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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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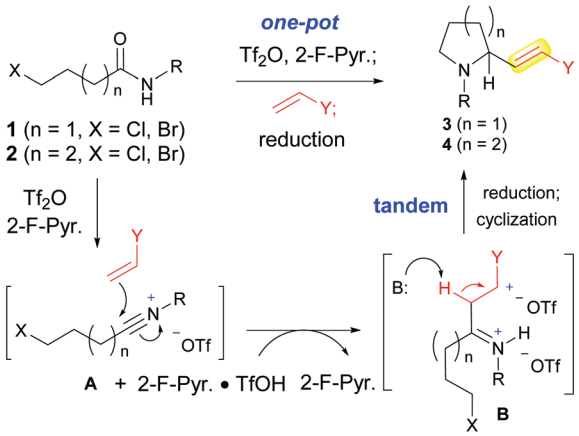
We report two efficient and versatile alkenylative cyclization methods for the one-pot synthesis of substituted pyrrolidine, piperidine, indolizidine, and quinolizidine ring systems, and enimino carbocycles, respectively. The first method consists of amide activation (Tf_2O) induced dehydrative coupling of halogenated secondary amides with alkenes and the $NaBH_4$ reduction triggered tandem cyclization reaction, while the second one features the Tf_2O-promoted novel modes of extended Bischler–Napieralski cyclization reactions of olefinic secondary amides. Taking advantage of triflic anhydride (Tf_2O) 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 δ-coniceine and 6-styrylpiperidin-2-one. When ethyl vinyl ether and enamides were used as functionalized alkenes, saturated 1,3-amino-ether/amido products $\mathbf{4A_1}$–$\mathbf{4A_3}$ were obtained in 73%–74% yields.

Introduction

Efficiency is essential to modern organic synthesis.[1] A tandem reaction[2] 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.[3] In comparison, this chemistry has been less explored for secondary amides.[4] In connection with our endeavor to develop amide-based C–C bond forming reactions,[5–7] very recently, we have disclosed a highly chemoselective, intermolecular C–H alkyliminylation and acylation of alkenes with secondary amides,[7a–c] which provides direct access to α,β-unsaturated ketimines (1-aza-1,3-dienes, enimines) and α,β-enones. As a continuation of this work, the tandem dehydrative alkenylation–reductive cyclization of secondary halogenated amides **1**/**2** to give 2-alkenylpyrrolidines **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.[8] Among them some possess a 2-alkenyl pyrrolidine[9]/piperidine[10] 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.[10a] This piperidine alkaloid has been shown to exhibit cytotoxic activity on the human cancer

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† In memory of the late Professor Zhi-Tang Huang.

‡ Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR Spectra of all products. See DOI: 10.1039/c6qo00720a

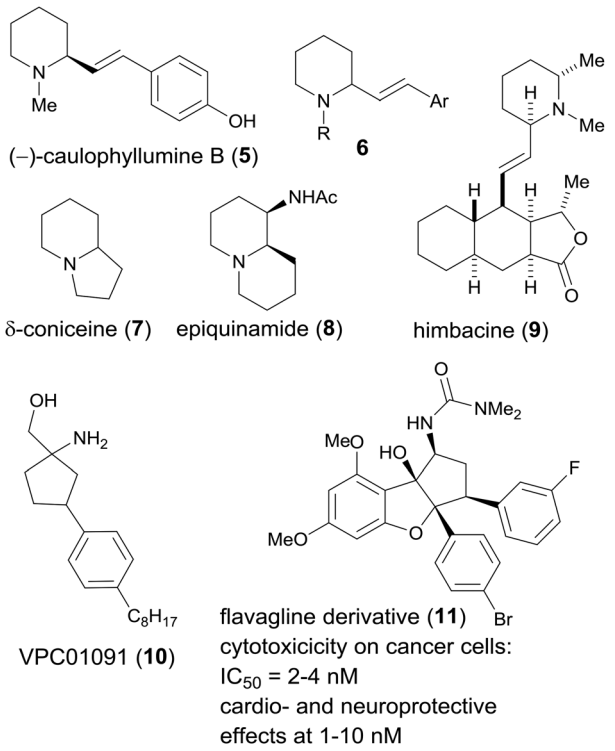
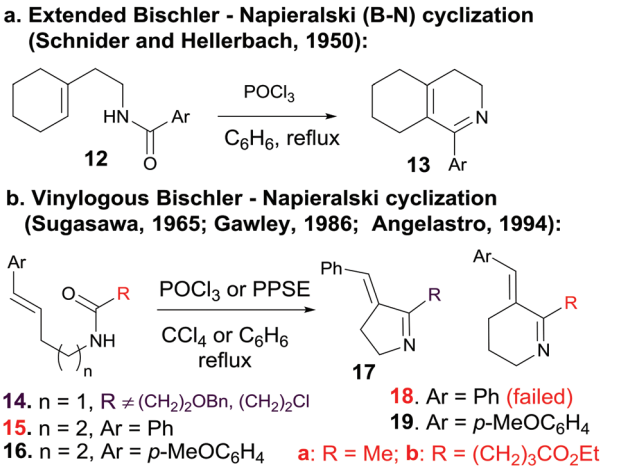


