Reductive Functionalization of Carboxamides: A Recent Update[#]

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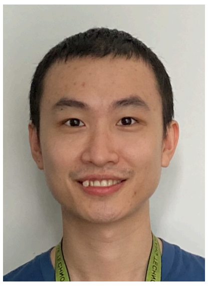
D. Y. Ong



J.-h. Chen

S. Chiba

Abstract

Carboxamides including lactams are readily available and bench-stable chemical feedstock, and thus their use in chemical synthesis for production of valuable compounds would be an attractive choice in various synthetic endeavors. This review highlights and discusses recent advances on deoxygenative reductive functionalization of carboxamides for the synthesis of α-branched amines, that is initiated by controlled single hydride delivery to the amide carbonyl group and terminated by downstream functionalization of the iminium intermediates. The protocols are categorized based on the types of the reduction processes including those with aluminum hydrides, the Schwartz reagent, transition metal-catalyzed/mediated hydrosilylation, and sodium hydride-iodide composite.

Keywords: Carboxamides, Amines, Reduction, Hydride, Hydrosilylation

1. Introduction

α-Branched (cyclic) amines and their derivatives are found as key structural and functional motifs in various pharmaceutical compounds and biologically active natural products. Figure 1 illustrated selected examples of clinically used drugs and biologically active natural products based on the α-branched amine scaffolds. Therefore, development of practical and user-friendly protocols that enable efficient construction of α-branched (cyclic) amines from readily available chemicals has been an important subject in the area of synthetic organic chemistry, and various variants have hitherto been developed and reported.[1]

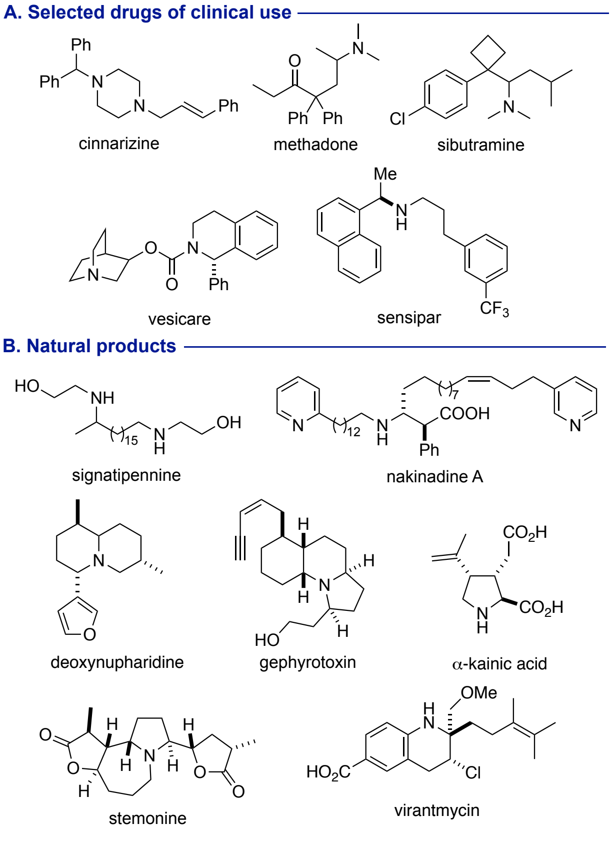


Figure 1. A. Selected α-branched amines of clinical use; B. Selected natural products based on α-branched amine scaffolds.

Reductive amination of ketones or aldehydes[2] and the related multicomponent approaches such as Mannich,[3] Petasis[4] and Strecker[5] reactions that engage respective carbon nucleophiles are classical yet powerful protocols of choice especially for the synthesis of acyclic α-branched amines (Figure 2A). Leveraging of organic free radical strategies in the multicomponent coupling of carbonyl compounds has recently emerged, allowing for use of alkenes and alkyl halides as a coupling partner and thus greatly widening the scope of the α-functionalization of amines (Figure 2B).[6]

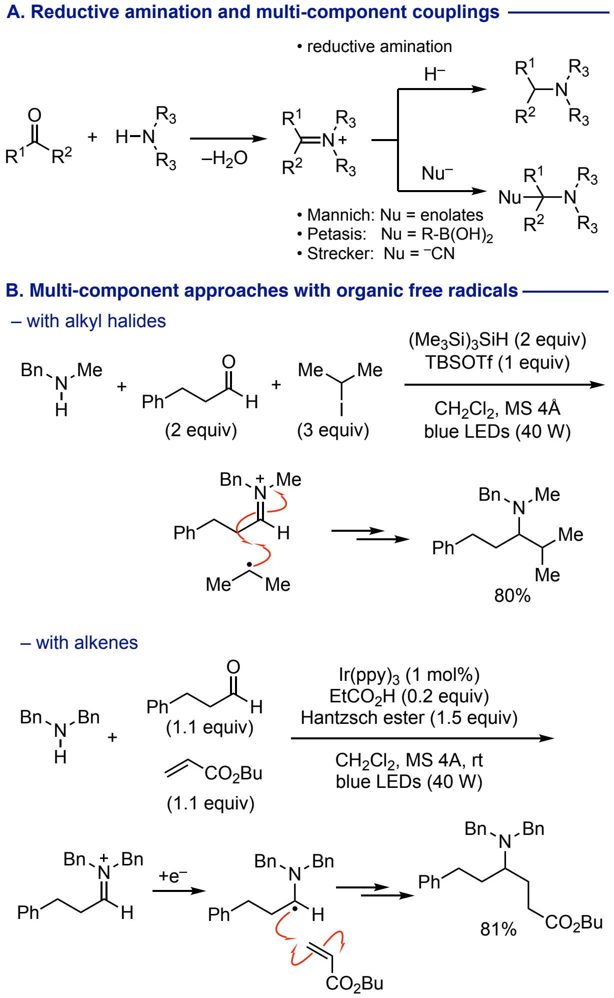


Figure 2. Reductive amination and the related multi-component approaches.

Cyclic amines are valued as the mainstream in small molecule libraries for drug discovery programs.[7,8] For the synthesis of α-branched cyclic amines, leveraging of deprotonative lithiation at the α-carbon of the nitrogen having an unreactive Lewis basic directing group (such as *tert*-butyloxycarbonyl; Boc) is one of the promising ways starting from the readily available simpler cyclic amine feedstock (Figure 3). Subsequent treatment of the resulting carbanion intermediates with reactive carbon electrophiles (E^+) allows for installation of various functionalities, although this protocol requires the use of strong organolithium reagents under cryogenic reaction conditions for the initial deprotonation.[9,10]

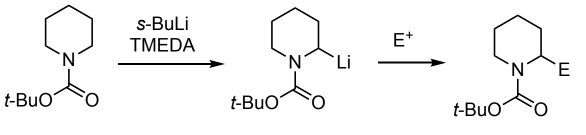


Figure 3. Synthesis of α-branched cyclic amines by lithiation followed by treatment with electrophiles.

