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Article

Keywords: Direct reductive amination, amine synthesis, iridium catalysis

Posted Date: November 11th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1010397/v1

Practical *N*-Alkylation *via* Homogeneous Iridium-Catalyzed Direct Reductive Amination

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Abstract. Direct reductive amination (DRA) is one of the most efficient methods for amine synthesis. Herein we report a practical homogeneous DRA procedure utilizing iridium catalysis. Applying simple, readily available and inexpensive PPh_3 and alike ligands at as low as 0.003 mol%, aldehydes and ketones reductively coupled with primary and secondary amines to efficiently form structurally and functionally diverse amine products, including a set of drugs and their late-stage manipulation. The reaction conditions were exceptionally mild and additive-free, and they tolerated oxygen, moisture, polar protic groups and multiple other functional groups. For targeted products, this methodology is versatile and could offer multiple synthetic routes in regard to the selection of starting materials. The 10 gram-scale synthesis further demonstrated the potential and promise of this procedure in practical amine synthesis.

Introduction

The amino group is a privileged structural motif presenting prevailingly in pharmaceuticals, agrochemicals, biomolecules and natural products, and playing essential roles in their functions.[1-4] In fact, 910 out of 1086 (84%) FDA approved small-molecule drugs until 2014 contains at least one nitrogen atom with the average number of nitrogen atoms per drug at 2.3,[5] and amines is a major constituent part of nitrogen-containing compounds. Thus, the development of efficient catalytic reactions for the selective and practical construction of C−N bond from readily available starting materials by utilizing green reagents is one major goal of chemical research. The direct reductive amination (DRA), a one-pot procedure in which aldehydes or ketones reacts with inorganic ammonia/ammonium or organic amines in the presence of reducing agents, is a pivotal transformation for the synthesis of *N*-H and *N*-alkyl amines in organic chemistry.[6-9] Since the first report by Leuckart in 1885,[10] reductive amination has been

developed into one of the most practical methods for the production of alkyl amino pharmaceuticals and fine and bulky chemicals over the past century. Actually, reductive amination accounts for 25% of the total C−N bond forming reactions in the pharmaceutical industry.[6] Common reducing agents include boron hydrides, formate, silanes, isopropyl alcohol, Hantzsch esters and H_2.[11-16] The B-H reagents and molecular hydrogen are most frequently utilized both in academia and industry. While the procedure using boron hydrides will generate copious waste and also pose a potential explosion hazard, transition metal-catalyzed DRA using inexpensive and abundantly available H_2 as the reducing reagent is highly attractive in terms of reaction waste control and atom-economy with H_2O as the sole by-product, especially on a large-scale.[17-19]

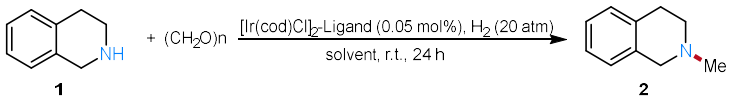
Reductive amination using heterogeneous catalysts based on group 10 metals (Ni, Pd, Pt) has been intensively investigated. In recent years remarkable progress was made in using nano-structured heterogeneous catalysts.[20-21] Although various heterogeneous catalytic systems have been widely applied in alkyl amine synthesis, oftentimes they are not compatible with many important functional groups, such as halogens (-F, -Cl, -Br, -I), nitro (-NO_2), nitrile (-CN), oxobenzyl (-OBn), and olefins (C=C). Besides, high catalyst loading and/or elevated reaction temperature are required in many catalytic systems. Compared with the heterogeneous catalysis, the homogeneous catalytic reductive amination is less developed. One of the major obstacles is the inhibitory effect on transition metals from the amine starting materials, imine/enamine intermediates and amine products. As a result, frequently those catalytic procedures suffer narrow substrate scope, requirement of excess additives, high catalyst loading, high reaction temperature and/or synthetically demanding catalytic complexes and ligands.[22-40] To date, successful universal catalytic systems with broad substrate scope are extremely scarce.[41-46] In this regard, highly efficient and practical homogeneous catalytic systems for more functional group tolerating with low catalyst loading and simplified and inexpensive ligands are immensely desired.

