JOC The Journal of Organic Chemistry

Note

A General Method for the One-pot Reductive Functionalization of Secondary Amides

Pei-Qiang Huang, Ying-Hong Huang, Kai-Jiong Xiao, Yu Wang, and Xiao-Er Xia

J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 05 Feb 2015

Just Accepted

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

A General Method for the One-pot Reductive Functionalization of Secondary Amides

Pei-Qiang Huang,*[a,b] Ying-Hong Huang,[a,‡] Kai-Jiong Xiao,[a,‡] Yu Wang,[a] and Xiao-Er Xia[a]

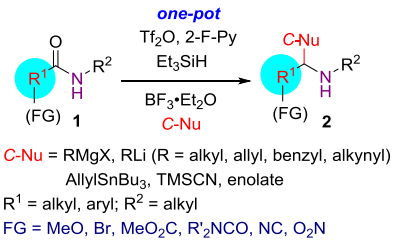
[a] *Department of Chemistry and Fujian Provincial Key Laboratory of Chemical Biology, Collaborative Innovation Centre of Chemistry for Energy Materials, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, P. R. China*

[b] *State Key Laboratory of Applied Organic Chemistry Lanzhou University, Lanzhou 730000, P. R. China*

Email: pqhuang@xmu.edu.cn.

‡ Y.-H. H. and K.-J. X. contributed equally to this work

In Memory of Professor Dr. Bertrand Castro



ABSTRACT: A one-pot reaction for the transformation of common secondary amides into amines with C-C bond formation is described. This method is consisted of *in situ* amide activation with Tf_2O – partial reduction – addition of *C*-nucleophiles. The method is general in scope, which allows employing both hard nucleophiles (RMgX, RLi) and soft nucleophiles, as well as enolates. The reaction proceeded with high chemoselectivity at secondary amide in the presence of ester, cyano, nitro and tertiary amide groups.

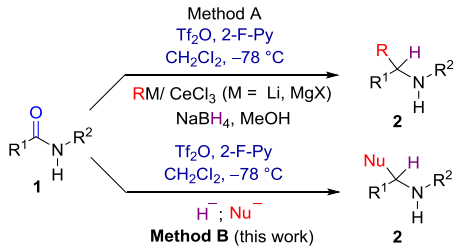
Due to the high stability and easy availability of amides,[1a] secondary amides[1b-e]

constitute a class of versatile synthetic intermediates in organic synthesis[2] and serve as valuable directing group in both modern C-H activation/ functionalization[3] and classical C-H lithiation/ functionalization reactions.[4] Since directing groups themselves seldom constitute a part of the target molecules, it is highly desirable to develop one-pot methods for their transformations into useful functional groups such as amines. However, little attention has been paid to the subsequent step-economical[5] transformations of the directing groups (amide groups) after C-H functionalizations.[3a,4b] Moreover, amino group plays a pivotal role for the bioactivity of pharmaceuticals and alkaloids.[6] Thus, there are multiple and urgent demands for methods allowing one-pot transformation of secondary amides into amines with C-C bond formation.

However, in contrast to that of tertiary amides,[7-10] the one-pot reductive alkylation of secondary amides remains a formidable challenge. Except for stepwise methods,[11] the reported one-pot methods only involve reductive di-allylation,[12a-c] Schwartz reagent-mediated reductive cyanation of secondary lactams,[12d,e] and reductive allylation of secondary amides.[9b] In 2012, our group disclosed a general method for the one-pot reductive alkylation of secondary amides,[13] which is based on the amide activation with trifluoromethanesulfonic anhydride (Tf_2O)[14]/ 2-fluoropyridine (2-F-Py)[15]–organocerium reagent addition - reduction sequence (Scheme 1, Method A). However the issue of chemoselectivity, one of the key challenges in modern organic synthesis,[16] has not yet been addressed in our previous method.[13,17] Thus, the development of a chemoselective alternative yet complementary partial reduction –

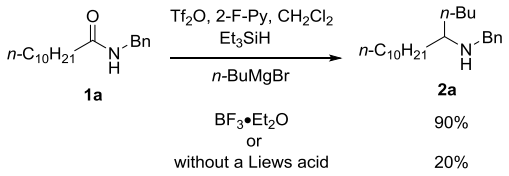
nucleophilic addition approach (Scheme 1, Method B) is highly desirable, which has been explored and the results are reported herein.

Scheme 1. Complementary Approaches for the General One-pot Reductive Alkylation of Secondary Amides



Recently,[18a] we have demonstrated that secondary amides, after activation with Tf_2O, can be reduced by $NaBH_4$ under mild conditions to give amines.[18] Lately, we have developed the first one-pot reductive coupling reaction of secondary amides,[19] which is based on the activations of secondary amides, partial reduction with triethylsilane (Et_3SiH)[20] and Kagan reagent (SmI_2)-mediated reductive coupling reactions. On the basis of these precedents, a more general one-pot reductive functionalization of secondary amides consisting of amide activation - partial reduction - addition of organometallic reagent was envisioned, and the reductive *n*-butylation of *N*-benzyl undecanamide **1a** was selected for screening reaction conditions (Table 1, entry 1). The optimal conditions were defined as: successive treatment of amide **1a** with 2-F-Py (1.2 equiv), Tf_2O (1.1 equiv) and Et_3SiH (1.1 equiv) at 0 °C, followed by addition of $BF_3{\cdot}OEt_2$ (1.5 equiv) and *n*-butyl Grignard reagent (4.0 equiv) at 0 °C for 2 h. In such a manner, amine **2a** was obtained in 90% yield. It is worth to note that in the absence of $BF_3{\cdot}OEt_2$, the product was obtained in a low yield (20%).

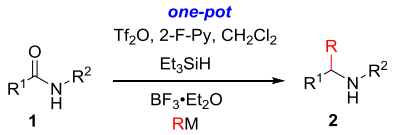
Scheme 2. One-pot Reductive Butylation of Amide 1a

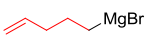


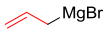
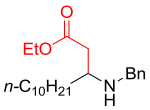
With the optimal conditions defined, the scope of the reaction was examined, and the results are summarized in Table 1. Similar to the reductive *n*-butylation of **1a** (Table 1, entry 1), *n*-butylation of aliphatic amides **1b** and **1c** produced the corresponding amines in 92% and 81% yield, respectively. The lower yield of **2c** compared with those of **2a** and **2b** is attributable to the volatility of the amine. Benzamides and *p*-methylbenzamide reacted similarly to give amines **2d-g** in 82-83% yields (entries 4-7). The reaction worked well with amides bearing different *N*-alkyl groups ranging from primary (Bn, *n*-Bu, Me) to secondary (*i*-Pr, *c*-hex) alkyl groups. The reductive alkylation of amide **1a** with Grignard reagents prepared from primary alkyl (entry 1), primary alkenyl (entry 8), and secondary alkyl (entry 9) halides worked similarly to give the corresponding amines **2a**, **2h**, and **2i** in 90-94% yields. Ethyl, benzyl, and allyl magnesium bromides also reacted smoothly to give the corresponding amines **2j-n** (entries 10-14). The reaction was shown to tolerate *para*-methoxy and *para*-bromo substituents on the phenyl ring of benzamides (68% and 62%, entries 15 and 16). It is noteworthy that, besides Grignard reagents, organolithium reagents can also serve as effective nucleophiles in the reductive functionalization (entries 17-20). In particular, reductive alkynylation proceeded smoothly to give the corresponding propargylamines **2q-s** (entries 18-20), which are important structural motifs in natural products and pharmaceuticals, and are versatile synthetic intermediates.[21] Surprisingly,

attempted introduction of simple ethenyl, ethynyl, and phenyl groups were at current stage unsuccessful (entries 21 and 22). Significantly, reductive functionalization of **1a** with enolate derived from ethyl acetate underwent smoothly to give β-aminoester **2t** in 82% yield (entry 23), thus providing an alternative method for the synthesis of biologically important β-amino acids.[22]

Table 1. One-pot Reductive Functionalization of Secondary Amides with Organometallic Reagents and Enolate



Entry	Amide	R^1	R^2	RM	Yield (%)[a]
1.	**1a**	*n*-$C_{10}H_{21}$	Bn	*n*-BuMgBr	**2a:** 90
2.	**1b**	*n*-$C_{11}H_{23}$	*n*-Bu	*n*-BuMgBr	**2b:** 92
3.	**1c**	Me	*c*-hex	*n*-BuMgBr	**2c:** 81
4.	**1d**	Ph	*n*-Bu	*n*-BuMgBr	**2d:** 89
5.	**1e**	Ph	Me	*n*-BuMgBr	**2e:** 82
6.	**1f**	Ph	*c*-hex	*n*-BuMgBr	**2f:** 83
7.	**1g**	4-Me-C_6H	*c*-hex	*n*-BuMgBr	**2g:** 90
			4		
8.	**1a**	*n*-$C_{10}H_{21}$	Bn		**2h:** 94
9.	**1a**	*n*-$C_{10}H_{21}$	Bn	*c*-hexMgBr	**2i:** 92
10.	**1f**	Ph	*c*-hex	EtMgBr	**2j:** 81
11.	**1f**	Ph	*c*-hex	BnMgBr	**2k:** 85

