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# One-pot synthesis of N-heterocycles and enimino carbocycles by tandem dehydrative coupling—reductive cyclization of halo-sec-amides and dehydrative cyclization of olefinic sec-amides†‡

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We report two efficient and versatile alkenylative cyclization methods for the one-pot synthesis of substituted pyrrolidine, piperidine, indolizidine, and quinolizidine ring systems, and enimino carbocycles, respectively. The first method consists of amide activation (Tf<sub>2</sub>O) induced dehydrative coupling of halogenated secondary amides with alkenes and the NaBH<sub>4</sub> reduction triggered tandem cyclization reaction, while the second one features the Tf<sub>2</sub>O-promoted novel modes of extended Bischler–Napieralski cyclization reactions of olefinic secondary amides. Taking advantage of triflic anhydride (Tf<sub>2</sub>O) as the amide activating reagent, the hitherto failed two-step process for the construction of the quinolizidine ring system *via* intramolecular vinylogous Bischler–Napieralski cyclization has been realized in one pot. The first method was applied to the protecting-group-free one-pot synthesis of the cytotoxic natural product caulophyllumine B (**5**) and its bioactive derivatives, and to the synthesis of  $\delta$ -coniceine and 6-styrylpiperidin-2-one. When ethyl vinyl ether and enamides were used as functionalized alkenes, saturated 1,3amino-ether/amido products **4A<sub>1</sub>–4A<sub>3</sub>** were obtained in 73%–74% yields.

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#### Introduction

Efficiency is essential to modern organic synthesis.<sup>1</sup> A tandem reaction<sup>2</sup> is a valuable tactic towards this goal. In this regard, tertiary amide-based tandem reactions have been proven to be a powerful strategy to access molecule complexity.<sup>3</sup> In comparison, this chemistry has been less explored for secondary amides.<sup>4</sup> In connection with our endeavor to develop amide-based C–C bond forming reactions,<sup>5–7</sup> very recently, we have disclosed a highly chemoselective, intermolecular C–H alkyliminylation and acylation of alkenes with secondary amides,<sup>7*a*-*c*</sup> which provides direct access to  $\alpha,\beta$ -unsaturated ketimines (1-aza-1,3-dienes, enimines) and  $\alpha,\beta$ -enones. As a continuation of this work, the tandem dehydrative alkenylation–reductive cyclization of secondary halogenated amides 1/2 to give 2-alkenyl-pyrrolidines 3 and 2-alkenylpiperidines 4 was envisioned (Scheme 1).

**Scheme 1** Designed tandem dehydrative coupling-reductive cyclization reaction of halogenated secondary amides.

2-Substituted pyrrolidines and piperidines are salient structural features found in a number of alkaloids and medicinal agents.<sup>8</sup> Among them some possess a 2-alkenyl pyrrolidine<sup>9</sup>/ piperidine<sup>10</sup> motif. For example, caulophyllumine B (5, Fig. 1) was isolated from *Caulophyllum thalictroides* (L.) Michx (Berberidaceae), an indigenous perennial plant found in north-eastern North America.<sup>10a</sup> This piperidine alkaloid has been shown to exhibit cytotoxic activity on the human cancer

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one-pot Tf<sub>2</sub>O, 2-F-Pyr.; 3 (n = 1) 1 (n = 1, X = CI, Br)reduction (n = 2) 2 (n = 2, X = CI, Br) reduction; Tf<sub>2</sub>O tandem cyclization 2-F-Pyr. B: OTf 2-F-Pyr. • TfOH 2-F-Pyr. в

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<sup>‡</sup> Electronic supplementary information (ESI) available: <sup>1</sup>H and <sup>13</sup>C NMR Spectra of all products. See DOI: 10.1039/c6q000720a



Fig. 1 Representative bioactive alkaloids and medicinal agents related to the present investigation.

cell lines of the lung, breast and ovary.<sup>10b,c</sup> Using caulophyllumine B (5) as a leading compound, several piperidine alkenealkaloids represented by the general structure **6** have found to possess higher growth inhibition activity than the standard drug cisplatin.<sup>10c</sup> Alkaloid himbacine (**9**) is a potent and selective antagonist of the muscarinic M<sub>2</sub> receptor, which constitutes an attractive lead compound of a drug for the treatment of Alzheimer's disease.<sup>10d</sup> In addition to their important biological profile, 2-substituted pyrrolidines and piperidines also serve as key intermediates for the synthesis of aza-bicyclic pyrrolizidine,<sup>9a,11</sup> indolizidine<sup>9a,12</sup> and quinolizidine<sup>12</sup> alkaloids such as  $\delta$ -coniceine<sup>13a</sup> (7) and epiquinamide,<sup>13b,c</sup> (**8**). The latter was isolated from the skin of Ecuadorian frog *Epipedobates tricolor*.<sup>13b</sup>

On the other hand, the Bischler–Napieralski (B–N) reaction<sup>14</sup> has been known over one century, and the  $P_2O_5$  or POCl<sub>3</sub>-mediated dehydrative cyclization of the secondary amide group onto an internal cyclohexenyl moiety (extended Bischler–Napieralski cyclization) (Scheme 2, eqn (a))<sup>15a</sup> or onto a styryl terminator (vinylogous Bischler–Napieralski cyclization) (Scheme 2, eqn (b))<sup>15b</sup> have been reported since 1950s. However, to date, this type of cyclization reactions are restricted to the synthesis of heterocycles **13**, **17**, and **19**,<sup>15,16</sup> and suffer from limited substrate scope and cyclization mode. Even the modern version utilizing PPSE (polyphosphoric acid trimethylsilyl ester) as a more efficient dehydrative cyclization agent, it has been reported that all attempts to undertake the dehydrative cyclization of **15** to **18** failed.<sup>16</sup> In addition, the a. Extended Bischler - Napieralski (B-N) cyclization (Schnider and Hellerbach, 1950):



b. Vinylogous Bischler - Napieralski cyclization (Sugasawa, 1965; Gawley, 1986; Angelastro, 1994):







Scheme 3 Designed novel modes of extended Bischler–Napieralskitype cyclization reactions.

harsh reaction conditions and hazardous solvent (benzene or  $CCl_4$ ) used in these methods render them with low functional group tolerance and make them environmentally harmful. In this regard, Gawley and Chemburker have noted that the substrate containing a benzyl ether [14:  $R = (CH_2)_2OBn$ ] or an ethyl chloride moiety [14:  $R = (CH_2)_2Cl$ ] was destroyed under the reaction conditions.<sup>16a,b</sup> Thus development of novel modes of extended Bischler–Napieralski-type cyclizations (*cf.* Scheme 3) and tandem reactions that allow access of diverse nitrogenous carbocycles (*cf.* Scheme 1) is highly desirable.

We anticipated that a new mode of dehydrative olefinic amide cyclization would provide direct access to enimino carbocycles 22 and 23 (Scheme 3), which could in turn serve as valuable building blocks for the synthesis of related alkaloids and medicinal agents such as VPC01091 (10, Fig. 1) and flavagline. VPC01091<sup>17a</sup> is a drug candidate developed by the scientists of Abbott Laboratories for the treatment of multiple sclerosis.<sup>17a</sup> Flavagline derivative **11** exhibited cytotoxicity on human cancer cell lines and the neuroprotection effect on culture models of Parkinson's disease and cisplatin-induced neurotoxicity.<sup>17b</sup> Investigations along these two lines (*cf.* Schemes 1 and 3) have been undertaken and the results are reported herein.

#### **Results and discussion**

We first investigated the tandem intermolecular dehydrative alkenylation-reductive cyclization of halo amides (Scheme 1). For this purpose, 5-chloro-N-(2,6-dimethylphenyl)pentanamide 2a was selected as a phenotype substrate, and the reaction conditions were optimized on the basis of those we previously established for the coupling of alkenes with amides.<sup>7a-c</sup> Thus, chloro-amide 2a was successively treated with trifluoromethanesulfonic anhydride (Tf<sub>2</sub>O, 1.1 equiv.) and 2-fluoropyridine<sup>18,6*i*-*k*</sup> (2-F-Pyr., 1.2 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (0 °C, 10 min), and styrene (1.2 equiv.) (Scheme 4). After the disappearance of the starting material as indicated by TLC monitoring, NaBH<sub>4</sub> and MeOH were added. The mixture was stirred at 0 °C for 30 min, and at RT for 3 hours. As shown in Scheme 4, when 1.5 equiv. of NaBH<sub>4</sub> was used, 1,2-disubstituted piperidine 4a and uncyclized intermediate chloro-enimine 24 were obtained in 15% and 71% yields, respectively. With the amount of NaBH4 increased to 2.0 equiv., the yield of 4a increased to 35% and that of 24 decreased to 46%. On further increasing the amount of NaBH<sub>4</sub> to 3.0 equiv., the yield of 4a increased to 88% and only a trace amount of 24 was observed. Thus 3.0 equiv. was determined to be the optimized amount for NaBH<sub>4</sub> (cf. Table 1, 4a).