Herein we demonstrate that simple and inexpensive PPh_3, SPhos and BrettPhos ligands along with iridium are capable of efficiently catalyzing the reductive amination reaction under remarkably mild conditions. Catalyzed by as low as 0.003 mol% of the Ir-monophosphine complex, readily available carbonyl compounds (aldehydes and ketones), amines and molecular hydrogen were efficiently transformed into functionalized and structurally diverse secondary and tertiary amines. The related amino acid derivative modification, late-stage manipulation of drugs containing multiple functional groups, and scale-up reactions were also performed.

Results

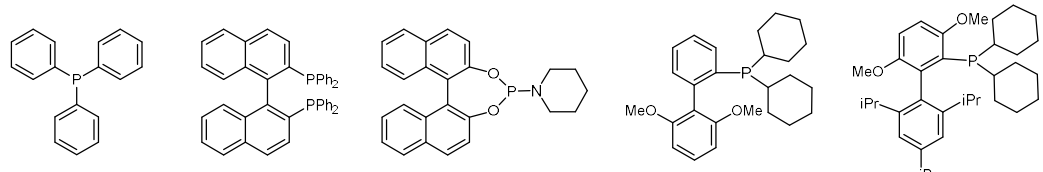
Reaction development. *N*-Methyl is a highly important structural domain in regulating the biological and pharmaceutical properties of bio-active molecules.[47-48] Traditionally *N*-methylamines are synthesized from SN_2 substitutions using methylation agents, such as methyl iodide, dimethyl sulfate and diazomethane, or by reductive amination of amines and formaldehyde. We set out our research to explore the DRA reaction of natural alkaloid tetrahydroisoquinoline **1** and paraformaldehyde (Table 1). To make this procedure more practical, we selected one of the simplest and most inexpensive phosphine ligands, triphenylphosphine (PPh_3), with $[Ir(cod)Cl]_2$ as the metal precursor, and set the initial catalyst loading at 0.05 mol%. With the *in situ* generated iridium-triphenyl phosphine complex as the catalyst and methanol as the solvent, the desired product *N*-methyltetrahydroisoquinoline **2** was obtained in 79% yield. Solvent

Table 1. Initial reaction development.[a]



1 2

Entry	Ligand	Cat. (mol%)	Solvent	Yield (%)
1	PPh_3	0.05	MeOH	79
2	PPh_3	0.05	CH_2Cl_2	41
3	PPh_3	0.05	EtOAc	16
4	PPh_3	0.05	THF	16
5	PPh_3	0.05	toluene	24
6	PPh_3	0.05	CF_3CH_2OH	99
7	BINAP	0.05	CF_3CH_2OH	98
8	PipPhos	0.05	CF_3CH_2OH	97
9	Brettphos	0.05	CF_3CH_2OH	19
10	SPhos	0.05	CF_3CH_2OH	52
11[b]	PPh_3	0.05	CF_3CH_2OH	98
12[c]	PPh_3	0.05	CF_3CH_2OH	98
13[d]	PPh_3	0.05	CF_3CH_2OH	98
14[e]	PPh_3	0.003	CF_3CH_2OH	95