12.	**1c**	Me	*c*-hex	BnMgBr	**2l:** 79
13.	**1h**	*c*-hex	*c*-hex	BnMgBr	**2m:** 77
14.	**1f**	Ph	*c*-hex		**2n:** 87
15.	**1i**	4-Br-C_6H_4	*c*-hex	*n*-BuMgBr	**2o:** 68
16.	**1j**	4-MeO-C_6H_4	*c*-hex	*n*-BuMgBr	**2p:** 62
17.	**1f**	Ph	*c*-hex	*n*-BuLi	**2f:** 75
18.	**1f**	Ph	*c*-hex		**2q:** 76
19.	**1c**	Me	*c*-hex		**2r:** 72
20.	**1g**	4-Me-C_6H_4	*c*-hex		**2s:** 81
21.	**1f**	Ph	*c*-hex		nd[b]
22.	**1f**	Ph	*c*-hex	PhMgBr	nd
23.	**1a**	*n*-$C_{10}H_{21}$	Bn		 **2t:** 82

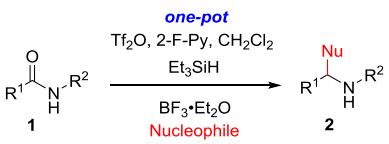
[a] Isolated yield. [b] No desired product isolated.

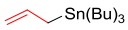
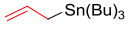
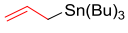
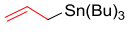
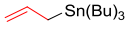
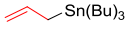
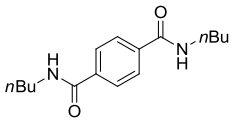
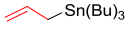
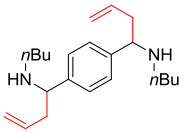
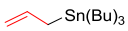
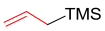
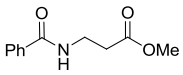
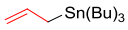
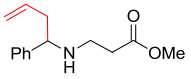
Having demonstrated the viability of the present method for the one-pot reductive alkylation of the C-H functionalization products, we next focused on issue of the chemoselective reductive alkylation of secondary amides. To simplify the problem, *para*-substituted benzamide derivatives were selected as substrates.[10d,11e] To further explore the functional group tolerance, use of softer carbon nucleophiles was investigated. As can be seen from Table 2, reductive allylation of **1a** with

allyltributyltin proceeded smoothly to give **2u** in 90% yield (Table 2, entry 1). For *p*-substituted benzamides bearing functional groups ranged from methoxyl, ester, cyano to nitro, the reductive allylation reactions proceeded chemoselectively on the secondary amide, producing the corresponding amines in good yields (entries 2-5). At appropriate activation temperatures, the reductive alkylation of secondary amides proceeded chemoselectively in the presence of tertiary amide, which remained intact (entry 6). When using 5.0 mol equiv of allyltributyltin, the di-*sec*-amide underwent bis-reductive allylation to give diamine **2aa** in 89% yield (entry 7). The reaction was incompatible with acetyl group (entry 8). Attempted addition of allyltrimethylsilane (entry 9) failed to give the desired product, instead, after work up, *p*-methoxybenzaldehyde was isolated in an 86% yield. Use of TMSCN as the carbon nucleophile also afforded the desired α-amino nitrile **2ab** in 53% yield (entry 10).

Encouraged by these results, we next turned to the more challenging chemoselective reductive alkylation of alicyclic amido ester **1q**. To our delight, the reductive allylation of amido ester **1q** proceeded uneventfully to give the amino ester **2ac** in 88% yield (entry 11). It is worthy of mentioning that *N*-*α*-allyl secondary amines are in turn useful substrates for the synthesis of *N*-heterocycles for which a number of methods have been developed.[23]

Table 2. Reductive Functionalization of Secondary Amides with Soft Carbon Nucleophiles



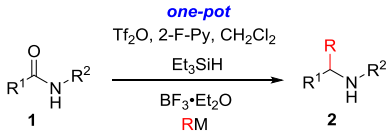
Entry	Amide	R^1	R^2	Nu (3 eq.)	Yield (%)[a]
1.	**1a**	*n*-$C_{10}H_{21}$	Bn		**2u:** 90
2.	**1j**	4-MeO-C_6H_4	*c*-hex		**2v:** 87
3.	**1k**	4-MeO_2C-C_6H_4	*c*-hex		**2w:** 87
4.	**1l**	4-NC-C_6H_4	*c*-hex		**2x:** 83
5.	**1m**	4-O_2N-C_6H_4	*c*-hex		**2y:** 81
6.	**1n**	4-$Et_2NC(O)$-C_6H_4	*c*-hex		**2z:** 77[b]
7.	**1o**				 **2aa:** 89
8.	**1p**	4-Ac-C_6H_4	*c*-hex		nd[c]
9.	**1j**	4-MeO-C_6H_4	*c*-hex		Nd[d]
10.	**1j**	4-MeO-C_6H_4	*c*-hex	TMSCN	**2ab:** 53
11.	**1q**				 **2ac:** 88

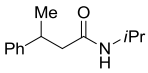
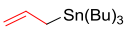
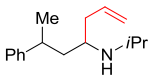
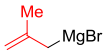
[a] Isolated yield. [b] Amide **1n** was activated at –78 °C, 20 min; then –20 °C, 20 min; and 0 °C 10 min. [c] No desired product was observed. [d] No desired product was observed, instead, after work up, *p*-methoxybenzaldehyde was isolated in an 86% yield.

To establish a tighter linkage between the present method with the secondary amide-directed C-H activation methodology, some substrates and/ or products of C-H

functionalization were tested for the reductive alkylation. We first examined the reaction of amide **1r**, prepared by Beak's amide directed C-H alkylation.[4b] Following the general procedure, the reductive alkylation proceeded smoothly to give the expected amine **2ad** in 84% yield as a 1: 1 diastereomeric mixture (Table 3, entry 1). *N*-Methyl and *N*-*iso*-propyl benzamides **1e** and **1s** are substrates used by Nakamura and Daugulis for the C-H activation and functionalization.[3a,c] Their reductive *n*-butylation proceeded smoothly to give amines **2e** and **2ae** in 82% and 80% yield, respectively (Table 3, entries 2 and 3). Subjection of benzamide **1t**, a C-H functionalization product prepared by Nakamura's method,[3c] to the reductive alkylation also gave amine **2af** in 77% yield (entry 4).

Table 3. Reductive Functionalization of Some C-H Functionalization Products/ Starting Materials



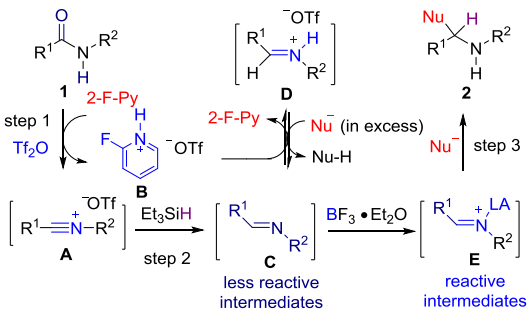
Entry	Amide	R^1	R^2	RM	Yield (%)[a]
1.	**1r**[b]				 **2ad:** 84 (*dr* = 1:1)[c]
2.	**1e**[d]	Ph	Me	*n*-BuMgBr	**2e:** 82
3.	**1s**[d]	4-Me-C_6H_4	*i*-Pr	*n*-BuMgBr	**2ae:** 80
4.	**1t**[b]	2-Et-C_6H_4	*i*-Pr		**2af:** 77

[a] Isolated yield. [b] C-H functionalization product. [c] The diastereomer ratio determine by ^{1}H NMR. [d] C-H functionalization starting material.

