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Air Stable Iridium Catalysts for Direct Reductive Amination of Ketones

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Abstract: Half-sandwich iridium complexes bearing bidentate urea-phosphorus ligands were found to catalyze the direct reductive amination of aromatic and aliphatic ketones under mild conditions at 0.5 mol% loading with high selectivity towards primary amines. One of the complexes was found to be active in both the Leuckart–Wallach (NH_4CO_2H) type reaction as well as in the hydrogenative (H_2/NH_4AcO) reductive amination. The protocol with ammonium formate does not require an inert atmosphere, dry solvents, as well as additives and in contrast to previous reports takes place in hexafluoroisopropanol (HFIP) instead of methanol. Applying NH_4CO_2D or D_2 resulted in a high degree of deuterium incorporation into the primary amine α-position.

Primary amines are key intermediates in fine and bulk chemical production,[1] in this regard, access to them from ketones in a single step is a desired but yet challenging chemical transformation. The classical uncatalyzed Leuckart–Wallach (LW) reaction utilizes ammonium formate both as a nitrogen source and as a reducing agent but requires high temperature (150–185 °C).[2] Additionally, the hydrolysis of the formed *N*-formyl side product to the corresponding primary amine decreases the yield significantly.

In the last two decades, the original reaction conditions have been improved via application of transition metal catalysis.[3a] One of the first reports on the catalytic LW-type direct reductive amination (DRA) utilized $[Cp^*RhCl_2]_2$ complex, which accelerated the conversion of a limited number of ketones and α-keto acids into the corresponding primary amines and amino acids.[3b] Soon after, a protocol of highly enantioselective Ru-catalyzed DRA of aryl ketones was published, yet the limited scope of substrates, high degree of formamide side product formation, and a necessity to add ammonia hampered its broad application.[3c] Significant breakthrough was achieved by utilizing iridium half-sandwich complexes.[3d–h] The performance of those catalysts bearing L-X type ligands was similar and demonstrated a high substrate to catalyst molar ratio (1000–20000) but demanded air-free conditions. The reactions take place in methanol and require addition of superstoichiomeric amounts of acetic acid or formic acid—triethylamine azeotrope in order to work at low catalyst loading. While the catalyst ligands can be extensively tuned to adjust steric or electronic effects, chiral variants have not been reported.

Besides the LW reaction, ketones can be converted into primary amines by reductive amination utilizing a combination of dihydrogen and ammonia or its equivalent (e.g., NH_4AcO).[4] Several protocols presented heterogeneous catalysts which operated at elevated temperatures (120 °C) in a high-pressure vessel setup.[4a–c] While the reaction can be practical in industrial applications, adapting this protocol for lab use can be laborious. The same holds true for a molecular Co-catalyst reported for hydrogenative DRA of aldehydes and ketones utilizing a triphosphine ligand.[4d] A significant breakthrough was achieved by employing a chiral diphosphine Ru-catalyst, which allowed access to highly enantioenriched primary amines using molecular hydrogen and ammonium acetate.[4e]

Herein, we present a simple Ir-based catalyst that is active in both types of reductive amination under mild conditions (50 °C) for a variety of substrates. The complex can be prepared in two simple steps, which makes it convenient for laboratory applications in primary amine synthesis and deuterium labeling.

Due to the straightforward assembly and high tunability, various P,N-chelating ligands have found utility in many catalytic hydrogenation reactions.[5] Preparation of **L1** and **L2** was achieved by treatment of *N*,*N*′-dimethylurea with the corresponding chlorophosphine or phosphorochloridate in the presence of a base (Figure 1). The carbamide moiety was used to build the rigid frame of the five-membered iridacycles.[6] After the reaction of $[Cp^*IrCl_2]_2$ with the corresponding ligands in the presence of triethylamine, the complexes **Ir-L1** and **Ir-L2** were isolated in good yields. The characterization was achieved via NMR and IR spectroscopies, as well as single-crystal XRD analysis. Comparison of the ν(CO) positions indicates that **L1** is more electron donating than **L2**. The molecular structures of **Ir-L1** and **Ir-L2** show a very similar distorted three-legged piano stool coordination geometry at the iridium center (Figure 1). Both complexes are bench-stable solids that can be stored for at least several months under an ambient atmosphere.

