

ORGANIC CHEMISTRY

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 alkynylation 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 κ -opioid antagonist aticaprant.

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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 allylation 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 chemoselective transformation of amides (9, 13, 14) a long-standing challenge in organic 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 phosphorylation of secondary amides using iridium/chiral thiourea relay catalysis (42). More recently, a highly enantioselective, catalytic reductive alkynylation 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 $[\text{IrCl}(\text{CO})(\text{PPh}_3)_2]$ -catalyzed hydrosilylation of amides with tetramethyldisiloxane, followed by CuI /chiral diphosphine ligand-catalyzed asymmetric alkynylation of the iminium ion intermediates (i) 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 alkynylation 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),

Department of Chemistry and Fujian Provincial Key Laboratory of Chemical Biology, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, Fujian, China.

*Corresponding author. Email: pqhuang@xmu.edu.cn

†These authors contributed equally to this work.

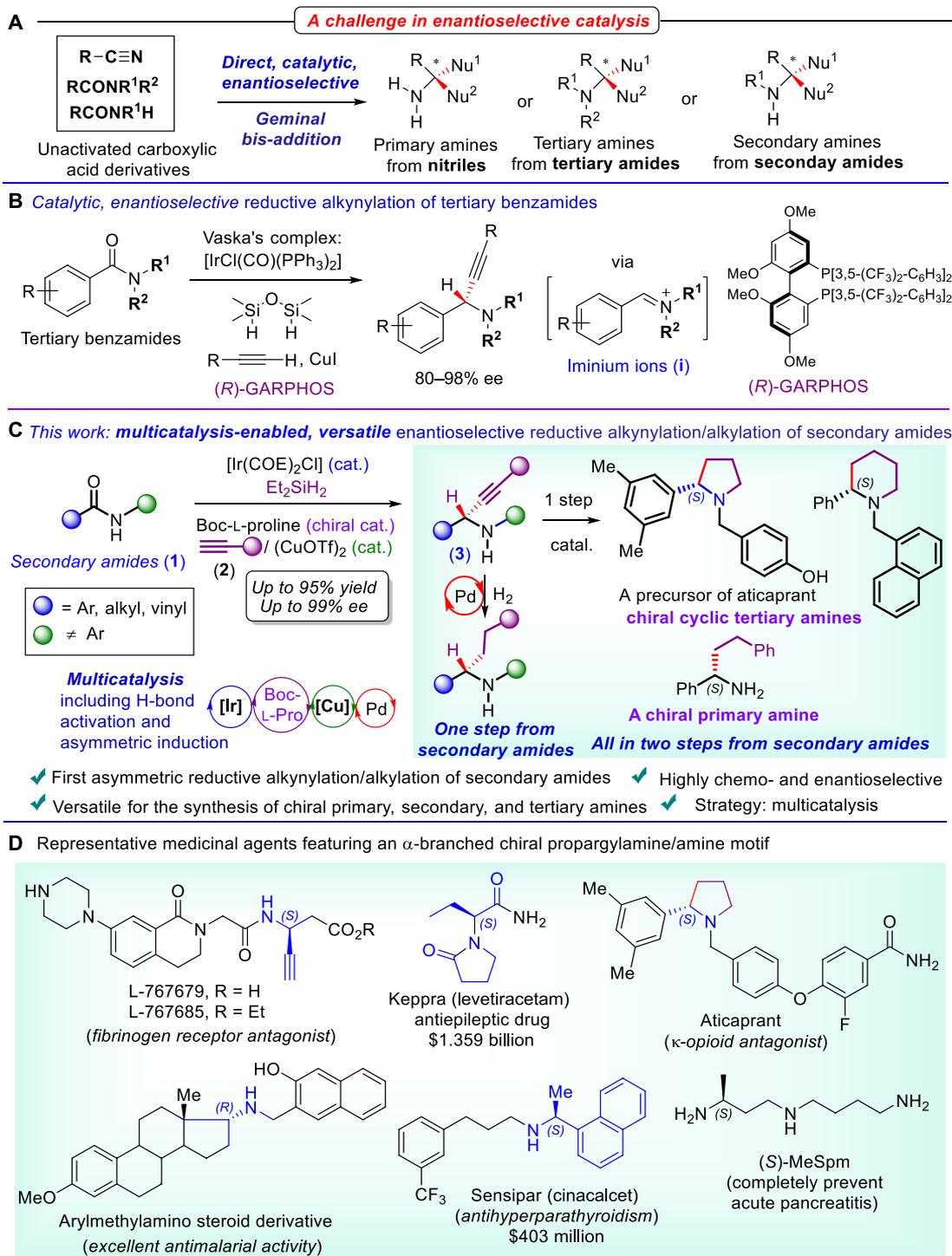


Fig. 1. The challenge and significance of the topic. (A) The challenge. (B) State of the art. (C) This work: versatile catalytic enantioselective transformations of secondary amides. (D) Significance of structurally diverse α -branched amines for medicinal chemistry/pharmaceutical industry. GARPHOS, ligand containing the skeleton of (4,4',6,6'-tetramethoxy-[1,1'-biphenyl]-2,2'-diyl)bis(diphenylphosphane).

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 hydrosilylation of a secondary amide, the presumed imine intermediate is much less reactive than the iminium

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 multistep 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 (pK_a = -15) is a much stronger acid than HBr (pK_a = -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.