In plausible mechanism for the one-pot reductive functionalization of secondary

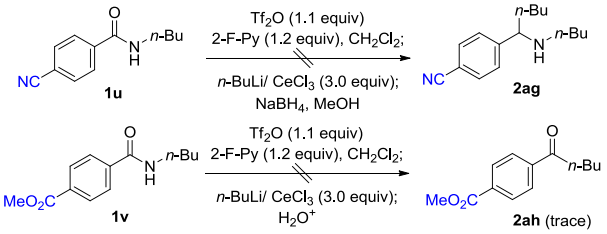
amides is depicted in Scheme 3. The IR evidence gained by Movassaghi,[15] and our previous supporting results[19b] allow us to suggest the formation of nitrinium ion intermediate **A** along with 2-fluoropyridinium salt **B** upon treatment of secondary amides with Tf_2O. The highly electrophilic nitrinium ion intermediate **A** is reduced with Et_3SiH to give imine **C**. A proton exchange between the protonated 2-F-pyridine **B** and more basic imine **C** results in iminium ion **D** and regenerates 2-F-pyridine. The iminium ion **D** consumes an equivalent of nucleophile by proton exchange to yield back imine **C**. The low reactivity of imines towards Grignard reagents is well-known. Thus, the employment of a Lewis acid is necessary to convert the imine **C** to the reactive chelating species **E**, which is subjected to nucleophilic addition to yield the desired amine **2**. The proton exchange between iminium ion **D** and non-basic nucleophiles is less evident. However, this is supported by the fact that in the absence of $BF_3{\cdot}OEt_2$ reductive allylation of **1a**, and reductive cyanation of **1j** gave the corresponding products **2u** and **2ab** in only 12% and 20% yield, respectively, whereas in the presence of $BF_3{\cdot}OEt_2$, the yields are 90% (Table 2, entry 1) and 53% (Table 2, entry 10), respectively.

Scheme 3. Plausible Mechanism for the One-pot Reductive Functionalization of Secondary Amides



Compared with our previous reductive alkylation method (Method A in Scheme 1), the advantages of the present method reside in its chemoselectivity. In fact, attempted reductive butylation of benzamide **1u** by Method A was unsuccessful (Scheme 4). Attempted deaminative butylation[19b] of benzamide **1v** with organocerium reagent produced only a trace of the desired ketone **2ah**. In addition, for stereoselective reductive alkylation of substrates bearing chiral elements, it can be expected that two methods, with inversed order of addition of two nucleophiles, will give complementary stereochemical outcomes.

Scheme 4. Unsuccessful Chemoselective Reductive Butylation of 1u and 1v by Method A.



Conclusion

In summary, we have developed a new and general method for the one-pot reductive functionalization of secondary amides, which is complementary to the method we developed recently.[13] This method allows using a variety of nucleophiles including hard nucleophiles such as RMgX and RLi, and soft nucleophiles such as TMSCN, allyltributyltin as well as enolate. The reaction tolerates many sensitive functional groups, and a number of functional groups bearing amines have been synthesized in one-pot. The method has been applied to the transformations of selected C-H functionalization products (**1r**, **1t**) and C-H functionalization starting materials (**1e**,

1s). We thus established a connection with the C-H functionalization products, which rends the latter methodology more step-economical.

Experimental Section

Mass spectra were recorded on a LC-MS apparatus. HRFABMS spectra were recorded on a 7.0 T FT-MS. ^{1}H NMR and ^{13}C NMR spectra were recorded on instruments (400 and 100 MHz, respectively). Chemical shifts (δ) are reported in ppm and respectively referenced to internal standard Me_4Si and solvent signals (Me_4Si, 0 ppm for ^{1}H NMR and $CDCl_3$, 77.0 ppm for ^{13}C NMR). Infrared spectra were measured using film KBr pellet techniques. Silica gel (300-400 mesh) was used for flash column chromatography (FC), eluting (unless otherwise stated) with ethyl acetate/ hexane mixture. Trifluoromethanesulfonic anhydride (Tf_2O) was distilled over phosphorus pentoxide and was stored for no more than a week before redistilling. All other commercially available compounds were used as received. Dry dichloromethane was distilled over calcium hydride under Argon. All reactions were carried out under Argon. All the Grignard reagents were titrated immediately before use.[24]

General procedure for the one-pot transformation of secondary amides 1 into secondary amines 2.

Into a dry 10-mL round-bottom flask equipped with a stirring bar were added successively an amide (1.0 mmol, 1.0 equiv), 4 mL of anhydrous dichloromethane and 2-fluoropyridine (116.5 mg, 103 μL, 1.2 mmol, 1.2 equiv.). After being cooled to

0 °C, trifluoromethanesulfonic anhydride (Tf_2O) (310 mg, 185 μL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at 0 °C and the reaction was stirred for 20 min. To the resulting mixture, triethylsilane (Et_3SiH) (128 mg, 176 μL, 1.1 mmol, 1.1 equiv) was added dropwise at 0 °C and the reaction was stirred for 10 min. The mixture was allowed to warm-up to room temperature and stirred for 5 h. After being cooled to 0 °C, $BF_3{\cdot}Et_2O$ (213 mg, 185 μL, 1.5 mmol, 1.5 equiv) was added, and the reaction mixture was stirred for 30 min. RMgX or RLi (4.0 mmol, 4.0 equiv) or allyltributyltin (3.0 mmol, 3.0 equiv) was added dropwise to the resultant mixture at 0 °C. Then the reaction mixture was warmed slowly to rt. and stirred for 2 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride and extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired amine **2**.

***N*-Benzylpentadecan-5-amine (2a)**

Following the general procedure, the reductive alkylation of amide **1a** (275 mg, 1.0 mmol) with *n*BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 50), amine **2a** (285 mg, yield: 90%). Colorless oil; IR (film) ν_{max}: 3349, 3026, 2924, 1494, 1454, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84-0.93 (m, 6H), 1.21-1.35 (m, 19H), 1.37-1.46 (m, 5H), 2.48-2.57 (m, 1H), 3.75 (s, 2H), 7.20-7.34 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (2C), 22.7, 23.0, 25.7, 27.9, 29.3, 29.6, 29.7 (2C), 29.9, 31.9, 33.7, 34.0, 51.2, 56.8, 126.7, 128.1 (2C),

128.3 (2C), 141.1 ppm; HRMS (ESI) calcd for $[C_{22}H_{40}N]^+$ ($M+H^+$): 318.3155; found: 318.3156.

***N*-Butylhexadecan-5-amine (2b)**

Following general procedure, the reductive alkylation of amide **1b** (255 mg, 1.0 mmol) with *n*BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 20), the known amine **2b**[13] (273 mg, 92%). Colorless oil. IR (film) ν_{max}: 3390, 2956, 2923, 2854, 1466, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85-0.95 (m, 9 H), 1.22-1.50 (m, 30 H), 2.40-2.49 (m, 1 H), 2.56 (t, *J* = 7.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 20.6, 22.6, 23.0, 25.7, 28.0, 29.3, 29.6 (3C), 29.6 (2C), 30.0, 31.9, 32.6, 33.8, 34.1, 46.9, 57.6 ppm; MS (ESI) *m/z* 298 ($M+H^+$, 100%); HRMS (ESI) calcd for $[C_{20}H_{44}N]^+$ ($M+H^+$): 298.3468; found: 298.3466.

***N*-(Hexan-2-yl)cyclohexanamine (2c)**

Following the general procedure, the reductive alkylation of amide **1c** (141 mg, 1.0 mmol) with *n*BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 30), amine **2c** (148 mg, yield: 81%). Colorless oil; IR (film) ν_{max}: 3304, 2954, 2927, 2853, 1450, 1377, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.1 Hz, 3H), 0.92-1.46 (m, 11H), 1.56-1.64 (m, 1H), 1.67-1.76 (m, 2H), 1.80-1.94 (m, 2H), 2.44-2.54 (m, 1H), 2.70-2.80 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.0, 22.9, 25.2, 25.3, 26.1, 28.3, 33.9, 34.5, 37.3, 49.3, 53.4 ppm; MS (ESI) *m/z* 184 ($M+H^+$, 100%); HRMS (ESI) calcd for $[C_{12}H_{26}N]^+$ ($M+H^+$): 184.2060; found: 184.2063.

***N*-Butyl-1-phenylpentan-1-amine (2d)**

Following general procedure, the reductive alkylation of amide **1d** (177 mg, 1.0 mmol) with *n*BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 20), the known amine **2d**[13] (195 mg, 89%). Colorless oil. IR (film) ν_{max}: 3320, 3083, 3062, 3025, 2957, 2928, 2858, 1493, 1454, 1125, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H), 1.08-1.46 (m, 8H), 1.54-1.78 (m, 2H), 2.34-2.43 (m, 2H), 3.53 (dd, *J* = 7.6, 6.2 Hz, 1H), 7.18-7.34 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (2C), 20.4, 22.7, 28.5, 32.4, 38.0, 47.4, 63.6, 126.7, 127.1 (2C), 128.2 (2C), 144.7 ppm; MS (ESI) *m/z* 220 ($M+H^+$, 100%); HRMS (ESI) calcd for $[C_{15}H_{26}N]^+$ ($M+H^+$): 220.2060; found: 220.2058.