With the optimized reaction conditions in hand, the reaction was extended to a series of substituted styrenes as well as 1-vinylnaphthalene and 1*H*-indene. As can be seen from Table 1, the reactions produced the corresponding 2-substituted piperidines **4b**-i in 90–98% yields. These results implicated that the reaction tolerated styrylic alkenes bearing either an electron-donating or an electron-withdrawing group, and these groups have little effects on the yield. Besides styrene and its derivatives, *gem*-dialkyl alkenes also reacted smoothly. Thus, the reaction of methylenecyclohexane afforded the corresponding product **4j** in 90% yield. The reaction also tolerated ester and  $\alpha$ , $\beta$ -unsaturated ester group bearing alkenes (**4k** and **4l**). Interestingly, the reaction of ethyl vinyl ether unexpectedly yielded saturated 2-ethoxyethylpiperidine **4A**<sub>1</sub> in



Scheme 4 The tandem dehydrative coupling-reductive cyclization reaction of chloro-amide 2a.

 
 Table 1
 The tandem dehydrative coupling-reductive cyclization reaction of chloro-amide 2a with functionalized alkenes<sup>a</sup>



<sup>*a*</sup> Reaction conditions: amide (1.0 equiv.), 2-F-Pyr. (1.2 equiv.),  $CH_2Cl_2$  (0.25 M), then 0 °C, Tf<sub>2</sub>O (1.1 equiv.), 10 min; alkene (1.2 equiv.), 2 h. NaBH<sub>4</sub> (3.0 equiv.), MeOH, 3 h. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> *E/Z* ratio determined by <sup>1</sup>H NMR.

74% yield. Similarly, the reactions of enamides 25b and 25c, aza-analogues of the enol form of acetaldehyde, produced the saturated 1,3-amino-amido products  $4A_2$  and  $4A_3$  in 73% and 74% yields, respectively. It is worth mentioning that 1,3-diamine is an important structural motif found in many natural products, pharmaceuticals,<sup>10a,19</sup> and chiral ligands.

A plausible mechanism for the formation of saturated 1,3-amino ether/amides when employing a vinyl ether or an enamide in lieu of an alkene as a nucleophile is depicted in Scheme 5. A vinyl ether or an enamide reacts with a nitrilium ion **A**, generated *in situ* from a chloro-amide and  $Tf_2O/2$ -F-Pyr.,



Scheme 5 A plausible mechanism for the formation of 1,3-amino ether/amides

1

2

3

5

6

to give an oxonium-iminium intermediate B-4A1 or *N*-acyliminium–iminium intermediates **B-4A**<sub>2</sub>, **B-4A**<sub>3</sub>. Bisreduction of the two electrophilic sites in B-4A<sub>1</sub>, B-4A<sub>2</sub>, B-4A<sub>3</sub> followed by tandem cyclization produces the 1,3-amino ether/ amides 4A.

Encouraged by these results, the effects of the N-substituent, ω-leaving group, and chain length were examined. The reaction of 4-chloro-N-(2,6-dimethylphenyl)butanamide 1a, a one-carbon lower homologue of 2a afforded (E)-2-styrylpyrrolidine derivative 3a in an unexpected lower yield (80%, Table 2, entry 1). The reaction of 4-bromo-N-(2,6-dimethylphenyl)butanamide gave 3a in the same yield (80%, entry 2) as that for its chloro analogue (entry 1). Thus the chloro and bromo amides displayed comparable reactivity in the tandem reaction. To our delight, the tandem reaction of N-n-butylamide 2b with styrene produced the desired piperidine derivative 4m in 70% yield along with the corresponding side chain-saturated product 4m' in 10% yield (entry 3). The reaction of its lower homologue 1c afforded the (E)-2-styrylpyrrolidine derivative 3b in 52% yield along with its saturated analogue 3b' in 12% yield (entry 4). Similar yields (56% and 50%) were obtained with N-allyl and N-benzyl chloro-amides, where the yields of the side products bearing saturated substituents were higher (21% and 27%, entries 5 and 6). The successful incorporation of the well-known N-protecting groups such as N-ally and N-benzyl groups will allow further elaboration via ring closing metathesis (RCM) and N-deprotection.

A tandem reaction on amido ester 26 was also attempted. The reductive addition with styrene gave α-styryl amino ester 27 in 70% yield along with 12% of its saturated analogue 27' (Scheme 6). Treatment of 27 with NaH at 80 °C yielded 6-styrylpiperidin-2-one 28 in 80% yield.

To demonstrate the synthetic value of this method, the synthesis of some simple targets were envisaged. Caulophyllumine B (5) and its analogues (cf. 6 in Fig. 1) appeared to be ideal targets for our methodology. To this end, amide 2d and *p*-methoxystyrene was subjected to the standard tandem reaction conditions, which provided compound 4n (Scheme 7). The caulophyllumine analogue 4n has been shown to exhibit Table 2 Effects of N-substituent, ω-leaving group, and chain length on the tandem reaction





Scheme 6 The stepwise dehydrative coupling-lactamization of amido ester 26

higher growth inhibition activity than the standard drug cisplatin.<sup>10c</sup> In addition, this compound has served as the immediate intermediate in a racemic synthesis of caulophyllu-



and 4n.

mine B (5).<sup>20a</sup> Although this approach is more efficient than the reported ones,<sup>20</sup> in view of developing procedure-economical synthesis,<sup>21</sup> an even more efficient one-pot access to racemic caulophyllumine B (5) was envisioned. According to the above mentioned plausible mechanism, the reaction medium is acidic. Thus we anticipated that if we use an acid cleavable *O*-protecting group such as TBS and THP, it would be possible to perform an *in situ O*-deprotection by the *in situ* generated acid. Indeed, subjecting chloro-amide 2d to the reaction with *p*-TBSO-styrene under slightly modified tandem reaction conditions (40 °C, 12 h) yielded 5 directly in 53% yield (Scheme 7). Under the same conditions, the reaction of *p*-THPO-styrene produced 5 in 57% yield. Significantly, the direct use of unprotected *p*-hydroxystyrene also afforded 5 in an appreciable yield of 48%.

Both approaches to caulophyllumine B (5) are highly efficient which merit comments. In the first approach, by judicious selection of the *O*-protecting group, three reactions took place sequentially in one pot. The fact that the *O*-deprotection was achieved by taking advantage of TfOH generated *in situ* from amide activation, without the need to use any additional reagent, implicates that in addition to being procedure-economical, the method also features a symbiotic catalysis.<sup>22</sup> Using *O*-unprotected 4-hydroxystyrene as a nucleophile, the second approach is not only procedure-economical, but also a protecting group-free synthesis, which are key elements of modern green synthesis.<sup>2a</sup>

We next addressed the construction of the indolizidine ring system by the established method. The synthesis started from **2e**, which was subjected to the tandem reaction to produce **4o** in 53% yield along with its saturated analogue **4o**' in 19% yield (Scheme 8). Treatment of **4o** with the Grubbs second generation catalyst and  $\text{Ti}(\text{O}^{i}\text{Pr})_{4}$  in CH<sub>2</sub>Cl<sub>2</sub> at reflux yielded 3,5,6,7,8,8a-hexahydroindolizine (**29**) in 82% yield. Catalytic hydrogenation of the latter produced the indolizidine alkaloid  $\delta$ -coniceine (7)<sup>13a</sup> in 93% yield. Hexahydroindolizine **29** can also be converted to indolizidinediol by dihydroxylation.<sup>23</sup>

Alternatively, a more efficient direct entry to the indolizidine ring system was also envisaged. Indeed, tandem dehrdracyclization-reductive cyclization of **1f** led to **3e** in 78% yield (Scheme 9). In view of the synthesis of 1-benzylideneoctahydro-2*H*-quinolizine **4p** as a potential synthetic intermediate of quinolizidine alkaloids<sup>12</sup> such as epiquinamide (**8**),<sup>13</sup> we



Scheme 8 The synthesis of racemic  $\delta$ -coniceine (7).



Scheme 9 One-pot construction of indolizidine and quinolizidine ring systems.

needed to challenge the previously reported unsuccessful vinylogous Bischler-Napieralski reaction (cf. Scheme 1).16 To this end, compound 2f was prepared and subjected to the standard tandem reaction conditions, which, to our delight, afforded the desired cyclization product 4p in 81% yield. In view of the failure in the previous attempts for the PPSE-promoted dehydrative cyclization of 15  $[R = (CH_2)_3CO_2Et]$  to give 18 (Scheme 1),<sup>16</sup> this result is significant. Gawley and Chemburker attributed the failure of dehydrative cyclization of 15 to the inability of the intermediate generated from 15 to achieve the correct orbital overlap geometry. On the other hand, by incorporating a p-methoxy substituent, Angelastro and co-workers have accomplished the six-membered ring formation of 16 via a vinylogous Bischlep-Napieralski cyclization.<sup>16c</sup> On the basis of the experimental results and in combination with semiempirical and ab initio molecular orbital calculations, they suggested that the overall reaction is under kinetic rather than thermodynamic control.<sup>16c</sup>



Scheme 10 Novel modes of dehydrative cyclization of olefinic amides (20a-c).

