EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202001097

Link to VoR: https://doi.org/10.1002/ejoc.202001097

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10.1002/ejoc.202001097

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One-Pot Transfer Hydrogenation Reductive Amination of Aldehydes and Ketones by Iridium Complexes "on Water"

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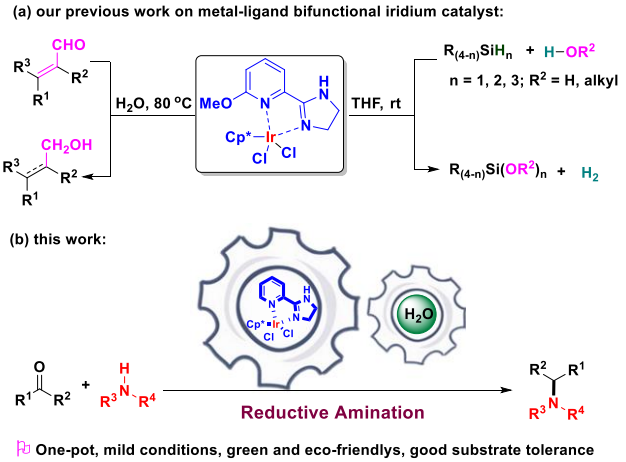
Abstract: An efficient and practical one-pot transfer hydrogenation reductive amination of aldehydes and ketones with amines has been developed by using iridium complexes as catalysts and formic acid as hydrogen source in aqueous, providing an environmentally friendly methodology for the construction of a wide range of functionalized amine compounds in excellent yields (80%~95%). This effective methodology can be scaled up to the grams with 0.1 mol% catalyst loading and also be employed in the synthesis of medical substance such as Meclizine.

The construction of C-N bond plays a paramount role in organic chemistry, providing wide application in the area of bioactive molecules, pharmaceuticals agents and natural products and multifunctional materials.[1] Therefore, the research on the formation of C-N bond has always been a research hotspot. There are many means to achieve this transformation. For example, the reduction of imines, [2] the reductive amination of aldehydes, [3] the borrowing hydrogenation of alcohols and amines, [4] the reduction of amides, [5] the coupling of halogenated hydrocarbons [6] and boric acids[7] to amines, and the addition of amines and alkynes, [8] etc.

Among the above-mentioned common synthetic methods, reductive amination is the most direct and efficient method for the construction C-N bond.[9] Studies show that more than a quarter of reactions for the C-N bond formation were proceeded via reductive amination in the field of medicament synthesis.[10] Until now, homogeneous transition metal catalysts such as Rh,[11] Ir, [12] Ru,[13] Co[14] and Fe[15] employed in reduction amination have been reported. In order to improve the recycling of the catalysts, there are also reports of the heterogeneous metal catalysts such as Ru, [16] Ir, [17] Pd, [18] Pt, [19], Mn [20] and Au. [21] Besides, metal-free reduction amination of aldehydes was also reported.[22] Therefore, reductive amination has been the chemist's most common tools for the preparation of C-N bond transformation.

The half-sandwich Ir^{III} complexes, which coordinate with Cp-type ligand, which have the features of controllability, flexility, stability and ease to synthesize, [23] had been the most attractive and powerful catalysts for efficient assembly of new chemical bonds.[24] For example, Xiao[25a] and others[25b~e] reported the iridium complexs-catalyzed transfer hydrogenation reductive amination of carbonyl compounds with amines. Although outstanding research results had been made in the field of half-sandwich Ir^{III} catalysts,[25, 26] further design and synthesis of this type of iridium catalyst applied in the research of organic synthesis reactions still have important theoretical guidance and practical value.

