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Intramolecular hydroamination of conjugated enynes

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ABSTRACT

An intramolecular hydroamination of conjugated enyne was developed using commercially available *n*-BuLi as a precatalyst. This hydroamination reaction led to products with allene and pyrrolidine functional groups. One of the enyne hydroamination products was successfully converted to natural products irniine and irnidine in three steps. The scope and mechanism of the enyne hydroamination are also discussed.

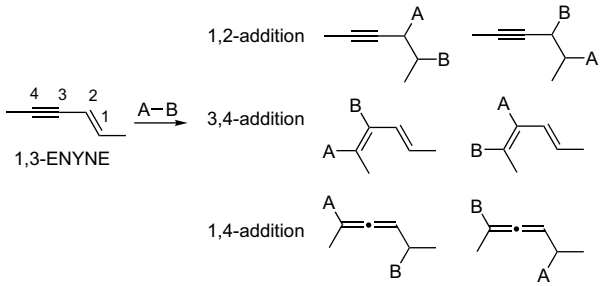
1. Introduction

Stereoselective additions to alkenes and alkynes are powerful methods for the introduction of functionality to organic compounds and have become one of the most influential fields in modern synthetic organic chemistry. We envision that conjugated 1,3-enyne may represent a new platform for the discovery of novel stereoselective addition reactions. Three possible additions may occur for conjugated 1,3-enynes: 1,2-addition to alkene, 3,4-addition to alkyne, and 1,4-addition across enyne (Scheme 1). While the regio-, diastereo-, and enantioselectivity for the addition to isolated alkenes and/or alkynes have been studied extensively, little is known about the 1,4-addition across conjugated enynes,[1] which may form a stereogenic center and a chiral allene[2] in a single step.

We first explored intramolecular hydroamination of conjugated enynes, which may produce substituted nitrogen heterocycles, an important class of pharmaceutical agents (Scheme 2). Tethering of the enyne and amine may simplify the regioselectivity issues illustrated in Scheme 1. However, both allenyl amine **2** and homopropargyl amine **3** can potentially be formed.

Impressive progress has been made recently for the transition metal catalyzed intramolecular additions of amides and sulfonamides to alkenes, allenes, and dienes.[3] The addition of unprotected amines to alkenes, arguably the most important donors and acceptors,[4] has been studied in very limited systems (Scheme 3). The intramolecular addition of unprotected amines to monosubstituted alkenes has been tested in a number of catalytic systems based on rare earth metals,[5] titanium and zirconium,[6,7] zinc,[8] alkali metals,[9–11] and late transition metals.[12] A few catalysts were developed for the intramolecular addition of unprotected amines to 1,1-disubstituted alkenes[13,14] and 1,2-disubstituted alkenes.[15] Hartwig's group recently reported a rhodium-based catalyst that promoted the intramolecular addition of unprotected amines to a variety of alkenes under mild conditions, which represents an important progress in the field of hydroamination.[16] To extend the scope of olefin substrates for the preparation of nitrogen heterocycles, highly reactive and sterically less encumbered aminoallenes have become attractive substrates for hydroamination using catalysts based on lanthanides,[17] group IV transition metals,[18] and late transition metals.[19] The conjugated aminodiene is another class of substrate that has been used to prepare nitrogen heterocycles with functionalized substituents.[20,21] The catalytic intramolecular addition of unprotected amines to conjugated vinyl arenes was also realized in several catalytic systems.[7,9,22]

Despite impressive progress on the hydroamination of carbon–carbon multiple bonds, the intramolecular hydroamination of conjugated enynes has never been explored.[23] Our group discovered the first intramolecular hydroamination of conjugated enyne **1**, which selectively affords allenyl amine **2**.[24] Herein, we report the scope, limitation, mechanistic studies, and synthetic applications of this novel hydroamination reaction.



Scheme 1. Possible regio-isomers from addition to conjugated enynes.

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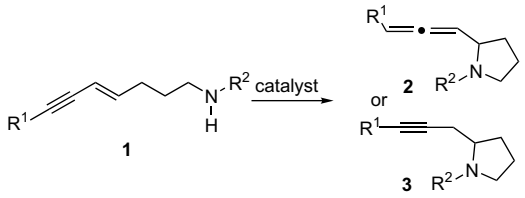
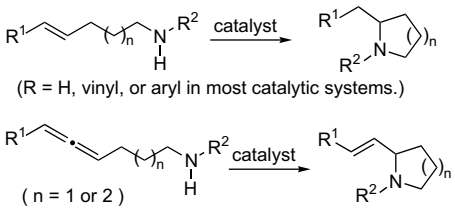


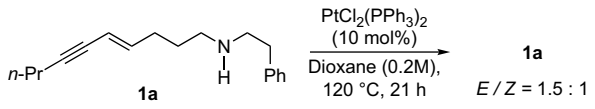
Scheme 2. Intramolecular hydroamination of enynes.