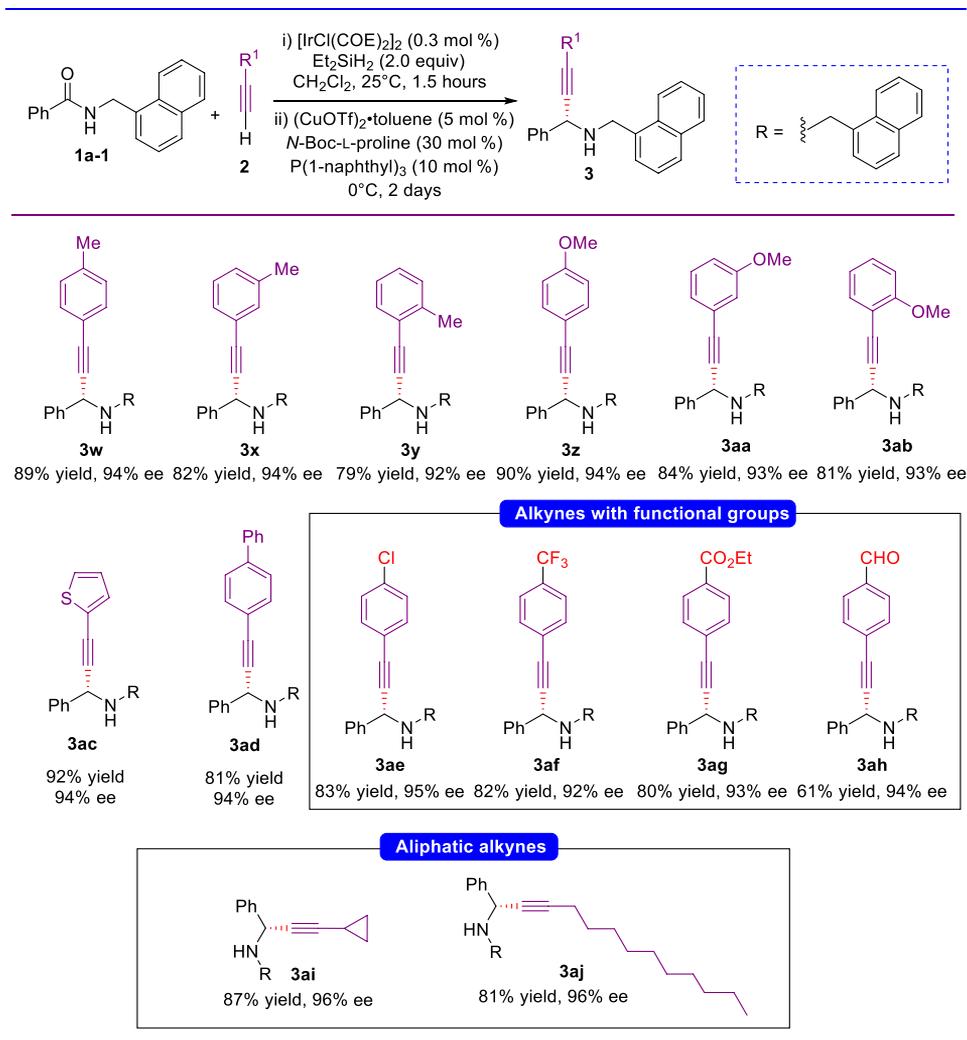


Fig. 3. Scope of alkynes. For reaction conditions, see footnote in Fig. 2.

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 alkylation 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**) (the structures of all amides used are listed in table S1) 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**, alkenyl 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)

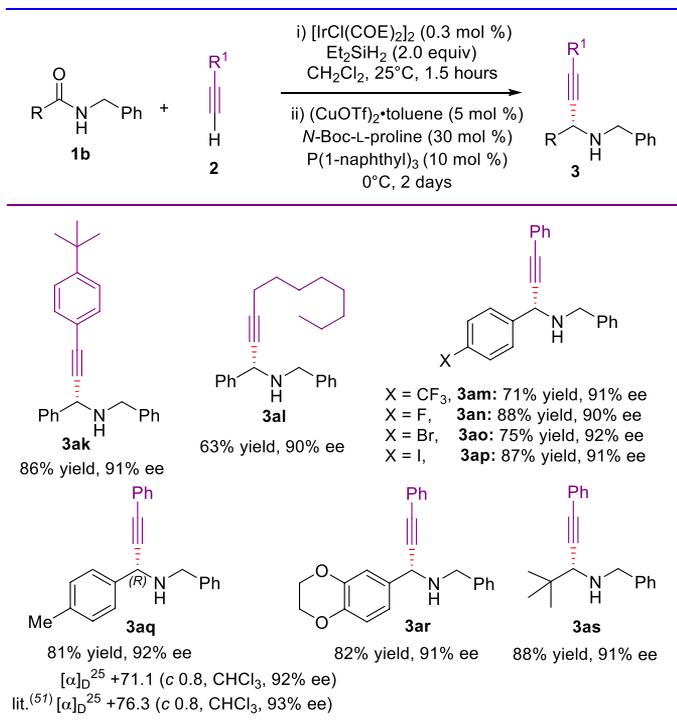


Fig. 4. The catalytic asymmetric reductive alkylation of *N*-benzyl amides. For reaction conditions, see footnote in Fig. 2.

