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Iridium-Catalyzed Reductive Alkylations of Secondary Amides

Wei Ou,[a] Feng Han,[a] Xiu-Ning Hu,[a]† Hang Chen,[a]† and Pei-Qiang Huang*[a,b]

Dedicated to Professor Guo-Qiang Lin on occasion of his 75th birthday

Abstract: We report the first direct, iridium-catalyzed reductive functionalization of secondary amides to give functionalized amines and heterocycles. The method is shown to have exceptionally broad scope with respect to suitable nucleophiles, which cover both hard and soft *C*-nucleophiles as well as a *P*-nucleophile. The reaction exhibits good chemoselectivity and tolerates several sensitive functional groups.

Carbon–carbon bond formation reactions constitute a core class of transformations in organic synthesis. In the field of total synthesis of alkaloids and *N*-containing medicinal agents, reductive alkylation of amides and lactams, namely, the transformations of amides into amines with C–C bond formation, has become one of the most important and fundamental transformations.[1,2] Indeed, from the selected classical synthesis of (perhydro)histrionicotoxin by Corey,[2a] Kishi,[2b] and Evans,[2c] respectively, (+)-pumiliotoxin C by Oppolzer,[2d] peduncularine by Speckamp,[2e] indolizomycin by Danishefsky,[2g] to the recent total synthesis of seven-membered-ring-containing lycopodium alkaloids by Shair (Figure 1, A),[2k] the reductive alkylation of amides has served as an indispensable transformation.[2] However, the high stability of amides means that it is necessary to pre-transform an amide into a more reactive intermediate before addition of a nucleophile and acid-mediated reduction. All these methods involve multiple-step transformations.

In recent years, the direct reductive alkylation of amides has attracted considerable attention, leading to the development of several synthetically useful methods[3,4] (Figure 1, B1). In these reactions, a stoichiometric amount of an activating agent/base combination [triflic anhydride (Tf_2O)/ 2-fluoropyridine (2-F-Pyr.)] or the Schwartz reagent [Cp_2ZrHCl] is required. In view of the increasing importance of catalysis as a green technology in both academic research and in the pharmaceutical industry,[5] the development of catalytic reductive functionalization of amides is highly desirable. In this context, breakthroughs in the catalytic reductive functionalization of tertiary amides have recently been achieved by the groups of Dixon, Chida/ Sato, Huang, and Adolfsson, respectively (Figure 1, B2).[6] However, the catalytic reductive functionalization of secondary amides leading to α-substituted amines remains unknown. Nevertheless, such transformations with broad nucleophile diversity are in high demand given the easy availability[7] and widespread use of secondary amides in organic synthesis,[1,2,8] and the presence of α-substituted secondary amine motifs in many medicinal agents[9a] and bioactive alkaloids.[9b] In this regard, medicinal agents such as fendiline (an anti-anginal agent in clinical use for the treatment of coronary heart disease) and tamsulosin (a selective α_1-adrenergic antagonist), and alkaloid histrionicotoxin (Figure 1, A) are just some representatives among many others. Among them, four entered the list of top 200 brand-name drugs by total US prescriptions in 2012.[9a] More importantly, known methods for the reductive functionalization of amides are generally restricted to some special classes of nucleophiles such as allyltrimethylsilane or allyltributyltin. Very often, several steps are required for the elaboration of the introduced allyl groups into the desired functionalized alkyl groups.

As part of our efforts to develop efficient C–C bond-forming reactions based on nucleophilic addition to amides,[4a,h-l,6a,h] herein, we report the $[IrCl(COE)_2]_2$-catalyzed reductive functionalization of secondary amides.