Our results might implicate that the activation of secondary amides 1f/2f by the  $Tf_2O/2$ -F-Pyr. system generates more reactive *O*-triflylimidate salt **H**, which can either undergo intramolecular cyclization with the styryl moiety to give intermediate **I** directly or generate more efficiently the highly reactive nitrilium intermediate **A-1f/A-2f** thus ensuing a successful cyclization reaction to take place.

We next turned our attention to explore novel modes of dehydrative cyclization of olefinic amides as those displayed in Scheme 3. To this end, compound 20a was prepared by Michael addition<sup>24</sup> and treated with Tf<sub>2</sub>O/2-F-Pyr. The reaction proceeded smoothly to produce the expected cyclization product 22a in 89% yield (Scheme 10). Similarly, the dehydrative cyclization of 20b afforded 1-imino-2-cyclopentene (22b) in 87% yield. Possessing two parochial functionalities, 1-imino-2cyclohexenes and 1-imino-2-cyclopentenes such as 22a and 22b could serve both as a versatile platform for enantiomeric synthesis and as building blocks for the synthesis of related natural products and medicinally relevant molecules such as VPC01091 (10). It is worth mentioning that although several methods for the synthesis of fused and poly-substituted 1-imino-2-cyclopentene derivatives have been reported,<sup>25</sup> a flexible method for direct synthesis of properly substituted and thus synthetically useful 1-imino-2-cyclopentenes from simple starting materials is rare.<sup>26</sup> Our approach thus provides an attractive transition-metal-free alternative, which is potentially applicable to the synthesis of related natural products. To demonstrate the versatility of this method, olefinic amide 20c was subjected to dehydrative cyclization and acidic hydro-



Scheme 11 A novel mode of dehydrative cyclization of olefinic amide (21).

lysis to give 3-phenylcyclohex-2-en-one **32** directly in 81% yield. Alternatively, subjecting **20c** to dehydrative cyclization and reduction with NaBH<sub>4</sub> to give 3-butylamino-phenylcyclohex-1-ene (**33**) directly in 80% yield.

Finally, another mode of dehydrative cyclization was investigated, for this purpose **21** was prepared and subjected to the Tf<sub>2</sub>O/2-F-Pyr.-mediated dehydrative cyclization to yield the expected cyclization product **23** in 76% yield (Scheme **11**). It is worth mentioning that although *N*-acyl/tosyl-1-aza-dienes are widely used in aza-[4 + 2]-cycloaddition reactions for the synthesis of heterocycles,<sup>27</sup> known methods for the synthesis of this type of bis-*exo*-cyclic 1-aza-dienes (enimines) either require the use of the corresponding enones as starting materials<sup>28</sup> or formed *in situ* as reactive intermediates (*o*-quinone methide imines, aza-*o*-quinone methides).<sup>29</sup> Our metal-free direct synthesis of enimino cyclohexane **23** from either *E* or *Z* olefinic amides is straightforward and high yielding.

#### Conclusions

In summary, we have developed, on one hand, a tandem reductive alkenylation-cyclization reaction starting from halogenated secondary amides and terminal alkenes,<sup>30</sup> and on the other hand, new cyclization modes of olefinic secondary amides to give two kinds of enimino carbocycles. Employing Tf2O as an amide activating reagent, the reactions were run under mild conditions, and the intermediates generated were more reactive than those using other activating reagents, allowing the hitherto failed vinylogous Bischler-Napieralski cyclization leading to the quinolizidine ring system. These methods provide efficient one-pot access to α-vinylic substituted pyrrolidines, piperidines, and 8-benzylideneindolizidine and 1-benzylidenequinolizidine, as well as to enimino carbocycles from easily available starting materials. The efficacy of the method was demonstrated by the one-pot synthesis of caulophyllumine B (5) and its bioactive derivatives 4n. The enimino carbocycles could serve as versatile scaffolds for many transformations such as asymmetric reduction/nucleophilic addition, aza-cycloaddition. Because the Tf2O-activated Vilsmeier-type intermolecular cross-coupling reaction of arenes with tertiary N,Ndimethylformamide has been reported,<sup>31</sup> it is expectable that the current method can be extended to the intermolecular coupling of alkenes with tertiary amides. In addition, the

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#### **Experimental section**

#### General method

Melting points were determined on Büchi M560 Automatic Melting Point apparatus and are uncorrected. Infrared spectra were recorded with a Nicolet Avatar 360 FT-IR spectrometer using film/KBr pellet techniques. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker spectrometer at 400 and 100 MHz (or at 500 and 125 MHz). Chemical shifts ( $\delta$ ) are reported in ppm and respectively referenced to internal standard Me<sub>4</sub>Si or solvent signals (Me<sub>4</sub>Si, 0 ppm for <sup>1</sup>H NMR and CDCl<sub>3</sub>, 77.0 ppm for <sup>13</sup>C NMR). Mass spectra were recorded on Bruker Dalton Esquire 3000 plus LC-MS apparatus (ESI direct injection). HRMS spectra were recorded on 7.0T FT-MS apparatus.

## General procedure A: tandem dehydrative coupling-reductive cyclization reaction of halogenated secondary amides

Into a dry 10 mL round-bottom flask equipped with a magnetic stirring bar were added successively a halo-amide (0.5 mmol, 1.0 equiv.), 2 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> and 2-fluoropyridine (0.6 mmol, 1.2 equiv.) under an argon atmosphere. After being cooled to 0 °C, trifluoromethanesulfonic anhydride (Tf<sub>2</sub>O) (155 mg, 93 µL, 0.55 mmol, 1.1 equiv.) was added dropwise via a syringe and the reaction was stirred for 10 min. To the resulting mixture, an alkene (0.6 mmol, 1.2 equiv.) was added dropwise at 0 °C. The reaction mixture was allowed to warm-up to room temperature and stirred for 2 h. Then the reaction mixture was cooled to 0 °C in an ice bath and stirred for 5 min. To the resulting mixture, sodium borohydride (57 mg, 1.5 mmol, 3.0 equiv.) and MeOH (3 mL) were added. The reaction mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched with a saturated NaHCO<sub>3</sub> aqueous solution and extracted with dichloromethane  $(3 \times 8 \text{ mL})$ . The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired saturated N-heterocycles.

#### General procedure B: dehydrative cyclization of olefinic amides

Into a dry 10 mL round-bottom flask equipped with a magnetic stirring bar were added successively a halo-amide (0.5 mmol, 1.0 equiv.), 2 mL of anhydrous  $CH_2Cl_2$  and 2-fluoropyridine (0.6 mmol, 1.2 equiv.) under an argon atmosphere. After being cooled to 0 °C, trifluoromethanesulfonic anhydride (Tf<sub>2</sub>O) (155 mg, 93 µL, 0.55 mmol, 1.1 equiv.) was added dropwise *via* a syringe and the reaction was stirred for 10 min. Then the mixture was allowed to warm-up to room temperature and stirred for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (FC) on silica gel (pre-neutralized with 2%  $Et_3N$  in *n*-hexane) to afford the desired  $\alpha$ , $\beta$ -unsaturated ketimine.

(*E*)-1-(2,6-Dimethylphenyl)-2-styrylpiperidine (4a). Following the general procedure A, the reductive cyclization reaction of amide 2a (120 mg, 0.5 mmol) with styrene gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1:10), 2-styrylpiperidine 4a (128 mg, yield: 88%). Colorless oil; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.54–1.67 (m, 3H), 1.73–1.86 (m, 3H), 2.27 (s, 6H), 3.52 (d, *J* = 6.7 Hz, 2H), 3.67–3.75 (m, 1H), 6.03 (dd, *J* = 15.8, 7.8 Hz, 1H), 6.28 (d, *J* = 15.8 Hz, 1H), 6.78 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 2H), 7.16–7.21 (m, 1H), 7.26 (m, 4H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  19.1 (2C), 23.6, 32.6, 35.8, 44.8, 59.6, 121.8, 126.2 (2C), 127.3, 128.5 (2C), 128.8 (2C), 129.4 (2C), 130.2, 131.6, 136.9, 144.4 ppm; IR (film)  $\nu_{max}$ : 3023, 2930, 2847, 1470, 1447, 740 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{21}H_{26}N]^+$  (M + H<sup>+</sup>): 292.2060; found: 292.2058.

(E)-1-(2,6-Dimethylphenyl)-2-(4-methoxystyryl)piperidine (4b). Following the general procedure A, the reductive cyclization reaction of amide 2a (120 mg, 0.5 mmol) with 4-methoxystyrene gave, after flash column chromatography on silica gel (eluent: EtOAc/n-hexane = 1/5), 2-(4-methoxystyryl)piperidine 4b (120 mg, yield: 75%). Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.56–1.67 (m, 3H), 1.74–1.86 (m, 3H), 2.27 (s, 6H), 3.53 (t, J = 6.7 Hz, 2H), 3.65-3.72 (m, 1H), 3.78 (s, 3H), 5.99 (dd, J = 15.8, 7.8 Hz, 1H), 6.22 (d, J = 15.8 Hz, 1H), 6.76-6.83 (m, 3H), 6.95 (d, J = 7.5 Hz, 2H), 7.18-7.23 (m, 2H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  19.1 (2C), 23.7, 32.7, 35.9, 44.8, 55.3, 59.7, 113.9 (2C), 121.7, 127.4 (2C), 128.8 (2C), 129.5, 129.5 (2C), 129.7, 129.8, 144.6, 159.0 ppm; IR (film)  $\nu_{\text{max}}$ : 3038, 3009, 2926, 2851, 1607, 1507, 1470, 1250, 1167, 1034, 765 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{22}H_{28}NO]^+$  (M + H<sup>+</sup>): 322.2165; found: 322.2170.

