Multicatalysis protocol enables direct and versatile enantioselective reductive transformations of secondary amides

Hang Chen†, Zhi-Zhong Wu†, Dong-Yang Shao, Pei-Qiang Huang*

The catalytic asymmetric geminal bis-nucleophilic addition to nonreactive functional groups is a type of highly desirable yet challenging transformation in organic chemistry. Here, we report the first catalytic asymmetric reductive/deoxygenative alkylation of secondary amides. The method is based on a multicatalysis strategy that merges iridium/copper relay catalysis with organocatalysis. A further combination with the palladium-catalyzed alkyne hydrogenation allows the one-pot enantioselective reductive alkylation of secondary amides. This versatile protocol allows the efficient synthesis of four types of α-branched chiral amines, which are prevalent structural motifs of active pharmaceutical ingredients. The protocol also features excellent enantioselectivity, chemoselectivity, and functional group tolerance to be compatible with more reactive functional groups such as ketone and aldehyde. The synthetic utility of the method was further demonstrated by the late-stage functionalization of two drug derivatives and the concise, first catalytic asymmetric approach to the α-opioid antagonist aticaprant.

INTRODUCTION

Despite the substantial advance made over the past decades on the catalytic asymmetric reactions, the catalytic enantioselective reductive functionalization of nonreactive functional groups at a high oxidation state such as amides and nitriles remains highly challenging (Fig. 1A). The challenge originates not only from the low reactivity of those functional groups but also from the need to undertake a geminal bis-addition of two different nucleophiles onto the same carbon in a highly enantioselective manner (>90% enantiomeric excess (ee)) and in one pot. For the functionalization of nitriles, Hoveyda and colleagues reported in 2019 an elegant catalytic enantioselective reductive alkylation methodology to yield chiral α,β-disubstituted homoallylic primary amines (cf. Fig. 1A) (1).

The catalytic, asymmetric reductive functionalization of highly stable amides represents an unsolved challenge. Because of the delocalization of the nitrogen lone pair into the carbonyl group, the carboxamide group is known as one of the least electrophilic carboxylic acid derivatives. Hence, the amide group is prevalent in proteins, peptides, medicinal agents, and materials (2). Amides are readily available from natural sources and through a variety of established methods from carboxylic acids and amines, as well as recently developed strategies such as amide-directed C–H bond activation and asymmetric coupling (3–5). These salient features of amides make them highly attractive starting materials for organic synthesis (6–12). Nevertheless, the inertness of amides renders the direct and chemo-selective transformation of amides (9, 13, 14) a long-standing challenge in synthetic synthesis and multistep protocols have to be used (6, 7). This is the case of the reductive alkylation of amides, an indispensable transformation for the synthesis of many biologically active alkaloids (6–12). During the past decade, considerable advancements on the direct transformations of amides have been achieved (14–18) either via the electrophilic activation of amides (19–31) or via catalytic partial reduction of amides (32–40). However, very few examples of the asymmetric transformations of amides have been reported (41–44), and those involving the catalytic asymmetric reductive transformation of the amide group itself is even more scarce (42, 43). Recently, we disclosed the catalytic asymmetric reductive cyanation and phosphonylation of secondary amides using iridium/chiral thiourea relay catalysis (42). More recently, a highly enantioselective, catalytic reductive alkylation of tertiary benzamides has been achieved by the collaborative research of Wang’s and Huang’s groups (43). The method consists of Vaska’s complex [IrCl(CO)(PPh₃)₂]-catalyzed hydroxysilylation of amides with tetramethyldisiloxane, followed by CuI/chiral diphosphine ligand-catalyzed asymmetric alkynylation of the iminium ion intermediates (1) to give tertiary propargylamines in up to 98% ee (Fig. 1B). Despite these notable progresses, several limitations exist, including the failure on secondary amides, incompatibility with the synthesis of α-branched chiral primary, secondary, and cyclic tertiary amines, and moderate functional group tolerance (43). These limitations originate from the fact that tertiary, secondary, and primary amides behave differently in many reactions. Many transformations developed for tertiary amides are not applicable to secondary amides (3, 19, 23, 25, 26) and vice versa (4, 5, 21, 22, 24).