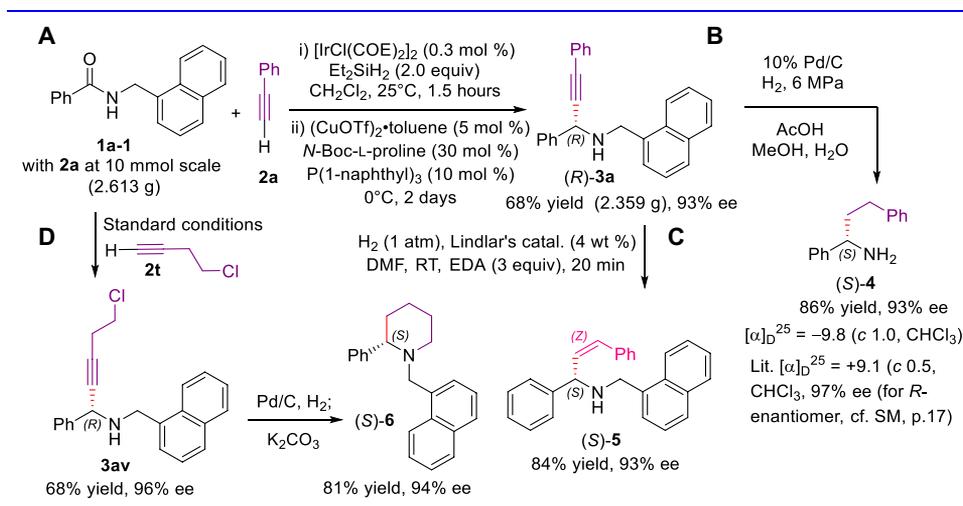


Fig. 5. Synthetic applications of the reaction. (A) Multigram-scale synthesis. (B) Determination of absolute configuration of propargylamine **3a**. (C) Selective synthesis of allylic amine (S)-5. (D) Two-step synthesis of 2-substituted piperidine (S)-6. wt %, weight %. DMF, Dimethylformamide; RT, room temperature; EDA, ethylenediamine.

