homogeneous metal-catalysed transfer-hydrogenative DRA of β-keto ethers has previously never been reported. Our protocol is mild and efficient, allowing direct access to β-amino ethers in a one-pot fashion. The results are presented in Table 4. As can be seen, 1-phenoxypropan-2-one, containing an aliphatic ketone and a phenoxy group, was aminated to give **10a** in a high yield (Table 4, entry 1). The amino ether product offers a valuable building block for the synthesis of various antiepileptic agents.[27] Aromatic β-keto ethers, regardless of the substituent nature, all reacted well under the present conditions (entries 2–4). Interestingly, unusual β-keto ethers bearing an aromatic ketone and fluoro-alkoxy group were also tolerated, leading to their corresponding amines in a good yield (entries 5–6). 2-Ethoxycyclohexanamine was also obtained in a good yield, showing again the excellent activity of **1i** towards the DRA of β-keto ethers (entry 7).

To further demonstrate the versatility of **1i**, the DRA of α-keto acids was targeted next and the results are summarised in Table 5. Non-natural α-amino acids are in the focus of inter-

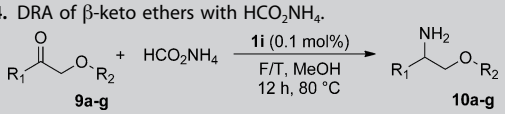
Table 3. DRA of aliphatic ketones with HCO_2NH_4.

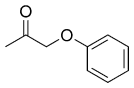
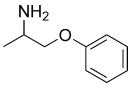
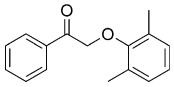
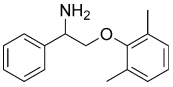
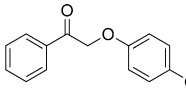
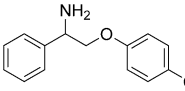
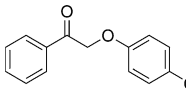
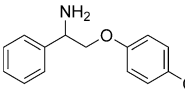
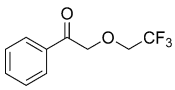
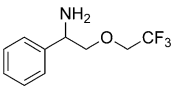
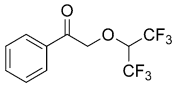
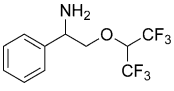
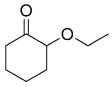
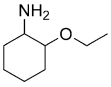


Entry[a]	Ketones	Amines		Yield [%][b]
1			**8a**	91
2			**8b**	93
3			**8c**	80
4			**8d**	83
5			**8e**	90
6			**8f**	80
7			**8g**	81
8			**8h**	83
9			**8i**	90
10			**8j**	87

[a] Reaction conditions: ketone (0.5 mmol), HCO_2NH_4 (5 mmol), catalyst (5×10^{-4} mmol), HCO_2H/Et_3N (5:2) azeotrope (0.5 mL) and MeOH (3 mL), stirred at 80 °C for 8 h. [b] Yield of isolated product.

Table 4. DRA of β-keto ethers with HCO_2NH_4.



Entry[a]	Ketones	Amines		Yield [%][b]
1			**10a**	87
2			**10b**	93
3			**10c**	90
4			**10d**	91
5			**10e**	74
6			**10f**	77
7[c]			**10g**	81

[a] Reaction conditions: ketone (0.5 mmol), HCO_2NH_4 (5 mmol), catalyst (5×10^{-4} mmol), HCO_2H/Et_3N (5:2) azeotrope (0.5 mL) and MeOH (3 mL), stirred at 80 °C for 12 h. [b] Yield of isolated product. [c] *syn/anti* ratio = 6:1.

est, as they are widely used as building blocks in drug synthesis, especially in the synthesis of semi-synthetic broad-spectrum antibiotics like Ampicillin and Amoxicillin.[28] Transfer-hydrogenative DRA of α-keto acids offers an easy way of generating these non-natural α-amino acids, in particular, as they cannot generally be synthesised through enzymatic methods.[16a,29] Electron neutral substrates, 2-oxo-2-phenylacetic acid and 2-(naphthalen-2-yl)-2-oxoacetic acid, were successfully aminated to their corresponding amines in near quantitative yields (Table 5, entries 1 and 5). Both electron-poor and -rich substrates gave excellent yields of their amines (entries 2–4). Interestingly, α-keto acids containing a heteroatom posed no poisoning effect on the catalyst, giving excellent yields (entries 6–7). The protocol is attractive not only because high yields are obtained, but also because the α-amino acid products precipitate from the reaction mixture and can be obtained by a simple filtration.