Scheme 3. Previous work on intramolecular hydroamination of alkenes.

2. Results and discussion

Aminoenyne **1a** (Scheme 4) was prepared in three steps involving addition of a terminal alkyne to acrolein, a Johnson–Claisen rearrangement, and a reductive amination according to the literature procedures.[25] Two strategies can be envisioned for the catalytic hydroamination of conjugated enynes: activation of the enyne or activation of the amine. Unfortunately, efforts toward activation of the enyne for nucleophilic attack failed to afford any hydroamination product. In most cases, only starting materials were recovered in the presence of catalysts based on gold, silver, and platinum. Interestingly, $PtCl_2(PPh_3)_2$ catalyst led to isomerization of enyne (Scheme 4).

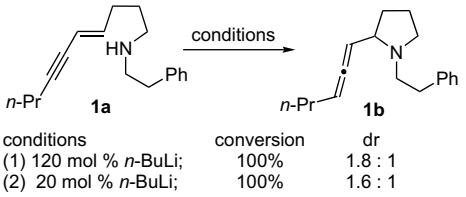


Scheme 4. Attempts for transition metal catalyzed enyne hydroamination.

We then focused on catalysts that can activate the amino group. Alkali metals have been used to catalyze the addition of amines to monosubstituted alkenes,[9–11] 1,1-disubstituted alkenes,[13] 1,3-butadienes,[21,26] and conjugated vinyl arenes[9,27] including electron-rich vinylarenes[28] via deprotonation of the amine followed by addition to the double bonds.[29] In an effort to develop a catalyst that is cost-effective and readily accessible, we decided to explore the potential of alkali metals for the intramolecular hydroamination of conjugated enynes.

When we first treated aminoenyne **1a** with 120 mol % *n*-BuLi at −78 °C in THF, aminoenyne **1a** was completely cycloisomerized to allenyl pyrrolidine **2a** with a 1.8:1 diastereomeric ratio after 1 h (Scheme 5). We then reduced the amount of *n*-BuLi to 20 mol % and increased the concentration of the aminoenyne to 0.4 M in THF. A 100% conversion was achieved at −78 °C with a 1.6:1 diastereomeric ratio after 1 h. No homopropargyl amine product was observed under these conditions.

We then investigated the scope of the hydroamination of conjugated aminoenynes using 20 mol % of *n*-BuLi as a precatalyst (Table 1). Aminoenynes with different substituents on the amino group all worked well under optimal conditions with no significant changes of the yields and diastereomeric ratios. Surprisingly, increasing the steric bulk of the alkyne improved the diastereomeric ratio from 2:1 to 5:1 (Table 1, entries 3 and 7). A phenyl substituted



Scheme 5. Base-catalyzed enyne hydroamination.

enyne also provided high yield of the hydroamination product (Table 1, entry 9). Substituted pyrrolidine **2j** was obtained as a mixture of two diastereomers, which yielded only the *cis*-1,2-disubstituted pyrrolidine upon hydrogenation (Table 1, entry 10). Efforts toward the formation of six-membered-ring heterocycles via hydroamination of enynes were not successful (Table 1, entry 11). It appeared that many olefin isomers were formed under this condition. In fact, olefin isomerization has been reported as a main competing pathway in base-catalyzed intramolecular hydroamination of monosubstituted alkenes.[10] We were surprised that *cis*-enyne **1l** did not undergo cyclization under our standard conditions (Table 1, entry 12). The *gem*-dimethyl group[30] did not facilitate the cyclization of enyne **1m** (Table 1, entry 13). The less nucleophilic aniline **1n** did not undergo cyclization (Table 1, entry 14). Addition of chelating nitrogen shuts down the hydroamination of enyne **1o** under catalytic condition (Table 1, entry 15). When 120 mol % *n*-BuLi was used, cyclization of enyne **1o** occurred with a 15% conversion even though the diastereoselectivity was improved significantly (Table 1, entry 16). Changing the chelating atom to oxygen shuts down the reaction completely (Table 1, entry 17).