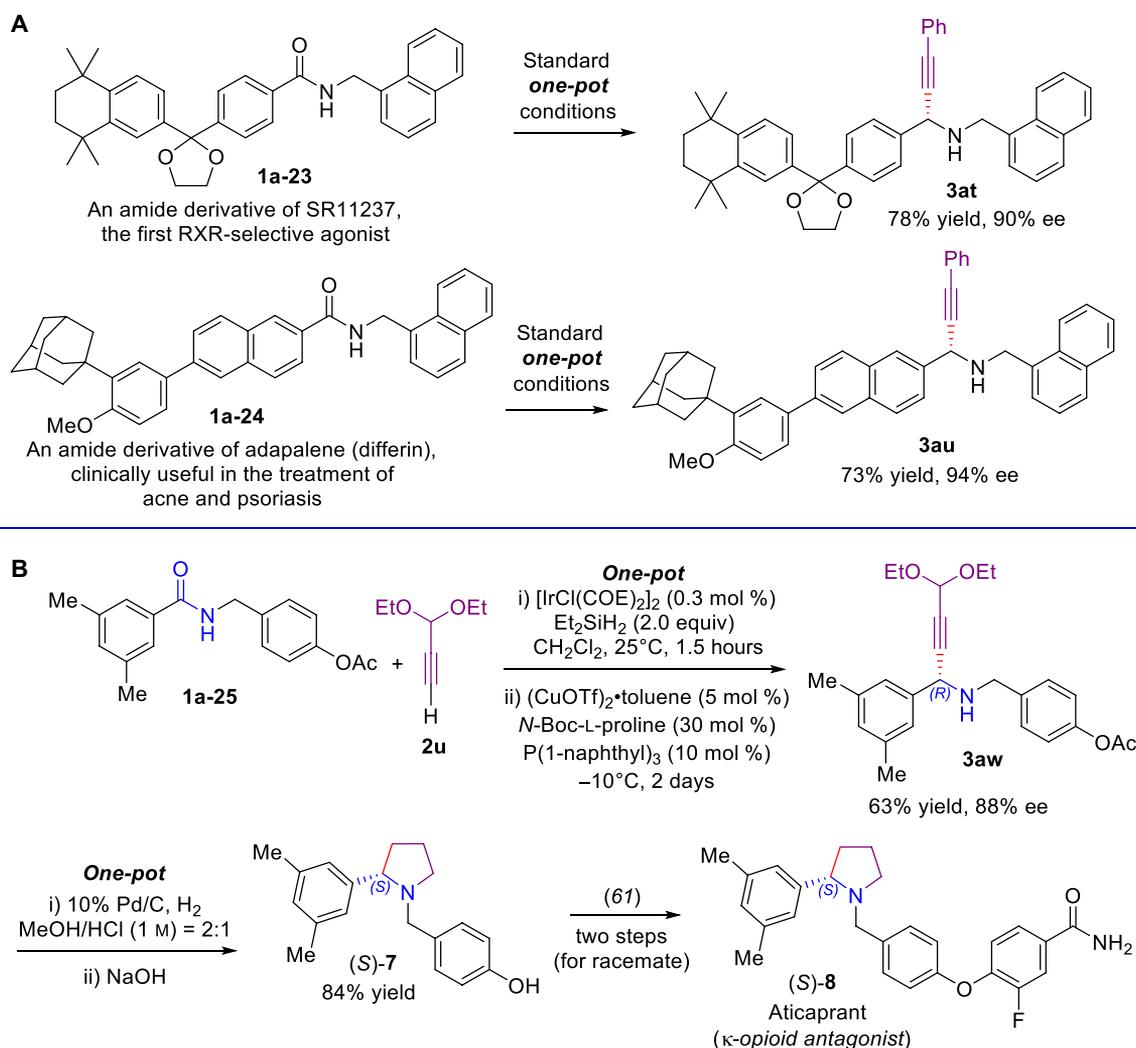


Fig. 6. Synthetic applications of the reaction to drug molecules. (A) Late-stage functionalization of drug derivatives and (B) catalytic asymmetric formal synthesis of the key intermediate of κ -opioid antagonist aticaprant. RXR, retinoid X receptor.

(Fig. 2). 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-ethynylthiophene (**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 alkylation 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

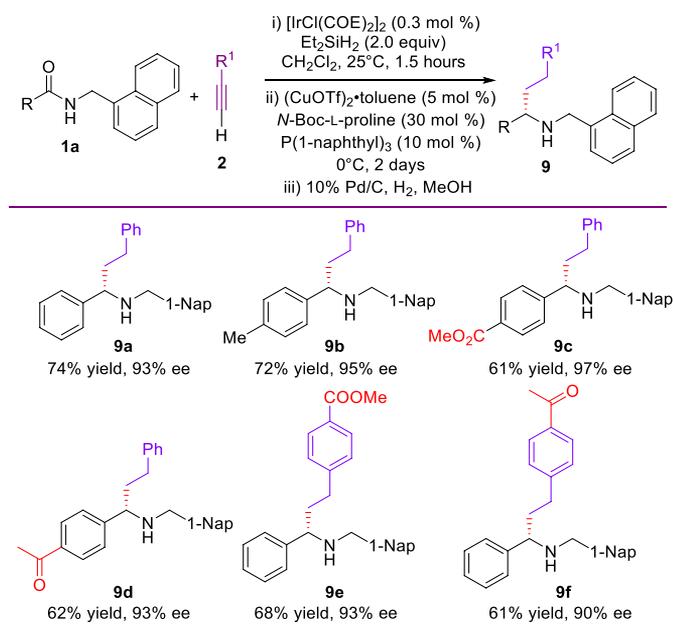


Fig. 7. One-pot, chemoselective, catalytic enantioselective reductive alkylation of secondary amides. Reaction conditions: amide (0.5 mmol), $[\text{Ir}(\text{COE})_2\text{Cl}]_2$ (0.3 mol %), Et_2SiH_2 (1.0 mmol), CH_2Cl_2 (2.5 mL), 25°C, 1.5 hours, then $(\text{CuOTf})_2 \cdot \text{toluene}$ (5 mol %), *N*-Boc-L-proline (30 mol %), $\text{P}(1\text{-naphthyl})_3$ (10 mol %), alkyne (2.0 mmol), 0°C, 2 days, and then 10% Pd/C, H_2 , MeOH.

afforded 2.359 g of **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 93% ee (Fig. 5C). By using functionalized alkyne **2t**, the resulting propargylamine **3av** 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 enantiomeric 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 enantiopurity (52).

To further demonstrate the synthetic utility of the method, the late-stage deoxygenative alkynylations 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 high-affinity and selective κ -opioid receptor antagonist (61, 62). Under standard conditions, the catalytic asymmetric reductive alkynylation of functionalized amide

1a-25 with 3,3-diethoxyprop-1-yne (**2u**) produced the desired propargylamine **3aw** in 63% yield and in 88% ee. Pd/C-catalyzed catalytic hydrogenation, hydrogenolysis, and reductive alkylation under acidic conditions proceeded in tandem to afford 2-arylpyrrolidine (*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**.

Catalytic enantioselective reductive alkylation of secondary amides

Considering that the catalytic asymmetric alkylation 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 H_2 (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.