***N*-Methyl-1-phenylpentan-1-amine (2e)**

Following general procedure, the reductive alkylation of amide **1e** (135 mg, 1.0 mmol) with *n*BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 20), the known amine **2e**[13] (145 mg, 82%). Colorless oil. IR (film) ν_{max}: 3301, 3083, 3062, 3025, 2956, 2930, 2857, 2788, 1493, 1453, 1134, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.2 Hz, 3H), 1.06-1.33 (m, 4H), 1.55-1.80 (m, 3H), 2.26 (s, 3H), 3.38 (dd, *J* = 7.7, 6.2 Hz, 1H), 7.20-7.34 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 28.5, 34.4, 37.6, 65.5, 126.8, 127.2 (2C), 128.2 (2C), 144.1 ppm; MS (ESI) *m/z* 178 ($M+H^+$, 100%); HRMS (ESI) calcd for $[C_{12}H_{20}N]^+$ ($M+H^+$): 178.1590; found: 178.1586.

***N*-(1-Phenylpropan-2-yl)cyclohexanamine (2f)**

Following general procedure, the reductive alkylation of amide **1f** (203 mg, 1.0 mmol) with *n*BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/

n-hexane = 1/ 20), the known amine **2f**[13] (203 mg, 83%). Colorless oil. IR (film) ν_{max}: 3304, 3043, 2957, 2933, 2861, 1458, 1289, 1241, 1165, 639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.2 Hz, 3H), 0.90-1.38 (m, 7H), 1.48-1.62 (m, 3H), 1.68-1.84 (m, 2H), 2.00-2.25 (m, 4H), 2.50-2.62 (m, 1H), 4.11-4.18 (m, 1H), 4.15 (dd, *J* = 10.8, 4.2 Hz, 1H), 7.38-7.50 (m, 5H), 7.93 (br s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 22.0, 24.3, 24.5, 24.6, 27.4, 27.8, 29.9, 33.6, 55.3, 60.5, 128.0 (2C), 129.5, 129.6 (2C), 133.9 ppm; MS (ESI) *m/z* 246 ($M+H^+$, 100%); HRMS (ESI) calcd for $[C_{17}H_{28}N]^+$ ($M+H^+$): 246.2216; found: 246.2214.

_N_-(1-_p_-Tolylpentyl)cyclohexanamine (2g)

Following general procedure, the reductive alkylation of amide **1g** (217 mg, 1.0 mmol) with *n*BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 20), the known amine **2g**[13] (233 mg, 90%). Colorless oil. IR (film) ν_{max}: 3314, 3039, 3015, 2926, 2853, 1512, 1449, 1124, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J* = 7.1 Hz, 3H), 0.96-1.32 (m, 9H), 1.48-1.72 (m, 6H), 1.93-2.02 (m, 1H), 2.19-2.28 (m, 1H), 2.34 (s, 3H, CH_3), 3.70 (dd, *J* = 7.6, 6.4 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.09-7.18 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.1, 22.7, 24.8, 25.2, 26.1, 28.7, 32.8, 34.6, 38.5, 53.4, 59.4, 127.0 (2C), 128.9 (2C), 136.1, 141.9 ppm; MS (ESI) *m/z* 260 ($M+H^+$, 100%); HRMS (ESI) calcd for $[C_{18}H_{30}N]^+$ ($M+H^+$): 260.2373; found: 260.2375.

_N_-Benzylhexadec-1-en-6-amine (2h)

Following the general procedure, the reductive alkylation of amide **1a** (275 mg, 1.0 mmol) with 4-pentenylmagnesium bromide gave, after flash column chromatography

on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 10), amine **2h** (309 mg, yield: 94%). Colorless oil. IR (film) ν_{max}: 3345, 3059, 3034, 2930, 2859, 1644, 1458, 910, 736, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.22-1.32 (m, 16H), 1.38-1.46 (m, 6H), 2.00-2.08 (m, 2H), 2.50-2.58 (m, 1H), 3.75 (s, 2H), 4.92-5.04 (m, 2H), 5.75-5.87 (m, 1H), 7.19-7.36 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 24.9, 25.6, 29.3, 29.6, 29.6 (2C), 29.9, 31.9, 33.4, 33.9, 34.0, 51.2, 56.6, 114.4, 126.8, 128.2 (2C), 128.3 (2C), 138.9, 141.0 ppm; HRMS (ESI) calcd for $[C_{23}H_{40}N]^+$ ($M+H^+$): 330.3155; found: 330.3155.

***N*-Benzyl-1-cyclohexylundecan-1-amine (2i)**

Following the general procedure, the reductive alkylation of amide **1a** (275 mg, 1.0 mmol) with cyclohexylmagnesium bromide gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 10), amine **2i** (316 mg, yield: 92%). Colorless oil. IR (film) ν_{max}: 3361, 3092, 3066, 3021, 2918, 2851, 1457, 736, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 6.8 Hz, 3H), 1.03-1.52 (m, 23H), 1.65-1.85 (m, 6H), 2.30-2.38 (m, 1H), 3.74-3.83 (m, 2H), 7.24-7.40 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 26.4, 26.8 (2C), 26.8, 29.0, 29.2, 29.3, 29.6, 29.7 (2C), 30.0, 30.9, 31.9, 40.8, 52.0, 62.0, 126.7, 128.2 (2C), 128.3 (2C), 141.3 ppm; HRMS (ESI) calcd for $[C_{24}H_{42}N]^+$ ($M+H^+$): 344.3312; found: 344.3314.

***N*-(1-Phenylpropyl)cyclohexanamine (2j)**

Following the general procedure, the reductive alkylation of amide **1f** (203 mg, 1.0 mmol) with EtMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 30), amine **2j** (176 mg, yield: 81%). Colorless oil; IR (film)

ν_{max}: 3497, 3062, 2929, 2857, 1607, 1492, 1456, 1289, 1242, 1167, 763, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.4 Hz, 3H), 0.98-1.42 (m, 5H), 1.54-2.10 (m, 7H), 2.41-2.50 (m, 1H), 3.91 (dd, *J* = 9.8, 4.8 Hz, 1H), 5.41 (br s, 1H), 7.32-7.44 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.4, 24.5, 24.8, 25.2, 29.0, 29.8, 31.9, 54.6, 61.6, 127.6 (2C), 128.2, 128.9 (2C), 138.3 ppm; MS (ESI) *m/z* 218 ($M+H^+$, 100%); HRMS (ESI) calcd for $[C_{15}H_{24}N]^+$ ($M+H^+$): 218.1903; found: 218.1904.

_N_-(1,2-Diphenylethyl)cyclohexanamine (2k)

Following the general procedure, the reductive alkylation of amide **1f** (203 mg, 1.0 mmol) with BnMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 30), the known amine **2k**[25a] (237 mg, yield: 85%). Colorless oil; IR (film) ν_{max}: 3326, 3083, 3061, 3026, 2925, 2851, 1494, 1452, 1264, 1120, 742, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76-1.16 (m, 5H), 1.44-1.88 (m, 5H), 2.18-2.27 (m, 1H), 2.82-2.97 (m, 2H), 4.05 (dd, *J* = 7.8, 6.3 Hz, 1H), 7.07-7.13 (m, 2H), 7.15-7.26 (m, 4H), 7.28-7.31 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 25.1, 26.0, 32.6, 34.7, 45.6, 53.4, 61.1, 126.2, 126.8, 127.2 (2C), 128.2 (2C), 128.2 (2C), 129.2 (2C), 140.0, 144.5 ppm; MS (ESI) *m/z* 280 ($M+H^+$, 100%); HRMS (ESI) calcd for $[C_{20}H_{26}N]^+$ ($M+H^+$): 280.2060; found: 280.2053.

_N_-(1-Phenylpropan-2-yl)cyclohexanamine (2l)

Following the general procedure, the reductive alkylation of amide **1c** (141 mg, 1.0 mmol) with BnMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 30), amine **2l** (172 mg, yield: 79%). Colorless oil; IR (film) ν_{max}: 3311, 3084, 3061, 3026, 2925, 2852, 1601, 1495, 1451, 1140, 744, 670 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.3 Hz, 3H), 0.86-1.30 (m, 5H), 1.54-1.74 (m, 3H), 1.80-1.95 (m, 2H), 2.52-2.64 (m, 2H), 2.80 (dd, *J* = 13.3, 6.3 Hz, 1H), 3.05-3.14 (m, 1H), 7.15-7.32 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 25.1, 25.2, 26.0, 33.1, 34.2, 43.6, 50.9, 53.5, 126.1, 128.3 (2C), 129.3 (2C), 139.4 ppm; MS (ESI) *m/z* 218 ($M+H^+$, 100%); HRMS (ESI) calcd for $[C_{15}H_{24}N]^+$ ($M+H^+$): 218.1903; found: 218.1908.