Encouraged by the relative high diastereoselectivity for the cyclization of aminoenyne **1o**, we tried to improve the diastereoselectivity of other enynes by the addition of external coordinating additives (Table 2). The addition of diisopropylamine slightly changed the ratio (Table 2, entries 1–7). Diethyl ether and toluene are not suitable solvents for the hydroamination reaction. Moderate improvement of the diastereoselectivity could be achieved by the addition of ethylenediamine (Table 2, entry 14). Additives clearly can impact the diastereoselectivity of the enyne hydroamination reaction. We also tried to quench the reaction with various proton sources after the treatment of 120 mol % of *n*-BuLi. However, no obvious improvement of the diastereoselectivity was observed.

The proposed mechanism for the base-catalyzed hydroamination of enynes is shown in Scheme 6.[29] The amine N–H was first deprotonated by *n*-BuLi to form lithium amide **4**, which presumably served as the catalytic species. A 5-*exo*-*trig* cyclization could generate propargyllithium **5** and/or allenyllithium **6**,[31] which could then be protonated by aminoenyne **1** to give allenyl amine **2** and catalyst **4**. The fact that no homopropargyl amine **3** was observed suggests that allenyllithium **6** is the predominant species or the protonation of allenyllithium **6** is much faster than propargyllithium **5**. In the case of *n*-BuLi-catalyzed intramolecular hydroamination of monosubstituted alkene, it was shown that the yield of the product dropped from 49% to 12% when *n*-BuLi was increased from 30 mol % to 120 mol %.[9] This suggests that the generation of β-aminoalkyl lithium anion from lithium amide is an unfavorable step and quenching of basic β-aminoalkyl lithium by amine is required for the high yield of the final product. In contrast, the enyne hydroamination reaction worked smoothly with 120 mol % *n*-BuLi (Scheme 5). This implies that the generation of propargyllithium **5** or allenyllithium **6** from metal amide **4** is a favorable step.

To probe the mechanism of the enyne hydroamination, we quenched the reaction with CD_3OD after 1 h (Scheme 7).

Table 1
Scope of the base-catalyzed enyne hydroamination[a]

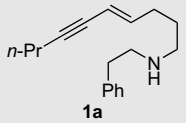
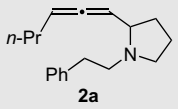
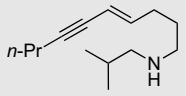
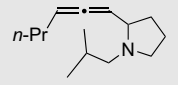
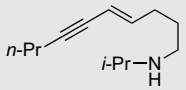
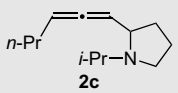
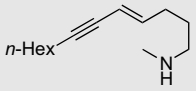
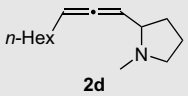
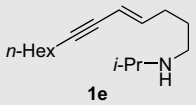
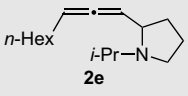
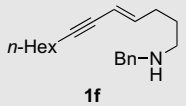
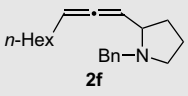
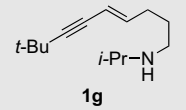
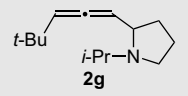
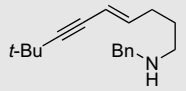
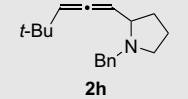
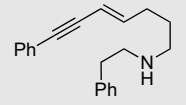
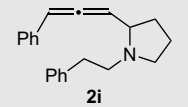
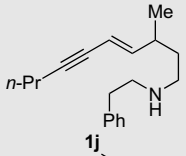
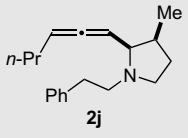
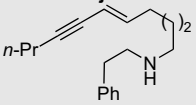
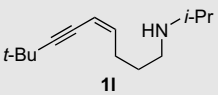
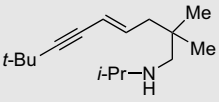
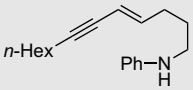
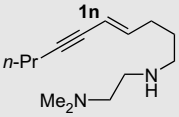
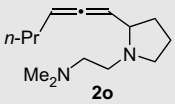
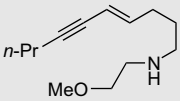
Entry	Enyne	Product	Yield (%) dr[b]
1	 **1a**	 **2a**	93 1.6:1
2	 **1b**	 **2b**	79 2.1:1
3	 **1c**	 **2c**	83 2.0:1
4	 **1d**	 **2d**	95 1.8:1
5	 **1e**	 **2e**	80 1.8:1
6	 **1f**	 **2f**	70 2.1:1
7	 **1g**	 **2g**	73 5.0:1
8	 **1h**	 **2h**	72 1.7:1
9	 **1i**	 **2i**	78 1.0:1
10	 **1j**	 **2j**	88 1.3:1
11	 **1k**	Complex mixture	
12	 **1l**	No reaction	
13	 **1m**	No reaction	

Table 1 (*continued*)

Entry	Enyne	Product	Yield (%) dr[b]
14	 **1n**	No reaction	
15		No reaction	
16[c]	 **1o**	 **2o**	15[d] 14:1
17[c]	 **1p**	No reaction	

[a] All reactions were performed at −78 °C with *n*-BuLi (20 mol %) in THF (0.4 M).
[b] Ratios were determined using NMR in CD_3COCD_3.
[c] *n*-BuLi (120 mol %), 0.1 M.
[d] Conversion estimated by ^1H NMR.