Complementary to the deprotonation strategy for α-functionalization of protected cyclic amines, Seidel recently developed α-C-H functionalization of unprotected cyclic amines that leverages hydride transfer from the lithium amide intermediates to external ketones as a hydride acceptor.[11] The resulting electrophilic imines could be trapped by various carbon nucleophiles, providing α-branched cyclic amines

(Figure 4A).[12] Moreover, ensuing treatment of the resulting cyclic imines with lithium diisopropylamide (LDA) can generate endocyclic aza-allyl anions, which undergo β-alkylation with alkyl halides to furnish β-functionalized cyclic imines (Figure 4B).[13] Thus, subsequent addition of another carbon-nucleophiles results in diastereoselective construction of α,β-disubstituted cyclic amines .

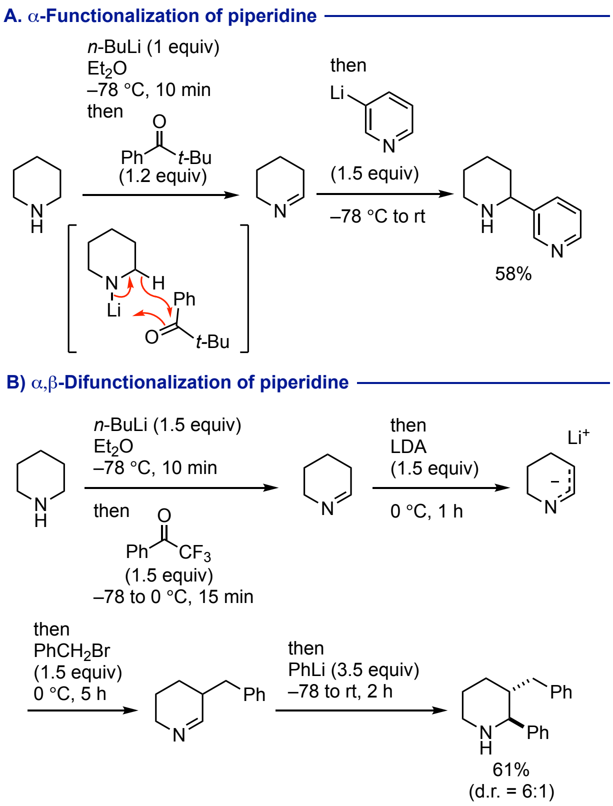


Figure 4. α-C-H functionalization of unprotected cyclic amines.

Nonetheless, leveraging of transition metal-catalyzed C-H functionalization[14,15] and free radical-based strategies[16,17] to install a desired functionality at the α-position of amine compounds are state-of-the-art approaches for the synthesis of α-branched amines. Recent development of visible-light photoredox catalysis has expanded the scope of the α-C-H functionalization of amines and offered milder reaction conditions and practical protocols.[18,19] Figure 5 exemplified construction of α-branched amines by means of photoredox catalysis in the combination with hydrogen atom transfer (HAT) catalysis (Figure 5A) and HAT catalysis & Ni-catalyzed cross-coupling (Figure 5B) as well as photocatalytic oxidation of amines followed by interception of the resulting iminium ions with a carbon nucleophile (Figure 5C).

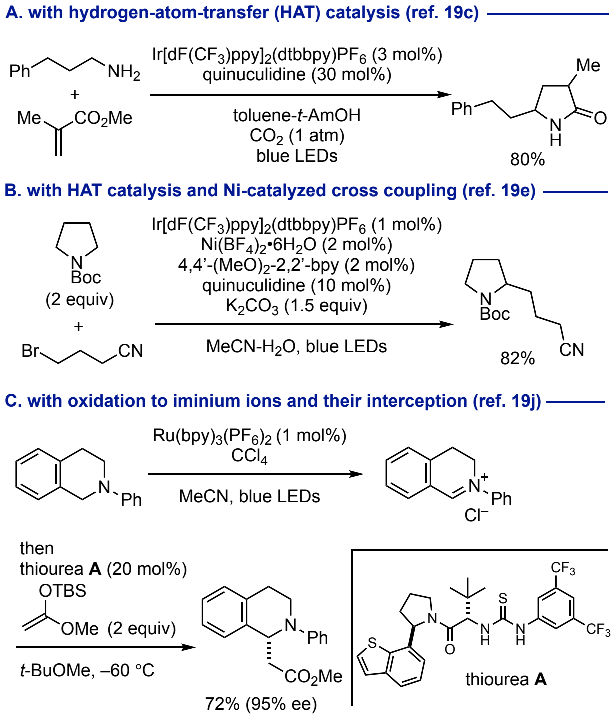


Figure 5. Synthesis of α-branched amines via photoredox catalysis.

Another promising approach to access to the α-branched amines is deoxygenative functionalization of readily available and bench-stable carboxamides and lactams.[20,21] In this context, several protocols have been developed by taking advantage of electron-rich and nucleophilic nature of tertiary and secondary carboxamides. For example, their electrophilic activation by triflic anhydride (Tf_2O)[22,23] allows for generation of imidoyl triflate salts from tertiary carboxamides (Figure 6A) or nitrilium ions from secondary ones (Figure 6B) and ensuing installation of two folds of nucleophiles including a hydride to deliver α-branched amines (Figure 6).

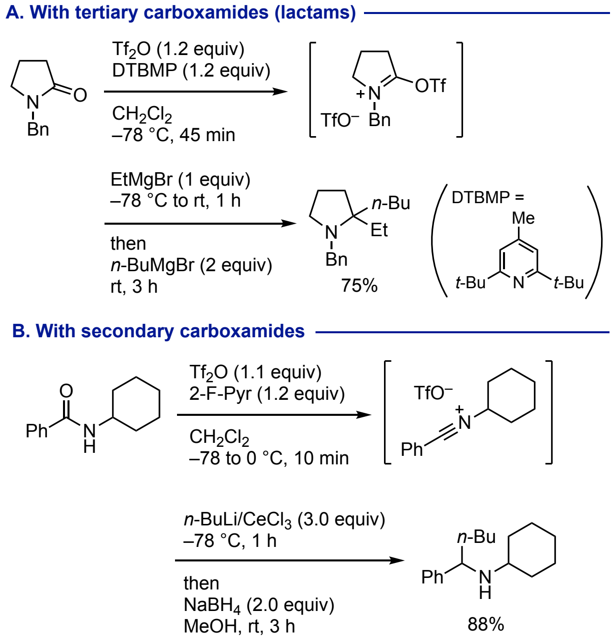


Figure 6. Electrophilic activation of carboxamides with triflic anhydride (Tf_2O).

