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One-pot reductive amination of carbonyl compounds and nitro compounds *via* Ir-catalyzed transfer hydrogenation†

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The formation of C–N bond is a vital synthetic tool for establishing molecular diversity, which is highly sought after in a wide range of biologically active natural products and drugs. Herein, we present a new strategy for the synthesis of secondary amines *via* iridium-catalyzed one-pot reductive amination of carbonyl compounds with nitro compounds. This method is demonstrated for a variety of carbonyl compounds, including miscellaneous aldehydes and ketones, which are compatible with this catalytic system, and deliver the desired products in good yields under mild conditions. In this protocol, the reduction of nitro compounds occurs *in situ* first, followed by reductive amination to form amine products, providing a new one-pot procedure for amine synthesis.

Amines, particularly secondary amines, are not only prevalent in dyestuff, and chemosynthesis plants as important industrial materials, but also exist in a wide range of biologically active natural products and drugs.¹ Thus, the establishment of strategies to facilitate the formation of C–N bond is of longstanding significance in organic synthesis. A simple strategy to construct amines is the alkylation of amines with alkyl halides² or alcohols.³ The successful preparation of C–N bond would also be realized by Buchwald-Hartwig⁴ or Ullman-type cross-coupling reactions.⁵ Notably, strategies of reductive amination⁶ and addition reactions to imines⁷ have been described as in the C–N bond synthesis. Additionally, the reduction of amides⁸ also enables the formation of amine products. Given the simple and easy accessibility of raw materials, reductive amination undoubtedly enables the practical and direct formation of the C–N bond,⁹ which is shown as a step and atomic economy.

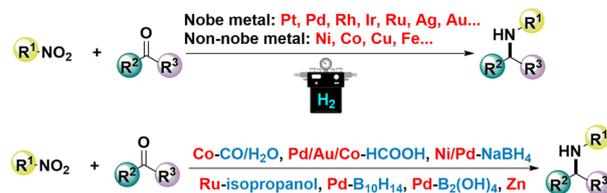
Nitro compounds, as readily available feedstocks, have been extensively employed for reductive amination with carbonyl compounds, in which the nitro compounds are converted into primary amines in advance, thereby avoiding the additional purification steps.¹⁰ In this context, a pioneering report on the reductive amination of carbonyl compounds with nitro compounds was described by Major's group in early 1931 with H₂ as the hydrogenation reagent.¹¹ Since this seminal work, extensive outstanding progress has been achieved over the past decades. In this regard, a heterogeneous catalytic system

utilizing noble metals (such as platinum,¹² palladium,¹³ rhodium,¹⁴ iridium,¹⁵ ruthenium,¹⁶ silver,¹⁷ and gold¹⁸) and non-noble metals (such as nickel,¹⁹ cobalt,²⁰ copper,²¹ and iron,²²) as catalysts have been established (Scheme 1a). Similarly, strategies based on the catalytic system with the form of metals, oxides, and other compounds as catalysts have been developed as well for the reductive amination of carbonyl derivatives with nitro compounds (Scheme 1a). However, synthetic methods for this one-pot reductive amination of nitro compounds were limited to H₂ as the hydrogen donor, which is inevitably constrained in the use of high-pressure devices and possesses potential safety issues.

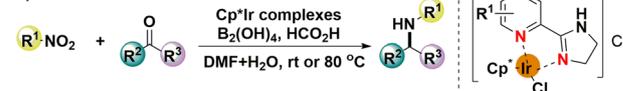
As a consequence, approaches for replacing hydrogen gas with other hydrogen donors, such as CO/H₂O,²³ HCO₂H,²⁴

Scheme 1a and 1b Reductive amination of carbonyl derivatives with nitro compounds.

a) Previous work:



b) This work:



Scheme 1 Reductive amination of carbonyl derivatives with nitro compounds.

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NaBH_4 ,²⁵ $\text{B}_{10}\text{H}_{14}$,²⁶ $\text{B}_2(\text{OH})_4$,²⁷ and Zn ,²⁸ for the reductive amination with nitro compounds have been established (Scheme 1a). However, great efforts to circumvent the harsh reaction conditions, narrow the substrate scope, long reaction times, complicated catalyst preparation processes, high catalyst loading, and well as side-reactions have been made in the past years.