Plausible mechanism of the reaction

Plausible mechanisms for the multicatalysis-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 **iii**, which eliminates diethylsilanol to generate imine intermediate **ii**; (ii) copper-catalyzed in situ generation of nucleophilic Cu-alkynylidene species **vi**; and (iii) *N*-Boc L-proline-catalyzed asymmetric alkynylation of imine **ii** in which *N*-Boc-L-proline (**A4**) serves as a Brønsted 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-alkynylidene **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 alkynyl group affords α -alkylated amine **7** in one pot.

To confirm the dual roles of *N*-Boc-L-proline (**A4**), we carried out the reductive alkynylation reactions of secondary amide **1a-1** with *N*-Boc-L-proline methyl ester or L-proline instead of *N*-Boc-L-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 alkynylation 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-L-proline methyl ester nor L-proline (being a zwitterion in the reaction medium) 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).

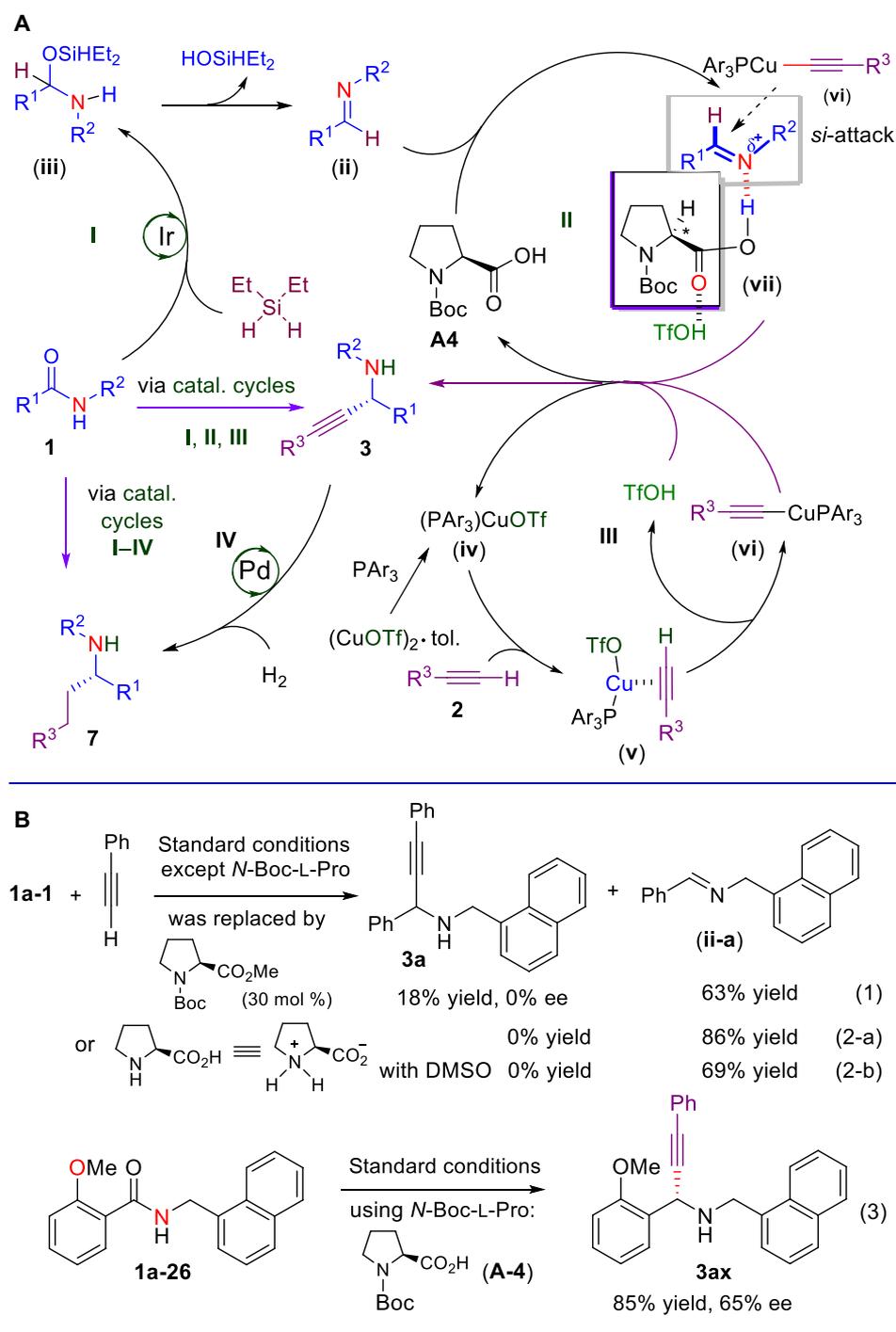


Fig. 8. Plausible reaction mechanisms. (A) Plausible mechanisms for the multicatalytic, one-pot asymmetric reductive alkylation/alkynylation of secondary amides. (B) Control experiments to probe the dual roles of *N*-Boc-L-proline (**A4**) in the catalytic asymmetric reductive alkylation of secondary amides. DMSO, dimethyl sulfoxide.

DISCUSSION

By designing a multicatalysis system, we have achieved the direct asymmetric reductive alkylation 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 ester, ketone, and aldehyde moieties. The observed unusual chemoselectivity can be understood from two aspects. First, the multistep 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 hydrosilylated, leading to the chemoselective asymmetric alkynylation 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 multistep strategy will be useful for the catalytic asymmetric transformations of other carboxylic acid derivatives.

MATERIALS AND METHODS

General procedure A (catalytic asymmetric reductive alkynylation of secondary amides)