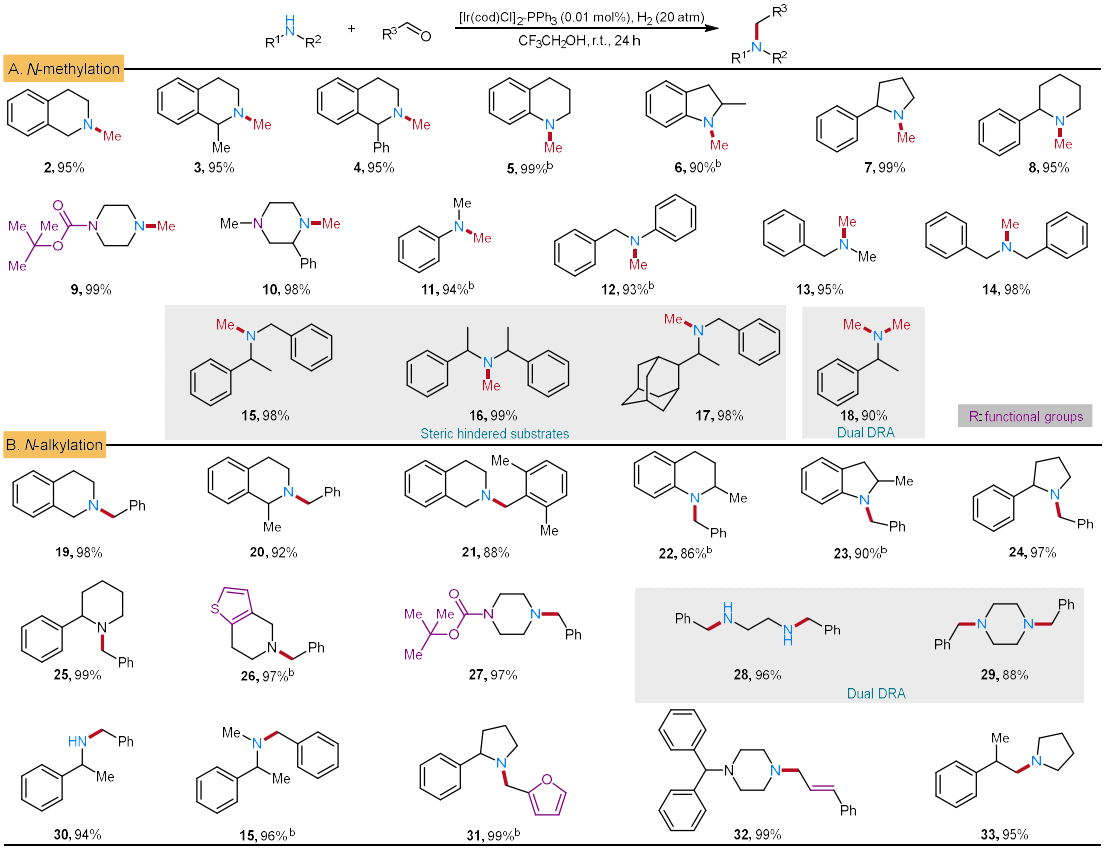
PPh_3 BINAP PipPhos SPhos Brettphos

[a] Reaction conditions: Ir–**L** 0.05 mol%, [Ir]/**L** (bisphosphine) = 1:1.1 or [Ir]/**L** (monophosphine) = 1:2.2; **1** 0.2 mmol, solvent 2 mL, H_2 20 atm, r.t., 24 h; Yields were determined by GC. [b] Operated under air atmosphere. [c] Formaldehyde water solution (1.5 equiv.) was used instead of paraformaldehyde. [d] H_2 pressure was 5 atm. [e] The reaction time was 30 h.

played a vital role in this transformation, in which the protic solvents outperformed the non-protic ones (Table 1, entries 1–6). Using trifluoroethanol as the solvent, the reaction underwent smoothly to afford **2** in 99% yield. Some other simple bidentate and monodentate phosphorus ligands were examined (Table 1, entries 7–10). The widely used BINAP and PipPhos both afforded great results, while more steric hindered SPhos and Brettphos did not provide satisfied yields. It is worth to mention that the reaction could be conducted under air atmosphere (Table 1, entry 11). When replacing paraformaldehyde with 37% formaldehyde aqueous solution as the coupling partner, the reaction proceeded without any difficulty. Under 5 atm of H_2, product **2** was obtained without any noticeable yield erosion. With the catalyst loading reduced to 0.003 mol%, the reaction still ran smoothly in 95% yield (Table 1, entry 14).