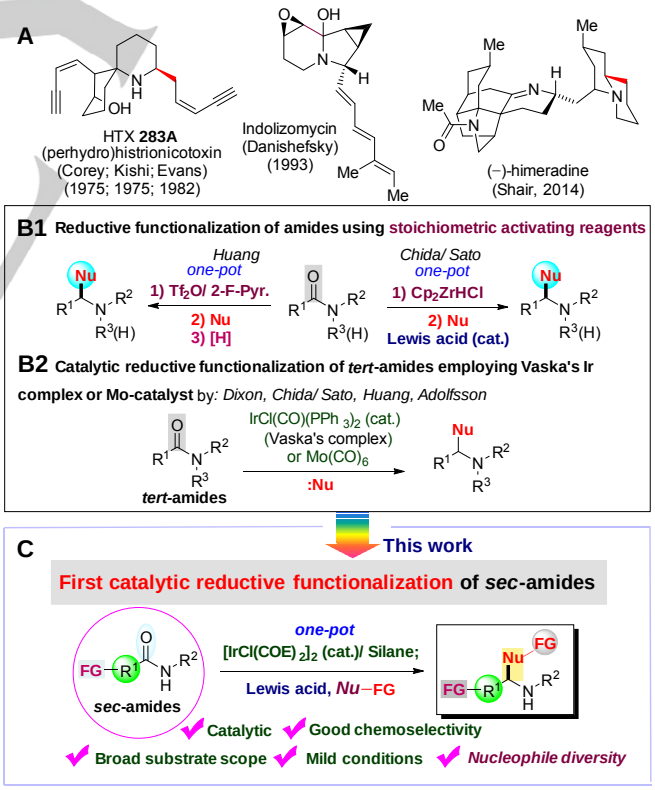

Figure 1. **A**) Representative alkaloids synthesized by employing multistep protocols for the reductive alkylation of amides. **B**) Recent methods for the direct reductive alkylation of amides. **C**) Our plan for the direct, Ir-catalyzed reductive alkylation of secondary amides. Nu = nucleophile, Cp = cyclopentadienyl, FG = functional group.

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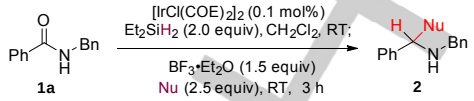
To develop an efficient method for the one-pot catalytic reductive functionalization of secondary amides, we needed a catalytic method for partial reduction of secondary amides. In 2012, Brookhart reported a catalytic reduction of secondary amides to either secondary amines or imines using catalytic $[IrCl(COE)_2]_2$, which is a commercially available complex.[10] Inspired by this work and by our own work,[6a,h] we devised a catalytic reductive functionalization of secondary amides that proceeds through sequential Ir-catalyzed reduction and Lewis acid-promoted nucleophilic trapping of imines generated *in situ*. The reductive allylation of **1a** using allyl magnesium bromide was chosen as a model reaction to identify optimal reaction conditions (Tables SI-1 and 2 in SI). The optimized conditions were found to involve treating amide **1a** (1.0 equiv) with 0.1 mol% of $[IrCl(COE)_2]_2$, 2.0 equiv of Et_2SiH_2, 1.5 equiv of $BF_3{\cdot}OEt_2$, and 2.5 equiv of allyl magnesium bromide at room temperature for 3 h. Under these conditions, the desired amine **2a** was isolated in 85% yield (Table 1, entry 1).

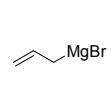
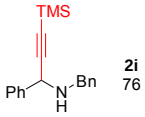
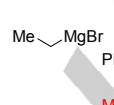
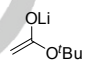
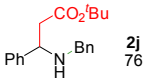
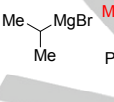
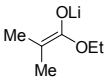
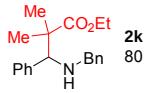
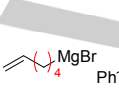
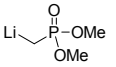
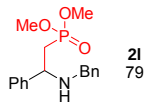
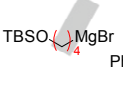
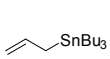
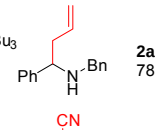
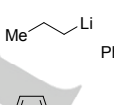
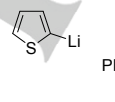
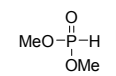
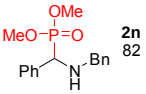
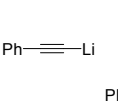
With the optimized reaction conditions in hand, the scope of the reaction was investigated by varying the nucleophilic trapping reagent and the amide. Using *N*-benzylbenzamide (**1a**) as a prototype amide substrate, we examined the scope of the nucleophile (Table 1). Simple and functionalized Grignard reagents including primary (entry 2), secondary (entry 3), and alkene- (entry 4) or siloxy-containing substrates (entry 5), proceeded efficiently to produce the corresponding amines (**2b–e**) in high yields (85–86%). Alkyl, heteroaryl, and alkynyl lithium reagents were also viable nucleophiles for the reductive functionalization reaction (**2f–i**, 66–85% yields; entries 6–9). Stabilized carbanions such as the lithium enolate of *t*-butyl acetate or the hindered lithium enolate derived from ethyl isobutyrate reacted to afford β-amino esters **2j** and **2k** in 76% and 80% yield, respectively (entries 10 and 11). (Dimethoxyphosphoryl)methyl]lithium reacted similarly, to provide *β*-amino phosphonate **2l** in 79% yield (entry 12).