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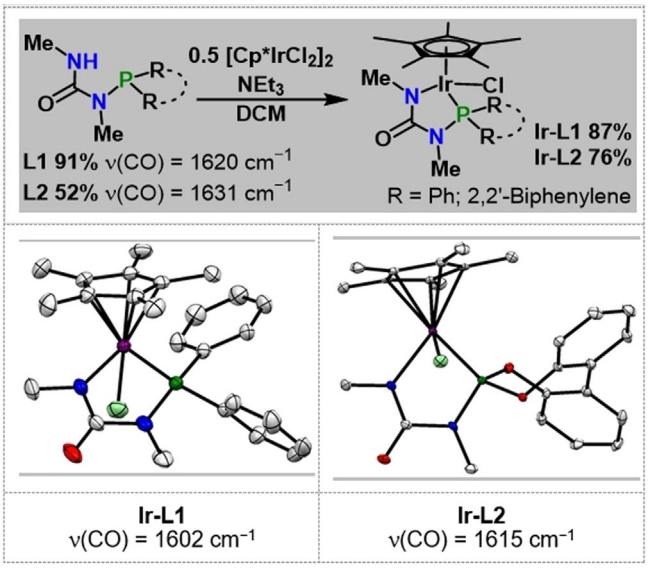
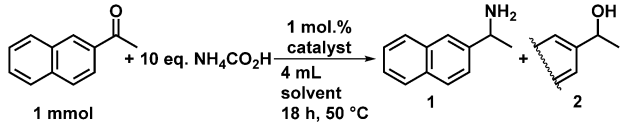


Figure 1. Synthesis of **Ir-L1** and **Ir-L2** complexes and MERCURY plots of their molecular structures.

In the initial optimization experiments, we carried out solvent screening using 1 mol% of **Ir-L1** at 50 °C with 2-acetonaphthone as a substrate (Table 1). The catalytic reaction was performed under an ambient atmosphere using solvents and starting materials as received from the suppliers. In the experiments using dry solvents and air-protective conditions, no effect on the yield or the selectivity was observed.

Surprisingly, the catalysts were almost inactive in methanol, which was previously reported as the most efficient solvent for DRA.[4] The performance increased significantly upon moving to trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP), respectively, with the complex **Ir-L1** showing slightly higher yields and selectivity compared to **Ir-L2** (Entry 3 and 6, Table 1). The better performance of the former complex can be attributed to the stronger donating ability of the ligand. Examination of additives such as *p*-TsOH or HCOOH/NEt_3 mixture as well as carrying out the reaction in nonafluoro-*tert*-butanol neither improved the yield nor the selectivity for **Ir-L2** (Table S1 in Supporting Information).

Table 1. Solvent screening in catalytic LW DRA of 2-acetonaphthone.



Entry	Catalyst	Solvent	Conversion [%]	Yield [%] 1	2
1	**Ir-L1**	methanol	9	9	0
2	**Ir-L1**	TFE	90	88	2
3	**Ir-L1**	HFIP	99	98	1
4	**Ir-L2**	methanol	0	0	0
5	**Ir-L2**	TFE	35	32	2
6	**Ir-L2**	HFIP	88	82	6

The crucial role of HFIP might be due to its previously reported facilitation of hydride transfer processes,[7a,b] or its ability to stabilize iminium cations.[7c] Further optimization demonstrated that the catalyst loading of **Ir-L1** could be reduced down to 0.5 mol% at 0.5 mmol mL^{-1} substrate concentration without affecting the performance (Table S2).[7a]

Next, we tested **Ir-L1** and **Ir-L2** in hydrogenative DRA in the presence of ammonium salts instead of ammonia (Table 2). Surprisingly, the **Ir-L1** complex showed high activity, while complex **Ir-L2** was almost inactive. Remarkably, only ammonium acetate provided conversion, while utilization of the corresponding carbonate, chloride and carbamate resulted in recovery of the ketone (Table S3). Similar to the catalytic LW protocol, the best result for **Ir-L1** was achieved in HFIP (Table 2).