Recently, we have strong interest in the design and synthesis of bis-nitrogen iridium complexes and their catalytic reactions. As our continuous effort in the development of iridium complexes-catalyzed organic transformation reactions, we developed the pH-dependent chemoselective transfer hydrogenation of *α*, *β*-unsaturated aldehydes[27] and selective hydroxylation and alkoxylation of silanes[28] (Scheme 1a).In our previous work, we found Tang's catalysts can efficiently catalyze the decomposition of formic acid to release carbon dioxide and hydrogen. In this catalytic system, formic acid can be used as a hydrogen source to generate active hydrogen in situ to realize the reduction of unsaturated compounds. There are two reaction processes for the reductive amination of carbonyl compounds and amines. Firstly, the amines react with the aldehydes and ketones to obtain imines. Then the imines are reduced to achieve reductive amination. According to preliminary research of our group and the reductive amination processes of carbonyls and amines, we envisaged using formic acid as the hydrogen source to generate active hydrogen in situ, realizing the one-pot

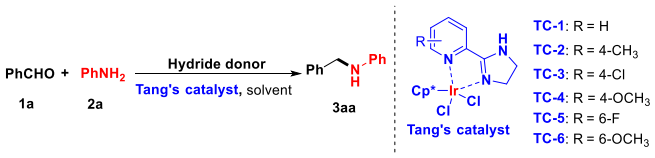


Scheme 1. Transfer hydrogenation and reductive amination of iridium complexes.

reductive amination of aldehydes and ketones. Herein, we reported transfer hydrogenation reductive amination of aldehydes and ketones via one-pot two-step procedure of various carbonyl compounds to synthesize functionalized amines in high yield under mild condition (Scheme 1b).

Compared with conventional method, one-pot two-step procedure method of carbonyl compounds with amine avoids the isolation of unstable imine intermediates, which has important value in terms of synthetic chemistry.[29]

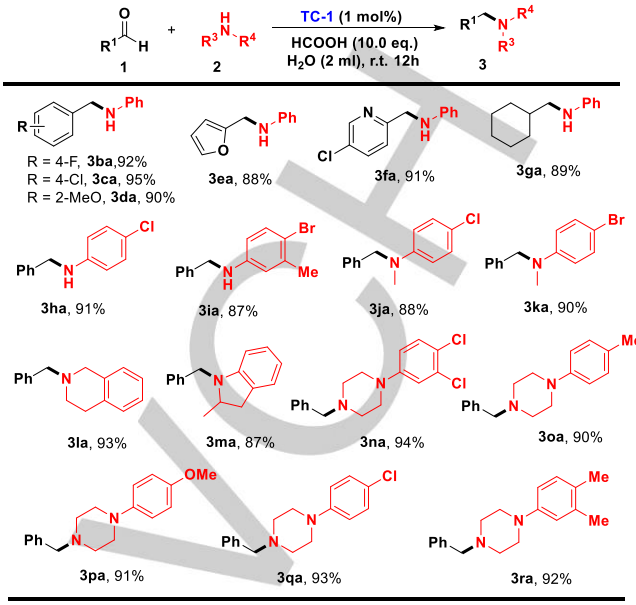
Table 1 Optimization of the reaction conditions. [a]



Entry	Catalyst	Hydrogen donor	Solvent	Yield (%)[b]
1	**TC-1**	HCOONa	MeOH	68
2[c]	**TC-1**	HCOOH/HCOONa	MeOH	56
3[d]	**TC-1**	HCOOH/NEt_3	MeOH	66
4	**TC-1**	HCOOH	MeOH	86
5	**TC-2**	HCOOH	MeOH	80
6	**TC-3**	HCOOH	MeOH	79
7	**TC-4**	HCOOH	MeOH	83
8	**TC-5**	HCOOH	MeOH	74
9	**TC-6**	HCOOH	MeOH	81
10	**TC-1**	HCOOH	toluene	55
11	**TC-1**	HCOOH	THF	86
12	**TC-1**	HCOOH	1,4-dioxane	78
13	**TC-1**	HCOOH	DCM	65
14	**TC-1**	HCOOH	Et_2O	77
15	**TC-1**	HCOOH	acetone	83
16	**TC-1**	HCOOH	DMF	78
17	**TC-1**	HCOOH	H_2O	95
18[e]	**TC-1**	HCOOH	H_2O	95(93)