Soft nucleophiles allyl tributyltin and TMSCN (TMS = trimethyl) participated in the reaction to give homoallylamine **2a** and α-aminonitrile **2m** in 78% and 76% yield, respectively (Table 1, entries 13 and 14). Moreover, dimethyl phosphonate reacted smoothly to yield α-amino phosphonate **2n** in 82% yield (entry 15).

We then investigated the scope of the reaction with respect to the amide. Benzamides bearing primary (**1b–d**, Table 2, A) and secondary (**1e**) alkyl *N*-substituents, as well as an *N*-phenyl group (**1f**) reacted smoothly with allyl magnesium bromide to yield the corresponding homoallylamines **2o–s** in high yields (80–85%, Table 2, B). The R^1 group of the amide could be more-hindered *o*-tolyl (**1g**), heteroaryl groups such as 2-furanyl (**1h**), or primary (**1i**), secondary (**1j** and **1l**), and tertiary (**1k**) alkyl groups. The reductive functionalization of **1g–l** afforded the corresponding functionalized amines **2t–ad** in 72–85% yields. In this manner, the anti-anginal agent fendiline (**2q**)[9a] was prepared in 82% yield. Notably, amide **1i** is a product of C–H functionalization,[11] and amide **1l** is a product of Fu's method.[7b] Moreover, the smooth reductive allylation of *N*-phenylbenzamide (**1f**) to give amine **2s** in high yield (80%) is significant in two respects: on the one hand, *N*-arylamides such as **1f** are common substrates for C–H functionalization,[12] and, on the other hand, attempted reductive allylation of **1f** using stoichiometric Tf_2O proved unsuccessful.[4h]

Table 1. Scope of the reaction with respect to the nucleophile used



Entry	Nucleophile	Product (%Yield)[a]	Entry	Nucleophile	Product (%Yield)[a]
1		**2a** 85	9		 **2i** 76
2		**2b** 86	10		 **2j** 76
3		**2c** 86	11		 **2k** 80
4		**2d** 85	12		 **2l** 79
5		**2e** 85	13		 **2a** 78
6		**2f** 85	14	TMSCN	 **2m** 76
7		**2g** 66	15		 **2n** 82
8		**2h** 73			

[a]Isolated yield. TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl.

The chiral induction deserves comments. Whereas the reductive allylation and alkynylation of chiral amide **1i** (racemic substrate used), and the reductive cyanation of amide (±)-**1l** yielded the corresponding products **2v**, **2w**, and **2ab** in poor diastereoselectivities (*dr* = 1.1–1.2:1), the reductive allylation of chiral amide (±)-**1l** produced the corresponding homoallylic amine **2ac** in excellent diastereoselectivities with *dr* = 24:1 (determined by HPLC, cf. SI; the relative stereochemistry undetermined).

Finally, the chemoselectivity and functional group tolerance of the method were examined. To our delight, besides electron-rich aroyl amides such as **1h**, the reaction also tolerated benzamide derivatives bearing an electron-withdrawing group such as CF_3 (**1m**) and ester (**1n**) groups, to give the desired products **2ae** and **2af** in 78% and 80% yield, respectively. In addition, amides bearing an OTBS group (**1o**) could survive the reaction using Grignard reagents as a nucleophile (**2ag**: 81%). Moreover, with the use of soft nucleophiles such as dimethyl phosphonate, the reaction took place chemoselectively at the amide group of **1n** and **1p** to give the corresponding α-amino phosphonates **2af** and **2ah**, respectively, in high yields, leaving the more reactive acetate and ester groups intact.