Substrate scope. Under the optimized reaction conditions, we explored the substrate scope of iridium/PPh_3-catalyzed reductive amination. Because of the importance of the *N*-methylamines, we first examined the reactions of various amines with paraformaldehyde under ambient temperature (Table 2A). With 0.01 mol% of the Ir-PPh_3 catalyst, some prevailingly natural-occuring *N*-heterocyclic compounds and important pharmacophores of many active pharmaceutical ingredients, tetrahydroisoquinolines, tetrahydroquinolines, indolines, piperidines, pyrrolidines and piperazine, smoothly underwent the DRA reaction with paraformaldehyde to form the corresponding *N*-methyl heterocycles (products **2**–**10**). The *N*-methylation reactions of acyclic substrates also worked very well (products **10**–**18**). For the primary 1-phenylethylamine substrate, the DRA reaction underwent twice to afford the tertiary amine **18**. Because of the weaker nucleophilicity of the *N*-Ar substrates, typically higher reaction temperature was required (products **5**–**6**, **11**–**12**). It is worth to mention that for highly steric-hindered substrates, the corresponding products were still obtained in excellent yields (products **15**–**17**). Since benzyl group is a ubiquitous protecting group for amino compounds in organic synthesis, we then utilized benzaldehyde as the coupling partner of some cyclic and acyclic secondary amines for this DRA reactions, in which the corresponding *N*-Bn products were obtained with high yields (Table 2B, products **19**–**30**, **15**). Surprisingly for ethyl diamine, a common bidentate ligand for iridium to form stable complex,[24,36] the reaction delivered the dual DRA product **28** without any difficulty. Similarly, piperazine reacted with 2.5 equiv. of benzaldehyde to afford 1,4-dibenzylpiperazine **29**. To our delight, the C-C double bond of α,β-unsaturated aldehyde survived during this DRA process (product **32**).

Table 2. Reductive amination of aldehydes.[a]