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), solvent (2 mL), catalyst (0.005 mmol), hydrogen donor (10 equiv) at room temperature under air for 12 h. [b] Determined by GC-MS using dodecane as the internal standard. The number in the parentheses was isolated yield. [c] The reaction was carried out with 5.0 equiv of HCOOH, 2.0 equiv of HCOONa. [d] The reaction was carried out with 5.0 equiv of HCOOH, 2.0 equiv of Et_3N. [e] The reaction was conducted for 6 h.

We began our studies by employing benzaldehyde (**1a**) and aniline (**2a**) as the template reaction for the optimization of the reaction conditions (Table 1). When the reaction was carried out with **TC-1** as the catalyst and HCOONa as the hydrogen donor in methanol at room temperature for 12 h, moderate yield of the desired product **3aa** was detected by GC-MS analysis (entry 1). Interestingly, we found that the use of different hydrogen sources, such as HCOOH/HCOONa, HCOOH/NEt_3 led to moderate yield of **3aa** (Table 1, entries 2 and 3). When HCOOH was used as the hydrogen source, the reaction could proceed smoothly and afforded the desired product **3aa** in 86% yield (Table 1, entry 4). Further screening of other Tang's catalyst with different substituted functional group found that **TC-1** was the best choice for this reductive amination (Table 1, entries 5-9). In order to further improve the catalytic efficiency, a range of solvents were checked, which showed that hydrophilic organic solvents exhibited good catalytic activity, giving **3aa** in excellent yield (Table 1, entries 10-17). It's well known water is a green and friendly reaction solvent to environment. When water was chosen as reaction solvent under the standard condition, **3aa** was obtained in the yield of 95%. In addition, with water as the reaction solvent, the reaction can be completely converted in a shorter time (Table 1, entry 18).

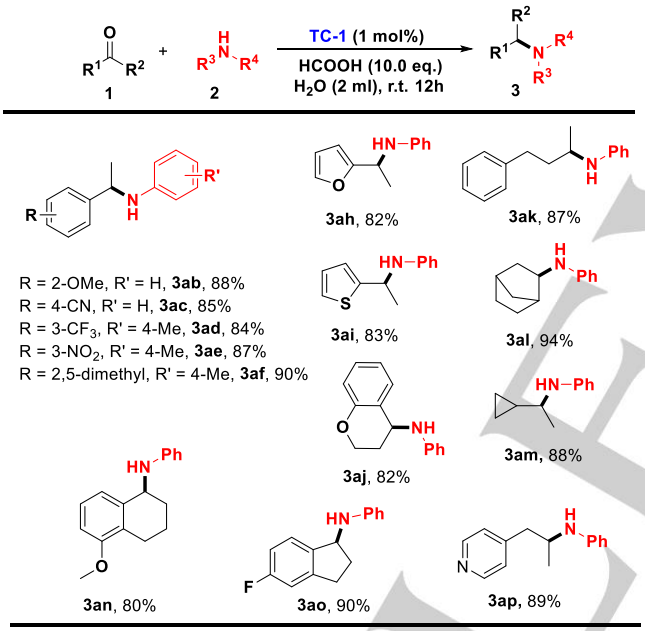


Scheme 2. Substrate scope of aldehydes and amines for reductive amination. Standard conditions: a solution of **1** (0.5 mmol), **2** (0.6 mmol), **TC-1** (0.005 mmol) and HCOOH (10 equiv) in H_2O (2 mL) at room temperature under air for 12 h. Yield of isolated product.