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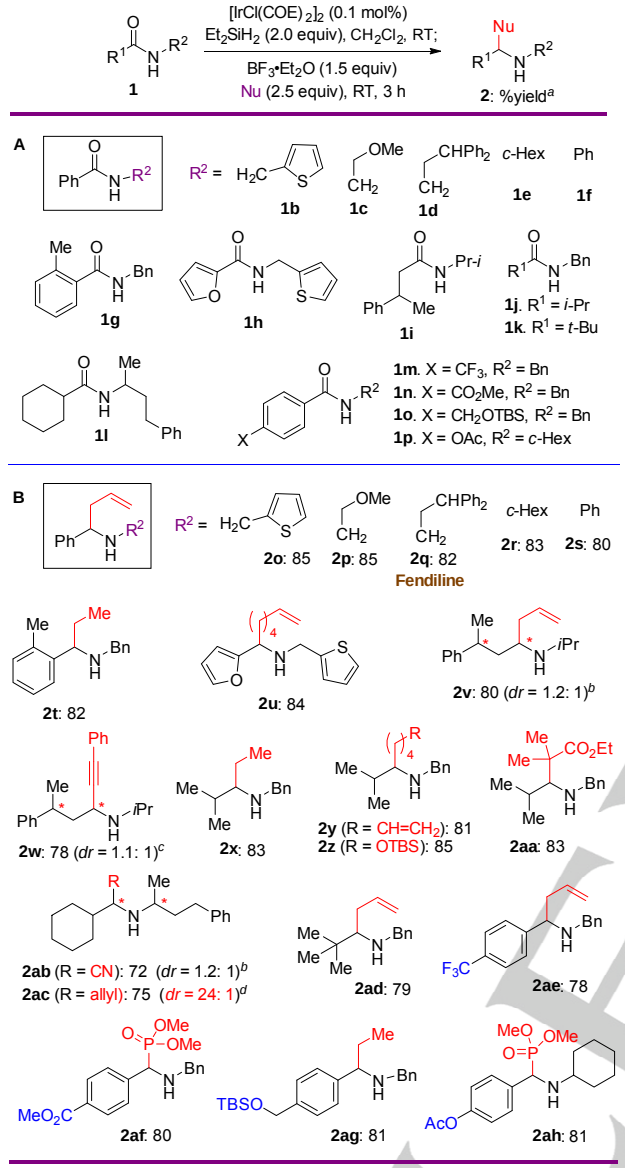
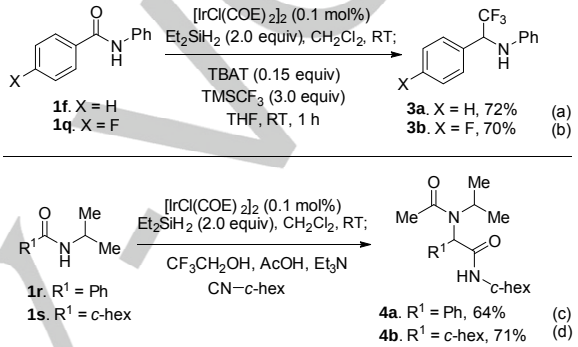
Table 2. Scope of the reaction with respect to the amide used



[a] Isolated yield; [b] Diastereoisomeric ratio (*dr*) determined by ^{1}H NMR; [c] *dr* determined via separation of diastereomers; [d] *dr* determined by HPLC analysis (cf. SI).

Attempts to further expand the reaction scope to catalytic reductive trifluoromethylation, reductive Ugi reaction, reductive lactamization, and reductive imino-Diels–Alder reaction were unsuccessful. Thus, we focused our attention on defining specific reaction conditions for each of these reactions. In view of the importance of trifluoromethylated amines in biological and medicinal chemistry as well as in the agrochemical field,[13] catalytic reductive trifluoromethylation of amides was first examined. It was found that, after the Ir-catalyzed partial reduction of amide **1f** in CH_2Cl_2, by switching the solvent to THF (form screening of solvent, see Table SI-3 in SI), and treating the imine intermediate with (trifluoromethyl)trimethylsilane ($TMSCF_3$) and with a catalytic amount of tetrabutylammonium triphenyl-difluorosilicate (TBAT),[14] the desired trifluoromethylated amine **3a**[4k] could be isolated in 72% yield (Scheme 1, a). Similarly, the Ir-catalyzed reductive trifluoromethylation of *N*-phenyl-*p*-fluorobenzamide (**1q**) produced tetrafluoroamine **3b**[4k] in 70% yield (Scheme 1, b).