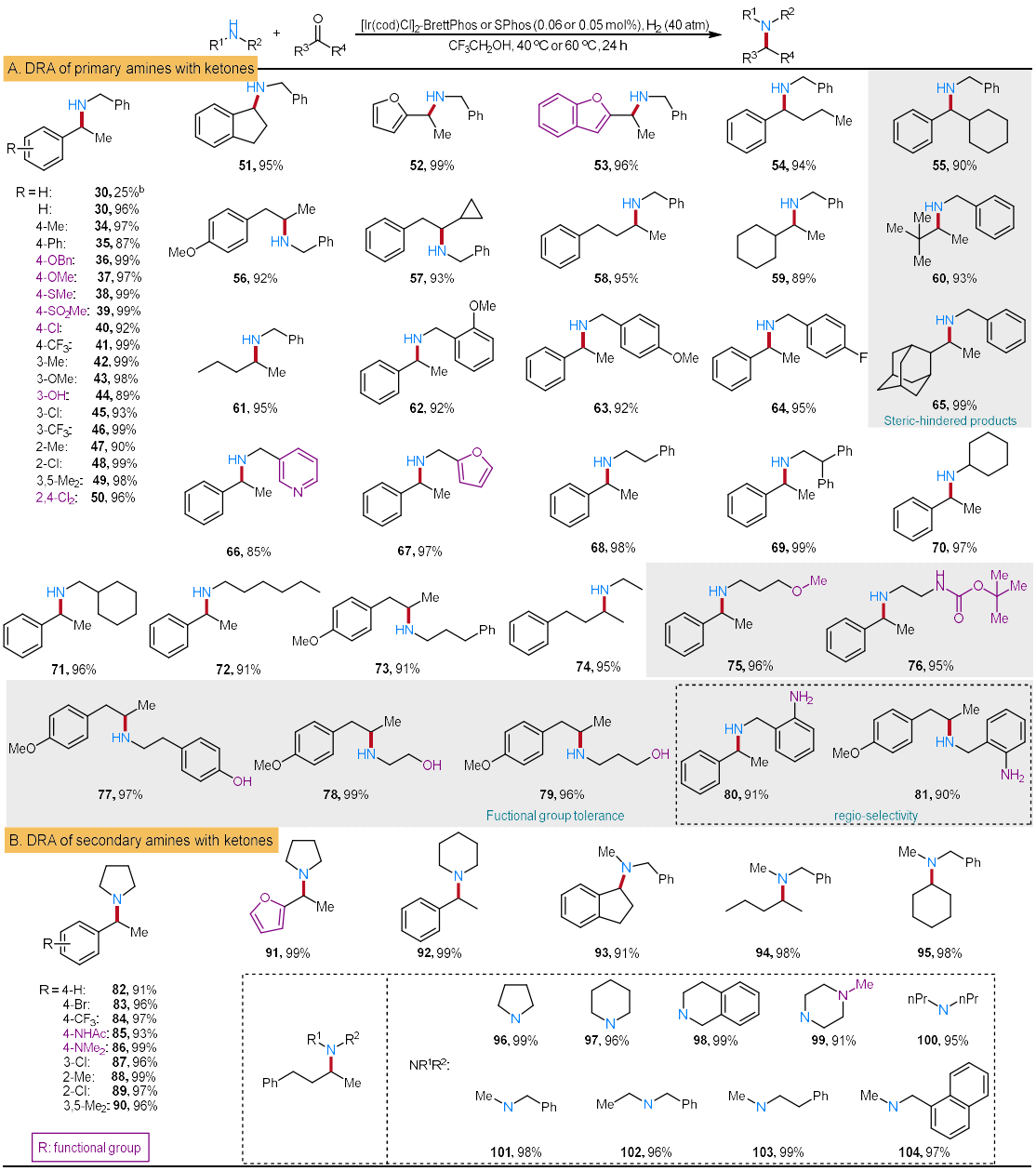


[a] Reaction conditions: Ir–PPh_3 0.01 mol%, amine 0.3 mmol, aldehydes 1.2 equiv. (2.5 equiv. in cases of dual reductive aminations), CF_3CH_2OH 1.5 mL, 20 atm H_2, r.t., 24 h. [b] Reaction temperature was 40 °C.

Next, the DRA reactions of ketone substrates with primary and secondary amines were conducted (Table 3). For this substrate category, more sterically hindered and electron-rich BrettPhos and SPhos displayed better catalytic reactivity than PPh_3. Utilizing 0.06 mol% of the *in situ* generated Ir-Brettphos complex, a variety of ketones and primary amines efficiently underwent the reductive condensation to afford the corresponding secondary amines in good to excellent yields (Table 3A). For the substituted arylethanones, in general the electronic property of the substituents on the aromatic ring of the ketone substrates appeared to have limited effects on the reaction yields. To our delight, various functional groups, such as chloride, ethers, thio-ether and sulphone, were all well-tolerated without being reduced (products **36**–**40**, **44**). For other aryl and aliphatic ketones, their DRA reactions with benzyl amine proceeded smoothly to afford the corresponding products. The substituted benzylamines or heteroaromatic methylamines also reacted with acetophenone successfully to furnish the products with high yields (products **62**–**64**, **66**–**67**). The above reactions opened doors for the efficient synthesis of primary amines after the *N*-benzyl deprotection.[49-50] The DRA reactions involving amine coupling

partners other than benzylamines also underwent as planned (products **68**–**79**). Remarkably, the aromatic ketone with a polar protic 3-OH substituent (product **44**) or amines partners with polar protic groups, including phenols, alcohols and anilines (products **77**–**81**), challenging substrates in organic transformations,[7] were well tolerated in this reaction. When both aliphatic and aromatic amino groups were presenting in the same nitrogen source, the more nucleophilic aliphatic nitrogen tended to react first to form the corresponding products (products **80**–**81**).

Table 3. Reductive amination of ketones.[a]