Thus, the catalytic, asymmetric reductive alkylation and reductive alkylation of secondary amides remain unconquered. Nevertheless, such transformations are in high demand, given the easy availability (4, 5, 45, 46) and widespread use of secondary amides in organic synthesis (7), and the presence of chiral α-branched secondary propargylamines (47–51) and chiral α-branched secondary amine motifs (52) in many medicinal agents (Fig. 1D) (53), bioactive alkaloids (54), and chiral catalyst (55). In the list of the top 200 brand-name drugs by total U.S. prescriptions in 2021, 26 contain a chiral secondary amine motif (53). Moreover, the chiral α-branched secondary propargylamines could be converted in one pot into chiral α-branched primary amines or cyclic tertiary amines (Fig. 1C),...
namely, nitrogen heterocycles, which are also active pharmaceutical ingredients (APIs) (Fig. 1D). The importance of the latter is highlighted by the fact that in U.S. Food and Drug Administration–approved drugs, 59% of unique small-molecule drugs contain a nitrogen heterocycle (56).

On the basis of abovementioned considerations, we decided to explore a catalytic, enantioselective reductive alkynylation of secondary amides. However, such transformations present several challenges: (i) After the planned Ir-catalyzed hydrosilation of a secondary amide, the presumed imine intermediate is much less reactive than the iminium
ion (ii in Fig. 1B) generated from a tertiary amide; (ii) the compatibility of all the reagents used in a one-pot environment to realize the fully catalytic and highly chemo- and enantioselective reaction; and (iii) high versatility and functional group tolerance are needed to cover both aromatic (benzamide-type) and aliphatic amides and diverse functionalized terminal alkynes.

**RESULTS**

Development of an enantioselective reductive alkynylation of secondary amides

To tackle the abovementioned multiple challenges, a multicatalysis (57–60) approach was envisioned. The multicatalysis is an emerging strategy

| Table 1. Optimization of reaction conditions. |
|---|---|---|---|---|
| Entry | Cu catal. | Organocatal. | Additive | Yield (%)* | ee % † |
| 1 | CuOTf | C1 | – | (84)‡ | – |
| 2 | CuOTf | C2 | – | (76)§ | – |
| 3 | CuOTf | A1 | – | 47 | 63 |
| 4 | CuOTf | A1 | P1 | 52 | 91|| |
| 5 | CuOTf | A2 | P1 | 52 | 76|| |
| 6 | CuOTf | A3 | P1 | 74 | 84|| |
| 7 | CuOTf | A4 | P1 | 65 | 93|| |
| 8 | CuOTf | A5 | P1 | 73 | 89|| |
| 9 | CuOTf | A6 | P1 | 53 | 87|| |
| 10 | CuOTf | A4 | P2 | 31 | 73|| |
| 11 | CuOTf | A4 | P3 | 81 | 73|| |
| 12 | CuOTf | A4 | P4 | 67 | 53|| |
| 13 | CuOTf | A4 | P1 | 76 | 93 |
| 14 | (CuOTf)•toluene | A4 | P1 | 78 | 93 |
| 15 | (CuOTf)2 | A4 | P1 | 70 | 92 |
| 16 | (CuOTf)2PF6 | A4 | P1 | 77 | 93 |
| 17 | CUBr | A4 | P1 | (87)¶ | – |

*Determined by GC using n-dodecane as an internal standard. †Determined by chiral high-performance liquid chromatography. ‡The imine intermediate obtained in 84% yield. §The imine intermediate obtained in 76% yield. ||Twenty mole percent of additive was used. ¶The imine intermediate obtained in 87% yield.
for developing unprecedented and challenging transformations that could not be achieved by a single catalytic system. Here, we disclose the results of this investigation, which include the first direct asymmetric transformation of secondary amides into $\alpha$-chiral secondary propargylamines or chiral $\alpha$-branched secondary amines. The methodology relies on the catalysis in trio or in quartet, namely, by merging Ir/Cu relay catalysis with Cu/N-protected l-proline cooperative catalysis, or further with sequential Pd-catalyzed hydrogenation of the chiral propargylamines (Fig. 1C).

**Fig. 2. Scope of secondary amides.** The structures of all amides and alkynes used are listed in tables S1 and S2. Reaction conditions: amide (0.25 mmol), [Ir(COE)$_2$Cl]$_2$ (0.3 mol %), Et$_2$SiH$_2$ (2.0 equiv), CH$_2$Cl$_2$, 25°C, 1.5 hours; then (CuOTf)$_2$-toluene (5 mol %), N-Boc-l-proline (30 mol %), P(1-naphthyl)$_3$ (10 mol %), 0°C, 2 days. ‡CuOTf instead of (CuOTf)$_2$-toluene. §Cu(OTf)$_2$ instead of (CuOTf)$_2$-toluene. ||Cu(MeCN)$_4$PF$_6$ instead of (CuOTf)$_2$-toluene. ¶Time for the Ir-catalyzed reduction: 0.5 hour. #0.5 mol % of [Ir(COE)$_2$Cl]$_2$ used. PMP, p-methoxyphenyl.
In view of the frequent occurrence of N-naphthylmethyl and N-benzyl secondary amine motifs in medicinal agents (cf. Fig. 1D), we opted for the reductive alkynylation of N-(naphthalen-1-ylmethyl)benzamide (1a) with phenylacetylene (2a) as the model reaction. Jacobsen’s chiral thiourea C1 and chiral phosphoric acid C2 were first evaluated as organocatalysts (42, 57) in our multicatalysis strategy (Table 1). Disappointingly, the desired propargylamine 3a was not observed, only the imine intermediate was obtained in 84 and 76% yield, respectively (Table 1, entries 1 and 2). Encouragingly, when N-Ac-L-proline (A1) was used both as a chiral catalyst and as an imine activator, the desired deoxygenative alkynylation reaction occurred to give the α-chiral propargylamine 3a in 47% yield with 63% ee (Table 1, entry 3).