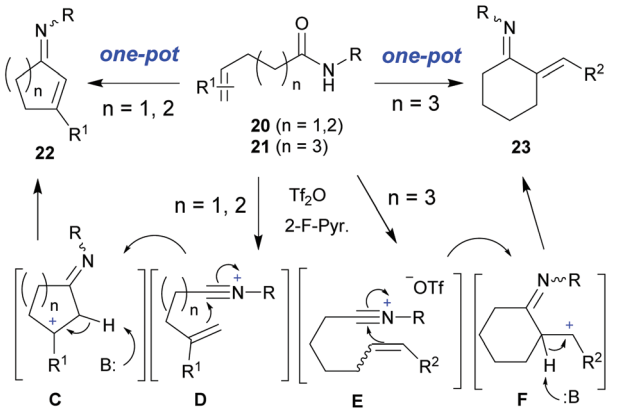
Fig. 1 Representative bioactive alkaloids and medicinal agents related to the present investigation.

cell lines of the lung, breast and ovary.[10b,c] Using caulophyllumine B (**5**) as a leading compound, several piperidine alkene-alkaloids represented by the general structure **6** have found to possess higher growth inhibition activity than the standard drug cisplatin.[10c] Alkaloid himbacine (**9**) is a potent and selective antagonist of the muscarinic M_2 receptor, which constitutes an attractive lead compound of a drug for the treatment of Alzheimer's disease.[10d] In addition to their important biological profile, 2-substituted pyrrolidines and piperidines also serve as key intermediates for the synthesis of aza-bicyclic pyrrolizidine,[9a,11] indolizidine[9a,12] and quinolizidine[12] alkaloids such as δ-coniceine[13a] (**7**) and epiquinamide,[13b,c] (**8**). The latter was isolated from the skin of Ecuadorian frog *Epipedobates tricolor*.[13b]

On the other hand, the Bischler–Napieralski (B–N) reaction[14] has been known over one century, and the P_2O_5 or $POCl_3$-mediated dehydrative cyclization of the secondary amide group onto an internal cyclohexenyl moiety (extended Bischler–Napieralski cyclization) (Scheme 2, eqn (a))[15a] or onto a styryl terminator (vinylogous Bischler–Napieralski cyclization) (Scheme 2, eqn (b))[15b] have been reported since 1950s. However, to date, this type of cyclization reactions are restricted to the synthesis of heterocycles **13**, **17**, and **19**,[15,16] 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.[16] In addition, the



Scheme 2 Known dehydrative cyclization of olefinic amides.



Scheme 3 Designed novel modes of extended Bischler–Napieralski-type 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.[16a,b] 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 [17a] is a drug candidate developed by the scientists of Abbott Laboratories for the treatment of multiple sclerosis.[17a] 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.[17b]

Investigations along these two lines (*cf.* Schemes 1 and 3) have been undertaken and the results are reported herein.