On the other hand, employment of controlled hydride reduction (including transition metal-catalyzed hydrosilylation) of carboxamides as the process initiation has enabled *in situ* generation of iminium ions and their downstream functionalization with prevention of undesired over-reduction, creating a new dimension for the synthesis of α-branched amines (Figure 7). This review highlights recent development of reductive functionalization of carboxamides and lactams for the synthesis of α-branched amines by categorizing them based on the types of the controlled hydride reduction as the process initiation. It should be noted that this review does not include reductive functionalization of thioamides[24] and imides.[25] Readers can find the representative examples in the corresponding references.

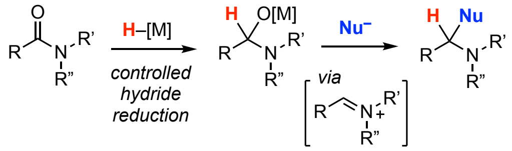


Figure 7. Reductive functionalization of carboxamides via controlled hydride reduction.

2. Aluminum hydrides

Aluminum hydrides have often been utilized for reduction of carboxamides into the corresponding amines via sequential delivery of two hydrides.[26] Controlled reduction of carboxamides is sometimes possible with stoichiometric use of aluminum hydrides under cryogenic reaction conditions to prevent collapse of the resulting tetrahedral anionic carbinol amine intermediates, and thus ensuing treatment with nucleophiles (often with acid activators) leads to their deoxygenative functionalization to afford α-branched amines via the corresponding iminium ion intermediates. An earlier example, dating back to 1999, could be found in the Suh's elegant total synthesis of fluvirucinine A$_1$ (Figure 8).[27] Reduction of 3-ethyl-2-piperidone **1** by LiAl(OEt)$_3$H (1.2 equiv) in Et$_2$O at 0 °C and subsequent treatment with vinylmagnesium bromide afforded 2-vinylated piperidine **2** in 70% yield with good trans-selectivity (*trans*:*cis* = 95:5). After conversion of **2** into amide **3**, treatment of **3** with lithium bis(trimethylsilyl)amide (LHMDS) in toluene under reflux conditions induced stereo-controlled aza-Claisen rearrangement of the resulting enolate, forming 10-membered ring lactam **4** having two stereogenic centers at C6 and C10 of fluvirucinine A$_1$.

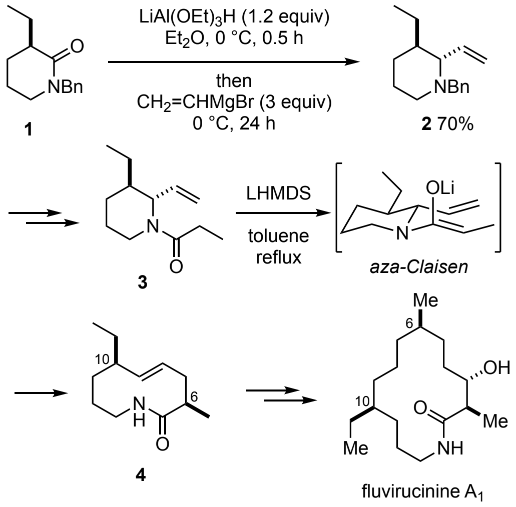


Figure 8. Synthesis of fluvirucinine A$_1$

However, use of aluminum hydrides has rarely been practiced for reductive functionalization of carboxamides and lactams probably due to the risk of over-reduction of the amide substrates. On the other hand, reduction of *N*-alkoxyamides by aluminum hydrides can provide relatively stable five-membered chelate intermediates.[28] Their subsequent deoxygenative functionalization with carbon-nucleophiles in the presence of acid activators was demonstrated independently by Chida/Sato (Figure 9A)[29] and Vincent/Kouklovsky (Figure 9B).[30]

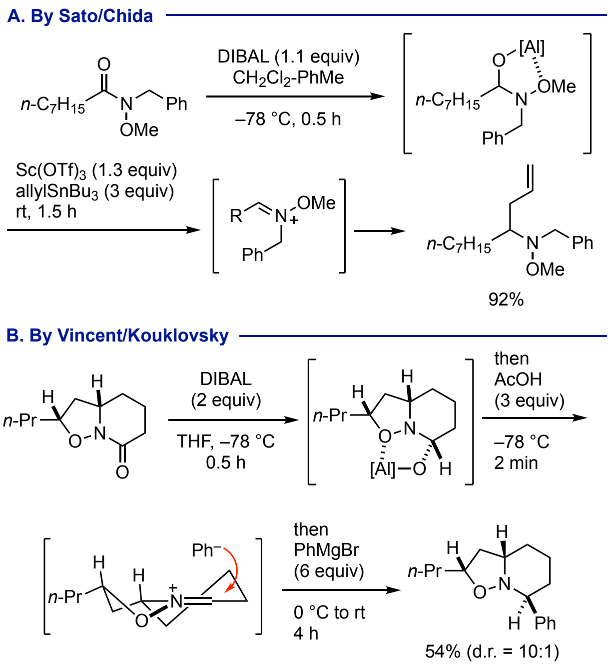


Figure 9. Reductive functionalization of *N*-alkoxyamides with aluminum hydrides.

3. Schwartz's reagent (Cp$_2$ZrHCl)

The Schwartz's reagent [Cp$_2$Zr(H)Cl] is capable of controlling delivery of a single hydride to a whole range of carboxamides (primary, secondary, and tertiary) for the synthesis of the corresponding aldehydes under milder reaction conditions. The protocol also exhibits much wider functional group compatibility than those with aluminum hydrides do.[31,32] The superior reactivity of the Schwartz's reagent was shown in reductive allylation of bicyclic *N*-methoxylactam **5** in the effort for the synthesis of gephyrotoxin by Sato/Chida (Figure 10).[33] Namely, use of diisobutylaluminum hydride (DIBAL) for the process initiation provided not only desired allylated *N*-methoxyamines **6** but also aldehyde **7** through undesired reduction of the *t*-butyl ester moiety (Figure 10A), whereas **6** was formed as a single product in the process with Cp$_2$ZrHCl (Figure 10B).