Notably, when P(1-naphthyl)3 was introduced as an additive, an excellent ee of 91% and a good yield of 52% were obtained (Table 1, entry 4). A survey of the effect of other N-protected L-proline derivatives A2 to A6 showed that all were effective affording 3a in good to excellent ee’s (76 to 93%). However, eight other P additives (cf. P2 to P4 and table S3 in the Supplementary Materials) turned out to be less effective for the reaction. Further examining the effect of copper catalyst showed that many copper salts such as CuOTf, (CuOTf)2-toluene, Cu(OTf)2, and Cu(MeCN)4PF6 were equally effective for the reaction, affording propargylamine 3a in excellent ee’s (92 to 93%) and good yields (70 to 78%). Unexpectedly, CuBr, which is the catalyst of choice for the deoxygenative alkynylation of tert amides (38), was totally ineffective for the current reaction. The striking difference between CuBr and CuOTf in the asymmetric induction may be explained by the acidity of corresponding acid (HBr versus TfOH) generated from an alkyne and CuBr/CuOTf. TfOH (pKₐ = −15) is a much stronger acid than HBr (pKₐ = −9) and forms a strong H-bond with the carbonyl of N-Boc-L-proline (A4). This hydrogen bonding enhances the imine N–H hydrogen bonding in the intermediate vii, thus enhancing the asymmetric induction (Fig. 8A).

Assessment of other reaction parameters including the amounts of reagents and additive, catalyst loadings as well as reaction temperature and time allowed defining the optimal reaction conditions (Table 1, entry 14). Several N-protected proline derivatives (entries 4 and 7 to 9) and copper salts (entries 13 to 16) are promising and efficient in catalyzing the enantioselective reaction. These results showed that the reaction is robust. Because (CuOTf)2-toluene is cheaper than the other copper salts and a stable solid, it was used for the subsequent investigations.

Fig. 3. Scope of alkynes. For reaction conditions, see footnote in Fig. 2.
Scope of the reaction and chemoselectivity
With the optimal reaction conditions in hands, we turned our attention to examine the reaction scope of this catalytic enantioselective reductive alkynylation reaction. The scope with respect to the amide was first examined. As shown in Fig. 2, the reaction proceeded with simple aryl amides such as p-tolyl (1a-2) and m-tolyl (1a-3) and was compatible with benzamides bearing either strong electron-donating (1a-4 to 1a-6) or electron-withdrawing groups (1a-7 and 1a-8) at the para- or meta-position of the phenyl ring providing the corresponding propargylamines 3b to 3h in good to excellent yields (68 to 95%) and with high enantioselectivities (90 to 95% ee). Heteroaromatic amides were also viable substrates providing the corresponding α-chiral propargylamines (3i and 3j) in 68 and 64% yields and with high enantioselectivity (93% ee). The reaction of 2-methylbenzamide also proceeded smoothly to give the desired propargylamine (3k) in excellent enantioselectivity (80% yield, 95% ee). In view of the importance of trifluoromethyl, fluoro, and heteroaromatic groups in biological and medicinal chemistry as well as in the agrochemical field, the smooth enantioselective synthesis of amines 3g to 3j is of value. The enantioselective reductive alkylation reaction showed remarkable chemoselectivity and functional group tolerance. For example, the amide substrates containing an ester moiety (1a-13 and 1a-14) or a keto group (1a-15) took place chemoselectively at the less electrophilic amide group, leaving the more reactive ester and ketone groups intact. The CuOTf, Cu(OTf)₂, and Cu(MeCN)₄PF₆ catalyzed syntheses of 3a, 3b, 3d, and 3g showed that they are also effective catalysts for the alkylation.