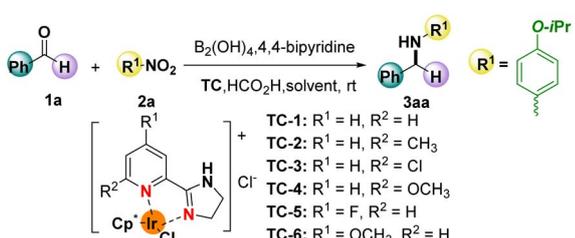
As such, transfer hydrogenation, which uses polyatomic molecules, including formic acid, alcohol, hydrazine hydrate, and silane as hydrogen donors, to migrate hydrogen to the unsaturated functional group directly with the assistance of catalysts. In this context, formic acid obtained from biomass, bearing the merits of high energy density, low cost, non-poisonousness, and stability, has been widely applied as a hydrogen source in transfer hydrogenation reactions. Recently, we have been working on the transfer hydrogenation of $\text{C}=\text{O}$, $\text{C}=\text{C}$, $\text{C}=\text{N}$ bonds using Cp^*Ir complexes as catalysts and formic acid as the hydrogen donor.²⁹ In these methods, we have demonstrated that these Cp^*Ir complexes could enable indirect and direct reductive amination for the construction of amine compounds.^{29a,d} However, reductive amination for the construction of $\text{C}-\text{N}$ bond *via* transfer hydrogenation with nitro compounds as the source of amine remains relatively limited. Herein, we present an iridium-catalyzed one-pot reductive amination of carbonyl compounds with nitro compounds (Scheme 1b). In this protocol, the reduction of nitro compounds occurs *in situ* first, followed by reductive amination to form the

amine products, providing a new one-pot procedure for amine synthesis.

To explore the possibility of the reaction, the reductive amination was started by using 1-isopropoxy-4-nitrobenzene (**2a**) and benzaldehyde (**1a**) as templates, and **TC** as the catalyst. As shown in Table 1, 98% conversion of the desired product **3aa** was observed using **TC-1** as a catalyst, 15.0 equiv. HCO_2H as the hydrogen donor, as well as DMF and H_2O as the mixed solvent ($v/v = 1:1$) after 4 h (Table 1, entry 1). Catalyst screening demonstrated the corresponding product **3aa** could be formed as well, though a lower conversion of the product was obtained (Table 1, entries 2–6). For instance, only moderate yields of the desired product were afforded when catalysts bearing methyl or chlorine substituents were employed (Table 1, entries 2 and 3). In contrast, good to excellent yields of the corresponding product were observed using fluorine or methoxyl-substituted catalysts (Table 1, entries 4–6). Of note, the increase in the reaction time had no influence on the yield of the product (Table 1, entry 7). However, a sharp decrease in the yield was observed when the catalyst loading of **TC-1** was decreased to 0.5 mol% (Table 1, entry 8). A similar negative influence on the yield of the product was also observed when different reaction media were loaded (Table 1, entries 9–12).

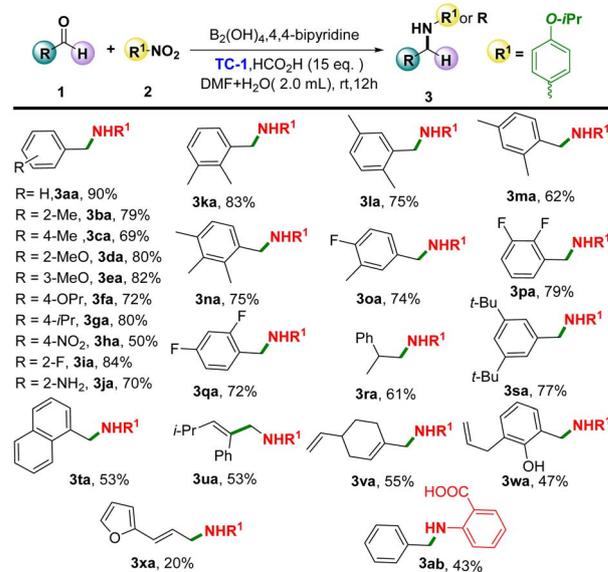
With the optimized conditions in hand, the substrate scope was investigated to explore its versatility (Scheme 2). Firstly, the 1-isopropoxy-4-nitrobenzene (**2a**) was loaded as an amination agent to react with various aldehydes. Gratifyingly, the desired reductive amination products of **3ba–3ga**, **3ia**, **3ja**, as well as **3sa** were afforded good yields with mono-substituted benzaldehydes as substrates. Of note, only a moderate yield of the corresponding product was achieved when 4-nitrobenzaldehyde