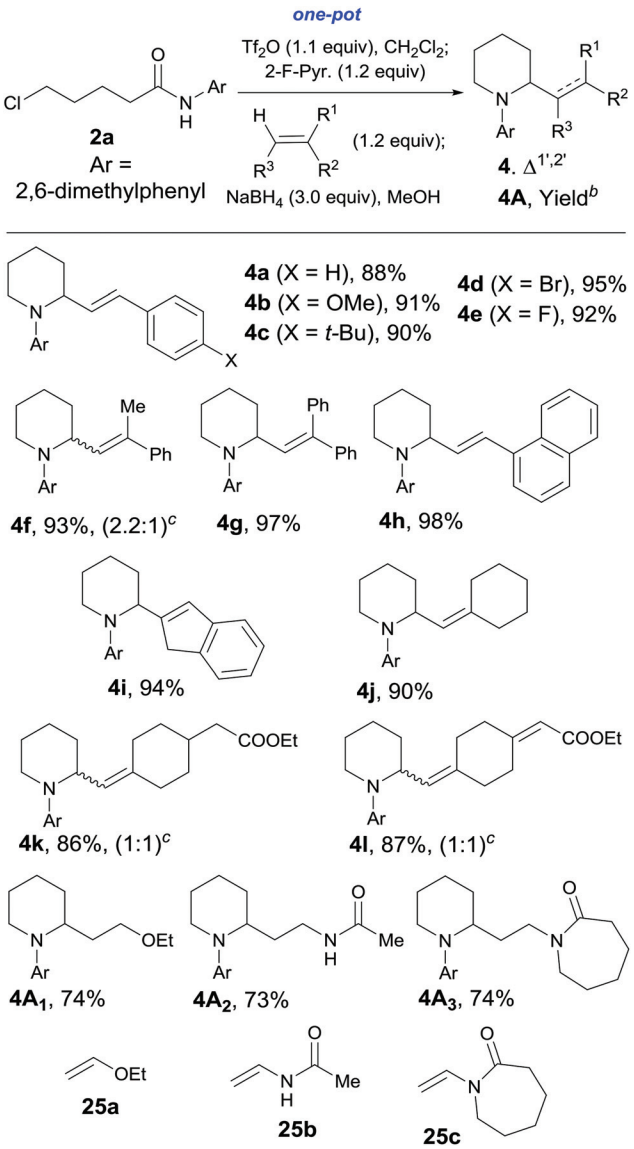
Results and discussion

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.[7a–c] Thus, chloro-amide **2a** was successively treated with trifluoromethanesulfonic anhydride (Tf_2O, 1.1 equiv.) and 2-fluoropyridine[18,6i–k] (2-F-Pyr., 1.2 equiv.) in CH_2Cl_2 (0 °C, 10 min), and styrene (1.2 equiv.) (Scheme 4). After the disappearance of the starting material as indicated by TLC monitoring, $NaBH_4$ 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 $NaBH_4$ 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 $NaBH_4$ 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 $NaBH_4$ 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 $NaBH_4$ (*cf.* Table 1, **4a**).

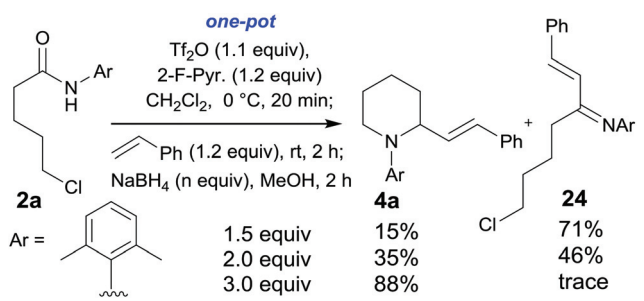
With the optimized reaction conditions in hand, the reaction was extended to a series of substituted styrenes as well as 1-vinylnaphthalene and 1*H*-indene. As can be seen from Table 1, the reactions produced the corresponding 2-substituted piperidines **4b–i** in 90–98% yields. These results implicated 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 α,β-unsaturated ester group bearing alkenes (**4k** and **4l**). Interestingly, the reaction of ethyl vinyl ether unexpectedly yielded saturated 2-ethoxyethylpiperidine $\mathbf{4A_1}$ in 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 $\mathbf{4A_2}$ and $\mathbf{4A_3}$ 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,[10a,19] 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.,

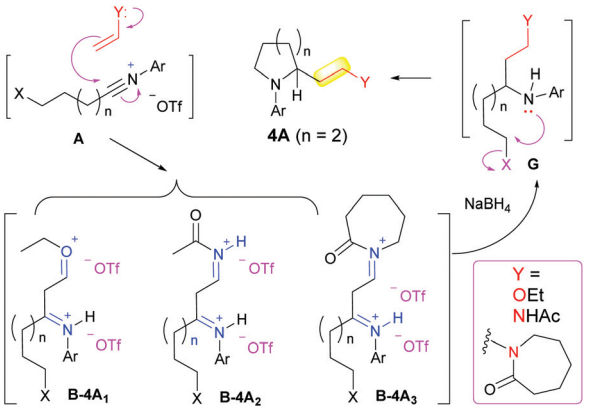
Table 1 The tandem dehydrative coupling–reductive cyclization reaction of chloro-amide **2a** with functionalized alkenes[a]



[a] Reaction conditions: amide (1.0 equiv.), 2-F-Pyr. (1.2 equiv.), CH_2Cl_2 (0.25 M), then 0 °C, Tf_2O (1.1 equiv.), 10 min; alkene (1.2 equiv.), 2 h. $NaBH_4$ (3.0 equiv.), MeOH, 3 h. [b] Isolated yield. [c] *E*/*Z* ratio determined by ^{1}H NMR.



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



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

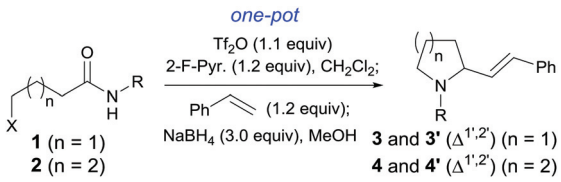
to give an oxonium–iminium intermediate **B-4A$_1$** or *N*-acyliminium–iminium intermediates **B-4A$_2$**, **B-4A$_3$**. Bis-reduction of the two electrophilic sites in **B-4A$_1$**, **B-4A$_2$**, **B-4A$_3$** followed by tandem cyclization produces the 1,3-amino ether/amides **4A**.