Surprisingly, we found that the deuterium content of proton H_a in product **2d** was about 85%, while proton H_b had almost no deuterium. This suggests that the allenyllithium **8** is the major lithium species. The coordination of nitrogen to lithium may shift the equilibrium from **7** to **8**. The inter-conversion of lithium species **7**, **8**, **9**, and **10** and the potential epimerization of each intermediate may complicate the diastereoselectivity issue of the enyne hydroamination reaction.[31]

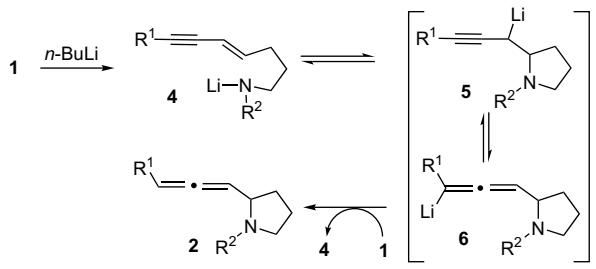
Substituted pyrrolidines exist in numerous natural products and pharmaceutical agents, and display a broad spectrum of biological activities.[32] For example, irniine **16** (Scheme 3) was isolated from the tubers of *Arisarum vulgare*, a toxic Amceae responsible for human and animal poisonings in Morocco.[33] Irniine[34] displayed significant antibacterial and antimycotic activity,[35] and a strong binding affinity for DNA.[36] From the same natural source, derivatives of irniine such as irnidine **17** have also been isolated.[37]

We envisioned that an alkyne-zipper reaction[38] could convert the allene functional group next to the pyrrolidine ring in **2a**–**j** to a terminal alkyne, which can then be further transformed to a desired functionality. Indeed, treatment of hydroamination product **2d** with excess potassium hydride in a solution of 1,3-

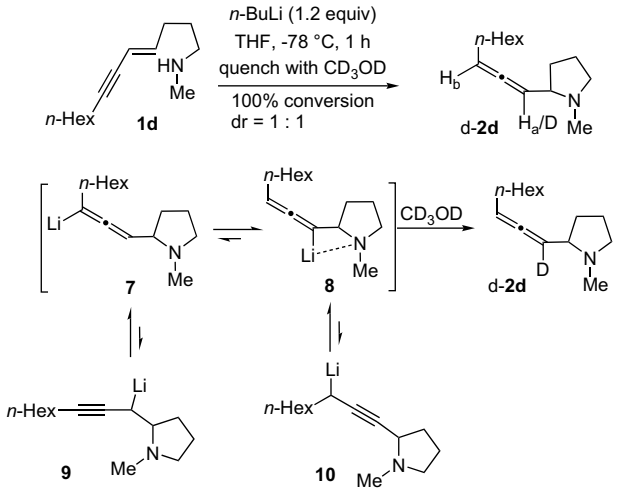
Table 2
Hydroamination of enyne **1a**[a]

Entry	*n*-BuLi (equiv)	Amine/equiv	Solvent	*T* (°C)	Time (h)	Conversion of **1a** to **2a** (%)	dr
1	1.0	*i*-Pr_2NH/8.0	THF	−78	1	100	1:1
2	1.0	*i*-Pr_2NH/4.0	THF	−78	1	100	1:1.1
3	1.0	*i*-Pr_2NH/1.0	THF	−78	1	100	1:1.5
4	1.0	*i*-Pr_2NH/1.0	Et_2O	−78	1	0	—
5	1.0	*i*-Pr_2NH/1.0	Et_2O	−78 to 0	1	22	1:2.2
6	1.0	*i*-Pr_2NH/1.0	PhMe	−78	1	33	1:1.1
7	0.5	*i*-Pr_2NH/4.0	THF	−78	1	100	1:1.1
8	1.0	Et_3N/1.0	THF	−78	1	27	1:1.4
9	1.0	TMEDA/1.0	THF	−78	1	56	1:1.7
10	0.5	TMEDA/0.5	THF	−78	1	100	1:2.2
11	0.5	TMEDA/1.0	THF	−78	1	100	1:1.8
12	1.0	TMP/1.0	THF	−78	1	100	1:2.3
13	1.0	$H_2N(CH_2)_3NH_2$/1.0	THF	−78	1	50	1:1.5
14	*1.0*	*$H_2N(CH_2)_2NH_2$/1.0*	*THF*	*−78*	*1*	*100*	*1:4.5*
15	1.0	$H_2N(CH_2)_2NH_2$/0.5	THF	−78	1	100	1:1.9
16	1.0	$H_2N(CH_2)_2NH_2$/2.0	THF	−78	1	60	1:2.8
17	0.5	$H_2N(CH_2)_2NH_2$/0.5	THF	−78	1	100	1:1.4