Table 1 Optimization of the conditions for Ir-catalysed reductive amination of aldehydes with nitro compounds^a



Entry	Catalyst	Solvent	HCO_2H (eq.)	Time (h)	Yield ^b (%)
1	TC-1	DMF + H_2O	15	4	98
2	TC-2	DMF + H_2O	15	4	66
3	TC-3	DMF + H_2O	15	4	48
4	TC-4	DMF + H_2O	15	4	92
5	TC-5	DMF + H_2O	15	4	89
6	TC-6	DMF + H_2O	15	4	76
7	TC-1	DMF + H_2O	15	12	99
8 ^c	TC-1	DMF + H_2O	15	12	54
9	TC-1	DMSO + H_2O	15	12	10
10	TC-1	H_2O	15	12	<5
11	TC-1	DMSO	15	12	<5
12	TC-1	DMF	15	12	<5

^a Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), solvent (2.0 mL), catalyst (0.005 mmol), HCO_2H (15.0 equiv.), $\text{B}_2(\text{OH})_4$ (6.0 equiv.), 4,4-bipyridine (0.05 mmol) at room temperature under air for 12 h. ^b Determined using GC-MS. ^c With 0.0025 mmol of the catalyst.



Scheme 2 Substrate scope of the aldehydes and nitro compounds. Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), solvent (2.0 mL), catalyst (0.005 mmol), HCO_2H (10.0 equiv.), $\text{B}_2(\text{OH})_4$ (6.0 equiv.), 4,4-bipyridine (0.05 mmol) at room temperature in air for 12 h. Yield of the isolated product.



was loaded as the substrate (**3ha**). Interestingly, the employment of multi-substituted benzaldehydes, including electron-donating or electron-withdrawing substituents on the phenyl group, could also enable the delivery of the corresponding products (**3ka–3pa**) in similar excellent yields. Obviously, the substrate **2w** bearing the potential oxidized hydroxyl group reacted smoothly as well under this system. Satisfactorily, employing aliphatic aldehydes, naphthaldehyde, as well as unsaturated aldehyde as substrates also furnished the corresponding products **3ra**, **3ta–3xa** in moderate to good yields. It is worth noting that the amino acid product of **3ab** was produced when 2-nitrobenzoic acid was loaded as the substrate.

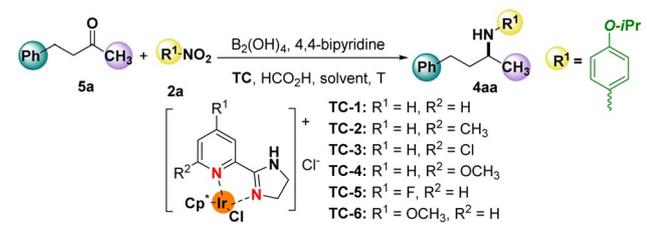
Encouraged by the results of the Ir-catalysed reductive amination of aldehydes with nitro compounds, the feasibility of using ketones as substrates was also investigated (Table 2). Firstly, 4-phenyl-2-butanone (**5a**) and 1-isopropoxy-4-nitrobenzene (**2a**) were chosen for the model reaction to optimize the reaction parameters. Catalyst screening (Table 2, entries 1–6) demonstrated that, unlike aldehydes, **TC-4** was found to be the optimal catalyst for the reductive amination of ketones, delivering 90% conversion of the desired product **4aa** at room temperature (Table 2, entry 4). Gratifyingly, the yield of

the product was slightly increased when the reaction temperature was increased to 80 °C (Table 2, entry 7). Similar to aldehydes, solvents have a significant influence on the reaction, producing completely different yields of the product in different reaction media (Table 2, entries 8–11). Of note, a similar high yield of the product was obtained even when the loading of the catalyst was decreased to 0.1 mol%, or the reaction time was shortened to 2 h (Table 2, entries 12–15). Control experiments evidenced that, indeed, a 30% yield of the corresponding reductive amination product of **4aa** could be afforded in the absence of $B_2(OH)_4$ under standard conditions (Table 2, entry 16). However, the iridium catalyst was essential for the formation of the desired product (Table 2, entry 17) (see ESI† for further details, F).