***N*-(1-Cyclohexyl-2-phenylethyl)cyclohexanamine (2m)**

Following general procedure, the reductive alkylation of amide **1h** (209 mg, 1.0 mmol) with BnMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 20), the known amine **2m**[13] (219 mg, 77%). Colorless oil. IR (film) ν_{max}: 3323, 3083, 3061, 3025, 2923, 2851, 1493, 1449, 1120, 744, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76-1.28 (m, 10H), 1.34-1.85 (m, 11H), 2.21-2.31 (m, 1H), 2.53 (dd, *J* = 13.2, 7.8 Hz, 1H), 2.63-2.71 (m, 1H), 2.77 (dd, *J* = 13.2, 5.4 Hz, 1H), 7.16-7.30 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 26.1, 26.6, 26.7, 26.8, 28.8, 29.1, 33.6, 34.2, 38.3, 41.0 (2C), 54.7, 61.4, 125.8, 128.2 (2C), 129.2 (2C), 140.6 ppm; MS (ESI) *m/z* 286 ($M+H^+$, 100%); HRMS (ESI) calcd for $[C_{20}H_{32}N]^+$ ($M+H^+$): 286.2529; found: 286.2530.

***N*-(1-Phenylbut-3-enyl)cyclohexanamine (2n)**

Following the general procedure, the reductive alkylation of amide **1f** (203 mg, 1.0 mmol) with allylmagnesium bromide gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 30), the known amine **2n**[25b] (199 mg, yield: 87%). Colorless oil; IR (film) ν_{max}: 3368, 3061, 3024, 2926, 2852, 1491, 1450, 1114,

759, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92-1.20 (m, 5H), 1.48-1.71 (m, 4H), 1.92-2.00 (m, 1H), 2.21-2.29 (m, 1H), 2.30-2.44 (m, 2H), 3.84 (dd, *J* = 7.6, 6.1 Hz, 1H), 5.00-5.11 (m, 2H), 5.63-5.76 (m, 1H), 7.20-7.34 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.2, 26.1, 32.9, 34.7, 43.5, 53.5, 59.0, 117.3, 126.7, 127.1 (2C), 128.2 (2C), 135.7, 144.7 ppm; MS (ESI) *m/z* 230 ($M+H^+$, 100%).

_N_-[1-(4-Bromophenyl)pentyl]cyclohexanamine (2o)

Following general procedure, the reductive alkylation of amide **1i** (281 mg, 1.0 mmol) with *n*BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 20), the known amine **2o**[13] (220 mg, 68%). Colorless oil. IR (film) ν_{max}: 3323, 3018, 2925, 2852, 1589, 1483, 1449, 1125, 1009, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J* = 7.1 Hz, 3H), 0.90-1.32 (m, 9H), 1.48-1.70 (m, 6H), 1.90-1.98 (m, 1H), 2.14-2.23 (m, 1H), 3.70 (dd, *J* = 7.2, 6.8 Hz, 1H), 7.13-7.18 (m, 2H), 7.40-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 24.8, 25.1, 26.1, 28.5, 32.9, 34.7, 38.5, 53.6, 59.2, 120.2, 128.9 (2C), 131.3 (2C), 144.3 ppm; MS (ESI) *m/z* 324 ($M+H^+$, 100%); HRMS (ESI) calcd for $[C_{17}H_{27}BrN]^+$ ($M+H^+$): 324.1321; found: 324.1321 and 326.1306.

_N_-[1-(4-Methoxyphenyl)pentyl]cyclohexanamine (2p)

Following general procedure, the reductive alkylation of amide **1j** (233 mg, 1.0 mmol) with *n*BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 20), the known amine **2p**[13] (170 mg, 62%). Colorless oil. IR (film) ν_{max}: 3323, 3061, 3028, 2996, 2926, 2852, 1510, 1463, 1246, 1039, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J* = 7.1 Hz, 3H, CH_3), 0.96-1.32 (m, 9H), 1.50-1.72 (m,

6H), 1.93-2.01 (m, 1H), 2.18-2.27 (m, 1H), 3.69 (dd, J = 7.2, 6.8 Hz, 1H, CH), 3.80 (s, 3H, CH_3), 6.83-6.89 (m, 2H), 7.15-7.21 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.7, 24.9, 25.2, 26.2, 28.7, 32.9, 34.7, 38.5, 53.4, 55.2, 59.0, 113.6 (2C), 128.1 (2C), 137.0, 158.3 ppm; MS (ESI) *m/z* 276 ($M+H^+$, 100%); HRMS (ESI) calcd for $[C_{18}H_{30}NO]^+$ ($M+H^+$): 276.2322; found: 276.2325.

***N*-(1-Phenylpropan-2-yl)cyclohexanamine (2q)**

Following general procedure, the reductive alkylation of amide **1f** (203 mg, 1.0 mmol) with lithium phenylacetylide gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 20), the known amine **2q**[13] (219 mg, 76%). Colorless oil. IR (film) ν_{max}: 3391, 3059, 2923, 2850, 1598, 1489, 1449, 1263, 1112, 756, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12-1.36 (m, 5H), 1.57-1.66 (m, 1H), 1.70-1.89 (m, 3H), 1.96-2.06 (m, 1H), 2.80-2.90 (m, 1H), 4.90 (s, 1H), 7.26-7.39 (m, 6H), 7.43-7.49 (m, 2H), 7.55-7.61 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 25.0, 26.1, 32.6, 33.9, 51.5, 54.3, 85.0, 89.8, 123.2, 127.5 (2C), 127.6, 128.0, 128.2 (2C), 128.5 (2C), 131.7 (2C), 141.0 ppm; MS (ESI) *m/z* 290 ($M+H^+$, 100%); HRMS (ESI) calcd for $[C_{21}H_{24}N]^+$ ($M+H^+$): 290.1903; found: 290.1907.

***N*-(4-Phenylbut-3-yn-2-yl)cyclohexanamine (2r)**

Following the general procedure, the reductive alkylation of amide **1c** (141 mg, 1.0 mmol) with lithium phenylacetylide gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 30), amine **2r** (163 mg, yield: 72%). Colorless oil; IR (film) ν_{max}: 3305, 3079, 3054, 2927, 2852, 1597, 1489, 1449, 1125, 755, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97-1.38 (m, 5H), 1.43 (d, J = 6.8 Hz,

3H), 1.59-1.68 (m, 1H), 1.70-1.86 (m, 3H), 1.95-2.04 (m, 1H), 2.79-2.88 (m, 1H), 3.84 (q, J = 6.8 Hz, 1H), 7.26-7.32 (m, 3H), 7.38-7.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 24.8, 25.2, 26.1, 32.5, 34.4, 42.4, 54.4, 82.5, 92.2, 123.4, 127.8, 128.2 (2C), 131.6 (2C) ppm; MS (ESI) *m/z* 228 ($M+H^+$, 100%); HRMS (ESI) calcd for $[C_{16}H_{22}N]^+$ ($M+H^+$): 228.1747; found: 228.1744.

_N_-[1-(_p_-Tolyl)non-2-yn-1-yl]cyclohexanamine (2s)

Following the general procedure, the reductive alkylation of amide **1g** (217 mg, 1.0 mmol) with 1-nonynyllithium gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 10), amine **2s** (252 mg, yield: 81%). Brown oil. IR (film) ν_{max}: 3328, 2930, 2847, 1507, 1453, 1113, 811, 715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 6.9 Hz, 3H), 1.11-1.97 (m, 18H), 2.21-2.27 (m, 2H), 2.33 (s, 3H), 2.69-2.78 (m, 1H), 4.61 (br s, 1H), 7.14 (d, J = 7.9 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 18.8, 21.0, 22.6, 24.8, 25.0, 26.1, 28.5, 28.8, 31.3, 32.7, 33.8, 50.8, 54.1 80.6, 85.1, 127.3 (2C), 129.0 (2C), 136.9, 138.8 ppm; HRMS (ESI) calcd for $[C_{22}H_{34}N]^+$ ($M+H^+$): 312.2686; found: 312.2685.

Ethyl 3-(benzylamino)tridecanoate (2t)

Following the general procedure, the reductive alkylation of amide **1a** (275 mg, 1.0 mmol) with EA enolate gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 5), amine **2ab** (284 mg, yield: 82%). Colorless oil. IR (film) ν_{max}: 3345, 3063, 3025, 2963, 2930, 2855, 1735, 1453, 1184, 735, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.20-1.36 (m, 21H), 1.38-1.57 (m, 2H), 1.69 (br s, 1H), 2.44 (d, J = 6.2 Hz, 2H), 2.97-3.06 (m, 1H), 3.78 (s, 2H), 4.13 (q, J =

7.1 Hz, 2H), 7.16-7.38 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 22.7, 25.6, 29.3, 29.5, 29.6 (2C), 29.7, 31.9, 34.3, 39.4, 51.0, 54.3, 60.2, 126.8, 128.1 (2C), 128.3 (2C), 140.6, 172.6 ppm; HRMS (ESI) calcd for $[C_{22}H_{38}NO_2]^+$ ($M+H^+$): 348.2897; found: 348.2892.