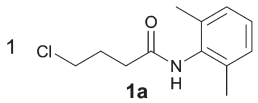
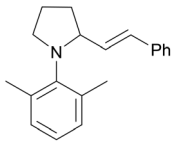
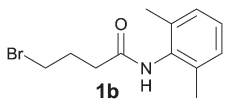
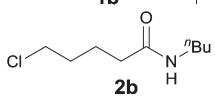
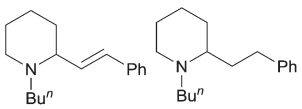
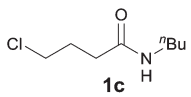
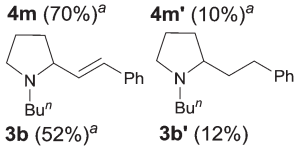
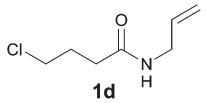
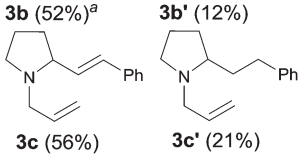
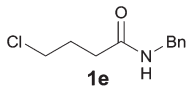
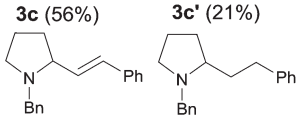
Encouraged by these results, the effects of the *N*-substituent, ω-leaving group, and chain length were examined. The reaction of 4-chloro-*N*-(2,6-dimethylphenyl)butanamide **1a**, a one-carbon lower homologue of **2a** afforded (*E*)-2-styrylpyrrolidine derivative **3a** in an unexpected lower yield (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-styryl-piperidin-2-one **28** in 80% yield.

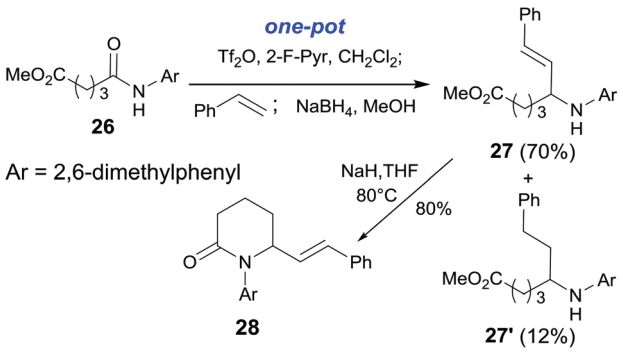
To demonstrate the synthetic value of this method, the synthesis of some simple targets were envisaged. Caulophyllumine B (**5**) and its analogues (*cf.* **6** in Fig. 1) appeared to be ideal targets for our methodology. To this end, amide **2d** and *p*-methoxystyrene was subjected to the standard tandem reaction conditions, which provided compound **4n** (Scheme 7). The caulophyllumine analogue **4n** has been shown to exhibit higher growth inhibition activity than the standard drug cisplatin.[10c] In addition, this compound has served as the immediate intermediate in a racemic synthesis of caulophyllu-

Table 2 Effects of *N*-substituent, ω-leaving group, and chain length on the tandem reaction

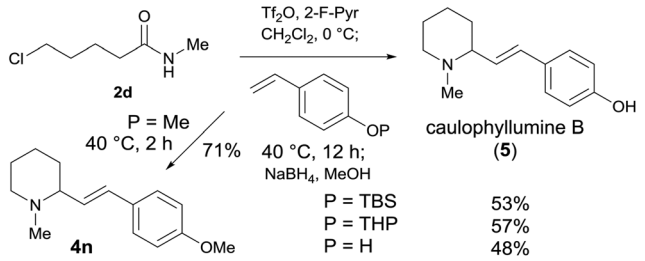


Entry	Substrate	Product
1	 1a	 **3a** (80%)[a]
2	 1b	**3a** (80%)[a]
3	 2b	 **4m** (70%)[a] **4m′** (10%)[a]
4	 1c	 **3b** (52%)[a] **3b′** (12%)
5	 1d	 **3c** (56%) **3c′** (21%)
6	 1e	 **3d** (50%) **3d′** (27%)

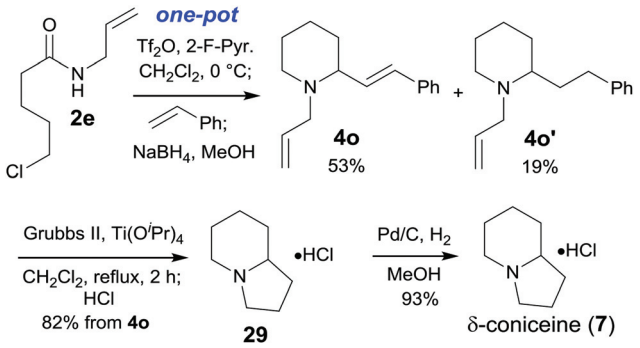
[a] Isolated yield.