Based on the above optimizations, the substrate scope of ketones and nitro compounds was investigated (Scheme 3).

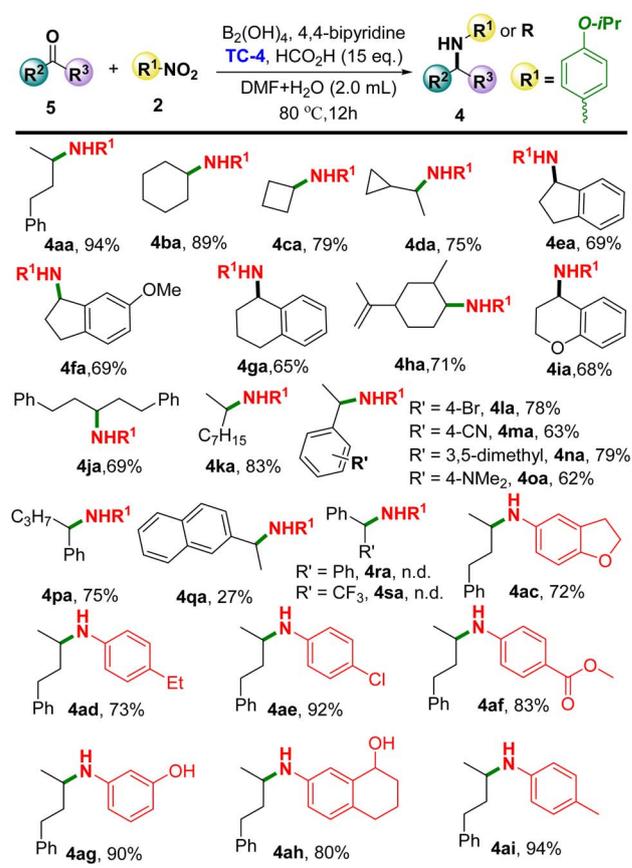
Firstly, the use of 4-phenylbutan-2-one (**5a**) as the substrate to react with 4-isopropyl nitrobenzene or heterocyclic nitrobenzene was explored to examine the versatility of this reductive amination. Gratifyingly, various cyclic aliphatic ketones loaded as substrates enabled the delivery of the target products (**4ba–4ga**) in moderate to good yields. Similar results were also

Table 2 Optimization of conditions for the Ir-catalysed reductive amination of ketone with nitro compounds^a



Entry	Cat.	T (°C)	Solvent	HCO ₂ H (eq.)	Time (h)	Yield ^b (%)
1	TC-1	rt	DMF + H ₂ O	15	12	59
2	TC-2	rt	DMF + H ₂ O	15	12	66
3	TC-3	rt	DMF + H ₂ O	15	12	38
4	TC-4	rt	DMF + H ₂ O	15	12	90
5	TC-5	rt	DMF + H ₂ O	15	12	34
6	TC-6	rt	DMF + H ₂ O	15	12	34
7	TC-4	80	DMF + H ₂ O	15	12	97
8	TC-4	80	DMF	15	12	34
9	TC-4	80	DMSO	15	12	<5
10	TC-4	80	H ₂ O	15	12	n.d.
11	TC-4	80	DMSO + H ₂ O	15	12	n.d.
12	TC-4	80	DMF + H ₂ O	10	12	95
13	TC-4	80	DMF + H ₂ O	12	12	97
14	TC-4	80	DMF + H ₂ O	15	2	97
15 ^c	TC-4	80	DMF + H ₂ O	15	12	94
16 ^d	TC-4	80	DMF + H ₂ O	15	12	30
17	—	80	DMF + H ₂ O	15	12	n.d.