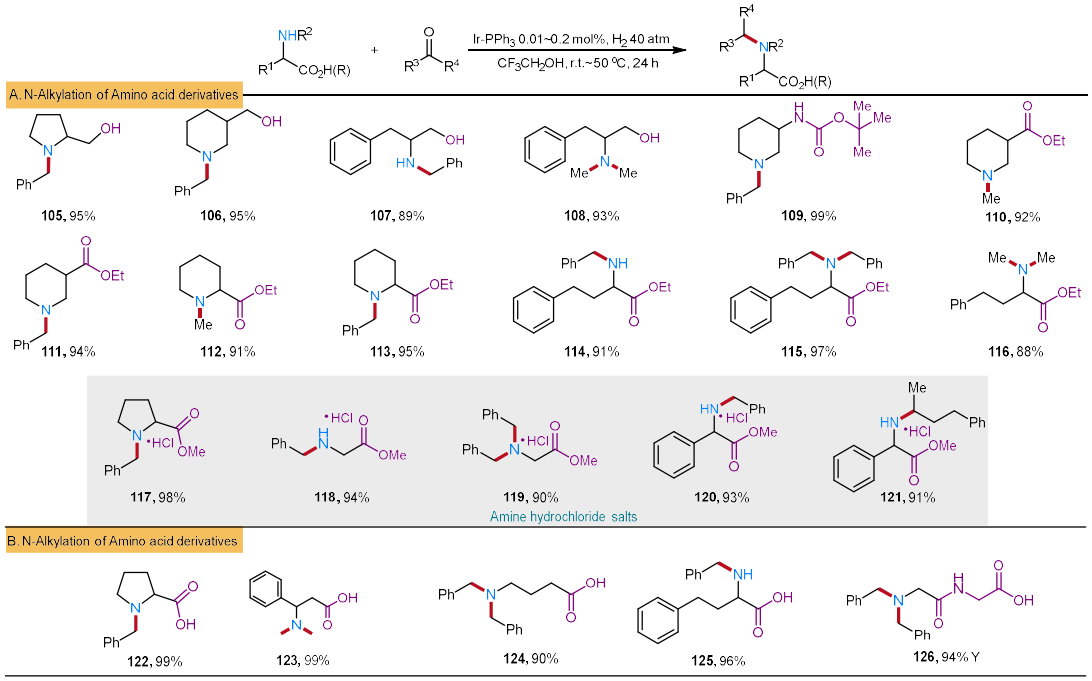


[a] Reaction conditions for Part A: Ir–BrettPhos 0.06 mol%, ketones 0.3 mmol, amines 1.2 equiv., CF_3CH_2OH 1.5 mL (containing 10 to 20 μL THF), 40 atm H_2, 40 °C, 24 h; Reaction conditions for Part B: Ir–SPhos 0.05 mol%, ketones 0.3 mmol, amines 1.2 equiv., CF_3CH_2OH 1.5 mL, 40 atm H_2, 60 °C, 24 h; Yields were isolated yields. [b] Ir–PPh_3 (0.06 mol%) was used.

Tertiary amines are important and prevailing constituents of many life science molecules. In fact, they account for 60% of the total number of medicinal related amines.[6] Thus, the efficient and practical synthetic routes are highly desired in pharmaceutical and agrochemical industries. Successful examples of reductive amination involving ketones and secondary amines are very limited.[35,41,51-54] Accomplishment in the reductive coupling of ketones with primary amines prompted us to validate this protocol for more challenging and space-demanding secondary amine substares. Fortunately, the iridium-SPhos catalytic system is found to be well functioned towards this substrate category (Table 3B). The DRA reaction yields of aromatic ethanones and aliphatic ketones with pyrrolidine, piperidine and *N*-methylbenzylamine ranged between 87% and 99%. 4-phenyl-2-butanone reacted with a ranged of cyclic and acyclic secondary amines to supply the corresponding products **96**–**104** in up to 99% yield.

Practical applications. After having successfully conducted the reductive amination of aldehydes and ketones with ordinary unfunctional and functional amines, we were interested in the applicability of this iridium catalysis in the modification of life-science important amino acids and their derivatives (Table 4). In comparison, the reductive amination of amino acid derivatives bearing polar protic groups with chelating capability, is more difficult. To our delight, the DRA reactions for amino alcohols, diamines,

Table 4. Modification of amino acid derivatives.[a]