***N*-Benzyltetradec-1-en-4-amine (2u)**

Following the general procedure, the reductive alkylation of amide **1a** (275 mg, 1.0 mmol) with $AllylSnBu_3$ gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 20), amine **2t** (271 mg, yield: 90%). Colorless oil. IR (film) ν_{max}: 3365, 3067, 3029, 2955, 2922, 2855, 1457, 73, 736, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.20-1.50 (m, 18H), 2.12-2.32 (m, 2H), 2.56-2.65 (m, 1H), 3.77 (s, 2H), 5.04-5.12 (m, 2H), 5.72-5.85 (m, 1H), 7.20-7.35 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 25.7, 29.3, 29.6 (3C), 29.9, 31.9, 33.9, 38.3, 51.2, 56.2, 117.1, 126.8, 128.1 (2C), 128.3 (2C), 135.8, 140.8 ppm; HRMS (ESI) calcd for $[C_{21}H_{36}N]^+$ ($M+H^+$): 302.2842; found: 302.2844.

***N*-[1-(4-Methoxyphenyl)but-3-en-1-yl]cyclohexanamine (2v)**

Following the general procedure, the reductive alkylation of amide **1j** (233 mg, 1.0 mmol) with $AllylSnBu_3$ gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 50), amine **2u** (255 mg, yield: 87%). Colorless oil. IR (film) ν_{max}: 3328, 3071, 2996, 2926, 2847, 1611, 1511, 1466, 1241, 1103, 827 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94-1.18 (m, 5H), 1.44-1.71 (m, 4H), 1.91-2.00 (m, 1H), 2.20-2.29 (m, 1H), 2.30-2.40 (m, 2H), 3.80 (s, 3H), 3.76-3.83 (m, 1H), 4.99-5.10 (m, 2H), 5.62-5.75 (m, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H) ppm; ^{13}C

NMR (100 MHz, $CDCl_3$) δ 24.9, 25.2, 26.1, 32.9, 34.7, 43.5, 53.4, 55.2, 58.3, 113.6 (2C), 117.2, 128.0 (2C), 135.8, 136.7, 158.4 ppm; HRMS (ESI) calcd for $[C_{17}H_{26}NO]^+$ ($M+H^+$): 260.2009; found: 260.2009.

Methyl 4-[1-(cyclohexylamino)but-3-en-1-yl]benzoate (2w)

Following the general procedure, the reductive alkylation of amide **1k** (261 mg, 1.0 mmol) with $AllylSnBu_3$ gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 20), amine **2v** (241 mg, yield: 84%). Colorless oil. IR (film) ν_{max}: 3324, 3083, 2976, 2926, 2847, 1723, 1611, 1433, 1279, 1109, 769, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92-1.18 (m, 5H), 1.30-1.70 (m, 4H), 1.89-1.98 (m, 1H), 2.16-2.26 (m, 1H), 2.28-2.43 (m, 2H), 3.90 (s, 3H), 3.87-3.93 (m, 1H), 5.01-5.11 (m, 2H), 5.61-5.74 (m, 1H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.99 (d, *J* = 8.3 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 25.1, 26.1, 32.9, 34.7, 43.3, 51.9, 53.9, 59.0, 117.8, 127.1 (2C), 128.7, 129.6 (2C), 135.1, 150.4, 167.1 ppm; HRMS (ESI) calcd for $[C_{18}H_{26}NO_2]^+$ ($M+H^+$): 288.1958; found: 288.1962.

4-[1-(Cyclohexylamino)but-3-en-1-yl]benzonitrile (2x)

Following the general procedure, the reductive alkylation of amide **1l** (228 mg, 1.0 mmol) with $AllylSnBu_3$ gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 10), amine **2w** (211 mg, yield: 83%). Colorless oil. IR (film) ν_{max}: 3328, 3075, 3046, 2926, 2847, 2221, 1607, 1263, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94-1.20 (m, 5H), 1.40-1.74 (m, 4H), 1.87-1.97 (m, 1H), 2.14-2.23 (m, 1H), 2.25-2.40 (m, 2H), 3.90 (dd, *J* = 7.8, 5.7 Hz, 1H), 5.03-5.12 (m, 2H), 5.60-5.74 (m, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz,

$CDCl_3$) δ 24.8, 25.1, 26.0, 32.9, 34.7, 43.3, 54.0, 59.0, 110.5, 118.2, 119.0, 127.9 (2C), 132.1 (2C), 134.6, 150.9 ppm; HRMS (ESI) calcd for $[C_{17}H_{22}N_2]^+$ ($M+H^+$): 255.1856; found: 255.1857.

_N_-[1-(4-Nitrophenyl)but-3-en-1-yl]cyclohexanamine (2y)

Following the general procedure, the reductive alkylation of amide **1m** (248 mg, 1.0 mmol) with $AllylSnBu_3$ gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 10), amine **2x** (222 mg, yield: 81%). Yellow oil. IR (film) ν_{max}: 3328, 3071, 2925, 2851, 1607, 1524, 1346, 857, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94-1.18 (m, 5H), 1.44-1.74 (m, 4H), 1.88-1.98 (m, 1H), 2.15-2.24 (m, 1H), 2.25-2.43 (m, 2H), 3.96 (dd, *J* = 7.8, 5.7 Hz, 1H), 5.04-5.12 (m, 2H), 5.62-5.75 (m, 1H), 7.52 (d, *J* = 8.7 Hz, 2H), 8.18 (d, *J* = 8.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 25.1, 26.0, 32.9, 34.7, 43.3, 54.1, 58.8, 118.3, 123.5 (2C), 127.9 (2C), 134.5, 146.9, 153.1 ppm; HRMS (ESI) calcd for $[C_{16}H_{23}N_2O_2]^+$ ($M+H^+$): 275.1754; found: 275.1758.

4-[1-(Butylamino)but-3-en-1-yl]-*N*,*N*-diethylbenzamide (2z)

Following the general procedure, change the activated procedure into: amide **1n** was activated at −78 °C, stirred for 20 min. then keeping −20 °C for 20 min, and 0 °C 10 min. The reductive alkylation of amides **1n** (276 mg, 1.0 mmol) with $AllylSnBu_3$ gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 2), amine **2y** (232 mg, yield: 77%). Colorless oil. IR (film) ν_{max}: 3320, 3083, 2959, 2926, 2864, 1636, 1466, 1300, 1101, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.4 Hz, 3H), 1.13 (br s, 3H), 1.19-1.35 (m, 5H), 1.37-1.47 (m, 2H), 1.66 (br s, 1H),

2.31-2.47 (m, 4H), 3.28 (br s, 2H), 3.55 (br s, 2H), 3.66 (dd, *J* = 7.4, 6.1 Hz, 1H), 5.02-5.13 (m, 2H), 5.64-5.77 (m, 1H), 7.34 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 13.9, 14.2, 20.4, 32.2, 39.2, 42.9, 43.2, 47.4, 62.4, 117.6, 126.4 (2C), 127.1 (2C), 135.2, 135.8, 145.4, 171.3 ppm; HRMS (ESI) calcd for $[C_{19}H_{31}N_2O]^+$ ($M+H^+$): 303.2431; found: 303.2429.

1,1'-(1,4-Phenylene)bis(*N*-butylbut-3-en-1-amine) (2aa)

Following the general procedure, the reductive alkylation of amide **1o** (276 mg, 1.0 mmol) with $AllylSnBu_3$ gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 10), amine **2z** (292 mg, yield: 89%). Colorless oil. IR (film) ν_{max}: 3324, 3075, 2959, 2926, 2868, 2851, 2810, 1644, 1466, 1122, 927 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.3 Hz, 6H), 1.24-1.47 (m, 8H), 1.53-1.72 (m, 2H), 2.33-2.49 (m, 8H), 3.62 (dd, *J* = 7.3, 6.3 Hz, 2H), 5.00-5.13 (m, 4H), 5.64-5.79 (m, 2H), 7.24 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (2C), 20.4 (2C), 32.2 (2C), 42.9 (2C), 47.4 (2C), 62.4 (2C), 117.3 (2C), 127.0 (4C), 135.6 (2C), 142.6 (2C) ppm; HRMS (ESI) calcd for $[C_{22}H_{37}N_2]^+$ ($M+H^+$): 329.2951; found: 329.2956.