^a Reaction conditions: **5a** (0.5 mmol), **2a** (0.75 mmol), solvent (2.0 mL), catalyst (1.0% mol), HCO₂H (15.0 equiv.), B₂(OH)₄ (2.25 mmol), 4,4-bipyridine (0.0375 mmol) at 80 °C in air for 12 h. ^b Determined using GC-MS. ^c The reaction was carried out using 0.0005 mmol of the catalyst. ^d Without B₂(OH)₄.



observed (**4ha** and **4ia**) when unsaturated ketones or heterocyclic ketones were employed in this catalytic system. Obviously, the use of aliphatic ketones with long carbon chains **5j** and **5k** as the substrates did not have an influence on the yields of the desired products (**4ja** and **4ka**). It should be noted that aromatic ketones were also well tolerated in this system to produce the corresponding products (**4la–4pa**). Nevertheless, only 27% of the target product (**4qa**) was provided using a more steric hindrance of 1-(naphthalen-2-yl)ethan-1-one (**5q**) as the substrate. Disappointingly, benzophenone (**5r**) or 2,2,2-trifluoro-1-phenylethan-1-one (**5s**) substrates could not be tolerated in this catalytic system. On the other hand, different substituted nitro compounds were also investigated in this system. Satisfyingly, heterocyclic substrates such as 5-nitro-2,3-dihydrobenzofuran (**2c**) were well tolerated to afford the desired product **4ac** in good yield. Interestingly, di-functional conversion products of **4ad** and **4ah** were observed when 1-ethynyl-4-nitrobenzene (**2d**) and 7-nitro-3,4-dihydronaphthalen-1(2H)-one (**2h**) were loaded, in which, both the alkyne and carbonyl groups were reduced simultaneously. It is notable that the chlorine (**2e**), methyl (**2i**), ester (**2f**), and even the readily oxidized phenol hydroxyl (**2g**) substituted nitro compounds were compatible with this system, delivering the corresponding products in excellent yields.

The model reaction was scaled up to investigate the practicability of this protocol (Scheme 4). Gratifyingly, 2.32 g target product of **4aa** was produced in 82% yield after 12 h by loading 10.0 mmol of **5a** as substrate under standard conditions, indicating that this protocol could be followed for scalable performance. Of note, this model reaction was also investigated with chiral **TC-7** as the catalyst, and only the racemic product **4aa** was afforded (see ESI† E).

According to the experiment and previous work,^{29d} a possible mechanism was proposed, as shown in Scheme 5. This catalytic

cycle involved two processes, in which amine **6** was produced *in situ* with $B_2(OH)_4$ as the catalyst, followed by condensation with carbonyl compounds to form the imine intermediate **A**. With the intermediate in hand, the second process occurred successively, in which the **Int-I** was formed firstly, then followed by transfer hydrogenation to afford the desired product **4** and the catalytic cycle.

Conclusions

In summary, we established a new strategy for the synthesis of secondary amines *via* the iridium-catalysed reductive amination of carbonyl compounds with nitro compounds. A wide range of carbonyl compounds, including aliphatic or aromatic aldehydes and ketones, were well tolerated in this catalytic system, delivering the desired products in moderated to excellent yields under mild conditions. In this transformation, first, the reduction of nitro compounds was realized *in situ* with $B_2(OH)_4$ as the reductant, followed by reductive amination of carbonyl compounds to afford amine products, providing a new one-pot procedure for amine synthesis.

Conflicts of interest

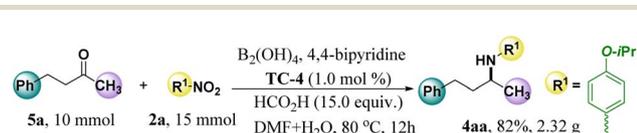
There are no conflicts to declare.

Acknowledgements

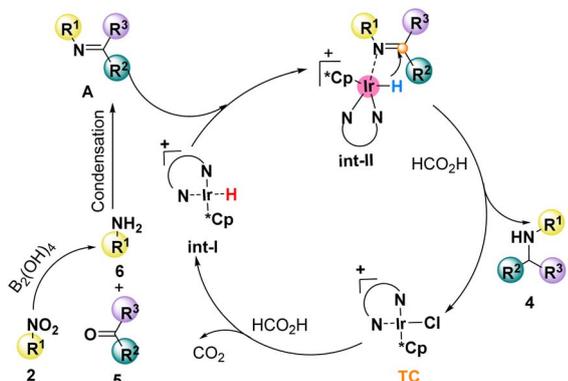
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Scheme 4 Scheme for the gram-scale experiment.



Scheme 5 Proposed mechanism.



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