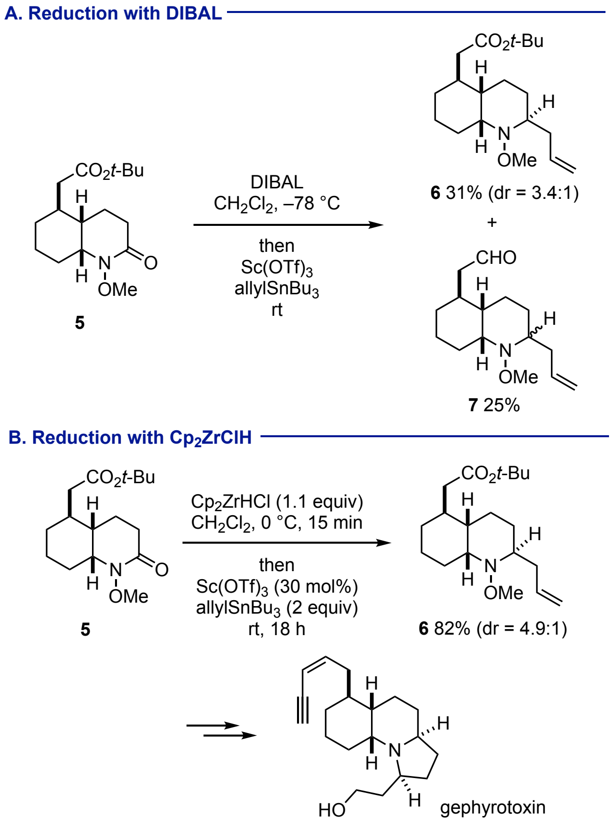


Figure 10. DIBAL vs the Schwartz's reagent.

Nonetheless, the Schwartz's reagent could be utilized in the reductive functionalization of secondary and tertiary carboxamides. For example, an earlier work by Ganem in the synthesis of α-kainic acid showed synthetic advantage in use of the Schwartz's reagent (Figure 11).[34] The late stage cyanation of lactam **7** was achieved to install a cyano group at C2 position of **8**, that was converted into α-kainic acid.

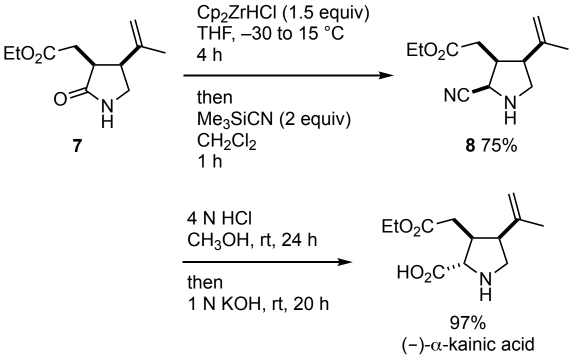


Figure 11. Synthesis of α-kainic acid.

Sato/Chida revealed that a range of neutral carbon-based nucleophiles in combination with acid activators are applicable in reductive functionalization of carboxamides initiated by the reduction using the Schwartz's reagent as shown in Figure 12.[35]

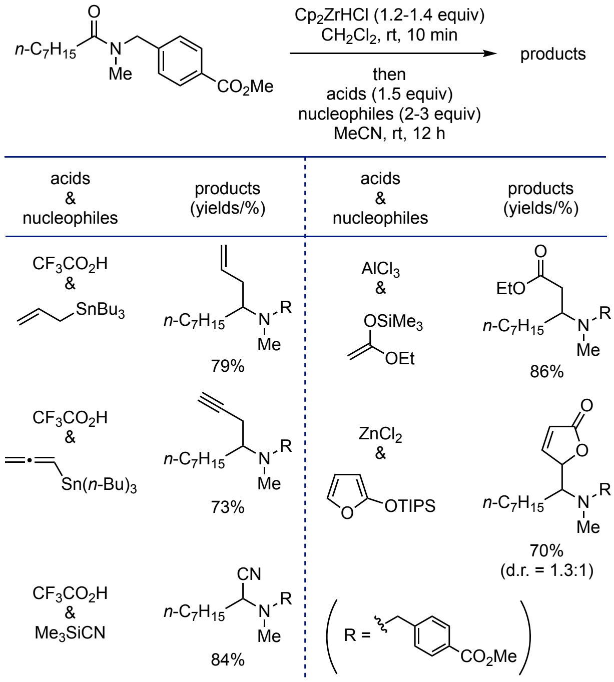


Figure 12. Use of neutral carbon-nucleophiles with the Schwartz' reagent.

In addition to carbon-based nucleophiles, diethyl phosphite was found to function as a phosphorous-centered nucleophile for the reductive functionalization of carboxamides initiated by the Schwartz's reagent (Figure 13).[36]

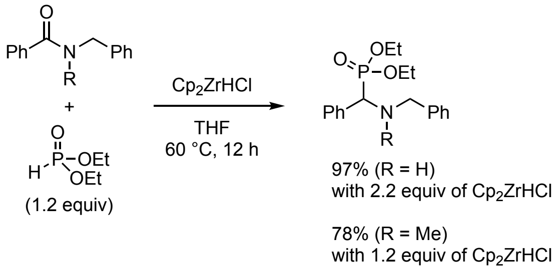


Figure 13. Reductive phosphination of carboxamides.

4. Metal-catalyzed hydrosilylation

Hydrosilylation of carboxamides catalyzed/mediated by transition-metal complexes is capable of single hydride delivery to the carbonyl group in a controlled manner with superior functional group compatibility to the conventional hydride reduction methods. The resulting O-silylated hemiaminal intermediates undergo deoxygenative functionalization under various reaction conditions. Therefore, leveraging of metal-catalyzed/mediated hydrosilylation has been utilized as the most promising tool for the initiation of the reductive functionalization of carboxamides.