2-(Cyclohexylamino)-2-(4-methoxyphenyl)acetonitrile (2ab)

Following the general procedure, the reductive alkylation of amide **1j** (233 mg, 1.0 mmol) with TMSCN gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 5), amine **2aa** (129 mg, yield: 53%). Colorless oil. IR (film) ν_{max}: 3338, 3071, 2996, 2926, 2847, 2221, 1511, 1466, 1241, 827 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07-1.38 (m, 5H), 1.59-1.67 (m, 1H), 1.70-1.82 (m, 3H), 1.93-2.03 (m, 1H), 2.79-2.90 (m, 1H), 3.81 (s, 3H), 4.78 (s, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.42

(d, J = 8.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 24.6, 25.9, 31.9, 33.8, 51.0, 54.7, 55.3, 114.2 (2C), 119.5, 128.4 (2C), 131.9, 159.9 ppm; HRMS (ESI) calcd for $[C_{15}H_{21}N_2O]^+$ ($M+H^+$): 245.1648; found: 245.1647.

Methyl 3-[(1-phenylbut-3-en-1-yl)amino]propanoate (2ac)

Following the general procedure, the reductive alkylation of amide **1q** (207 mg, 1.0 mmol) with $AllylSnBu_3$ gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 2), amine **2ac** (205 mg, yield: 88%). Colorless oil. IR (film) ν_{max}: 3332, 3079, 3025, 2976, 2942, 2922, 2843, 1727, 1445, 1167, 765, 711 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (br s, 1H), 2.31-2.52 (m, 4H), 2.64-2.77 (m, 2H), 3.62-3.70 (m, 4H), 5.01-5.13 (m, 2H), 5.65-5.78 (m, 1H), 7.20-7.37 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.5, 42.7, 43.0, 51.5, 62.3, 117.5, 127.0, 127.1 (2C), 128.2 (2C), 135.3, 143.6, 173.2 ppm; HRMS (ESI) calcd for $[C_{14}H_{19}NNaO_2]^+$ ($M+Na^+$): 256.1308; found: 256.1303.

***N*-Isopropyl-6-phenylhept-1-en-4-amine (2ad)**

Following the general procedure, the reductive alkylation of amide **1r** (205 mg, 1.0 mmol) with $AllylSnBu_3$ gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 5), amine **2ad** (194 mg, *dr* = 1:1, yield: 84%). Colorless oil. IR (film) ν_{max}: 3320, 3083, 3067, 3025, 2959, 2930, 2868, 1453, 1379, 1176, 765, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, J = 6.3 Hz, 3H), 1.01 (d, J = 6.3 Hz, 3H), 1.23 (d, J = 7.0 Hz, 3H), 1.48-1.57 (m, 1H), 1.67-1.77 (m, 1H), 2.04-2.19 (m, 2H), 2.44-2.52 (m, 1H), 2.74-2.85 (m, 1H), 2.86-2.96 (m, 1H), 4.98-5.10 (m, 2H), 5.64-5.78 (m, 1H), 7.14-7.22 (m, 3H), 7.25-7.32 (m, 2H) ppm; ^{13}C NMR (100 MHz,

$CDCl_3$) δ 23.0, 23.2, 23.9, 36.7, 38.8, 43.4, 45.2, 51.7, 117.2, 125.9, 127.1 (2C), 128.3 (2C), 135.4, 147.4 ppm; HRMS (ESI) calcd for $[C_{16}H_{26}N]^+$ ($M+H^+$): 232.2060; found: 232.2055.

_N_-Isopropyl-1-(_p_-tolyl)pentan-1-amine (2ae)

Following the general procedure, the reductive alkylation of amide **1s** (177 mg, 1.0 mmol) with *n*BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 20), amine **2ae** (175 mg, yield: 80%). Colorless oil. IR (film) ν_{max}: 3316, 3046, 2955, 2926, 2859, 1462, 1375, 1176, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.3 Hz, 3H), 1.00 (d, *J* = 6.3 Hz, 3H), 1.06-1.13 (m, 1H), 1.20-1.30 (m, 3H), 1.51-1.61 (m, 1H), 1.65-1.80 (m, 2H), 2.33 (s, 3H), 2.54-2.62 (m, 1H), 3.63 (dd, *J* = 8.0, 5.9 Hz, 1H), 7.08-7.16 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.0, 21.9, 22.7, 24.2, 28.6, 38.4, 45.4, 60.0, 127.0 (2C), 128.9 (2C), 136.2, 141.8 ppm; HRMS (ESI) calcd for $[C_{15}H_{26}N]^+$ ($M+H^+$): 220.2060; found: 220.2061.

1-(2-Ethylphenyl)-_N_-isopropyl-3-methylbut-3-en-1-amine (2af)

Following the general procedure, the reductive alkylation of amide **1t** (191 mg, 1.0 mmol) with 2-methylallylmagnesium chloride gave, after flash column chromatography on silica gel (eluent: EtOAc/ *n*-hexane = 1/ 20), amine **2af** (178 mg, yield: 77%). Colorless oil. IR (film) ν_{max}: 3316, 3067, 3021, 2963, 2930, 2868, 1657, 1470, 1445, 1371, 898, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.3 Hz, 3H), 1.02 (d, *J* = 6.3 Hz, 3H), 1.26 (t, *J* = 7.6 Hz, 3H), 1.77 (s, 3H), 2.18-2.30 (m, 2H), 2.52-2.63 (m, 1H), 2.64-2.81 (m, 2H), 4.22 (dd, *J* = 8.7, 4.9 Hz, 1H), 4.80-4.88 (m,

2H), 7.13-7.24 (m, 3H), 7.56-7.62 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 22.0, 22.3, 24.3, 25.2, 46.0, 47.3, 52.1, 113.2, 126.0, 126.4, 126.4, 128.4, 141.1, 142.6, 143.0 ppm; HRMS (ESI) calcd for $[C_{16}H_{26}N]^+$ ($M+H^+$): 232.2060; found: 232.2059.

Acknowledgment: The authors are grateful for financial support from the National Natural Science Foundation of China (21332007 and 21472153) and the Program for Changjiang Scholars and Innovative Research Team in University of Ministry of Education, China.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: pqhuang@xmu.edu.cn.

Author Contributions

‡ Y.-H. H. and K.-J. X. contributed equally to this work.

Notes

The authors declare no competing financial interest.

References

1. For a recent review on the recent developments in amide synthesis, see: (a) Lanigan, R. M.; Sheppard, T. D. *Eur. J. Org. Chem.* **2013**, 7453. (b) Yoo, W.-J.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 13064. (c) Nordstrøm, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*,

17672. (d) Allen, C. L.; Davulcu, S.; Williams, J. M. J. *Org. Lett.* **2010**, *12*, 5096. (e) Jiang, H., Liu, B.; Li, Y.; Wang, A.; Huang, H. *Org. Lett.* **2011**, *13*, 1028.

2. (a) Huang, L.; Wang, Q.; Wu, W.; Jiang, H. *J. Org. Chem.* **2014**, 79, 7734. (b) Song, L.; Liu, K.; Li, C. *Org. Lett*. **2011**, *13*, 3434. (c) Sakuma, S. Miyaura, N. *J. Org. Chem*. **2001**, *66*, 8944.

3. (a) Shabashov, D.; Daugulis, O. *Org. Lett.* **2006**, *8*, 4947. (b) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428. (c) Chen, Q.; Ilies, L.; Yoshikai, N.; Nakamura, E. *Org. Lett.* **2011**, *13*, 3232. (d) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc*. **2011**, *133*, 15362. (e) Zhang, L.-S.; Chen, K.; Chen, G.-H.; Li, B.-J.; Luo, S.; Guo, Q.-Y.; Wei, J.-B.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 10. (f) Ryu, J.; Kwak, J.; Shin, K.; Lee, D.; Chang, S. *J. Am. Chem. Soc.* **2013**, *135*, 12861. (g) Schoonen, A. K.; Fernández-Ibáñez, M. Á.; Fañanás-Mastral, M.; Teichert, J. F.; Feringa, B, L. *Org. Biomol. Chem.* **2014**, *12*, 36. (h) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216.

4. For a review, see: (a) Beak, P.; Basu, A.; Gallagher, D. J.; Peak, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. For selected examples, see: (b) Lutz, G. P.; Du, H.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 4542. (c) Smith, K.; El-Hiti, G. A.; Alshammari, M. B. *J. Org. Chem.* **2012**, *77*, 11210.

5. Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505.

6. For a review, see: Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785.

7. For a comprehensive review, see: (a) Pace, V.; Holzer, W.; Olofsson, B. *Adv. Synth. Catal.* **2014**, *356*, 3697. For related reviews, see: (b) Sato, T.; Chida, N. *Org. Biomol. Chem.*

2014, *12*, 3147. (c) Pace, V.; Holzer, W. *Aust. J. Chem.* **2013**, *66*, 507. See also: (d) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789.