(E)-2-[4-(tert-Butyl)styryl]-1-(2,6-dimethylphenyl)piperidine (4c). Following the general procedure A, the reductive cyclization reaction of amide 2a (120 mg, 0.5 mmol) with 4-tert-butylstyrene gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/5), 1,2-disubstituted piperidine 4c (156 mg, yield: 90%). Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.29 (s, 9H), 1.52–1.66 (m, 3H), 1.72–1.85 (m, 3H), 2.27 (s, 6H), 3.51 (t, J = 6.6 Hz, 2H), 3.66-3.74 (m, 1H), 5.99 (dd, J = 15.8, 7.8 Hz, 1H), 6.26 (d, J = 15.8 Hz, 1H), 6.77 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 7.5 Hz, 2H), 7.18–7.23 (m, 2H), 7.27–7.32 (m, 2H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  19.1 (2C), 23.6, 31.2, 32.6, 34.5, 35.9, 44.8, 59.7, 121.7, 125.4 (2C), 125.9 (2C), 128.8 (2C), 129.4 (2C), 130.0, 130.9, 134.2, 144.5, 150.4 ppm; IR (film)  $\nu_{\text{max}}$ : 3092, 3034, 2963, 2859, 1516, 1478, 1267, 1101, 964, 769 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{25}H_{34}N]^+$  (M + H<sup>+</sup>): 348.2686; found: 348.2690.

(*E*)-2-(4-Bromostyryl)-1-(2,6-dimethylphenyl)piperidine (4d). Following the general procedure A, the reductive cyclization reaction of amide 2a (120 mg, 0.5 mmol) with 4-bromostyrene gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/5), 1,2-disubstituted piperidine 4d (175 mg, yield: 95%). Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.56–1.67 (m, 3H), 1.74–1.86 (m, 3H), 2.26 (s, 6H), 3.53 (t, *J* = 6.6 Hz, 2H), 3.66–3.73 (m, 1H), 6.02 (dd, *J* = 15.8, 7.6 Hz, 1H),

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6.20 (d, *J* = 15.8 Hz, 1H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.93–6.98 (m, 2H), 7.09–7.14 (m, 2H), 7.35–7.40 (m, 2H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  19.0 (2C), 23.6, 32.6, 35.7, 44.8, 59.5, 121.0, 121.9, 127.7 (2C), 128.8 (2C), 129.1, 129.5 (2C), 131.6 (2C), 132.4, 135.9, 144.3 ppm; IR (film)  $\nu_{max}$ : 3038, 3017, 2921, 2851, 1586, 1486, 1466, 1067, 1002, 964, 806, 765 cm<sup>-1</sup>; HRMS-ESI calcd for [C<sub>21</sub>H<sub>25</sub>BrN]<sup>+</sup> (M + H<sup>+</sup>): 370.1165 and 372.1144; found: 370.1173 and 372.1153.

(*E*)-1-(2,6-Dimethylphenyl)-2-(4-fluorostyryl)piperidine (4e). Following the general procedure A, the reductive cyclization reaction of amide 2a (120 mg, 0.5 mmol) with 4-fluorostyrene gave, after flash column chromatography on silica gel (eluent: EtOAc/n-hexane = 1/5), 1,2-disubstituted piperidine 4e (142 mg, yield: 92%). Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.53–1.72 (m, 3H), 1.76–1.86 (m, 3H), 2.28 (s, 6H), 3.53 (t, J = 6.6 Hz, 2H), 3.66-3.74 (m, 1H), 5.96 (dd, J = 15.8, 7.8 Hz, 1H), 6.23 (d, J = 15.8 Hz, 1H), 6.81 (t, J = 7.4 Hz, 1H), 6.92-6.98 (m, 4H), 7.18–7.25 (m, 2H) ppm;  $^{13}$ C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  19.0 (2C), 23.6, 32.6, 35.6, 44.8, 59.9, 115.3 (d, J = 21.5 Hz, 2C), 122.1, 127.7 (d, J = 8.0 Hz, 2C), 128.9 (2C), 129.5, 129.6 (2C), 131.0, 131.0, 133.0 (d, J = 3.0 Hz), 162.1 (d, J = 246.6 Hz) ppm; IR (film) v<sub>max</sub>: 3042, 2930, 2859, 1607, 1511, 1470, 1229, 1159, 964, 769 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{21}H_{25}FN]^+$  (M + H<sup>+</sup>): 310.1966; found: 310.1969.

1-(2,6-Dimethylphenyl)-2-(2-phenylprop-1-en-1-yl)piperidine (4f). Following the general procedure A, the reductive cyclization reaction of amide 2a (120 mg, 0.5 mmol) with  $\alpha$ -methylstyrene gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/5), 1,2-disubstituted piperidine 4f (142 mg, yield: 93%) as a 69:31 inseparable mixture of E/Z isomers. Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, data of the two geometric isomers) δ 1.40-1.65 (m, 3.5H), 1.70 (s, 2.5H), 1.75-1.87 (m, 2.6H), 1.91 (s, 0.7H), 2.00 (s, 1.6H), 2.29 (s, 4.4H), 3.45-3.59 (m, 2.3H), 3.95-4.05 (m, 0.7H), 5.23 (d, J = 9.6 Hz, 0.3H), 5.53 (d, J = 9.6 Hz, 0.7H), 6.54-6.61 (m, 0.5H), 6.76-6.84 (m, 1H), 6.89 (d, J = 7.4 Hz, 0.5H), 6.95 (d, J = 7.4 Hz, 1.5H), 7.09–7.32 (m, 4.5H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, data of the two geometric isomers)  $\delta$  16.1, 18.6, 18.9, 23.5, 23.6, 25.7, 32.6, 32.7, 36.1, 36.3, 44.8, 44.9, 55.2, 55.4, 121.8, 122.0, 125.7, 126.4, 126.9, 127.6, 127.7, 128.1, 128.5, 128.7, 129.5, 129.8, 130.2, 130.5, 136.7, 139.1, 141.4, 143.5, 144.3, 144.6 ppm; IR (film) *v*<sub>max</sub>: 3079, 3050, 3021, 2922, 2855, 1474, 1441, 1101, 765, 699 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{22}H_{28}N]^+$  (M + H<sup>+</sup>): 306.2216; found: 306.2217.

**1-(2,6-Dimethylphenyl)-2-(2,2-diphenylvinyl)piperidine (4g).** Following the general procedure A, the reductive cyclization reaction of amide **2a** (120 mg, 0.5 mmol) with 1,1-diphenylethylene gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/5), 1,2-disubstituted piperidine **4g** (178 mg, yield: 97%). Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.54–1.67 (m, 3H), 1.70–1.81 (m, 3H), 2.01 (s, 6H), 3.53 (t, *J* = 6.6 Hz, 2H), 3.61–3.70 (m, 1H), 5.86 (d, *J* = 9.9 Hz, 1H), 6.58 (d, *J* = 7.4 Hz, 2H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 7.4 Hz, 2H), 7.07–7.25 (m, 8H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 18.3 (2C), 23.6, 32.6, 36.3, 44.8, 55.4, 122.0, 126.8, 126.9 (2C), 127.2, 127.8 (2C), 128.1 (2C), 128.6 (2C), 129.6 (2C), 130.2 (2C), 131.0, 139.2, 141.6, 142.9, 144.1 ppm; IR (film)  $\nu_{\text{max}}$ : 3075, 3054, 3013, 2918, 2847, 1482, 1441, 1097, 761, 699 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{27}H_{30}N]^+$  (M + H<sup>+</sup>): 368.2373; found: 368.2370.

(E)-1-(2,6-Dimethylphenyl)-2-(2-(naphthalen-1-yl)vinyl) piperidine (4h). Following the general procedure A, the reductive cyclization reaction of amide 2a (120 mg, 0.5 mmol) with 1-vinylnaphthalene gave, after flash column chromatography on silica gel (eluent: EtOAc/n-hexane = 1/5), piperidine 4h (167 mg, yield: 98%) as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.68–1.80 (m, 3H), 1.85–1.96 (m, 3H), 2.35 (s, 6H), 3.61 (t, J = 6.6 Hz, 2H), 3.86-3.95 (m, 1H), 5.99 (d, J = 15.5 Hz, 1H), 6.86–6.92 (m, 1H), 6.93 (d, J = 15.5 Hz, 1H), 7.05 (d, J = 7.4 Hz, 2H), 7.40-7.50 (m, 4H), 7.66 (d, J = 8.2 Hz, 1H), 7.72-7.78 (m, 1H), 7.82 (d, J = 8.2 Hz, 1H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  19.1 (2C), 23.7, 32.6, 35.8, 44.9, 59.7, 121.9, 123.7, 124.1, 125.5, 125.7, 125.8, 127.6, 128.2, 128.4, 128.9 (2C), 129.5 (2C), 131.1, 133.4, 134.9, 135.1, 144.5 ppm; IR (film)  $\nu_{\text{max}}$ : 3050, 3013, 2926, 2853, 1478, 1437, 1101, 806, 777 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{25}H_{28}N]^+$  (M + H<sup>+</sup>): 342.2216; found: 342.2219.