4.1. Ir-catalyzed hydrosilylation. Nagashima reported that hydrosilylation of tertiary carboxamides **9** with 1,1,3,3-tetramethyldisiloxane (TMDS) was efficiently catalyzed by the Vaska's complex, $IrCl(CO)(PPh_3)_2$ and its derivatives, providing the corresponding enamines **10** (Figure 14).[37] The catalytic cycle is generally considered as follows: i) oxidation addition of the H-Si bond to the Ir(I) center to form H-Ir(III)-Si species **11**; ii) insertion of the amide carbonyl group to the

Ir(III)-Si bond to afford the α-silyoxy organo-Ir(III) hydride **12**; iii) H-C reductive elimination to liberate O-silylated hemiaminal intermediate **13** with regeneration of the Ir(I) catalyst. The resulting O-silylated hemiaminal intermediate **13** undergoes elimination of a siloxide to generate iminium ion **14**, which is further converted into the corresponding enamines via α-deprotonation. Use of various nucleophiles in combination with this Ir-catalyzed hydrosilylation of tertiary carboxamides allows for interception of iminium intermediate **14**, enabling synthesis of α-branched amines.

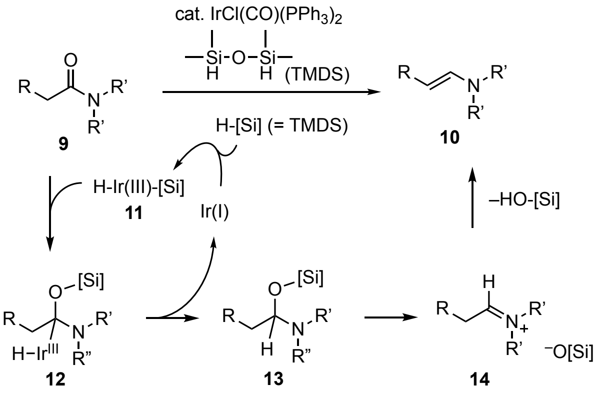


Figure 14. Ir-catalyzed hydrosilylation of tertiary carboxamides.

Capturing the iminium ion by an intramolecular nucleophile results in facile construction of complex heterocyclic molecular scaffolds. For example, Dixon demonstrated the reductive intramolecular aza-Henry reaction of *N*-nitroalkyl tethered lactam **15**, where initially formed enamine **16** via the Ir-catalyzed hydrosilylation were protonated to generate iminium ion **17** and subsequent basification promoted cyclization to form aza-bicyclic product **18** (Figure 15).[38]

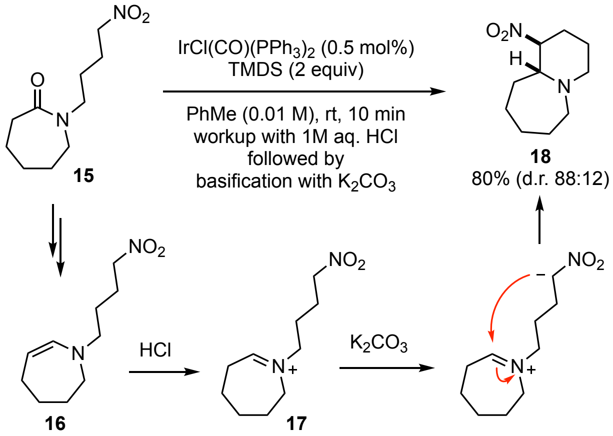
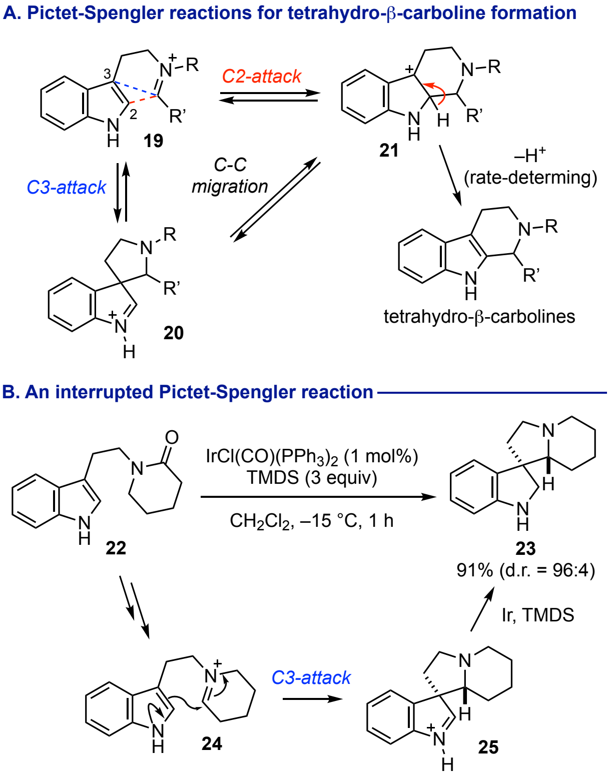


Figure 15. Reductive intramolecular aza-Henry reaction

Formation of tetrahydro β-carbolines via intramolecular Friedel Crafts type C-C bond formation of iminium ions **19** derived from tryptamine and carbonyl compounds is known as the Pictet-Spengler reaction (Figure 16A). The mechanistic studies implicated that the process involves both C3- and C2-attack of the indole moiety to form spiro-indolenium ions **20** and pentahydro β-carbolinium ions **21**, respectively as the intermediates which are linked under equilibrium via C-C bond migration.[39] The pentahydro β-carbolinium ion intermediates **21** undergo deprotonative aromatization to form tetrahydro β-carbolines, which is generally considered as a rate-determining process. On the other hand, Dixon recently reported an interrupted Pictet-Spengler process by taking advantage of the Ir-catalyzed hydrosilylation of indole-tethered tertiary lactams (Figure 16B).[40] For example, treatment of lactam **22** under the Ir-catalyzed hydrosilylation reaction conditions afforded azaspiro indoline **23** predominantly. In the process, the spiro-indolenium intermediate **25** formed via C3-attack in the iminium intermediate **24** could be efficiently reduced under the present hydridic reaction conditions, thus outcompeting the conventional deprotonative aromatization observed in the Pictet-Spengler process.


A. Pictet-Spengler reactions for tetrahydro-β-carboline formation

B. An interrupted Pictet-Spengler reaction

Figure 16. The Pictet-Spengler reaction and its interrupted process.

Dixon also demonstrated total syntheses of aspidosperma alkaloids by taking advantage of formal [4+2]-cycloaddition of the enamine intermediates, which were obtained *in situ* by the Ir-catalyzed hydrosilylation of indole-tethered lactams.[41] For example, synthesis of vincadifformine was accomplished from δ-lactam **26** under Ir-catalyzed hydrosilylation reaction conditions (Figure 17). Enamine **27** underwent intramolecular 1,4-addition to the α,β-unsaturated ester moiety to form the 1st C-C bond and ensuing trapping of the resulting iminium cation **28** with the C3 carbon of the indole moiety to construct the 2nd C-C bond in diastereoselective fashion, liberating vincadifformine in one-pot fashion.