8. For one-pot reductive dialkylation of *N*,*N*-dialkylformamides, see: (a) Tomashenko, O.; Sokolov, V.; Tomashevskiy, A.; Buchholz, H. A.; Welz-Biermann, U.; Chaplinski, V.; de Meijere, A. *Eur. J. Org. Chem.* **2008**, 5107. For one-pot reductive cyclopropanation of amides, see: (b) Chaplinski, V.; de Meijere, A. *Angew. Chem. Int. Ed.* **1996**, ***35***, 413. (c) Chaplinski, V.; Winsel, H.; Kordes, M.; de Meijere, A. *Synlett* **1997**, 111. (d) Lee, J.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 1584. (e) Ouhamou, N.; Six, Y. *Org. Biomol. Chem.* **2003**, *1*, 3007.

9. For one-pot reductive alkylation of common amides, see: (a) Xiao, K.-J.; Luo, J.-M.; Ye, K.-Y.; Wang, Y.; Huang, P.-Q. *Angew. Chem. Int. Ed.* **2010**, *49*, 3037. (b) Oda, Y.; Sato, T.; Chida, N. *Org. Lett.* **2012**, *14*, 950. (c) Huang, S.-Y.; Chang, Z.; Tuo, S.-C.; Gao, L.-H.; Wang, A.-E; Huang, P.-Q. *Chem. Commun*. **2013**, *49*, 7088. (d) Xiao, K.-J.; Wang, Y.; Huang, Y.-H.; Wang, X.-G.; Huang, P.-Q. *J. Org. Chem*. **2013**, *78*, 8305.

10. For one-pot reductive alkylation of *N*-alkoxylamides, see: (a) Shirokane, K.; Kurosaki, Y.; Sato, T.; Chida, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 6369. (b) Vincent, G.; Guillot, R.; Kouklovsky, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 1350. (c) Yanagita, Y.; Nakamura, H.; Shirokane, K.; Kurosaki, Y.; Sato, T.; Chida, N. *Chem. Eur. J.* **2013**, *19*, 678. (d) Shirokane, K.; Wada, T.; Yoritate, M.; Minamikawa, R.; Takayama, N.; Sato, T.; Chida, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 512.

11. For stepwise reductive alkylation of secondary amides/ lactams, see: (a) Suh, Y.-G.; Kim, S.-A.; Jung, J.-K.; Shin, D.-Y.; Min, K.-H.; Koo, B.-A.; Kim, H.-S. *Angew. Chem. Int. Ed.* **1999**, *38*, 3545. (b) Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett.*

2000, *2*, 3901. (c) Lee, Y.-S.; Jung, J.-W.; Kim, S.-H.; Jung, J.-K.; Paek, S.-M.; Kim, N.-J.; Chang, D.-J.; Lee, J.; Suh, Y.-G. *Org. Lett.* **2010**, *12*, 2040. (d) Deng, H.-Q.; Qian, X.-Y.; Li, Y.-X.; Zheng, J.-F.; Xie, L.-F.; Huang, P.-Q. *Org. Chem. Front*. **2014**, *1*, 258. (e) Nakajima, M.; Oda, Y.; Wada, T.; Minamikawa, R.; Shirokane, K.; Sato, T.; Chida, N. *Chem. Eur. J*. **2014**, *20*, 17565.

12. For one-pot reductive diallylation, see: (a) Bubnov, Y. N.; Pastukhov, F. V.; Yampolsky, I. V.; Ignatenko, A. V. *Eur. J. Org. Chem.* **2000**, 1503. (b) Li, Z.-F.; Zhang, Y.-M. *Tetrahedron Lett.* **2001**, *42*, 8507. (c) Nieczypor, P.; Mol, J. C.; Bespalova, N. B.; Bubnov, Y. N. *Eur. J. Org. Chem.* **2004**, 812. For one-pot reductive cyanation of secondary γ-lactams, see: (d) Xia, Q.; Ganem, B. *Org. Lett.* **2001**, *3*, 485. (e) Xia, Q.; Ganem, B. *Tetrahedron Lett.* **2002**, *43*, 1597.

13. For one-pot reductive alkylation of secondary amides, see: Xiao, K.-J.; Wang, A.-E; Huang, P.-Q. *Angew. Chem. Int. Ed.* **2012**, *51*, 8314.

14. For a recent review, see: (a) Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2000**, *56*, 3077. For selected examples on amide activation with Tf_2O for C-C bond formation, see: (b) Falmagne, J.-B.; Escudero, J.; Saa, T.-S.; Ghosez, L. *Angew. Chem. Int. Ed.* **1981**, *20*, 879. (c) Martinez, A. G.; Alvarez, R. M.; Barcina, J. O.; Cerero, S. M.; Vilar, E. T.; Fraile, A. G.; Hanack, M.; Subramanian, L. R. *J. Chem. Soc., Chem. Commun.* **1990**, 1571. (d) Barbaro, G.; Battaglia, A.; Bruno, C.; Giorgianni, P.; Guerrini, A. *J. Org. Chem*. **1996**, *61*, 8480. (e) Bélanger, G.; Larouche-Gauthier, R.; Ménard, F.; Nantel, M.; Barabé, F. *J. Org. Chem.* **2006**, *71*, 704. (f) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 14254. (g) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096. (h) Cui, S.-L.; Wang, J.; Wang, Y.-G. *J. Am. Chem. Soc.* **2008**, *130*, 13526. (i)

Bélanger, G.; O'Brien, G.; Larouche-Gauthier, R. *Org. Lett.* **2011**, *13*, 4268. (j) Bechara, W. S.; Pelletier, G.; Charette, A. B. *Nat. Chem.* **2012**, *4*, 228. (k) Medley, J. W.; Movassaghi, M.; *Angew. Chem. Int. Ed*. **2012**, *51*, 4572. (l) Valerio, V.; Petkova, D.; Madelaine, C.; Maulide, N. *Chem. Eur. J.* **2013**, *19*, 2606. (m) Pace, V.; Castoldi, L.; Holzer, W. *Chem. Commun.* **2013**, *49*, 8383. (n) Peng, B.; Geerdink, D.; Maulide, N. *J. Am. Chem. Soc.* **2013**, *135*, 14968. (o) Peng, B.; Geerdink, D.; Farès, C.; Maulide, N, *Angew. Chem. Int. Ed*. **2014**, *53*, 5462. (p) Pace, V.; Castoldi, L.; Mamuye, A. D.; Holzer, W. *Synthesis* **2014**, *46*, 2897.

15. Medley, J. W.; Movassaghi, M. *J. Org. Chem.* **2009**, *74*, 1341.
16. Shenvi, R. A.; O'Malley D. P.; Baran, P. S. *Acc. Chem. Res.* **2009**, *42*, 530.
17. While this manuscript was in preparation, Sato/ Chida reported a highly chemoselective method for the one-pot reductive nucleophilic addition to tertiary amides, which shows reasonable functional group tolerance for secondary amides: ref. 10e.
18. (a) Xiang, S.-H.; Xu, J.; Yuan, H.-Q.; Huang, P.-Q. *Synlett* **2010**, 1829. For a related work, see: (b) Pelletier, G.; Bechara, W. S.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 12817.
19. (a) Huang, P.-Q.; Lang, Q.-W.; Wang, A.-E; Zheng, J.-F. *Chem. Commun.* **2015**, *51*, 1096. (b) Xiao, K.-J.; Huang, Y.-H.; Huang, P.-Q. *Acta Chim. Sinica* **2012**, *70*, 1917.
20. (a) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633. (b) Huang, P.-Q. *Synlett* **2006**, 1133.
21. (a) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, *42*, 4263. (b) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917.
22. (a) *Enantioselective Synthesis of Amino Acids*, Eds. Juaristi, E., Soloshonok, V. A., 2nd ed.; Wiley-VCH: Weinheim, 2005. (b) Seebach, D. Gardiner, J. *Acc. Chem. Res*. **2008**, *41*, 1366.

23. (a) Feula, A.; Dhillon, S. S.; Byravan, R.; Sangha, M.; Ebanks, R.; Salih, M. A. H.; Spencer, N.; Male, L.; Magyary, I.; Deng, W.-P.; Müller, F.; Fossey, J. S. *Org. Biomol. Chem.* **2013**, *11*, 5083. (b) Diaba, F.; Bonjoch, J. *Chem. Commun.* **2011**, *47*, 3251. (c) Feula, A.; Male, L.; Fossey, J. S. *Org. Lett.* **2010**, *12*, 5044.

24. Love, B. E., Jones, E. G. *J. Org. Chem.* **1999**, *64*, 3755.

25. (a) Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2001**, 4411. (b) Schumann, H.; Kaufmann, J.; Dechert, S.; Schmalz, H.-G. *Tetrahedron Lett.* **2002**, *43*, 3507.