The catalytic reductive alkylation of aliphatic amides in high enantioselectivity presents a formidable challenge because of the absence of a rigid aromatic ring that appears to be a valuable control element for the enantioselective addition. Moreover, for α-hydrogen-containing amides, the situation may be further complicated by the possible isomerization of the imine intermediates to unreactive enamines. The reported enantioselective reductive alkylation of tertiary amides is only compatible with benzamide derivatives (43). To our delight, the current catalytic enantioselective reaction tolerated both α,β-unsaturated amide 1a-12 and aliphatic amides. For 1a-12, alkynyl propargylamine 3l was obtained in 74% yield with 96% ee (Fig. 2). For aliphatic amides, not only hindered pivalamide 1a-16 and adamantane-1-carboxamide 1a-17 but also less hindered α-hydrogen-containing secondary amides 1a-18 to 1a-22 reacted to afford the desired secondary propargylamines 3p to 3v in good yields (62 to 76%) and excellent enantioselectivities (89 to 99% ee)
To the best of our knowledge, the synthesis of 3r to 3v represents the first examples of catalytic asymmetric synthesis of α-hydrogen-containing secondary propargylamines in high enantioselectivity. Note that for the syntheses of 3i and 3r to 3t, the reaction time of the Ir-catalyzed hydrosilylation was shortened to 0.5 hours to avoid over reduction.

Scope of alkynes and functional group tolerance of the reaction

The alkyne coupling partner also tolerated variation. The reactions were compatible with phenylacetylene derivatives bearing substituents at the para- (2b, 2e, and 2i), meta- (2c, 2f), and ortho-position (2d and 2g) of the benzene ring and 2-ethylthiophene (2h) (Fig. 3) (the structures of all alkynes used are listed in Table S2). Notably, phenylacetylene derivatives that contain on the benzene ring a chloro (2j), trifluoromethyl (2k), ester (2l), or even an aldehyde (2m) group all reacted successfully to give the desired products 3ae to 3ah in good yields and excellent enantioselectivities. Last, alkylacetylenes (2n and 2o) were proven to be viable substrates.

Extension to N-benzylamides

Besides N-(naphthalen-1-ylmethyl)amides, N-benzylamides were also suitable substrates for the catalytic enantioselective reductive alkynylation reaction to afford the corresponding chiral propargylamines (3ak to 3as) in 63 to 88% yields and 90 to 92% ee (Fig. 4). The absolute configuration of the propargylamines was determined as R by comparing the specific optical rotation data of amine 3aq with that reported in (51).

Synthetic applications of the reaction

The practical utility of our method was demonstrated by the preparation of propargylamine 3a in multigram scale. The 10-mmol scale reaction
afforded 2.359 g of propargylamine 3a (68% yield) without losing enantioselectivity (93% ee) (Fig. 5A). The absolute configuration of propargylamine 3a, a representative of the series of N-(naphthalen-1-ylmethyl)propargylamines, was determined as R by comparing the specific optical rotation data of its hydrogenation product (S)-4 (Fig. 5B) with that reported for its enantiomer (see the Supplementary Materials). To showcase the versatility of propargylamines in organic synthesis, derivatization of 3a was performed. Thus, 3a was partially hydrogenated with Lindlar’s catalyst to allylic amine (S)-5 in 84% yield and 19% ee (Fig. 5C). By using functionalized alkyl 2t, the resulting propargylamine 3aw was synthesized in excellent ee (96%) (Fig. 5D), which was further converted, in one pot, into 2-substituted piperidine (S)-6 in 94% ee, demonstrating the value of current method for the asymmetric synthesis of chiral, cyclic tertiary amines in high enantioselective excess. Note that motifs such as α-substituted tertiary amine (S)-6 are inaccessible by the method previously developed for tertiary benzamides (43), and the present synthesis is among the most efficient methods for its asymmetric synthesis in high enantipurity (52).

To further demonstrate the synthetic utility of the method, the late-stage deoxyenative alkynylation of amide derivatives (1a-23 and 1a-24) of two drugs SR11237 and adapalene were undertaken. Under the standard conditions, the catalytic asymmetric alkynylation reactions proceeded without incident to yield the desired propargylamines 3at and 3au in 78 and 73% yield and in 90 and 94% ee, respectively (Fig. 6). Next, we addressed the catalytic asymmetric synthesis of aticaprant (S)-8 (formerly known as LY-2456302 and CERC-501), a highly-affinity and selective κ-opioid receptor antagonist (61, 62). Under standard conditions, the catalytic asymmetric reductive alkynylation of functionalized amide afforded 2.359 g of 3a with 93% ee. Reaction conditions: amide (0.5 mmol), [Ir(COE)2Cl2] (0.3 mol %), Et3SiH2 (1.0 mmol), CH3Cl (2.5 ml), 25°C, 1.5 hours, then (CuOTf)2-toluene (5 mol %), N-Boc-c-proline (30 mol %), P(1-naphthyl)2 (10 mol %), alkylene (2.0 mmol), 0°C, 2 days, and then 10% Pd/C, H2, MeOH.