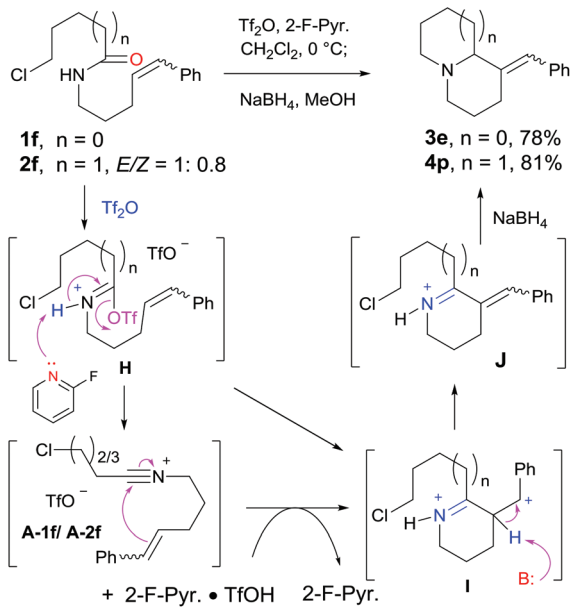
Scheme 6 The stepwise dehydrative coupling–lactamization of amido ester **26**.



Scheme 7 The one-pot racemic syntheses of caulophyllumine B (**5**) and **4n**.



Scheme 8 The synthesis of racemic δ-coniceine (**7**).



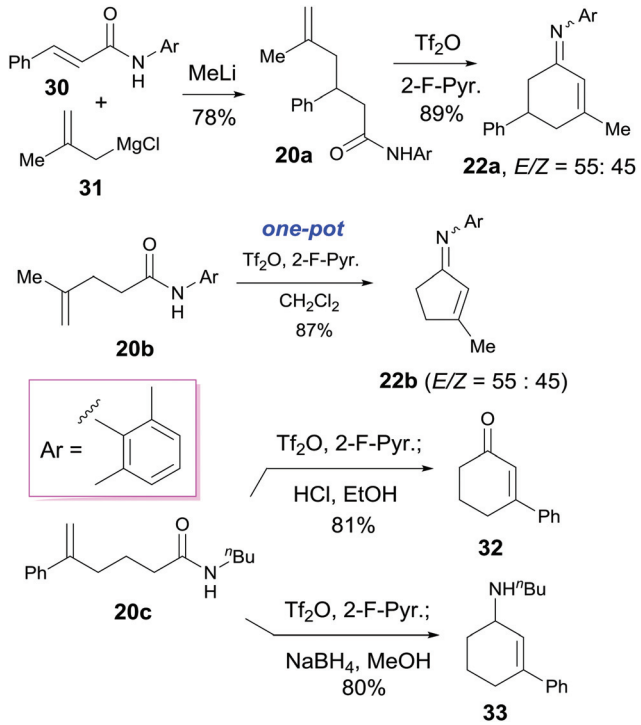
Scheme 9 One-pot construction of indolizidine and quinolizidine ring systems.

mine B (**5**).[20a] Although this approach is more efficient than the reported ones,[20] in view of developing procedure-economical synthesis,[21] 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.[22] 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.[2a]

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 $Ti(O^iPr)_4$ in CH_2Cl_2 at reflux yielded 3,5,6,7,8,8a-hexahydroindolizine (**29**) in 82% yield. Catalytic hydrogenation of the latter produced the indolizidine alkaloid δ-coniceine (**7**)[13a] in 93% yield. Hexahydroindolizine **29** can also be converted to indolizidinediol by dihydroxylation.[23]

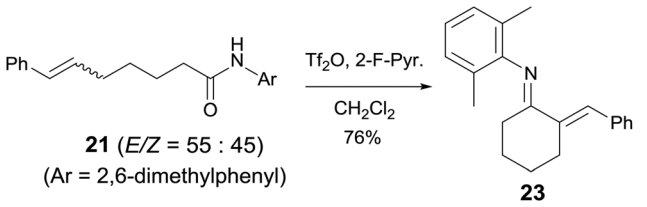
Alternatively, a more efficient direct entry to the indolizidine ring system was also envisaged. Indeed, tandem dehrdracyclization–reductive cyclization of **1f** led to **3e** in 78% yield (Scheme 9). In view of the synthesis of 1-benzylideneoctahydro-2*H*-quinolizine **4p** as a potential synthetic intermediate of quinolizidine alkaloids[12] such as epiquinamide (**8**),[13] we 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),[16] 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.[16c] 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.[16c]



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[24] and treated with Tf_2O/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-2-cyclohexenes 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,[25] a flexible method for direct synthesis of properly substituted and thus synthetically useful 1-imino-2-cyclopentenes from simple starting materials is rare.[26] 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 hydrolysis to give 3-phenylcyclohex-2-en-one **32** directly in 81% yield. Alternatively, subjecting **20c** to dehydrative cyclization and reduction with $NaBH_4$ to give 3-butylamino-phenylcyclohex-1-ene (**33**) directly in 80% yield.