Ugi multicomponent reactions[15] offer a powerful approach to the preparation of functionalized compounds. We were interested in exploring the possibility of merging the Ir-catalytic reductive transformation of amides with the Ugi reaction. Pleasingly, subjecting the imine, generated in situ by Ir-catalytic reduction of *N*-isopropylbenzamide **1r**, to the modified Ugi reaction conditions (in the absence of $BF_3{\cdot}OEt_2$, for optimization of reaction conditions, see Table SI-4 in SI) afforded the expected product **4a**[4j] in 64% yield (Scheme 1, c). Similarly, the Ir-catalytic reductive transformation of aliphatic amide **1s** provided **4b** in 71% yield (Scheme 1, d).

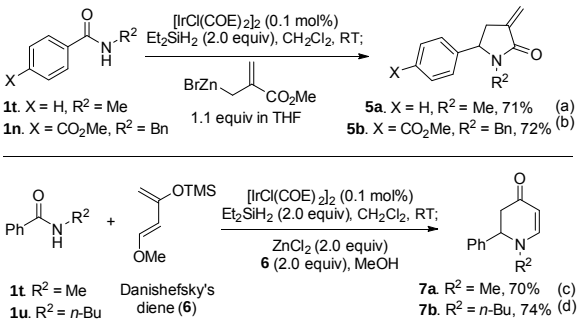


Scheme 1. Catalytic reductive trifluoromethylation combined with the Ugi reaction. TBAT = tetrabutylammonium triphenyl-difluorosilicate.

We then investigated the catalytic reductive annulation and reductive cycloaddition of amides. Organozinc reagents are a class of versatile and chemoselective organometallic reagents for C–C bond formation.[16] Villiéras and co-workers have reported the annulation of imines with functionalized allylic zinc reagent generated in situ from methyl 2-(bromomethyl)acrylate.[17] Considering the important bioactivity and multiple functionality possessed by α-methylene γ-lactams,[18a] which are attractive for the total synthesis of structurally complex alkaloids,[18b] the direct transformation of amides into α-methylene γ-lactams was investigated. By subjecting *N*-methylbenzamide **1t** to the catalytic partial reduction followed by reaction with (methoxycarbonyl)allyl)zinc(II) bromide (1.1 equiv) at room temperature for 3 h, the expected α-*exo*-methylene-γ-lactam **5a** was produced in 71% yield (Scheme 2, a). Remarkably, when ester-group-bearing benzamide derivative **1n** was employed as a substrate, the tandem reaction proceeded chemoselectively at the amide group to yield ester-lactam **5b** in 72% yield (Scheme 2, b).

Finally, the direct catalytic reductive cycloaddition of amides with Danishefsky's diene (**6**)[19] was investigated. The established conditions consist of the Ir-catalyzed partial reduction of amide **1t** in CH_2Cl_2, switching the solvent to MeOH,[20] and treating the presumed imine intermediate with anhydrous $ZnCl_2$ and Danishefsky's diene (**6**). In this manner, the cycloadduct **7a**[4l] was isolated in 70% yield (Scheme 2, c). Similarly, the reductive

cycloaddition of amide **1u** produced **7b**[4l] in 74% yield (Scheme 2, d).



Scheme 2. Catalytic reductive annulation/cycloaddition

In summary, a mild, versatile, and efficient method has been developed for the direct catalytic reductive functionalization of secondary amides. This method validates secondary amides as a class of stable and reliable building blocks that undergo direct and chemoselective transformation into a diverse variety of multiply functionalized amines. The successful relay transformation of the amides prepared by other synthetic methods demonstrated the potential of the current method as a strategy for late-stage transformation of amides in both natural product synthesis and medicinal chemistry. Work on this direction is ongoing in our laboratory.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: reductive alkylation • catalysis • secondary amides • C-C bond formation • one-pot reaction • chemoselective reaction

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COMMUNICATION

A versatile, direct, Ir-catalyzed reductive functionalization reactions of secondary amides to give functionalized amines and heterocycles is developed. A broad substrate scope for both the amide and nucleophile was observed. Viable nucleophiles include reactive and soft C-nucleophiles as well as a P-nucleophile. The reaction exhibited good chemoselectivity and tolerated several sensitive functional groups.

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