Fig. 7. One-pot, chemoselective, catalytic enantioselective reductive alklylation of secondary amides. Reaction conditions: amide (0.5 mmol), [Ir(COE)2Cl2] (0.3 mol %), Et3SiH2 (1.0 mmol), CH3Cl (2.5 ml), 25°C, 1.5 hours, then (CuOTf)2-toluene (5 mol %), N-Boc-c-proline (30 mol %), P(1-naphthyl)2 (10 mol %), alkylene (2.0 mmol), 0°C, 2 days, and then 10% Pd/C, H2, MeOH.

Plausible mechanism of the reaction

Plausible mechanisms for the multicalysis-based asymmetric reductive alkynylation/alkylation of secondary amides are outlined in Fig. 8A. For the asymmetric reductive alkynylation of secondary amides, it involves three catalytic cycles: (i) Ir-catalyzed hydrosilylation of a secondary amide with diethylsilane to give O-silyl hemiaminal intermediate ii, which eliminates diethylsilanol to generate imine intermediate iii; (ii) copper-catalyzed in situ generation of nucleophilic Cu-alkynylide species vi; and (iii) N-Boc-c-proline-catalyzed asymmetric alkynylation of imine ii in which N-Boc-c-proline (A4) serves as a Bronsted acid to activate the nonreactive imine intermediate ii via hydrogen bonding (see vii) and as an asymmetric inducer to block re-face of vii. The addition of Cu-alkynylide vi to reactive intermediate vii then occurs preferentially from si-face to afford (R)-propargylamine 3. Further merging of this tris-catalysis with Pd-catalyzed hydrogenation of the alkyne group affords α-alkylated amine 7 in one pot.

To confirm the dual roles of N-Boc-c-proline (A4), we carried out the reductive alkynylation reactions of secondary amide 1a-1 with N-Boc-c-proline methyl ester or c-proline instead of N-Boc-c-proline (A4) (Fig. 8B-1). In the first case, the expected propargylamine 3a was obtained in only 18% yield in racemic form along with imine ii-a in 63% yield (Fig. 8B-1). In the second case, only imine ii-a was obtained in 86% yield (Fig. 8B-2a). To increase the solubility of proline, in the alkylation step, a 20% (v/v) of dimethyl sulfoxide was added as a cosolvent. However, only imine was formed in 69% yield (Fig. 8B-2b). These control experiments showed that neither Boc-c-proline methyl ester nor c-proline (being a zwitterion in the reaction media) can promote the alkynylation or provide any asymmetric induction even when the alkynylation occurs as a side reaction, likely because none of them can activate imine ii through H-bonding. An additional evidence for the H-bond asymmetric catalysis was provided by the catalytic reductive alkynylation of o-methoxybenzamide 1a-26, a substrate bearing an additional H-bond acceptor (OMe) at the ortho-position of the phenyl group (Fig. 8B-3). This amide reacted with moderate stereoselectivity (65% ee) reflecting the competing H-bonding effect of the appropriately positioned OMe (Fig. 8B-3).

Catalytic enantioselective reductive alklylation of secondary amides

Considering that the catalytic asymmetric alkynylation of amides remains unknown, we investigated the catalytic alkynylation, followed by complete reduction in one pot. Thus, after the catalytic alkynylation under standard conditions, the resulting reaction mixture was subjected to Pd/C-catalyzed hydrogenation under H2 (1 atm). In this manner, α-substituted chiral amines 9a to 9f were obtained in good yields and excellent enantioselectivity (Fig. 7). Notably, more reactive functional groups such as ester, ketone, and aldehyde on the amide or alkyne coupling partner were tolerated.

1a-25 with 3,3-dioxyprop-1-ylne (2u) produced the desired propargylamine 3aw in 63% yield and in 88% ee. Pd/C-catalyzed catalytic hydrogenation, hydrogenolysis, and reductive alklylation under acidic conditions proceeded in tandem to afford 2-arylpyrrrolidine (S)-7 in 84% yield. Because racemic 7 has previously been converted into aticaprant (S)-8 by a two-step protocol followed by resolution (61, 62), this work constitutes the first formal catalytic asymmetric total synthesis of aticaprant (S)-8.
**DISCUSSION**

By designing a multicatalysis system, we have achieved the direct asymmetric reductive alkynylation and reductive alkylation of secondary amides to yield chiral α-branched secondary propargylamines and α-branched secondary amines, respectively. The method is characterized by mild reaction conditions, wide scope for both amides and alkynes, good yields, and high enantioselectivities. Another notable feature of our method is the exceptional chemoselectivity and functional group tolerance to allow the reactions to take place preferentially at the less reactive amide group over the more reactive alkyne group.