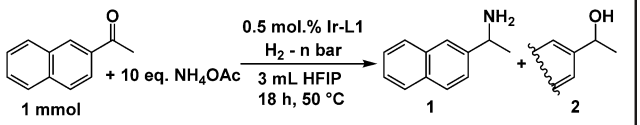
Addition of benzylamine or *p*-methoxy aniline instead of ammonium acetate did not result in the secondary amine formation and the starting materials were recovered. This feature of the catalytic system contributes to the selectivity towards the sole formation of primary amines.

The substrate scope was examined using both catalysts and both types of optimized reaction conditions (Figure 2). The substituted acetophenones bearing -NO_2 and -CN groups were successfully converted into the corresponding amines **3** and **4** in good yields, highlighting the high tolerance and selectivity of the catalytic system. Conversion of heterocyclic ketones occurred in good to excellent yields (Entries 7–9, Figure 2), where only in the case of 3-acetylpyridine 21% of the amine was obtained. The cyclic and benzylic ketones, such as tetralone and 2-phenylacetophenone reacted selectively to provide **10** and **11**. We were delighted that aliphatic ketones showed high reactivity, even cyclic ketones were successfully converted into the corresponding amines, such as cyclooctane-1-amine **15** and 2-aminoindan **16**. Remarkably, the 1,4-dioxaspiro[4.5]decan-8-amine **14** was isolated in 99% yield without the acetal deprotection.

A diastereoselectivity of $>$1:20 towards 3-methylcyclohexane-1-amine **12** was achieved. In the case of α-benzylideneacetone, the reduction of the C=C double bond along with amine formation were observed utilizing both catalytic conditions giving 4-phenylbutane-2-amine **17**.

To emphasize the utility and scalability of our catalytic system, we performed the LW DRA of 2,6-diacetyl pyridine with 0.1 mol% of **Ir-L1** loading to obtain 3.26 g of *rac*-α,α'-di-

Table 2. Influence of hydrogen pressure on the catalytic DRA of 2-acetonaphthone with **Ir-L1**.



Entry	Pressure of H_2 [bar]	Conversion [%]	Yield [%] 1	2
1	1	33	33	0
2	2	72	50	12
3	30	99	99	0
4	50	99	99	0