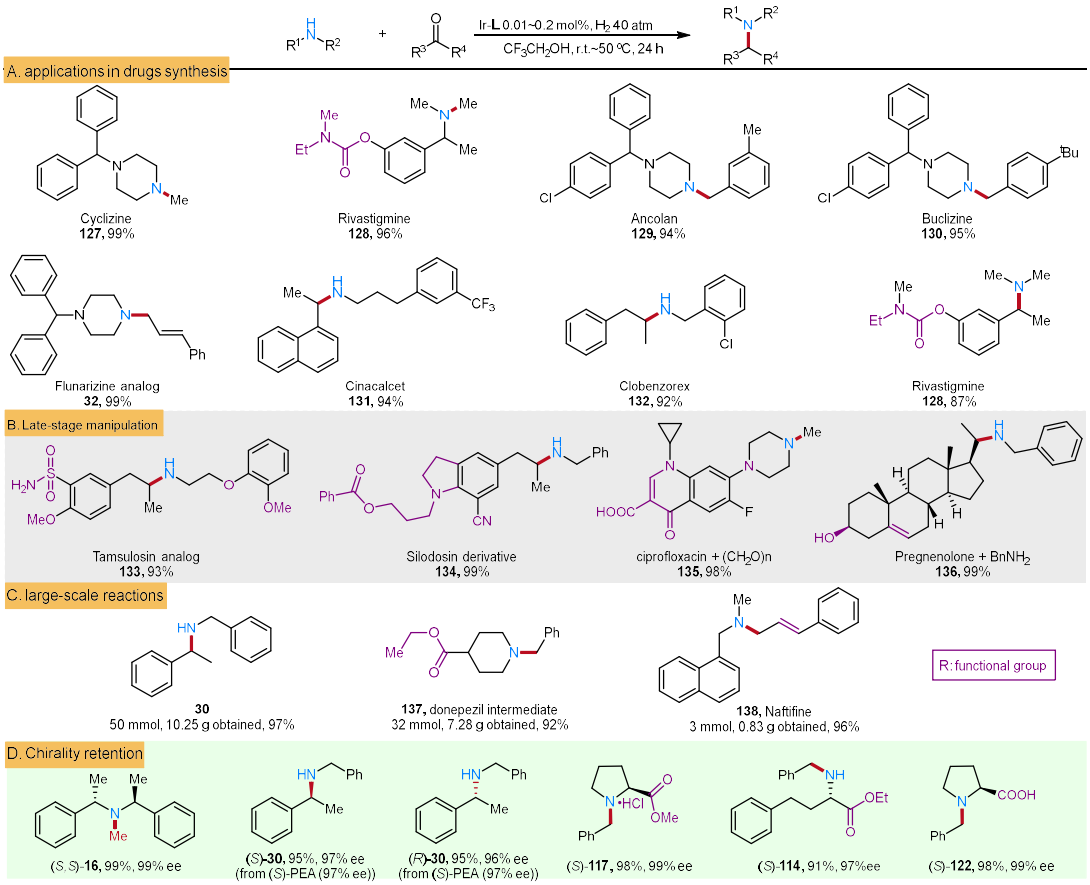


[a] For the reaction of amines and aldehydes: amine 0.3 mmol, aldehydes 1.2 equiv. (2.5 equiv. in cases of dual reductive aminations), CF_3CH_2OH 1.5 mL. For the reaction of amines and ketones: ketone 0.3 mmol, amine 1.2 equiv., CF_3CH_2OH 1.5 mL. Other reacion conditions please see the Supplementary Information.

amino esters went through fluently to provide the *N*-alkyl amino acid derivatives. Noticeably the hydrochloride salts of several amino esters were also suitable in this procedure to effectively afford products **117**–**121**. Besides, glycylglycine peptide also could get alkylated via the developed DRA process.

To further demonstrate the valuable applications of the iridium catalysis, the preparation of existing drugs and their key intermediates was carried out. As shown in Table 5A, a collection of related drugs (products **127**–**132**, **137**–**138**), were efficiently synthesize *via* this procedure in high yields. Extraordinarily, the late-stage functionalization of bioactive compounds, which contain multiple functional groups, was accomplished using the same one-step protocol, further highlighting the synthetic utility of this process (Table 5B, products **133**–**136**). To showcase the practical utility and manifest the potential for industrial production of this protocol, gram-scale synthesis of several *N*-alkyl amines was

Table 5. Application in drug synthesis.[a]



[a] For the reaction of amines and aldehydes: amine 0.3 mmol, aldehydes 1.2 equiv. (2.5 equiv. in cases of dual reductive aminations), CF_3CH_2OH 1.5 mL. For the reaction of amines and ketones: ketone 0.3 mmol, amine 1.2 equiv., CF_3CH_2OH 1.5 mL. Other reacion conditions please see the Supplementary Information.

performed (Table 5C, products **30**, **137**–**138**). Catalyzed by 0.04 mol% Ir-Brettphos complex, 50 mmol of acetophenone was efficiently converted to 10.25 gram of *N*-benzyl-1-phenylethan-1-amine, which could be further transformed into 1-phenylethanamine,[49-50] a very important building block. Under similar mild conditions, 7.28 gram of Donepezil intermediate and 0.83 gram of antifungal agent Naftifine were obtained through this catalytic path. We also monitored the ee values for chiral substrates (Table 5D). To our delight, the chirality of examined substrates remained during this transformation. For the 3 selected secondary and primary substrates, their corresponding products (*S,S*)-**16**, (*S*)- and (*R*)-**30** were obtained without any erosion on ee values. Very importantly, the *N*-alkylation of amino acids and their derivatives, which are frequently problematic with the racemization issue under other alkylation methods,[55-56] proceeded successfully with no obvious degradation in steric purity.