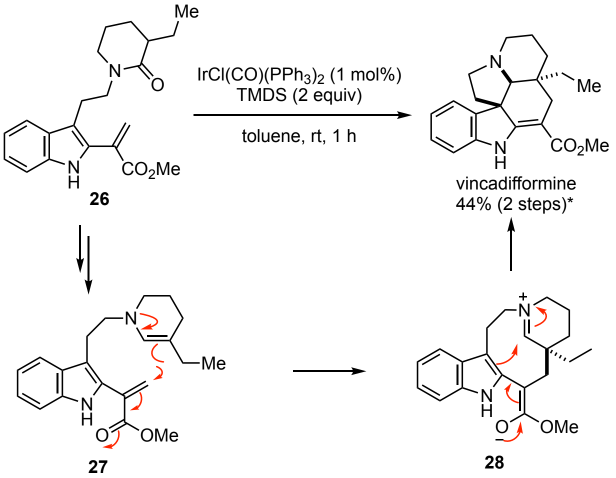


Figure 17. Synthesis of vincadifformine. *The process was commenced with N-Boc derivative of **26** with the deprotection of the Boc group.

On the other hand, various external nucleophiles were engaged in combination with the Ir-catalyzed hydrosilylation for reductive functionalization of tertiary carboxamides. As for the use of neutral carbon nucleophiles, Sato/Chida employed ketene silyl acetals, 2-siloxyfuran, and allyl tributylstannane in the presence of Brønsted or Lewis acid for reductive functionalization of *N*-methoxy-*N*-benzylamides[42] and tertiary carboxamides.[43] Figure 18 illustrated the reductive vinylogous functionalization of stemonamide (**29**) for the synthesis of stemonine. Use of 2-siloxyfuran in the presence of 2-nitrobenzoic acid in combination with the Ir-catalyzed hydrosilylation gave **30** in excellent yield. It should be noted that other controlled reduction protocols for the process initiation were incompatible for the reductive functionalization of stemonamide (**29**). For example, the Schwartz reagent (section 3) resulted in undesired reduction of the lactam moiety which is exceptionally highly reactive due to the strained *trans*-fused 5/7 ring system.

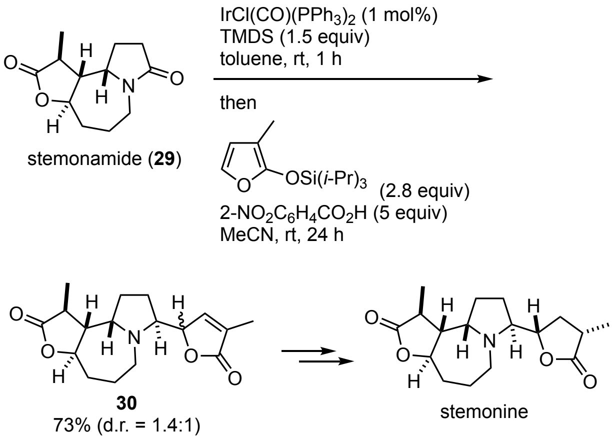


Figure 18. Reductive functionalization of stemonamide (**29**)

In addition, Dixon[44] and Sato/Chida[43a] independently disclosed that employment of trimethylsilyl cyanide as a nucleophile allows for reductive Strecker cyanation to prepare α-amino nitriles (Figure 19A). Sato/Chida recently applied this protocol as one of the key steps for the synthesis of fasicularin (Figure 19B).[45] On the other hand, it was reported by Dixon that use of isocyanides in the presence of acetic acid enables Ugi-type reductive coupling for the synthesis of α-amino amides (Figure 19C).[46]

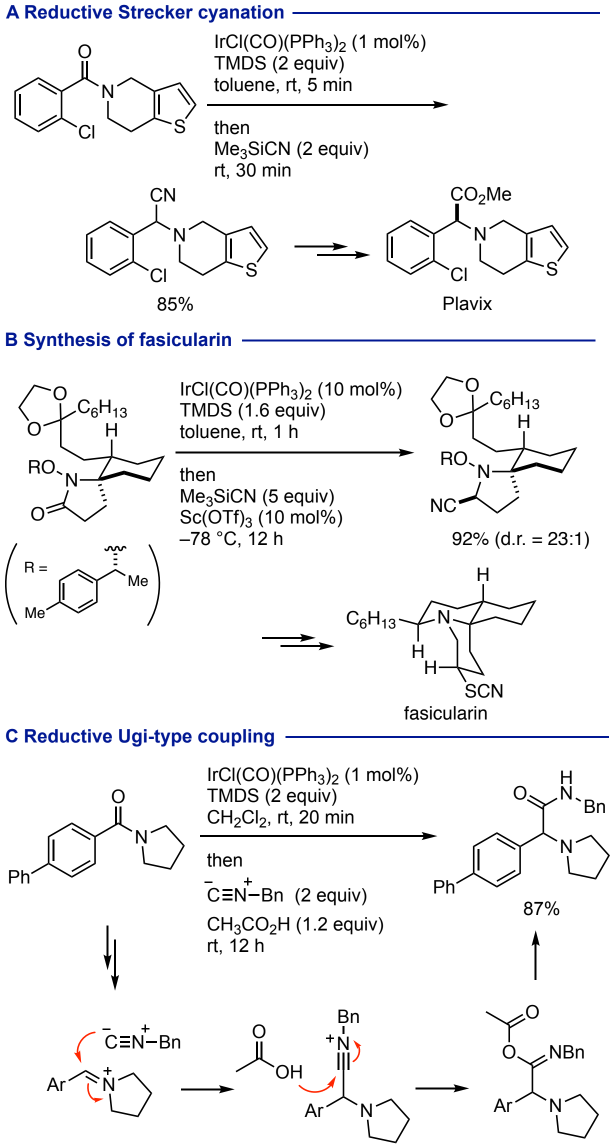


Figure 19. Reductive Strecker cyanation and Ugi-type couplings.