With the optimized reaction conditions in hand, the scope of transfer hydrogenation reductive amination of different aldehydes and amines was investigated by using Tang's catalyst on water (Scheme 2). To our delight, a range of aldehydes and amines, including aliphatic and aromatic aldehydes, aliphatic and aromatic amines, primary and secondary amines, could be compatible with this catalytic system, delivering the corresponding products in excellent yields under the standard reaction conditions. It is worth mentioning that aromatic aldehydes possessing halogen group could also undergo the reaction smoothly in high yields (**3ba**, **3ca**), in particular for the ortho position with steric hindrance on aromatic ring of aldehyde (**3da**). Furthermore, this reductive amination process could also be applied to heteroaromatic aldehydes such as furan, pyridine and aliphatic aldehydes, providing the desired products (**3ea**, **3fa, 3ga**) in high yields. Different kinds of amines were also proceeded for this strategy, which found the halogen substituted anilines and *N*-methylaniline conducted efficiently (**3ha-3ka**). In addition, the cyclic secondary amines such as tetrahydroisoquinoline and indoline, did not affect the formation of the desired products absolutely, leading to the corresponding amines in good yield (**3la**, **3ma**). Meanwhile, this catalytic system was also applicable for the reductive amination of different substituted *N*-phenyl piperazines under standard conditions, obtaining the corresponding amines in 90%-94% yields (**3na**-**3ra**).

Due to the excellent catalytic ability of this catalytic system for aldehydes and amines, various ketones with amines were also tested through Ir-catalyzed transfer hydrogenation reductive amination under standard conditions. According to the test results, the catalytic system was also compatible with various ketones. Ketones with the electron-donating group (EDGs) or

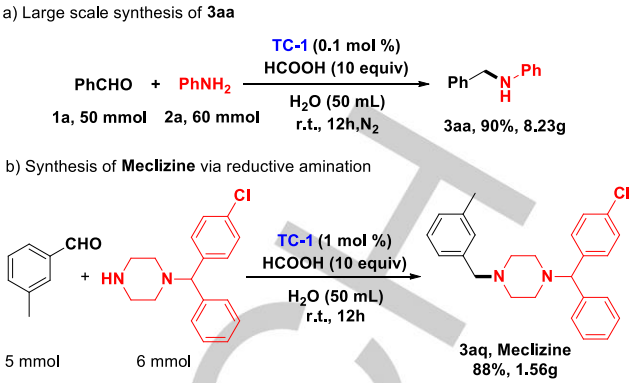
electron-withdrawing group (EWGs) on aromatic ring all undergoes smoothly under this catalytic symstem (Scheme 3). For example, using acetophenones substituted with EDGs such as methoxyl or methyl group as the substrates, desired amines products were achieved in high catalytic efficiency (**3ab**, **3af**). Meanwhile, substrates substituted with EWGs such as CN, NO_2, and CF_3 were practicable under standard condition in good yield (**3ac-3ae**). Interestingly, when heteroaromatic ketones were employed as the substrates with aniline under the standard condition, the corresponding products **3ah**, **3ai**, **3aj** could also be afforded in good yields. To further explore the practicability of this reductive amination, various aliphatic ketones, such as cyclopropyl methyl ketone, phenylacetone, 2-norbornanone, 5-fluoro-1-indanone, (4-pyridyl)acetone (**3ak-3am, 3ap**), were also subjected to the reaction. Fortunately, high yields were also obtained, which indicated execellent substrates tolerance. Besides, the reductive amination of cyclic ketones with aniline were also studied under aboving optimized conditions. Results showed that the corresponding amine (**3an**, **3ao**) were isolated in high yield.



Scheme 3. Substrate scope of ketones and amines for reductive amination. Standard conditions: a solution of **1** (0.5 mmol), **2** (0.6 mmol), **TC-1** (0.005mmol) and HCOOH (10 equiv) in H_2O (2 mL) at room temperature under air for 12 h. Yield of isolated product.