---

**Fig. 8. Plausible reaction mechanisms.** (A) Plausible mechanisms for the multicatalytic, one-pot asymmetric reductive alkynylation/alkylation of secondary amides. (B) Control experiments to probe the dual roles of N-Boc-L-proline (A4) in the catalytic asymmetric reductive alkynylation of secondary amides. DMSO, dimethyl sulfoxide.
reactive ester, ketone, and aldehyde moieties. The observed unusual chemoselectivity can be understood from two aspects. First, the multicatalysis protocol avoids the direct nucleophilic addition to amides, instead, it involves an Ir-catalyzed O-silylation of the amide carbonyl (partial reduction) as the first step of the reaction sequence. Second, due to the delocalization of the nitrogen lone pair of an amide, the oxygen of the amide C=O is more electron rich as compared with those of aldehyde, ketone, and ester and thus is more reactive vis-à-vis electrophilic silyl species (34). Consequently, the amide carbonyl can be chemoselectively hydroisilylated, leading to the chemoselective asymmetric alknylation reaction. The products can be elaborated in one step into two other types of α-branched amines: chiral primary amines and chiral tertiary aza-heterocycles. This method is expected to find applications in the total synthesis of alkaloids and N-containing medicinal agents, and the multicatalysis strategy will be useful for the catalytic asymmetric transformations of other carboxylic acid derivatives.