1-(2,6-Dimethylphenyl)-2-(1H-inden-2-yl)piperidine (4i). Following the general procedure A, the reductive cyclization reaction of amide 2a (120 mg, 0.5 mmol) with indene gave, after flash column chromatography on silica gel (eluent: EtOAc/n-hexane = 1/5), 2-(1H-inden-2-yl)piperidine 4i (142 mg, vield: 94%) as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.45–1.55 (m, 2H), 1.73–1.92 (m, 4H), 2.23 (s, 6H), 3.31 (br s, 2H), 3.49 (t, J = 6.7 Hz, 2H), 4.15 (dd, J = 7.8, 5.9 Hz, 1H), 6.61 (br s, 1H), 6.77 (t, J = 7.4 Hz, 1H), 6.95 (d, J = 7.4 Hz, 2H), 7.09-7.15 (m, 1H), 7.19-7.25 (m, 1H), 7.28 (d, J = 7.4 Hz, 1H), 7.37 (d, J = 7.4 Hz, 1H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  19.1 (2C), 23.9, 32.5, 35.2, 38.4, 44.7, 57.3, 120.7, 121.4, 123.6, 124.3, 126.3, 127.6, 128.5 (2C), 129.0 (2C), 142.9, 144.6, 144.7, 151.0 ppm; IR (film)  $\nu_{\text{max}}$ : 3063, 3013, 2918, 2847, 1474, 1453, 1097, 757, 719 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{22}H_{26}N]^+$  (M + H<sup>+</sup>): 304.2060; found: 304.2059.

2-(Cyclohexylidenemethyl)-1-(2,6-dimethylphenyl)piperidine (4j). Following the general procedure A, the reductive cyclization reaction of amide 2a (120 mg, 0.5 mmol) with methylenecyclohexane gave, after flash column chromatography on silica gel (eluent: EtOAc/n-hexane = 1/5), 1,2-disubstituted piperidine 4j (127 mg, yield: 90%). Colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.05-1.15 (m, 1H), 1.30-1.41 (m, 1H), 1.46-1.62 (m, 7H), 1.70-1.79 (m, 2H), 1.80-1.96 (m, 5H), 2.29 (s, 3H), 2.32 (s, 3H), 2.82-2.89 (m, 1H), 3.04-3.12 (m, 1H), 3.18-3.27 (m, 1H), 5.25-5.31 (m, 1H), 6.88 (d, J = 7.4 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 7.01 (d, J = 7.4 Hz, 1H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 19.6 (2C), 22.5, 23.0, 25.0, 25.3, 27.2, 28.8, 32.5, 42.9, 51.5, 56.3, 123.2, 125.0, 128.1 (2C), 128.9 (2C), 135.1, 137.7, 138.9, 147.5 ppm; IR (film)  $\nu_{\text{max}}$ : 3046, 2926, 2855, 2826, 1594, 1474, 1445, 1263, 1217, 1100, 765 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{20}H_{30}N^+]^+$  (M + H<sup>+</sup>): 284.2373; found: 284.2376.

Ethyl 2-{4-{[1-(2,6-dimethylphenyl)piperidin-2-yl]methylene} cyclohexyl} acetate (4k). Following the general procedure A, the

reductive cyclization reaction of amide 2a (120 mg, 0.5 mmol) with ethyl 2-(4-methylenecyclohexyl)acetate gave, after flash column chromatography on silica gel (eluent: EtOAc/n-hexane = 1/5), 1,2-disubstituted piperidine 4k (159 mg, yield: 86%) as a 50:50 inseparable mixture of E/Z isomers. Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, data of the two geometric isomers)  $\delta$  1.12–1.39 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.46–2.16 (m, 13H), 2.19-2.24 (m, 2H), 2.24 (s, 6H), 3.31-3.42 (m, 1H), 3.47-3.54 (m, 2H), 4.12 (q, J = 7.1 Hz, 2H), 6.35-6.43 (m, 1H), 6.76 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 7.5 Hz, 2H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, data of the two geometric isomers)  $\delta$  14.2, 19.2, 23.3, 23.3, 27.8, 28.0, 28.6, 28.7, 30.3, 30.6, 31.4, 31.5, 32.7, 32.8, 34.5, 34.7, 40.7, 40.9, 44.3, 44.6, 44.9, 54.1, 54.2, 60.1, 121.0, 122.3, 122.5, 128.4, 128.4, 128.9, 128.9, 134.9, 135.0, 172.9, 172.9 ppm; IR (film)  $\nu_{\text{max}}$ : 3042, 2918, 2853, 1731, 1478, 1445, 1155, 1097, 765 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{24}H_{36}NO_2]^+$  (M + H<sup>+</sup>): 370.2741; found: 370.2732.

Ethyl 2-{4-{[1-(2,6-dimethylphenyl)piperidin-2-yl]methylene} cyclo-hexylidene} acetate (41). Following the general procedure A, the reductive cyclization reaction of amide 2a (120 mg, 0.5 mmol) with ethyl 2-(4-methylenecyclohexylidene)acetate gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/5), 1,2-disubstituted piperidine 4l (158 mg, yield: 87%) as a 50:50 inseparable mixture of E/Z isomers. Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, data of the two geometric isomers)  $\delta$  1.25 (t, J = 7.2 Hz, 3H), 1.29–1.38 (m, 1H), 1.44-1.82 (m, 5H), 1.98-2.34 (m, 4H), 2.24 (s, 3H), 2.25 (s, 3H), 2.50-2.72 (m, 2H), 2.93-2.98 (m, 1H), 3.02-3.07 (m, 1H), 3.32-3.42 (m, 1H), 3.46-3.54 (m, 2H), 4.09-4.17 (m, 2H), 5.41-5.49 (m, 0.6H), 5.50-5.58 (m, 0.6H), 5.62-5.67 (m, 0.4H), 5.69-5.74 (m, 0.4H), 6.72-6.81 (m, 1H), 6.92-6.99 (m, 2H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, data of the two geometric isomers) & 14.2, 14.3, 19.2, 23.3, 23.3, 26.8, 27.2, 29.9, 30.2, 32.7, 32.8, 34.5, 42.5, 42.7, 43.5, 44.9, 54.1, 54.5, 60.5, 60.5, 120.7, 121.1, 121.1, 121.2, 122.7, 122.7, 128.3, 128.5, 128.6, 128.9, 129.4, 131.9, 135.5, 144.4, 171.4, 171.5 ppm; IR (film)  $\nu_{\rm max}$ : 3054, 2934, 2859, 1731, 1470, 1267, 1159, 773, 736 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{24}H_{34}NO_2]^+$  (M + H<sup>+</sup>): 368.2584; found: 368.2581.

1-(2,6-Dimethylphenyl)-2-(2-ethoxyethyl)piperidine (4A<sub>1</sub>). Following the general procedure A, the reductive cyclization reaction of amide 2a (120 mg, 0.5 mmol) with ethoxyethene gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1:10, 1,2-disubstituted piperidine  $4A_1$ (97 mg, yield: 74%) as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.18 (t, J = 7.0 Hz, 3H), 1.41–1.53 (m, 4H), 1.60–1.67 (m, 1H), 1.68-1.77 (m, 2H), 1.82-1.91 (m, 1H), 2.25 (s, 6H), 3.37-3.46 (m, 3H), 3.48 (t, J = 6.7 Hz, 2H), 3.51-3.57 (m, 2H), 6.76 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 7.5 Hz, 2H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 15.2, 19.2 (2C), 23.5, 32.7, 34.8, 35.3, 44.9, 53.6, 66.2, 67.7, 121.0, 128.4 (2C), 129.0 (2C), 144.8 ppm; IR (film)  $\nu_{\text{max}}$ : 2975, 2933, 2860, 1473, 1474, 1114, 764 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{17}H_{28}NO]^+$  (M + H<sup>+</sup>): 262.2165; found: 262.2167.

*N*-{2-[1-(2,6-Dimethylphenyl)piperidin-2-yl]ethyl}acetamide (4A<sub>2</sub>). Following the general procedure A, the reductive cyclization reaction of amide 2a (120 mg, 0.5 mmol) with N-vinylacetamide gave, after flash column chromatography on silica gel (eluent: EtOAc/n-hexane = 1/5), 1,2-disubstituted piperidine 4A<sub>2</sub> (100 mg, yield: 73%). Colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.14-1.47 (m, 5H), 1.55-1.70 (m, 1H), 1.75-1.96 (m, 2H), 1.84 (s, 3H), 2.28 (s, 6H), 2.77-2.92 (m, 1H), 2.95-3.02 (m, 4H), 5.31 (br s, 1H), 6.79-7.12 (m, 3H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  19.4, 19.6, 23.1, 24.9, 26.9, 32.6, 33.5, 36.5, 51.5, 56.4, 125.1, 128.3, 129.2, 137.5, 138.7, 147.1 ppm; IR (film)  $\nu_{\text{max}}$ : 3282, 3075, 3013, 2922, 2859, 2793, 1653, 1553, 1445, 1288, 769 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{17}H_{26}N_2NaO]^+$  (M + Na<sup>+</sup>): 297.1937; found: 297.1932.