To showcase the synthetic utility of the DRA, we applied the protocol to a synthesis of Mexiletine, a class Ib antiarrhythmic agent that interferes with the sodium channel (Figure 3).[30] 1-(2,6-Dimethylphenoxy)propan-2-one was synthesised by reacting 2,6-dimethylphenol with chloroacetone.[30a] Transfer-hydrogenative DRA of the resulting β-keto ether by **1i** afforded the target Mexiletine with an overall yield of 77%. This two-step synthesis is economical and high-yielding under mild reaction conditions. A conventional three-step method, by using Raney nickel under hydrogenative conditions, has been described in the patents.[31]

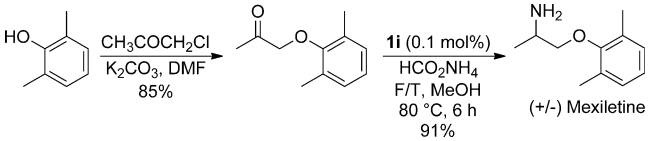
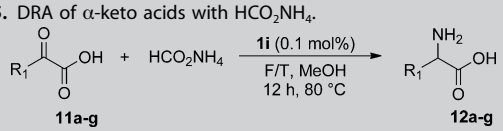


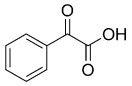
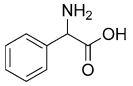
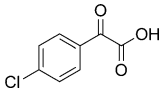
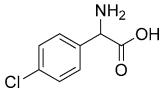
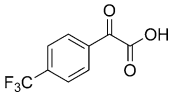
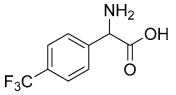
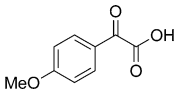
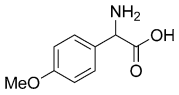
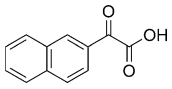
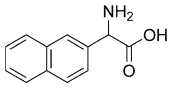
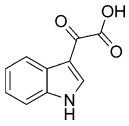
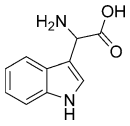
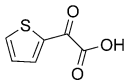
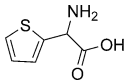
Figure 3. Synthesis of mexiletine by transfer-hydrogenative DRA.

A reaction mechanism for the DRA is proposed in Figure 4. Reduction by the catalyst **1i** most likely proceeds by the ionic mechanism,[32] as the catalyst does not offer metal–ligand bifunctionality.[33] Complex **1i** is first converted into **I** in the presence of formic acid. The decarboxylation of formate by iridium leads to the iridium hydride species **II**.[34] Simultaneously, an imine is generated through the condensation of a ketone with ammonia. This imine is protonated under the acidic conditions and enters the catalytic cycle as the iminium ion, where it is re-

Table 5. DRA of α-keto acids with HCO_2NH_4.



11a-g 12a-g

Entry[a]	Ketones	Amines		Yield [%][b]
1			**12a**	95
2			**12b**	91
3			**12c**	90
4			**12d**	88
5			**12e**	96
6			**12f**	94
7			**12g**	92

[a] Reaction conditions: ketone (0.5 mmol), HCO_2NH_4 (5 mmol), catalyst (5×10^{-4} mmol), HCO_2H/Et_3N (5:2) azeotrope (0.5 mL) and MeOH (3 mL), stirred at 80 °C for 12 h. [b] Yield of isolated product.

duced to the product by direct hydride transfer to the protonated C=N bond.[32,35]

In our preliminary studies, we monitored the DRA reaction of acetonaphthone **2a** in situ by ^1H NMR spectroscopy under the normal catalytic conditions but at room temperature. Formation of hydride **II** was confirmed and shown to be instantaneous. However, no other new species were observed at this temperature, which indicated that hydride transfer or imine generation may be more difficult than the hydride formation in the overall DRA.[36] Complex **II** was isolated and characterized by X-ray diffraction (Figure 5; see the Supporting Information for details). Our previous study suggests that the imine is reduced by the cyclometalated iridium hydride at room temperature only when it is present in its protonated but not neutral form.[34a] These results are in agreement with the proposed ionic mechanism.