**REFERENCES AND NOTES**

1. S. Zhang, J. del Pozo, F. Romiti, Y. Mu, S. Torker, A. Hoveyda, Delayed catalyst function enables direct enantioselective conversion of nitrites to NH-aminines. *Science* **364**, 45–51 (2019).
2. A. Greenberg, C. M. Breneman, J. F. Liebman, *Eds.*, *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science* (Wiley, 2003).
3. H.-H. Huo, B. J. Gorsline, G. C. Fu, Catalyst-controlled doubly enantioconvergent coupling of racemic aliphatic nitriles and electrophiles. *Science* **367**, 559–564 (2020).
4. R.-Y. Zhu, M. E. Farmer, Y.-Q. Chen, J.-Q. Yu, A simple and versatile amide directing group for C-H functionalizations. *Angew. Chem. Int. Ed.* **55**, 10578–10599 (2016).
5. X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S.-H. Li, K. M. Engle, J.-Q. Yu, Ligand-enabled metal-C-H activation using a transient mediator. *Nature* **519**, 334–338 (2015).
6. C. H. Heathcock, *The enchanting alkaloids of Yuzurina*. *Angew. Chem. Int. Ed.* **31**, 665–681 (1992).
7. A. S. Lee, B. B. Liu, M. D. Shair, A unified strategy for the synthesis of 7-membered-ring-containing Lycopodium alkaloids. *J. Am. Chem. Soc.* **136**, 13442–13452 (2014).
8. C. Piemontesi, Q. Wang, J. Zhu, Enantioselective total synthesis of (−)-terengganensine A. *Angew. Chem. Int. Ed.* **55**, 6556–6560 (2016).
9. M. Yoritate, Y. Takahashi, H. Tajima, C. Ogihara, T. Yokoyama, Y. Soda, T. Oishi, T. Sato, N. Chida, Unified total synthesis of stereoamine-type alkaloids by chemoselective assembly of five-membered building blocks. *J. Am. Chem. Soc.* **139**, 18386–18391 (2017).
10. L.-D. Guo, J.-P. Hou, W.-T. Tu, Y. Zhang, Y. Zhang, L.-X. Chem, J. Xu, Total synthesis of dapholdhamine B and dapholdhamine B lactone. *J. Am. Chem. Soc.* **141**, 11713–11720 (2019).
11. X.-Z. Huang, L.-H. Gao, P.-Q. Huang, Enantioselective total syntheses of (−)-temfolamine and three congeners based on a biogenetic hypothesis. *Nat. Commun.* **11**, 5314 (2020).
12. P. Gabriel, Y. A. Almehmadi, Z. R. Wong, D. J. Dixon, A general iridium-catalyzed reductive dienamine synthesis allows a five-step synthesis of cattanethone via the elusive dehydrocattanethone. *J. Am. Chem. Soc.* **143**, 10828–10835 (2021).
13. M. T. Peruzzi, Q. Mei, S. J. Leeb, M. R. Gagné, Chemoselective amide reductions by heteroleptic fluoroaryl boron Lewis acids. *Chem. Commun.* **54**, 5855–5858 (2018).
14. V. Pace, W. Holzer, Chemoselective activation strategies of amide carbonyls towards nucleophilic reagents. *Aust. J. Chem.* **66**, 507–510 (2013).
15. V. Pace, W. Holzer, B. Oflofsson, Increasing the reactivity of amides towards organometallic reagents: an overview. *Adv. Synth. Catal.* **356**, 3697–3736 (2014).
16. T. Sato, M. Yoritate, H. Tajima, N. Chida, Total synthesis of complex alkaloids by nucleophilic amide addition to alkaloids. *Org. Biomol. Chem.* **16**, 3864–3875 (2018).
17. D. Kaiser, A. Bauer, M. Lemmerera, N. Maulere, Amide activation: An emerging tool for chemoselective synthesis. *Chem. Soc. Rev.* **47**, 7899–7925 (2018).
18. P. J. Czerwiński, B. Furrman, Reductive functionalization of amides in synthesis and for modification of bioactive compounds. *Front. Chem.* **9**, 65589 (2021).
19. J.-B. Falmagne, J. Escudero, S. Taleb-Sahraoui, L. Ghosez, Cyclobutanone and cyclobutenone derivatives by reaction of tertiary amines with alkynes or alkenes. *Angew. Chem. Int. Ed.* **20**, 879–880 (1981).
20. A. B. Charette, M. Gremon, Spectroscopic studies of the electrophilic activation of amides with trifluoroacetyl and pyridine. *Can. J. Chem.* **79**, 1694–1703 (2001).
21. M. Movassaghi, M. D. Hill, Synthesis of substituted pyridine derivatives via the ruthenium-catalyzed cycloisomerization of 3-azaidenynes. *J. Am. Chem. Soc.* **128**, 4592–4593 (2006).
22. M. Movassaghi, M. D. Hill, O. K. Ahmad, Direct synthesis of pyridine derivatives. *J. Am. Chem. Soc.* **129**, 10096–10097 (2007).
23. G. Babe, A. B. Charette, Highly chemoselective metal-free reduction of tertiary amines. *J. Am. Chem. Soc.* **130**, 18–19 (2008).
24. G. Pelletier, W. S. Bechara, A. B. Charette, Controlled and chemoselective reduction of secondary amides. *J. Am. Chem. Soc.* **132**, 12817–12819 (2010).
25. C. Madelaine, V. Valerio, N. Maulere, Unexpected electrophilic rearrangements of amides: A stereoselective entry to challenging substituted lactams. *Angew. Chem. Int. Ed.* **49**, 1583–1586 (2010).
26. K.-J. Xiao, J.-M. Luo, K.-Y. Ye, Y. Wang, P.-Q. Huang, Direct, one-port sequential reductive alkylation of lactams/amides with Grignard and organolithium reagents through lactam/amide activation. *Angew. Chem. Int. Ed.* **49**, 3037–3040 (2010).