1-{2-[1-(2,6-Dimethylphenyl)piperidin-2-yl]ethyl}azepan-2-one (4A<sub>3</sub>). Following the general procedure A, the reductive cyclization reaction of amide 2a (120 mg, 0.5 mmol) with N-vinylcaprolactam gave, after flash column chromatography on silica gel (eluent: EtOAc/n-hexane = 1/5), 1,2-disubstituted piperidine 4A<sub>3</sub> (121 mg, yield: 74%). Colorless oil; <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.37–1.80 (m, 14H), 2.25 (s, 6H), 2.45-2.51 (m, 2H), 3.14-3.35 (m, 4H), 3.50 (t, J = 6.7 Hz, 2H), 3.56-3.68 (m, 1H), 6.77 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 7.5 Hz, 2H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  19.2 (2C), 23.3, 23.4, 28.5, 29.9, 32.6, 33.7, 35.0, 37.2, 44.9, 45.7, 49.5, 54.3, 121.1, 128.5 (2C), 128.9 (2C), 175.6 ppm; IR (film)  $\nu_{\text{max}}$ : 3046, 2934, 2855, 1636, 1478, 1445, 1254, 1205, 773 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{21}H_{32}N_2NaO]^+$  (M + Na<sup>+</sup>): 351.2407; found: 351.2402.

(E)-1-(2,6-Dimethylphenyl)-2-styrylpyrrolidine (3a). Following the general procedure A, the reductive cyclization reaction of amide **1a** (113 mg, 0.5 mmol) or amide **1b** (113 mg, 0.5 mmol) with styrene gave, after flash column chromatography on silica gel (eluent: EtOAc/n-hexane = 1/5), 2-styrylpyrrolidine 3a (111 mg, yield: 80%). Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.81-1.92 (m, 1H), 1.94-2.12 (m, 2H), 2.19-2.29 (m, 1H), 2.30 (s, 6H), 3.09-3.18 (m, 1H), 3.36-3.44 (m, 1H), 4.10-4.18 (m, 1H), 6.09 (dd, J = 15.7, 7.5 Hz, 1H), 6.17 (d, J = 15.7 Hz, 1H), 6.90-7.02 (m, 3H), 7.09-7.16 (m, 1H), 7.17-7.25 (m, 4H) ppm;  $^{13}$ C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  19.2 (2C), 25.3, 34.1, 51.4, 64.0, 125.3, 126.2 (2C), 126.9, 128.3 (2C), 128.6 (2C), 128.8, 134.0, 137.4, 144.3 ppm; IR (film)  $\nu_{\text{max}}$ : 3058, 3025, 2963, 2925, 2855, 1499, 1470, 1445, 1275, 1159, 959, 773, 740, 690  $\text{cm}^{-1}$ ; HRMS-ESI calcd for  $[C_{20}H_{24}N+]^+$  (M + H<sup>+</sup>): 278.1903; found: 278.1909.

(E)-1-n-Butyl-2-styrylpiperidine (4m). Following the general procedure A, the reductive cyclization reaction of amide 2b (96 mg, 0.5 mmol) with styrene gave, after flash column chromatography on silica gel (eluent: EtOAc/n-hexane = 1/5), 2-styrylpiperidine 4m (85 mg, yield: 70%) and 4m' (13 mg, yield: 10%). 4m: Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.87 (t, J = 7.3 Hz, 3H), 1.27–1.78 (m, 10H), 2.01–2.09 (m, 1H), 2.13-2.21 (m, 1H), 2.69-2.80 (m, 2H), 2.99-3.06 (m, 1H), 6.20 (dd, J = 16.0, 8.8 Hz, 1H), 6.47 (d, J = 16.0 Hz, 1H), 7.21-7.24 (m, 1H), 7.28-7.33 (m, 2H), 7.34-7.39 (m, 2H) ppm;  $^{13}\mathrm{C}$  NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  14.1, 20.8, 23.9, 25.9, 28.1, 33.6, 52.2, 55.6, 65.9, 126.2 (2C), 127.2, 128.5 (2C), 130.3, 133.6, 137.3 ppm; IR (film)  $\nu_{\text{max}}$ : 3083, 3058, 3029, 2959, 2930, 2851,

2784, 1445, 968, 748, 690 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{17}H_{26}N]^+$  (M + H<sup>+</sup>): 244.2060; found: 244.2061.

(E)-1-n-Butyl-2-styrylpyrrolidine (3b). Following the general procedure A, the reductive cyclization reaction of amide 1c (89 mg, 0.5 mmol) with styrene gave, after flash column chromatography on silica gel (eluent: EtOAc/n-hexane = 1/5), 2-styrylpyrrolidine 3b (60 mg, yield: 52%) and 3b' (14 mg, yield: 12%). **3b**: Colorless oil; <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ )  $\delta$  0.89 (t, J = 7.4 Hz, 3H), 1.22-1.36 (m, 2H), 1.44-1.53 (m, 2H),1.64-1.81 (m, 2H), 1.84-1.92 (m, 1H), 1.94-2.07 (m, 2H), 2.13 (t, J = 8.7 Hz, 1H), 2.74-2.86 (m, 2H), 3.19-3.27 (m, 1H), 6.12(dd, J = 15.8, 8.4 Hz, 1H), 6.47 (d, J = 15.8 Hz, 1H), 7.18-7.24 (m, 1H), 7.27-7.34 (m, 2H), 7.38 (d, J = 7.5 Hz, 1H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  14.0, 20.9, 22.2, 30.9, 31.8, 53.6, 54.3, 68.7, 126.3 (2C), 127.3, 128.5 (2C), 131.3, 132.6, 137.2 ppm; IR (film) v<sub>max</sub>: 3083, 3058, 3033, 2963, 2921, 2863, 2780, 1490, 1453, 972, 744, 690 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{16}H_{24}N]^+$  (M + H<sup>+</sup>): 230.1903; found: 230.1899.

(E)-1-Allyl-2-styrylpyrrolidine (3c). Following the general procedure A, the reductive cyclization reaction of amide 1d (81 mg, 0.5 mmol) with styrene gave, after flash column chromatography on silica gel (eluent: EtOAc/n-hexane = 1/5), 2-styrylpyrrolidine 3c (60 mg, yield: 56%) and 3c' (23 mg, yield: 21%). 3c: Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.70–1.82 (m, 2H), 1.83–1.93 (m, 1H), 1.97–2.07 (m, 1H), 2.25 (dt, J = 9.0, 8.7 Hz, 1H), 2.74 (dd, J = 13.2, 7.9 Hz, 1H), 2.97 (dt, J = 7.9, 7.9 Hz, 1H), 3.17 (t, J = 7.9 Hz, 1H), 3.51 (dd, J = 13.3, 5.1 Hz, 1H), 5.14 (dd, J = 13.3, 8.0 Hz, 2H), 5.84–5.96 (m, 1H), 6.14 (dd, J = 15.8, 8.6 Hz, 1H), 6.49 (d, J = 15.8 Hz, 1H), 7.23–7.40 (m, 5H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  22.1, 31.8, 53.4, 57.0, 67.8, 116.9, 126.3 (2C), 127.4, 128.5 (2C), 131.8, 132.1, 135.9, 137.0 ppm; IR (film)  $\nu_{\text{max}}$ : 3079, 3058, 3017, 2971, 2921, 2863, 2789, 1494, 1449, 964, 914, 748, 694 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{15}H_{20}N]^+$  (M + H<sup>+</sup>): 214.1590; found: 214.1591.

(*E*)-1-Benzyl-2-styrylpyrrolidine (3d). Following the general procedure A, the reductive cyclization reaction of amide 1e (106 mg, 0.5 mmol) with styrene gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/5), the known 2-styrylpyrrolidine  $3d^{33}$  (66 mg, yield: 50%) and 3d' (36 mg, yield: 27%). 3d: Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.90–1.66 (m, 3H), 2.22–1.94 (m, 2H), 3.02–2.92 (m, 2H), 3.13 (d, *J* = 12.8 Hz, 1H), 4.06 (d, *J* = 12.8 Hz, 1H), 6.19 (dd, *J* = 15.9, 8.5 Hz, 1H), 6.55 (d, *J* = 15.9 Hz, 1H), 7.42–7.18 (m, 10H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  22.1, 31.7, 53.3, 58.3, 67.8, 126.2 (2C), 126.7, 127.3, 128.1 (2C), 128.5 (2C), 128.9 (2C), 131.6, 132.5, 137.1, 139.3 ppm; IR (film)  $\nu_{max}$ : 3087, 3058, 3025, 2925, 2855, 2789, 1656, 1494, 1453, 964, 748, 694 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{19}H_{22}N+]^+$  (M + H<sup>+</sup>): 264.1747; found: 264.1743.