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

Finally, another mode of dehydrative cyclization was investigated, for this purpose **21** was prepared and subjected to the Tf_2O/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,[27] 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[28] or formed *in situ* as reactive intermediates (*o*-quinone methide imines, aza-*o*-quinone methides).[29] 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,[30] and on the other hand, new cyclization modes of olefinic secondary amides to give two kinds of enimino carbocycles. Employing Tf_2O 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 Tf_2O-activated Vilsmeier-type intermolecular cross-coupling reaction of arenes with tertiary *N*,*N*-dimethylformamide has been reported,[31] it is expectable that the current method can be extended to the intermolecular coupling of alkenes with tertiary amides. In addition, the

enantioselective version[32] of these reactions will be explored. The results of the investigations along these lines will be reported in due course.

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. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 and 100 MHz (or at 500 and 125 MHz). Chemical shifts (δ) are reported in ppm and respectively referenced to internal standard Me_4Si or solvent signals (Me_4Si, 0 ppm for ^{1}H NMR and $CDCl_3$, 77.0 ppm for ^{13}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_2Cl_2 and 2-fluoropyridine (0.6 mmol, 1.2 equiv.) under an argon atmosphere. After being cooled to 0 °C, trifluoromethanesulfonic anhydride (Tf_2O) (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 $NaHCO_3$ aqueous solution and extracted with dichloromethane (3 × 8 mL). The combined organic layers were washed with brine, 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 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_2O) (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 α,β-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; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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; ^{13}C NMR (125 MHz, $CDCl_3$) δ 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) ν_{max}: 3023, 2930, 2847, 1470, 1447, 740 cm^{-1}; HRMS-ESI calcd for $[C_{21}H_{26}N]^+$ (M + H$^+$): 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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) ν_{max}: 3038, 3009, 2926, 2851, 1607, 1507, 1470, 1250, 1167, 1034, 765 cm^{-1}; HRMS-ESI calcd for $[C_{22}H_{28}NO]^+$ (M + H$^+$): 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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) ν_{max}: 3092, 3034, 2963, 2859, 1516, 1478, 1267, 1101, 964, 769 cm^{-1}; HRMS-ESI calcd for $[C_{25}H_{34}N]^+$ (M + H$^+$): 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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),

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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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) ν_{max}: 3038, 3017, 2921, 2851, 1586, 1486, 1466, 1067, 1002, 964, 806, 765 cm^{-1}; HRMS-ESI calcd for $[C_{21}H_{25}BrN]^+$ (M + H$^+$): 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) ν_{max}: 3042, 2930, 2859, 1607, 1511, 1470, 1229, 1159, 964, 769 cm^{-1}; HRMS-ESI calcd for $[C_{21}H_{25}FN]^+$ (M + H$^+$): 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 α-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; ^{1}H NMR (400 MHz, $CDCl_3$, 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; ^{13}C NMR (100 MHz, $CDCl_3$, data of the two geometric isomers) δ 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) ν_{max}: 3079, 3050, 3021, 2922, 2855, 1474, 1441, 1101, 765, 699 cm^{-1}; HRMS-ESI calcd for $[C_{22}H_{28}N]^+$ (M + H$^+$): 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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; ^{13}C NMR (100 MHz, $CDCl_3$) 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) ν_{max}: 3075, 3054, 3013, 2918, 2847, 1482, 1441, 1097, 761, 699 cm^{-1}; HRMS-ESI calcd for $[C_{27}H_{30}N]^+$ (M + H$^+$): 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. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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) ν_{max}: 3050, 3013, 2926, 2853, 1478, 1437, 1101, 806, 777 cm^{-1}; HRMS-ESI calcd for $[C_{25}H_{28}N]^+$ (M + H$^+$): 342.2216; found: 342.2219.

1-(2,6-Dimethylphenyl)-2-(1*H*-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-(1*H*-inden-2-yl)piperidine **4i** (142 mg, yield: 94%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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) ν_{max}: 3063, 3013, 2918, 2847, 1474, 1453, 1097, 757, 719 cm^{-1}; HRMS-ESI calcd for $[C_{22}H_{26}N]^+$ (M + H$^+$): 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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; ^{13}C NMR (100 MHz, $CDCl_3$) 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) ν_{max}: 3046, 2926, 2855, 2826, 1594, 1474, 1445, 1263, 1217, 1100, 765 cm^{-1}; HRMS-ESI calcd for $[C_{20}H_{30}N+]^+$ (M + H$^+$): 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; ^{1}H NMR (400 MHz, $CDCl_3$, data of the two geometric isomers) δ 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; ^{13}C NMR (100 MHz, $CDCl_3$, data of the two geometric isomers) δ 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) ν_{max}: 3042, 2918, 2853, 1731, 1478, 1445, 1155, 1097, 765 cm^{-1}; HRMS-ESI calcd for $[C_{24}H_{36}NO_2]^+$ (M + H$^+$): 370.2741; found: 370.2732.