Use of organometallic nucleophiles has also been explored for the downstream C-C bond formation. For example, installation of alkynyl moieties was developed by Huang using terminal alkynes and CuBr as a catalyst (Figure 20).[47]

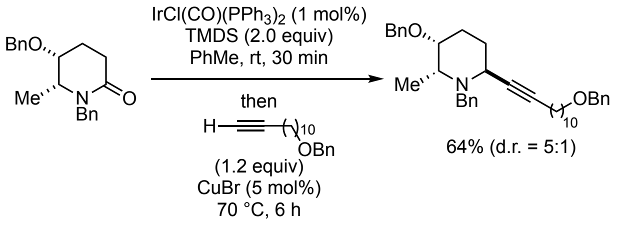


Figure 20. Reductive functionalization with terminal alkynes.

Dixon disclosed that Grignard reagents can functionalize the hydrosilylated intermediates generated *in situ* from tertiary carboxamides, allowing for facile, rapid and scalable (up to 0.1 mol) access to a series of α-branched amines (Figure 21).[48]

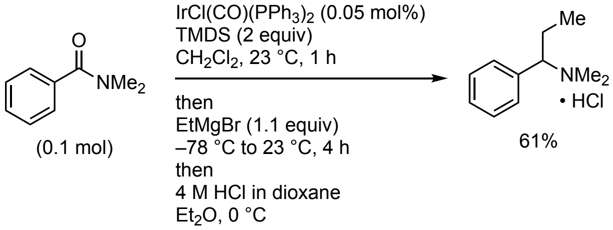


Figure 21. Reductive functionalization with Grignard reagents.

Despite wider functional group compatibility and milder reaction conditions offered by the Vaska's catalyst for the hydrosilylation, it is limited to the transformations of tertiary carboxamides or *N*-methoxy-*N*-benzylamides. To overcome this drawback, Huang[49] and Sato/Chida[50] independently reported that the combination of [Ir(COE)$_2$Cl]$_2$ and diethylsilane (Et$_2$SiH$_2$) that was originally reported by Brookhart,[51] can be utilized for reductive functionalization of secondary carboxamides with various nucleophiles (Figure 22).

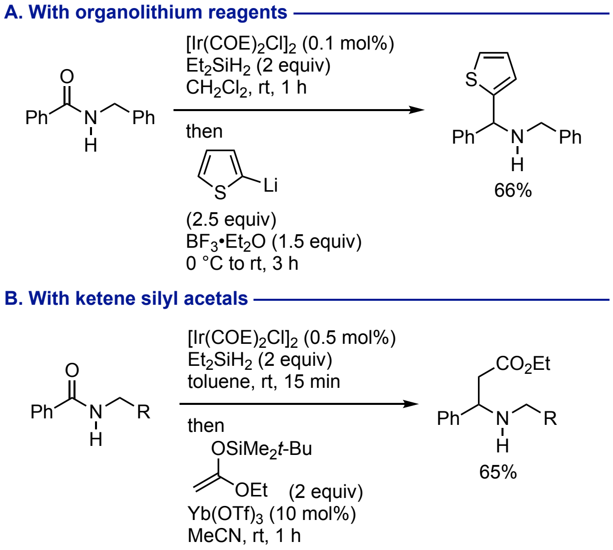


Figure 22. Reductive functionalization of secondary carboxamides.

4.2. Mo(CO)$_6$-catalyzed hydrosilylation. Recently, Adolfsson revealed that molybdenum hexacarbonyl is capable in catalyzing controlled and chemoselective hydrosilylation of tertiary carboxamides with TMDS to provide the corresponding O-silylated hemiaminal intermediates, which are converted into the aldehydes through aqueous workup.[52] On the other hand, ensuing treatment of the resulting O-silylated hemiaminal intermediates with TMSCN allowed for reductive Strecker cyanation to form α-amino nitriles (Figure 23).[53]

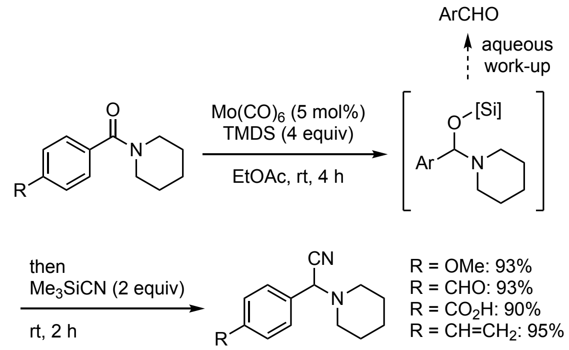


Figure 23. Reductive Strecker cyanation in combination with Mo(CO)$_6$-catalyzed hydrosilylation of tertiary carboxamides.

4.3. Ti(O*i*-Pr)$_4$-medaited hydrosilylation. Buchwald developed reduction of secondary and tertiary aliphatic carboxamides into aldehydes by combined use of Ti(O*i*-Pr)$_4$ and diphenyl silane (Ph$_2$SiH$_2$) (Figure 24A).[54] The methodology exhibited robust functional group tolerance on the aliphatic carbon chain on the carboxamides, while it needs α-enolizable proton(s) and stoichiometric quantity of Ti(O*i*-Pr)$_4$. The reduction of α-quaternary carboxamides provided not only aldehydes but also alcohols through hydrolysis of the iminium intermediates and consecutive reduction of the resulting aldehydes. On the other hand, Dixon demonstated that reductive aza-Henry cyclization of spirocyclic α-quaternary lactam **31** having a nitroalkane tether proceeded predominantly through quick intramolecular interception of the iminium ions, providing **32**, a key intermediate toward the synthesis of manzamine alkaloids (Figure 24B).[55] Recently, Tokuyama applied the protocol with a slight modification for reductive allylation of spirocyclic secondary lactams using allylmagnesium chloride and zinc chloride in the synthetic studies of histrionicotoxins[56] and lepadiformine.[57] For example, reductive allylation of lactam **33** resulted in stereoselective installation of the allyl group to construct the 1-azaspiro[5,5]undecane core **34** of the histrionicotoxin family (Figure 24C). Furthermore, Tokuyama revealed that reductive crotylation of secondary lactam **35** proceeded stereospecifically via rigid 6-membred ring pseudo-chair transition state **36** formed between the crotylzinc reagent and the half-chair cyclic imines, affording branched adduct **37** as a single diastereomer.[58] This was eventually converted to castoramine (Figure 24D).