27. K. Shirokane, Y. Kurosaki, T. Sato, N. Chida, A direct entry to substituted N-methoxymethanes from N-methoxyamines via O-methoxyamines. *Angew. Chem. Int. Ed.* **49**, 6369–6372 (2010).
28. W. S. Bechara, G. Pelletier, A. B. Charette, Chemoselective synthesis of ketones and ketimines by addition of organometallic reagents to secondary amides. *Nat. Chem.* **4**, 228–234 (2012).
29. M. Mewald, J. W. Medley, M. Movassaghi, Concise and enantioselective total synthesis of (−)-mebranine, (−)-methylenebismbranine, and related Aspidosperma alkaloids. *Angew. Chem. Int. Ed.* **53**, 11634–11639 (2014).
30. S. Heinild, M. Riomet, J. Matyasovsky, M. Lemmerer, N. Malzer, N. Maulere, Chemoselective γ-oxidation of β,γ-unsaturated amides with TEMPO. *Angew. Chem. Int. Ed.* **60**, 19123–19127 (2021).
31. J. Jiao, X.-M. Wang, Merging electron transfer with 1,2-metalate rearrangement: Deoxygenative arylation of aromatic amides with aryboronic esters. Angew. Chem. Int. Ed. 60, 17088–17093 (2021).
32. L. J. Donnelly, J.-C. Berthet, T. Cantat, Selective reduction of secondary amides to imines catalyzed by Schwartz's reagent. Angew. Chem. Int. Ed. 61, e202206170 (2022).
33. D. Mathieu-Raven, P. Gabriel, J. A. Leitch, Y. A. Almezehadi, K. Yamazaki, D. J. Dixon, Catalytic reductive functionalization of tertiary amides using Vaska's complex: Synthesis of complex tertiary amine building blocks and natural products. ACS Catal. 10, 8880–8897 (2020).
34. C. Cheng, M. Brookhart, Iridium-catalyzed reduction of secondary amides to secondary amines and imines by diethyliamine. J. Am. Chem. Soc. 134, 11304–11307 (2012).
35. A. W. Gregory, A. Chambers, A. Hawkins, P. Jakubec, D. Dixon, Iridium-catalyzed reductive nitro-Mannich cyclization. Chem. Eur. J. 21, 111–114 (2015).
36. M. Nakajima, T. Sato, N. Chida, Iridium-catalyzed chemoselective reduction of nucleophilic addition to N-methoxymidams. Org. Lett. 17, 1696–1699 (2015).
37. S. Katahara, S. Kobayashi, K. Fujita, T. Matsumoto, T. Sato, N. Chida, An iridium-catalyzed reductive approach to nitriles from N-hydroxymidams. J. Am. Chem. Soc. 138, 5246–5249 (2016).
38. P.-Q. Huang, W. Ou, F. Han, Chemoselective reductive alkenylation of tertiary amides by bi- and Cu(i) bis-metal sequential catalysis. Chem. Commun. 52, 11967–11970 (2016).
39. Á. L. Fuentes de Arriba, E. Lenci, M. Sonawane, O. Formyee, D. Dixon, Iridium-catalyzed reductive Strecker reaction for late-stage amide and lactam cyanation. Angew. Chem. Int. Ed. 56, 3655–3659 (2017).
40. L.-G. Xie, D. J. Dixon, Iridium-catalyzed Ugi-type reactions of tertiary amides. Nat. Commun. 9, 2841 (2018).
41. L. Ji, M. Berger, W. Zawodny, M. Simaan, N. Maulide, A chemo- and regioselective α-oxitriflation enables the direct asymmetric arylation of amides. Chem. 5, 1883–1891 (2019).
42. D. H. Chen, W. T. Sun, C. J. Zhu, G. S. Lu, A. E. Wang, P.-Q. Huang, Enantioselective reductive cyanation and phosphonation of secondary amides by iridium and chiral thiourea sequential catalysis. Angew. Chem. Int. Ed. 60, 8827–8831 (2021).
43. Z. Li, F. Zhao, W. Ou, P.-Q. Huang, X. M. Wang, Asymmetric deoxygenative alkenylation of tertiary amides enabled by iridium/copper bimetallic relay catalysis. Angew. Chem. Int. Ed. 60, 26604–26609 (2021).
44. M. Feng, I. Mosiagin, D. Kaiser, B. Maryasin, N. Maulide, Deployment of sulfinimines as N-catalyst for the amidation of aryl halides and the selective hydrosilylation of secondary amides catalyzed by an iridium(III) metalloenzyme: Development and mechanistic investigation. ChemCatChem 9, 2009–2017 (2017).
45. A. Klapper, J. C. Antilla, X.-H. Huang, S. L. Buchwald, A general and efficient copper catalyst for the amidation of aryl halides and the N-arylation of nitrogen heterocycles. J. Am. Chem. Soc. 123, 7727–7729 (2001).
46. M. I. Lavrov, V. I. Lapteva, V. V. Grigor‘ev, V. A. Palyulin, S. O. Bachurin, N. S. Zefirov, Synthesis and AMPA-receptor modulating activity of benzodiazepinobenzamide and piperazinobenzamide derivatives. Pharm. J. 46, 92–95 (2012).
47. P.-Q. Ye, Y.-L. Shao, X.-Z. Ye, F.-J. Zhang, R.-H. Li, P. Hasegawa, D. G. Guiney, M. Pellecchia, Small molecule dnak modulators targeting the β-domain. Chem. Biol. Drug Des. 74, 349–357 (2009).
48. K. Lauder, A. Toscani, N. Scalacci, D. Castagnolo, Synthesis and reactivity of N-hydroxyamides. J. Org. Chem. 5246–5249 (2010).
49. W.-J. Yoo, L. Zhao, C.-J. Li, The A 3-coupling (aldehyde–alkyne–amine) reaction: A versatile method for the preparation of racemic compounds. All authors discussed the results and commented on the manuscript. Supporting information for this article is available at https://doi.org/10.1126/sciadv.ade3431.