Methyl (*E*)-5-[(2,6-dimethylphenyl)amino]-7-phenylhept-6enoate (27). Following the general procedure A, the reaction of amide 28 (125 mg, 0.5 mmol) with styrene and reduction gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/5), amido ester 27 (118 mg, yield: 70%) and 27' (20 mg, yield: 12%). 27: Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.57–1.71 (m, 1H), 1.73–1.84 (m, 3H), 2.27 (s, 6H), 2.33–2.39 (m, 2H), 3.65 (s, 3H), 3.68–3.76 (m, 1H), 6.03 (dd, J = 15.8, 7.8 Hz, 1H), 6.27 (d, J = 15.8 Hz, 1H), 6.78 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 7.5 Hz, 2H), 7.15–7.22 (m, 1H), 7.23–7.31 (m, 4H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  19.0 (2C), 21.8, 34.0, 35.9, 51.5, 59.5, 121.8, 126.2 (2C), 127.3, 128.4 (2C), 128.8 (2C), 129.5 (2C), 130.4, 131.4, 136.9, 144.4, 173.8 ppm; IR (film)  $\nu_{max}$ : 3382, 3059, 3025, 2926, 2851, 1740, 1267, 740, 703 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{22}H_{27}NNaO_2]^+$  (M + Na<sup>+</sup>): 360.1934; found: 360.1929.

**Methyl** 5-[(2,6-dimethylphenyl)amino]-7-phenylheptanoate (27'). 27': Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.39–1.61 (m, 2H), 1.64–1.85 (m, 4H), 2.20 (s, 6H), 2.29 (t, *J* = 7.4 Hz, 2H), 2.59–2.78 (m, 2H), 3.25 (quart, *J* = 6.2 Hz, 1H), 3.65 (s, 3H), 6.76 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 7.5 Hz, 2H), 7.13–7.19 (m, 1H), 7.21–7.28 (m, 2H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 19.2 (2C), 21.5, 32.4, 34.1, 35.0, 37.3, 51.5, 55.4, 120.9, 125.8, 128.3 (2C), 128.3, 129.0 (2C), 142.1, 173.9 ppm; IR (film)  $\nu_{max}$ : 3440, 3079, 3059, 3034, 2922, 2859, 1740, 1453, 769, 699 cm<sup>-1</sup>; HRMS-ESI calcd for [C<sub>22</sub>H<sub>29</sub>NNaO<sub>2</sub>]<sup>+</sup> (M + Na<sup>+</sup>): 362.2091; found: 362.2079.

(E)-1-(2,6-Dimethylphenyl)-6-styrylpiperidin-2-one (28). To a solution of the amido ester 27 (35 mg, 0.1 mmol) in dry THF (5 mL) was added sodium hydride (60% in mineral oil, 10 mg, 0.25 mmol). The reaction mixture was refluxed under argon until the disappearance of starting material. The reaction was quenched with a saturated aqueous solution of NH<sub>4</sub>Cl, extraction of the aqueous solution with ethyl acetate  $(3 \times 5 \text{ mL})$ , drying of the organic phases over MgSO<sub>4</sub>, and filtered. Solvent was removed under reduced pressure. The residue was purified by column chromatography (eluent: EtOAc/n-hexane = 1:10) to give 6-styryl-8-lactam 28 in 80% yield (24 mg). Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.66–1.72 (m, 1H), 1.76–1.85 (m, 3H), 2.27 (s, 6H), 2.36-2.44 (m, 2H), 3.69-3.74 (m, 1H), 6.02 (dd, J = 15.8, 7.9 Hz, 1H), 6.26 (d, J = 15.8 Hz, 1H), 6.77 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 7.5 Hz, 2H), 7.15–7.22 (m, 1H), 7.24–7.28 (m, 4H) ppm;  $^{13}$ C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  19.0 (2C), 21.6, 33.9, 35.7, 59.7, 122.0, 126.3 (2C), 127.4, 128.5 (2C), 128.8 (2C), 129.6 (2C), 130.6, 131.2, 136.9, 144.1, 178.9 ppm; IR (film)  $\nu_{\text{max}}$ : 3033, 2923, 2847, 1707, 1473 cm<sup>-1</sup>; HRMS calcd for  $[C_{21}H_{23}NNaO]^+$  (M + Na<sup>+</sup>): 328.1672; found: 328.1675.

(*E*)-2-(4-Methoxystyryl)-1-methylpiperidine (4n). Following the general procedure A, the reductive cyclization reaction of amide 2d (75 mg, 0.5 mmol) with 4-methoxystyrene gave, after flash column chromatography on silica gel (eluent: MeOH/CH<sub>2</sub>Cl<sub>2</sub> = 1/10), the known 2-(4-methoxystyryl)piperidine 4n<sup>20a</sup> (82 mg, yield: 71%). Pale yellow wax. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.36–1.41 (m, 1H), 1.63–1.84 (m, 5H), 2.23 (t, *J* = 11.5 Hz, 1H), 2.35 (s, 3H), 2.70 (t, *J* = 9.4 Hz, 1H), 3.03–3.10 (m, 1H), 3.78 (s, 3H), 6.06 (dd, *J* = 15.8, 7.0 Hz, 1H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  23.5, 25.1, 32.7, 43.7, 55.4, 56.3, 68.5, 114.2 (2C), 127.4 (2C), 128.3, 129.4, 132.1, 159.4 ppm; MS (ESI) *m*/*z* 232 (M + H<sup>+</sup>, 100%).

(±)-4-(2-(1-Methylpiperidin-2-yl)-vinyl)-phenol (caulophyllumine B, 5). Following the general procedure A, the reductive cyclization reaction of amide 2d (75 mg, 0.5 mmol) with 4-vinylphe-

nol/p-TBSO-styrene/p-THPO-styrene gave, after flash column chromatography on silica gel (eluent: MeOH/CH<sub>2</sub>Cl<sub>2</sub> = 1/10), (±)-caulophyllumine B (5)<sup>20b</sup> (52 mg, yield: 48%)/(57 mg, yield: 53%)/(62 mg, yield: 57%).

(±)-Caulophyllumine B (5): Brown powder. IR (film)  $\nu_{\text{max}}$ : 3334, 3030, 2927, 2847, 2789, 1518, 1457, 1137, 1073 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.30–1.42 (m, 1H), 1.57–1.84 (m, 5H), 2.13–2.23 (m, 1H), 2.33 (s, 3H), 2.58–2.67 (m, 1H), 3.01–3.09 (m, 1H), 5.98 (dd, J = 15.8, 9.0 Hz, 1H), 6.43 (d, J = 15.8 Hz, 1H), 6.78–6.83 (m, 2H), 7.18–7.23 (m, 2H), 7.39 (br s, 1H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  23.5, 25.1, 32.6, 43.9, 56.3, 68.5, 116.2 (2C), 127.6 (2C), 127.9, 128.1, 131.9, 157.1 ppm; MS (ESI) *m/z* 218 (M + H<sup>+</sup>, 100%).

(*E*)-1-Allyl-2-styrylpiperidine (40). Following the general procedure A, the reductive cyclization reaction of amide 2e (88 mg, 0.5 mmol) with styrene gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/10), 2-styrylpiperidine 4o (60 mg, yield: 53%) and 4o' (22 mg, yield: 19%). 4o: Colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.27–1.39 (m, 1H), 1.50–1.80 (m, 5H), 2.01 (td, *J* = 11.5, 3.0 Hz, 2H), 2.73–2.81 (m, 2H), 2.97–3.04 (m, 1H), 3.45–3.53 (m, 1H), 5.09–5.16 (m, 2H), 5.82–5.94 (m, 1H), 6.20 (dd, *J* = 15.9, 8.8 Hz, 1H), 6.49 (d, *J* = 15.9 Hz, 1H), 7.18–7.24 (m, 1H), 7.27–7.33 (m, 2H), 7.34–7.38 (m, 2H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  23.9, 25.8, 33.6, 52.3, 59.0, 65.8, 117.6, 126.2 (2C), 127.3, 128.5 (2C), 130.9, 133.1, 135.2, 137.1 ppm; IR (film)  $\nu_{max}$ : 3058, 3026, 2930, 2862, 1447, 1143, 970, 909, 743, 688 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{16}H_{22}N]^+$  (M + H<sup>+</sup>): 228.1747; found: 228.1747.