The accomplishments of the developed procedure in the RA reactions of aldehydes/ketones and primary and secondary amines expand the versatility of this methodology in amine synthesis. For example, to achieve the synthesis of target compound **101**, there are up to 5 various routes available, either from ketone **139** or from primary amine **140** (Figure 1). The flexibility in selecting the appropriate approach and/or inexpensive starting materials make this process very practical in preparation of amines.

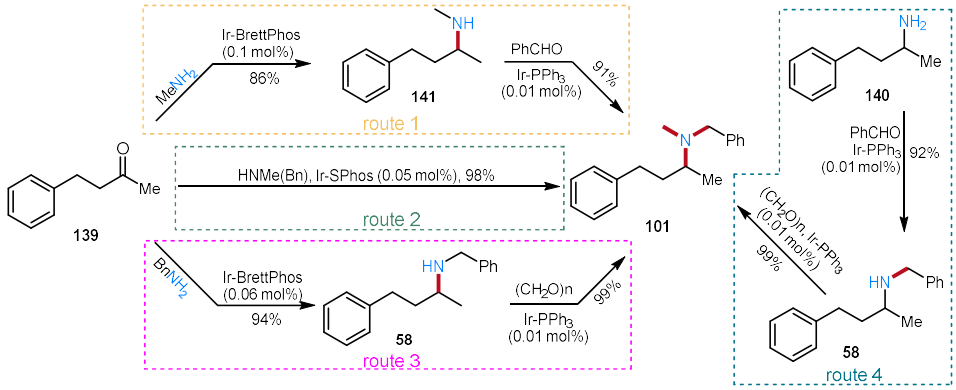


Figure 1. Synthetic versatility in amine preparation.

Discussion

In summary, we demonstrated a practical and highly potential protocol for the synthesis of amines through the iridium-catalyzed direct reductive amination. With the simple and readily available PPh_3, SPhos or BrettPhos, functionalized and unfunctionalized aldehydes and ketones reductively couple with primary and secondary amines to provide secondary and tertiary amine products under mild and additive-free conditions. Importantly the catalyst loading could be lowered to 0.003 mol%. Furthermore,

this reaction system tolerated oxygen, moisture, polar protic groups and multiple other functional groups. Utilizing this procedure, amino acid derivatives including peptide could be conveniently alkylated to further demonstrate the practical and potential application in drug synthesis.

Methods

General procedure for direct reductive amination. In a nitrogen–filled glovebox, $[Ir(cod)Cl]_2$ (2.0 mg, 3 μmol) and PPh_3 (3.5 mg, 13.2 μmol) were dissolved in anhydrous trifluoroethanol (2 mL) in a 10 mL vial equipped with a stir bar. The above solution was stirred at room temperature for 20 minutes to *in situ* generate the Ir-PPh_3 complex. To a 5mL vial equipped with a stir bar were added amine (0.3 mmol) and aldehyde (0.36 mmol) substrates, followed by the addition of anhydrous trifluoroethanol (1.5 mL) and the Ir-PPh_3 complex solution (10 μL, 0.01 mol%). The resulting vial was transferred to an autoclave, which was purged with H_2 3 times and then charged with H_2 (20 atm), and stirred at room temperature for 24 h. The hydrogen gas was released slowly and the solution was concentrated to give the crude products, which were purified by column chromatography to afford the final product. For the reaction of ketones and amines, due to the low solubility of the Ir-BrettPhos and Ir-Sphos complexes in trifluoroethanol, THF was instead used for the *in situ* generation of the catalyst.

Data availability. Experimental procedure and characterization data of new compounds are available within Supplementary Information. Any further relevant data are available from the authors upon reasonable request.

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Acknowledgements

Financial support from the National Natural Science Foundation of China (21772155 and 21402155), Scientific Fund of Northwest A&F University and Postdoctoral Science Foundation of China (2019M663827) is gratefully acknowledged.

Author contributions

J.W. and X.Y. established the reaction conditions. J.W., X.Y. and J.L. expanded the substrate scope. J.W. performed the applications. M.C. conceived and supervised the project and wrote the manuscript. All the authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

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