Ethyl 2-{4-{[1-(2,6-dimethylphenyl)piperidin-2-yl]methylene} cyclo-hexylidene} acetate (4l). 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; ^{1}H NMR (400 MHz, $CDCl_3$, data of the two geometric isomers) δ 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; ^{13}C NMR (100 MHz, $CDCl_3$, data of the two geometric isomers) δ 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) ν_{max}: 3054, 2934, 2859, 1731, 1470, 1267, 1159, 773, 736 cm^{-1}; HRMS-ESI calcd for $[C_{24}H_{34}NO_2]^+$ (M + H$^+$): 368.2584; found: 368.2581.

1-(2,6-Dimethylphenyl)-2-(2-ethoxyethyl)piperidine (4A$_1$). 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. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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; ^{13}C NMR (100 MHz, $CDCl_3$) 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) ν_{max}: 2975, 2933, 2860, 1473, 1474, 1114, 764 cm^{-1}; HRMS-ESI calcd for $[C_{17}H_{28}NO]^+$ (M + H$^+$): 262.2165; found: 262.2167.

***N*-{2-[1-(2,6-Dimethylphenyl)piperidin-2-yl]ethyl}acetamide (4A$_2$).** 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$_2$** (100 mg, yield: 73%). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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) ν_{max}: 3282, 3075, 3013, 2922, 2859, 2793, 1653, 1553, 1445, 1288, 769 cm^{-1}; HRMS-ESI calcd for $[C_{17}H_{26}N_2NaO]^+$ (M + Na$^+$): 297.1937; found: 297.1932.

1-{2-[1-(2,6-Dimethylphenyl)piperidin-2-yl]ethyl}azepan-2-one (4A$_3$). 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$_3$** (121 mg, yield: 74%). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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) ν_{max}: 3046, 2934, 2855, 1636, 1478, 1445, 1254, 1205, 773 cm^{-1}; HRMS-ESI calcd for $[C_{21}H_{32}N_2NaO]^+$ (M + Na$^+$): 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) δ 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) ν_{max}: 3058, 3025, 2963, 2925, 2855, 1499, 1470, 1445, 1275, 1159, 959, 773, 740, 690 cm^{-1}; HRMS-ESI calcd for $[C_{20}H_{24}N+]^+$ (M + H$^+$): 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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) ν_{max}: 3083, 3058, 3029, 2959, 2930, 2851,

2784, 1445, 968, 748, 690 cm^{-1}; HRMS-ESI calcd for $[C_{17}H_{26}N]^+$ ($M + H^+$): 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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) ν_{max}: 3083, 3058, 3033, 2963, 2921, 2863, 2780, 1490, 1453, 972, 744, 690 cm^{-1}; HRMS-ESI calcd for $[C_{16}H_{24}N]^+$ ($M + H^+$): 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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) ν_{max}: 3079, 3058, 3017, 2971, 2921, 2863, 2789, 1494, 1449, 964, 914, 748, 694 cm^{-1}; HRMS-ESI calcd for $[C_{15}H_{20}N]^+$ ($M + H^+$): 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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) ν_{max}: 3087, 3058, 3025, 2925, 2855, 2789, 1656, 1494, 1453, 964, 748, 694 cm^{-1}; HRMS-ESI calcd for $[C_{19}H_{22}N+]^+$ ($M + H^+$): 264.1747; found: 264.1743.

Methyl (*E*)-5-[(2,6-dimethylphenyl)amino]-7-phenylhept-6-enoate (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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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) ν_{max}: 3382, 3059, 3025, 2926, 2851, 1740, 1267, 740, 703 cm^{-1}; HRMS-ESI calcd for $[C_{22}H_{27}NNaO_2]^+$ ($M + Na^+$): 360.1934; found: 360.1929.