(±)-δ-Coniceine hydrochloride salt (7). A 100 mL flask was charged with CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and diene 40 (114 mg, 0.5 mmol), and the solution was bubbled with a flow of argon for 2 h. Ti( $O^{i}Pr$ )<sub>4</sub> (30 µL, 0.1 mmol) was added to the mixture, then the solution was heated to 40 °C and a solution of the Grubbs' second generation catalyst (51 mg, 0.06 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added over 10 min. The mixture was stirred for 3 h at 40 °C before being cooled to room temperature and stirred for 1 h in air. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: MeOH/CH<sub>2</sub>Cl<sub>2</sub> = 1/20) and 2M HCl in MeOH (1 mL) was added to the mixture, and stirred for 0.5 h to yield compound 29 (65 mg, yield: 82%). Then a 25 mL flask was charged with MeOH (6 mL), 29 (65 mg, 0.41 mmol) and palladium on carbon (10% Pd on carbon, 65 mg). The reactor was purged with H<sub>2</sub> and the suspension was stirred under H<sub>2</sub> (1 atm) for 12 h. The reaction mixture was filtered through a plug of SiO<sub>2</sub> topped with Celite (eluent: EtOAc). Evaporation under reduced pressure gave  $(\pm)$ - $\delta$ -coniceine hydrochloride  $(7)^{13a}$  (61 mg, yield: 92%). White solid, mp: 175–176 °C; IR (film)  $\nu_{\text{max}}$ : 3396, 2945, 1644, 1549 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.73–2.44 (m, 10H), 2.54–2.96 (m, 3H), 3.53-3.88 (m, 2H), 11.33-12.34 (m, 1H, NH) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  19.7, 22.8, 22.9, 27.6, 28.5, 52.2, 52.6, 67.3 ppm; MS (ESI) m/z 126 (M + H<sup>+</sup>, 100%).

**8-Benzylideneoctahydroindolizine (3e).** Following the general procedure A, the reductive cyclization reaction of amide **1f** (133 mg, 0.5 mmol) gave, after flash column chromatography

on silica gel (eluent: MeOH/CH<sub>2</sub>Cl<sub>2</sub> = 1/50), indolizidine **3e** (83 mg, yield: 78%). Colorless oil; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.66–2.07 (m, 8H), 2.25–2.42 (m, 2H), 2.61–2.70 (m, 1H), 2.88–2.95 (m, 1H), 3.18–3.26 (m, 2H), 6.39 (br s, 1H), 7.19–7.23 (m, 3H), 7.29–7.34 (m, 2H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  20.3, 26.0, 26.3, 27.1, 52.8, 54.8, 67.8, 122.6, 126.3, 128.1 (2C), 129.0 (2C), 137.6, 139.1 ppm; IR (film)  $\nu_{max}$ : 3048, 3029, 2924, 2776, 1356, 1162, 701 cm<sup>-1</sup>. HRMS-ESI calcd for  $[C_{15}H_{20}N]^+$  (M + H<sup>+</sup>): 214.1590; found: 214.1594.

**1-Benzylideneoctahydro-1***H***-quinolizine** (**4p**). Following the general procedure A, the reductive cyclization reaction of amide **2f** (140 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/1), quinolizidine **4p** (92 mg, yield: 81%). Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.35–1.50 (m, 1H), 1.66–2.04 (m, 8H), 2.30–2.50 (m, 2H), 2.65–2.80 (m, 1H), 2.86–2.96 (m, 1H), 3.05–3.16 (m, 2H), 6.48 (br s, 1H), 7.15–7.25 (m, 3H), 7.28–7.35 (m, 2H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 21.6, 22.8, 23.6, 26.6, 31.9, 44.7, 47.0, 67.6, 127.2, 128.3, 128.4 (2C), 128.8 (2C), 135.9, 137.0 ppm; IR (film)  $\nu_{max}$ : 3055, 3016, 2927, 2856, 1450, 1274, 704 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{16}H_{22}N]^+$  (M + H<sup>+</sup>): 228.1747; found: 228.1747.

2,6-Dimethyl-N-(5-methyl-1,6-dihydro-[1,1'-biphenyl]-3(2H)ylidene)aniline (22a). Following the general procedure B, the intramolecular reaction of amide 20a (154 mg, 0.5 mmol) with alkene gave, after flash column chromatography on silica gel (eluent: EtOAc/n-hexane = 1:10), enimine 22a (129 mg, yield: 89%) as a 55:45 inseparable mixture of E/Z isomers. Brown oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, data of the two geometric isomers)  $\delta$  1.80 (s, 1.3H), 1.96 (s, 3.0H), 2.00 (s, 1.7H), 2.01-2.05 (m, 3.5H), 2.33-2.47 (m, 2.6H), 2.81-2.88 (m, 0.45H), 2.93-2.98 (m, 0.45H), 3.00-3.08 (m, 0.55H), 3.22-3.30 (m, 0.45H), 5.62 (s, 0.45H), 6.33 (s, 0.55H), 6.79-6.84 (m, 0.55H), 6.86-6.90 (m, 0.45H), 6.93-7.03 (m, 2H), 7.11-7.38 (m, 5H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, data of the two geometric isomers) & 17.8, 18.0, 18.1, 18.2, 24.0, 24.1, 35.0, 38.8, 39.3, 40.5, 40.5, 40.6, 117.9, 122.4, 122.5, 122.5, 126.1, 126.3, 126.5, 126.5, 126.7, 126.8, 126.8, 126.9, 127.6, 127.6, 127.7, 128.6, 128.6, 144.1, 144.1, 148.2, 148.4, 150.4, 152.3, 165.2, 166.6 ppm; IR (film)  $\nu_{\text{max}}$ : 3071, 3033, 2917, 2847, 1639, 1620, 1595, 771, 704 cm<sup>-1</sup>. HRMS-ESI calcd for  $[C_{21}H_{24}N]^+$  (M + H<sup>+</sup>): 290.1903; found: 290.1904.

**2,6-Dimethyl-***N***-(3-methylcyclopent-2-en-1-ylidene)aniline (22b).** Following the general procedure B, the intramolecular reaction of amide **20b** (119 mg, 0.5 mmol) with alkene gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1 : 20), enimine **22b** (173 mg, yield: 87%) as a 55 : 45 inseparable mixture of *E*/*Z* isomers. Brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, data of the two geometric isomers)  $\delta$  1.91–1.94 (m, 1H), 2.00–2.12 (m, 9H), 2.42–2.49 (m, 1H), 2.51–2.58 (m, 1H), 2.79–2.85 (m, 1H), 5.51–5.56 (m, 0.45H), 6.17–6.25 (m, 0.55H), 6.86 (t, *J* = 7.5 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 2H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, data of the two geometric isomers)  $\delta$  17.8, 18.0, 18.2, 18.4, 29.5, 32.4, 34.0, 34.5, 122.3, 122.4, 123.5, 126.0, 127.2, 127.5, 127.8, 129.9, 149.9, 165.0, 166.6, 177.9, 179.4 ppm; IR (film)  $\nu_{max}$ : 3062, 3014, 2953, 2930, 2866,

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1739, 1704, 1678, 1476 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{14}H_{18}N]^+$  (M + H<sup>+</sup>): 200.1434; found: 200.1438.

*N-n*-Butyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-amine (33). Following the general procedure A, the intramolecular reaction of amide 20c (123 mg, 0.5 mmol) with alkene and hydrolysis gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1 : 10), allylic amine 33 (92 mg, yield: 80%). Colorless oil; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.93 (t, *J* = 7.3 Hz, 3H), 1.33–1.41 (m, 2H), 1.45–1.56 (m, 3H), 1.65–1.74 (m, 1H), 1.88–2.00 (m, 2H), 2.34–2.48 (m, 2H), 2.73 (t, *J* = 7.3 Hz, 2H), 3.34–3.40 (m, 1H), 6.11 (br s, 1H), 7.21–7.26 (m, 1H), 7.28–7.33 (m, 2H), 7.38–7.42 (m, 2H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 14.0, 20.6, 20.8, 27.7, 29.0, 32.4, 46.6, 53.9, 125.3 (2C), 126.8, 127.0, 128.2 (2C), 138.6, 141.9 ppm; IR (film)  $\nu_{max}$ : 3305, 3055, 3033, 2924, 2853, 1447, 752, 691 cm<sup>-1</sup>. HRMS-ESI calcd for [C<sub>16</sub>H<sub>24</sub>N]<sup>+</sup> (M + H<sup>+</sup>): 230.1903; found: 230.1906.

*N*-[(*E*)-2-Benzylidenecyclohexylidene]-2,6-dimethylaniline (23). Following the general procedure B, the intramolecular reaction of amide 21 (154 mg, 0.5 mmol) with alkene gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1:20), enimine 23 (110 mg, yield: 76%). Brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.70–1.76 (m, 4H), 2.09 (s, 6H), 2.10–2.16 (m, 2H), 2.79–2.86 (m, 2H), 6.89 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 2H), 7.26–7.31 (m, 1H), 7.32–7.42 (m, 5H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 18.0, 24.7, 25.2, 29.5, 31.9, 122.6, 126.0 (2C), 127.2, 127.7 (2C), 128.1 (2C), 129.0, 129.7 (2C), 136.8, 139.2, 148.1, 171.4 ppm; IR (film)  $\nu_{max}$ : 3063, 3025, 2922, 2851, 1686, 1590, 1449, 1254, 1134, 765, 699 cm<sup>-1</sup>; HRMS-ESI calcd for  $[C_{21}H_{24}N]^+$  (M + H<sup>+</sup>): 290.1903; found: 290.1910.

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