In a glove box, to a stirring solution of a secondary amide **1** (0.25 mmol, 1.0 equiv) and [IrCl(COE)₂]₂ (0.75 μ mol, 0.3 mole percent (mol %)) (0.5 mol % for amides **1a-21** and **1a-22**) in anhydrous CH₂Cl₂ (1.25 ml, 0.25 M) was added Et₂SiH₂ (0.5 mmol, 2.0 equiv, 65 μ l) at room temperature under an Ar atmosphere. After being stirred for 1.5 hours (30 min for amides **1a-9**, **1a-18**, **1a-19**, and **1a-20**), the resulting mixture was transferred out of the glove box and added to a mixture of *N*-Boc-L-proline (0.075 mmol, 30 mol %), (CuOTf)₂-toluene (0.0125 mmol, 5 mol %), and P(1-naphthyl)₃ (0.025 mmol, 10 mol %) and stirred for 30 min at 0 °C. To the resultant mixture, an alkyne (1.0 mmol, 4 equiv) was added, and the reaction mixture was stirred at 0 °C for 2 days. The solvent was evaporated under vacuum, and the residue was purified by flash column chromatography on silica gel to give the desired enantioenriched α -chiral propargylamine **3**.

General procedure B (catalytic asymmetric reductive alkylation of secondary amides)

In a glove box, to a stirring solution of a secondary amide (0.25 mmol, 1.0 equiv) and [IrCl(COE)₂]₂ (0.75 μ mol, 0.3 mol %) in anhydrous CH₂Cl₂ (1.25 ml, 0.25 M) was added EtSiH₂ (0.5 mmol, 2.0 equiv, 65 μ l) at room temperature under an Ar atmosphere. After being stirred for 1.5 hours, the resulting mixture was transferred out of the glove box and added to a mixture of *N*-Boc-L-proline (0.075 mmol, 30 mol %), (CuOTf)₂-toluene (0.0125 mmol, 5 mol %), and P(1-naphthyl)₃ (0.025 mmol, 10 mol %) and stirred for 30 min at 0 °C. To the resultant mixture, an alkyne (1.0 mmol, 4 equiv) was added, and the reaction mixture was stirred at 0 °C for 2 days. Then, CH₂Cl₂ was removed, and Pd/C (10 weight %) and MeOH (2 ml) were added. The mixture was stirred under a H₂ atmosphere at room temperature until the propargylamine intermediate was completely consumed. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel to give the desired enantioenriched chiral α -branched amine **7**.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at <https://science.org/doi/10.1126/sciadv.a43431>

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