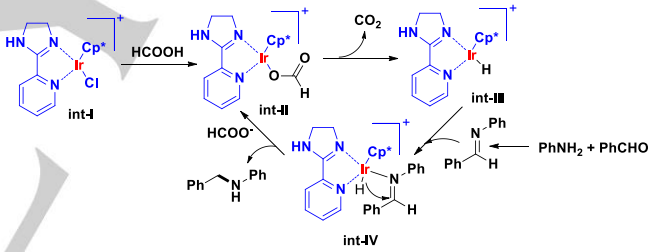
Encouraged by the above results, we next focused on the practical synthetic applications of this reductive amination. A scale-up experiment (**1a**, 50 mmol) and (**2a**, 60 mmol) was carried out under above established conditions with 0.1 mol% **TC-1** loading, giving **3aa** in the yield of 90% (Scheme 4a).

Meclizine is a blocker of H_1 histamine receptors by reducing the vasodilating and spasmogenic effect of histamine [30]. We envisage applying above effective methodology to the synthesis of this medical molecule. To our delight, Meclizine was afforded in the yield of 88% by this one-pot reductive amination (Scheme 4b).



Scheme 4. Large scale experiment and synthesis of Meclizine.

On the basic of experimental results and previous reports, we proposed a reaction mechanism as showed in Scheme 5. As we know, imines were obtained from carbonyl compounds and amines through dehydration condensation and subsequently reductive amination of imines happened. Details as follows, Firstly, **int-I** was transformed into **int-II** in the presence of the formate ion [31]. Decarboxylation of **int-II** was happened and produced the active **int-III**. Then, imines were trapped by **int-III** and generated a four-membered transition intermediate **int-IV** [32]. The desired products were achieved via the ligand exchange of **int-IV**, and **int-I** was released for the next catalytic cycles.



Scheme 5. Proposed mechanism for the transformation.

In summary, we have successfully developed a practical reductive amination between aldehydes/ketones and amines. The broad substrate scope, simple operation, good functional group tolerance and excellent yield are the attractive features of this transformation. Moreover, the using of water as reaction medium makes this methodology for the synthesis of various amines eco-friendly. In addition, the catalytic efficiency is high with the TOF up to 1000. The synthesis of Meclizine demonstrates this useful method has great potential synthetic applications. Ongoing studies are focused on further exploring the asymmetric hydrogenation and the results will be reported in due course.

Acknowledgements

The authors thank the National Natural Science Foundation of China (21961002, 21962004, and 21562004), Jiangxi provincial department of science and technology (20192BAB203004), Fundamental Research Funds for Gannan Medical University (QD201810), and the COVID-19 emergency project of Gannan Medical University (YJ202027) for financial support.

Keywords: reductive amination • transfer hydrogenation • aldehydes and ketones • amines • iridium complexes

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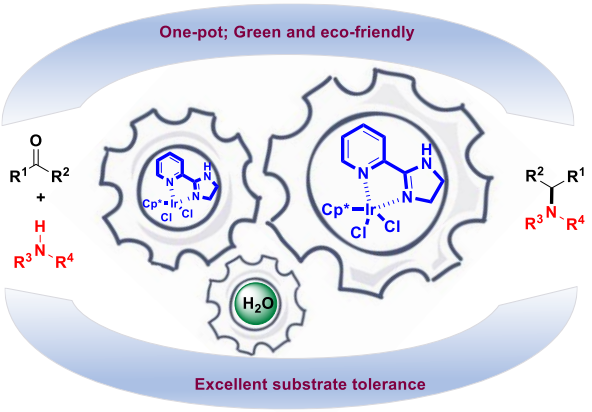
Reductive amination (key topic)



This is a practical reductive amination between aldehydes/ketones and amines for the construction of a variety of amine compounds in excellent yields. Moreover, the attractive features of this transformation are simple operation, good functional group tolerance and high catalytic efficiency. In addition, this useful method can be applied to the synthesis of Meclizine demonstrates.