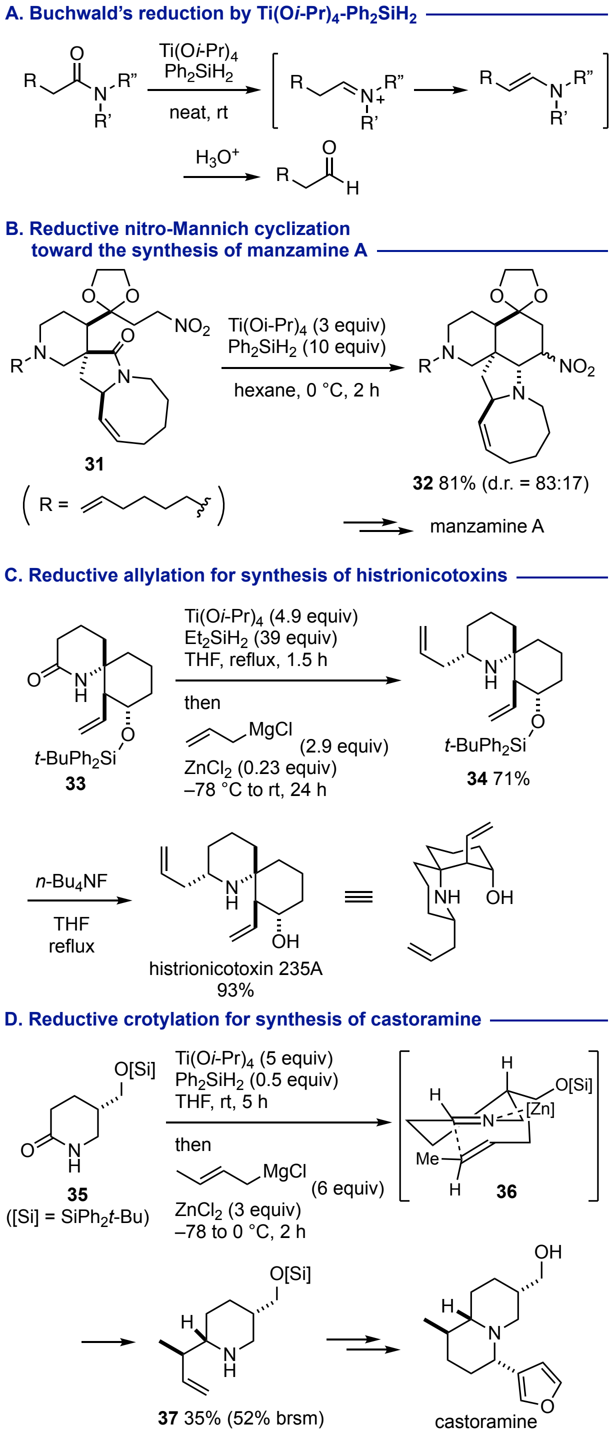


Figure 24. Ti(O*i*-Pr)$_4$-mediated reductive functionalization of carboxamides.

5. NaH-NaI composite

In 2016, our group reported a controlled hydride reduction of tertiary carboxamides into aldehydes using a combination of NaH and NaI in THF (Figure 25A).[59] The detailed mechanistic study revealed that the anionic hemi-aminal intermediates **36** formed via single hydride delivery to the tertiary carboxamides **35** from the activated NaH are kept stable under the reaction conditions (prior to aqueous work-up).[26] Thus, subsequent silylation of the anionic hemi-aminals with trimethylsilyl chloride (TMSCl) followed by addition of carbon-based nucleophiles allowed for overall production of α-branched amines from tertiary carboxamides under a transition-metal free manner.[60] In this context, a series of Grignard reagents were found amenable to the downstream C-C bond formation (Figure 26B). In this process, MgBr$_2$ present in the Grignard reagents (due to the Schlenk equilibrium) likely functions as a Lewis acid to assist generation of the iminium ion. Moreover, the reaction conditions were found compatible for reductive Strecker reaction using tetrabutylammonium cyanide (Figure 26C).

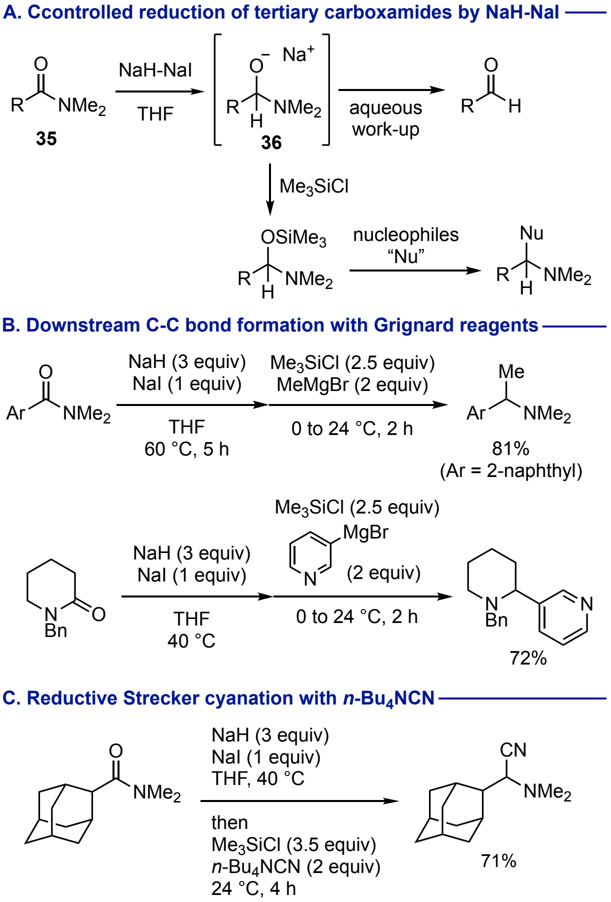


Figure 25. NaH-mediated reductive functionalization of carboxamides.

6. Conclusion

This review summarized recent development on reductive functionalization of carboxamides for the synthesis of α-branched amines. The controlled single hydride delivery to an amide carbonyl group and subsequent addition of nucleophiles enabled downstream deoxygenative functionalization via interception of the iminium ion intermediates generated *in situ* by the aid of acid activators or Lewis acidity of the nucleophiles themselves. A wide array of nucleophiles (both in organometallic ionic and covalent neutral states) could be engaged, enhancing molecular complexity in the α-branched amines scaffolds. Nonetheless, there is no all-around method that can be applicable to universal substrates, and each of the reported protocols has merits and demerits. The merits of demand in the protocol are varied in the opportunities and purposes, as the targeted products, α-branched amines are versatile in various fields such as target-oriented synthesis, medicinal chemistry, and process manufacturing. Therefore, it is our strong belief that the research for the development of new protocols on the reductive functionalization of carboxamides continues to flourish and thus further expands the choices for the synthetic chemists.

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