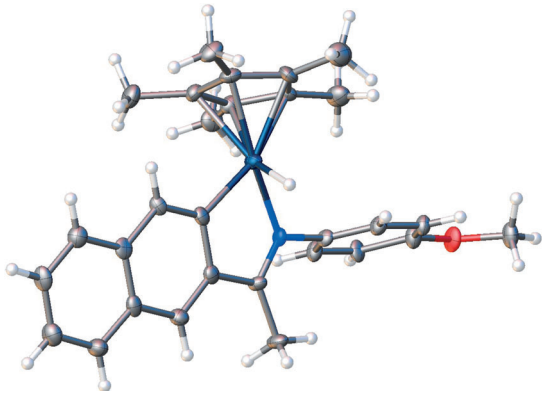


Figure 5. Molecular structure of the hydride **II** determined by X-ray diffraction. Thermal ellipsoids are displayed at the 50% probability (see the Supporting Information for details).

Conclusion

This paper demonstrates that primary amines can be readily accessed by the DRA of various ketones by using economic, safe and easy-to-handle ammonium formate. Cyclometalated iridium complexes hold the key, allowing the DRA to proceed with high productivity and excellent chemoselectivity toward primary amines under mild transfer-hydrogenative conditions. Aromatic ketones, aliphatic ones, α-keto acids and β-keto ethers are all viable substrates under the current conditions, showing the versatility of the iridicycle catalyst identified.

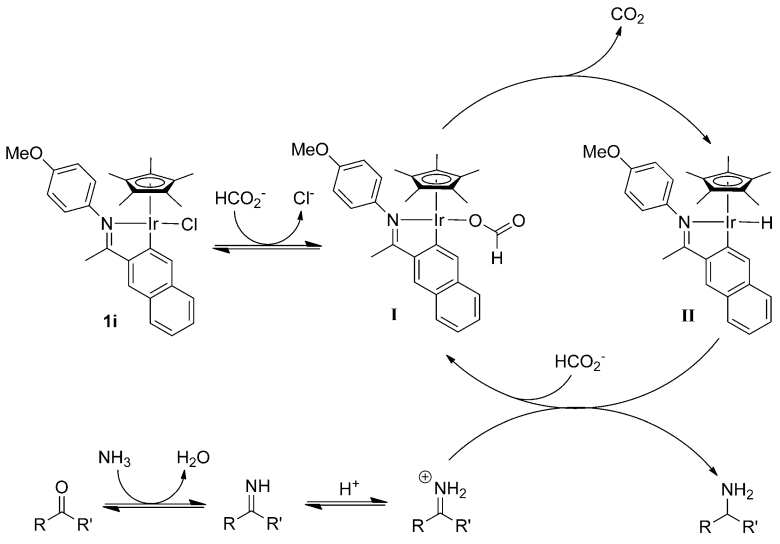


Figure 4. Proposed DRA mechanism under the present conditions.

Experimental Section

Typical procedure for the DRA of an aromatic/aliphatic ketone: 2-Acetonaphthone (85.1 mg, 0.5 mmol), **1i** (0.3 mg, 5×10^{-4} mmol) and HCO_2NH_4 (315.2 mg, 5 mmol) were placed in a carousel reaction tube. MeOH (3 mL) was introduced with a syringe and the resulting mixture was bubbled with nitrogen for 2 min. The F/T azeotrope (0.5 mL) was then added and the mixture

stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature and the solvent evaporated under vacuum. HCl solution (1 M) was added to the resulting residue and the mixture was washed with diethyl ether (2×15 mL) to remove the neutral compounds. The aqueous layer was basified with dilute KOH solution and bought to a pH of 10–12. It was then extracted with dichloromethane (3×30 mL) and the combined organic layers were dried over anhydrous sodium sulphate. Filtration followed by evaporation of solvent under reduced pressure gave **3a** in 93% yield.

Typical procedure for the DRA of a α-keto acid: 2-Oxo-2-phenylacetic acid (75.1 mg, 0.5 mmol), **1i** (0.32 mg, 5×10^{-4} mmol) and ammonium formate (315.2 mg, 5 mmol) were placed in a carousel reaction tube. MeOH (3 mL) was introduced with a syringe and the resulting mixture was bubbled with nitrogen for 2 min. The F/T azeotrope (0.5 mL) was then added and the mixture stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature and the resulting precipitate filtered off and washed with MeOH to give 2-amino-2-phenylacetic acid in 95% yield.

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Keywords: amines · iridium · ketones · reductive amination · transfer hydrogenation

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[36] Condensation of **2a** with ammonia was not observed even after heating the sample at 50 °C for 10 min.

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