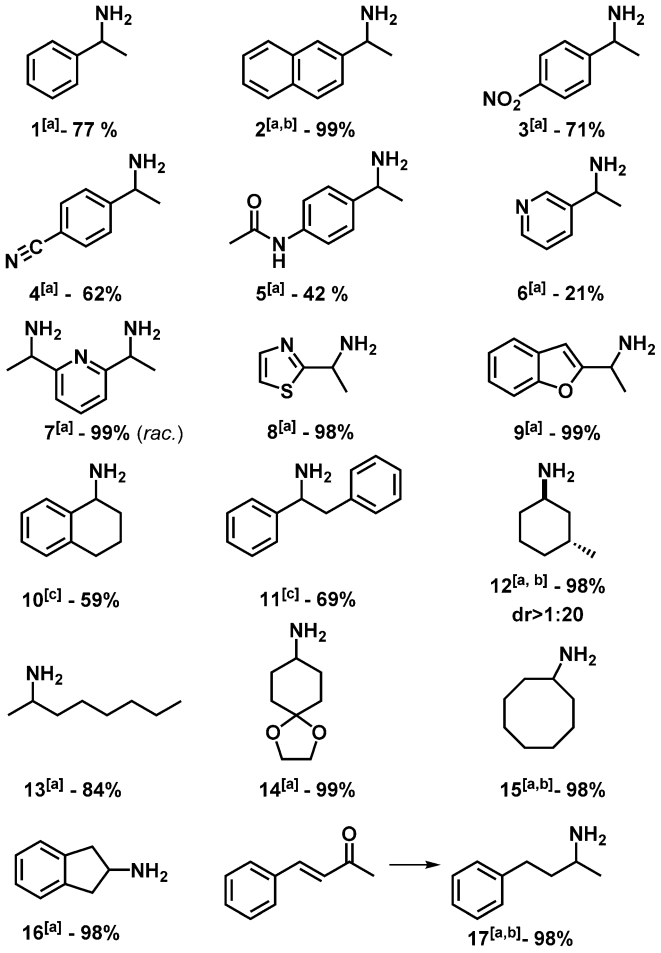


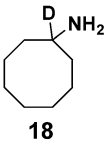
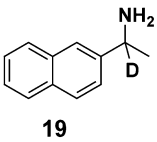
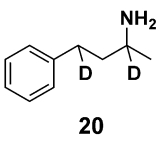
Figure 2. Scope of substrates for DRA using both catalytic conditions. Reaction conditions: a) 0.5 mol.% **Ir-L1**, 1 mmol. of substrate, 10 mmol. NH_4CO_2H, 4 mL HFIP, 50 °C, 18 h; b) 0.5 mol% **Ir-L1**, 1 mmol. of substrate, 10 mmol. NH_4AcO, 50 bar H_2, 3 mL HFIP, 50 °C, 18 h; c) 0.5 mol.% **Ir-L2**, 1 mmol. of substrate, 10 mmol. NH_4CO_2H, 4 mL HFIP, 50 °C, 18 h.

amino-1,3-dimethyl pyridine **7** in 98% yield. Important to note that no *meso*-byproduct formation was detected.

To get insight into the reaction mechanism, an excess of ammonium formate was added in an HFIP solution of **Ir-L2** which led to an immediate color change from orange to pale yellow. In the ^1H NMR spectrum a doublet at $\delta = -11.6$ ppm ($^2J_{P,H} = 37.2$ Hz) appeared, additionally, in the ^{31}P NMR spectrum a shift of the signal was observed from $\delta = 100.9$ ppm to $\delta = 104.6$ ppm, accompanied by a significant line broadening from $W_{1/2} = 21.3$ to 47.3 Hz. This result indicates iridium hydride complex formation, which is consistent with the NMR data of similar previously reported complexes.[8]

We decided to perform deuterium labeling experiments applying both catalytic protocols. Using D_2, the primary amines were isolated in excellent yields with 79–91% deuterium incorporation at the α-position (Table 3). In case of NH_4CO_2D, the degree of deuterium incorporation was slightly lower (42–60%).[3f] It is noteworthy, that due to keto-enol tautomerization, only the C1 and C3 positions were deuterated for the benzylideneacetone substrate in both catalytic protocols utilizing **Ir-L1** with D_2 gas and deuterated ammonium acetate or **Ir-L2** with ammonium formate. (Table 3). This observation additionally corroborates the previous reports that in the case of enones, the C=C double bond gets reduced first in the reaction.[3c]

Table 3. D-labeled amines obtained in DRA with D_2 and NH_4CO_2D.

Product/Reaction	 18	 19	 20
D_2, % of D	91	79	90
NH_4CO_2D, % of D	42	60	53

Reaction conditions: D_2 1 mol% **Ir-L1**, 1 mmol. of the substrate, 10 mmol. NH_4OAc, 3 mL HFIP, 18 bar D_2, 50 °C, 24 h. NH_4CO_2D −0.5 mol%. **Ir-L2**, 1 mmol. of the substrate, 10 mmol. NH_4CO_2D, 4 mL HFIP, 50 °C. In all cases, the amines were isolated in over 99% yield.

In this work, we demonstrated that bench-stable half-sandwich iridium complexes with a readily available P-N chelating ligands act as highly efficient catalysts in the reductive amination of ketones. **Ir-L1** was found to be active in LW type reaction as well as in hydrogenative DRA, showing its high potential for further development. The Ir-catalysts provide a convenient method for the synthesis of the primary amines from aromatic, aliphatic and heterocyclic ketones. The protocol with ammonium formate does not require a protective atmosphere and exclusion of moisture, which makes it convenient in laboratory applications. Utilizing D_2 or NH_4CO_2D allows a significant degree of deuterium incorporation to the α-position of the amine. Modification of the P-N ligand in a chiral fashion to access enantioenriched primary amines is currently being developed in our group.

Experimental Section

Full experimental details of ligand and complex synthesis, catalytic evaluation and characterization can be found in the Supporting Information.

Deposition Numbers 2064118 (for **Ir-L1**) and 2064119 (for **Ir-L2**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Conflict of interest

The authors declare no conflict of interest.

Keywords: deuteration · iridium catalysis · primary amines · reductive amination

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