Methyl 5-[(2,6-dimethylphenyl)amino]-7-phenylheptanoate (27′). **27′**: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 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; ^{13}C NMR (100 MHz, $CDCl_3$) 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) ν_{max}: 3440, 3079, 3059, 3034, 2922, 2859, 1740, 1453, 769, 699 cm^{-1}; HRMS-ESI calcd for $[C_{22}H_{29}NNaO_2]^+$ ($M + Na^+$): 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_4Cl, extraction of the aqueous solution with ethyl acetate (3 × 5 mL), drying of the organic phases over $MgSO_4$, 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-δ-lactam **28** in 80% yield (24 mg). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) ν_{max}: 3033, 2923, 2847, 1707, 1473 cm^{-1}; HRMS calcd for $[C_{21}H_{23}NNaO]^+$ ($M + Na^+$): 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_2Cl_2 = 1/10), the known 2-(4-methoxystyryl)piperidine **4n**[20a] (82 mg, yield: 71%). Pale yellow wax. ^{1}H NMR (500 MHz, $CDCl_3$) δ 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; ^{13}C NMR (125 MHz, $CDCl_3$) δ 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 ($M + H^+$, 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_2Cl_2 = 1/10), (±)-caulophyllumine B (**5**)[20b] (52 mg, yield: 48%)/(57 mg, yield: 53%)/(62 mg, yield: 57%).

(±)-Caulophyllumine B (**5**): Brown powder. IR (film) ν_{max}: 3334, 3030, 2927, 2847, 2789, 1518, 1457, 1137, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 ($M + H^+$, 100%).

(*E*)-1-Allyl-2-styrylpiperidine (4o). 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. ^1H NMR (400 MHz, $CDCl_3$) δ 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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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) ν_{max}: 3058, 3026, 2930, 2862, 1447, 1143, 970, 909, 743, 688 cm^{-1}; HRMS-ESI calcd for $[C_{16}H_{22}N]^+$ ($M + H^+$): 228.1747; found: 228.1747.

(±)-δ-Coniceine hydrochloride salt (7). A 100 mL flask was charged with CH_2Cl_2 (30 mL) and diene **4o** (114 mg, 0.5 mmol), and the solution was bubbled with a flow of argon for 2 h. $Ti(O^iPr)_4$ (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_2Cl_2 (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_2Cl_2 = 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_2 and the suspension was stirred under H_2 (1 atm) for 12 h. The reaction mixture was filtered through a plug of SiO_2 topped with Celite (eluent: EtOAc). Evaporation under reduced pressure gave (±)-δ-coniceine hydrochloride (**7**)[13a] (61 mg, yield: 92%). White solid, mp: 175–176 °C; IR (film) ν_{max}: 3396, 2945, 1644, 1549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 22.8, 22.9, 27.6, 28.5, 52.2, 52.6, 67.3 ppm; MS (ESI) m/z 126 ($M + H^+$, 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_2Cl_2 = 1/50), indolizidine **3e** (83 mg, yield: 78%). Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 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; ^{13}C NMR (125 MHz, $CDCl_3$) δ 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) ν_{max}: 3048, 3029, 2924, 2776, 1356, 1162, 701 cm^{-1}. HRMS-ESI calcd for $[C_{15}H_{20}N]^+$ ($M + H^+$): 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; ^1H NMR (400 MHz, $CDCl_3$) 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; ^{13}C NMR (100 MHz, $CDCl_3$) 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) ν_{max}: 3055, 3016, 2927, 2856, 1450, 1274, 704 cm^{-1}; HRMS-ESI calcd for $[C_{16}H_{22}N]^+$ ($M + H^+$): 228.1747; found: 228.1747.

2,6-Dimethyl-*N*-(5-methyl-1,6-dihydro-[1,1′-biphenyl]-3(2*H*)-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. ^1H NMR (500 MHz, $CDCl_3$, data of the two geometric isomers) δ 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; ^{13}C NMR (125 MHz, $CDCl_3$, data of the two geometric isomers) δ 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) ν_{max}: 3071, 3033, 2917, 2847, 1639, 1620, 1595, 771, 704 cm^{-1}. HRMS-ESI calcd for $[C_{21}H_{24}N]^+$ ($M + H^+$): 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. ^1H NMR (400 MHz, $CDCl_3$, data of the two geometric isomers) δ 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; ^{13}C NMR (100 MHz, $CDCl_3$, data of the two geometric isomers) δ 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) ν_{max}: 3062, 3014, 2953, 2930, 2866,

1739, 1704, 1678, 1476 cm^{-1}; HRMS-ESI calcd for $[C_{14}H_{18}N]^+$ ($M + H^+$): 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; ^1H NMR (500 MHz, $CDCl_3$) 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; ^{13}C NMR (125 MHz, $CDCl_3$) 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) ν_{max}: 3305, 3055, 3033, 2924, 2853, 1447, 752, 691 cm^{-1}. HRMS-ESI calcd for $[C_{16}H_{24}N]^+$ ($M + H^+$): 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. ^1H NMR (400 MHz, $CDCl_3$) 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; ^{13}C NMR (100 MHz, $CDCl_3$) 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) ν_{max}: 3063, 3025, 2922, 2851, 1686, 1590, 1449, 1254, 1134, 765, 699 cm^{-1}; HRMS-ESI calcd for $[C_{21}H_{24}N]^+$ ($M + H^+$): 290.1903; found: 290.1910.

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