[a] Reaction concentration was 0.1 M, THF was dry from the column, and quenched by MeOH (0.1 mL) at −78 °C. TMEDA=tetramethylethylenediamine, TMP=tetramethylpiperidine.

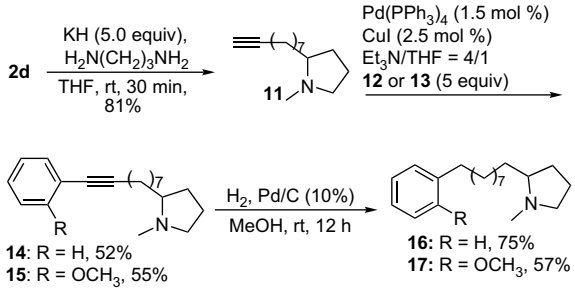


Scheme 6. A proposed mechanism for the base-catalyzed enyne hydroamination.



Scheme 7. Deuterium labeling of the enyne hydroamination product.

diaminopropane completely isomerized allene **2d** to terminal alkyne **11** shown in Scheme 8. Sonogashira cross-coupling[39] between alkyne **11** and iodobenzene **12** or 1-iodo-2-methoxybenzene **13** provided penultimate intermediates **14** and **15**. Palladium catalyzed hydrogenation of alkyne **14** and **15** then cleanly afforded natural products irniine **16** and its congener irnidine **17**.



Scheme 8. Synthesis of irniine and irnidine.

3. Conclusion

In summary, we reported the scope and limitations of a base-catalyzed intramolecular hydroamination of conjugated enynes. The reaction was catalyzed by lithium amide to yield allenyl substituted five-membered pyrrolidines in up to 95% yield. A stereogenic center and an axial chiral allene were generated in this cycloisomerization reaction and a diastereomeric ratio of up to 5:1 was achieved. Attempts to make six-membered piperidines led to significant olefin isomerization. *cis*-Enynes did not undergo cyclization under our standard conditions. The low cost of commercially available *n*-BuLi precatalyst and the mild conditions make this hydroamination feasible for large scale production of substituted pyrrolidines. The deuterium labeling study indicated that the product could be further deprotonated leading to multiple lithium species. We also showed that the diastereoselectivity could be improved by the addition of amine additives. This result encourages further development of a catalytic, diastereo-, and enantioselective hydroamination method for conjugated enynes using chiral additives. The resulting allenyl substituted pyrrolidines could be further functionalized as demonstrated in the divergent synthesis of the natural products irniine and irnidine. The sequential enyne hydroamination followed by alkyne-zipper reaction should be applicable to the synthesis of other pyrrolidines with remote functional groups, such as the family of broussonetine iminosugars.[32]

4. Experimental

4.1. General experimental procedures

All reactions in non-aqueous media were conducted under a positive pressure of dry argon within glassware that had been oven dried prior to use unless otherwise noted. Anhydrous solutions of reaction mixtures were transferred via an oven dried syringe or cannula. All solvents were dried prior to use. Thin layer chromatography was performed using precoated silica gel plates (EMD Chemical Inc. 60, F_{254}). Flash column chromatography was performed with silica gel (Sillicycle, 40–63 μm). Infrared spectra (IR) were obtained as neat oils on a Bruker Equinox 55 Spectrophotometer. ^{1}H and ^{13}C nuclear magnetic resonance spectra (NMR) were obtained on a Varian Unity-Inova 400 MHz (400 and 100 MHz, respectively) and are recorded in parts per million (δ) downfield of TMS (δ=0) in $CDCl_3$, CD_3COCD_3. The NMR spectra indicate that final products have >95% purity. High resolution mass spectra (HRMS) were performed by Analytical Instrument Center at the School of Pharmacy on an IonSpec ProMALDI Fourier transform ion cyclotron resonance (FTICR) mass spectrometer.

4.2. Experimental procedures

4.2.1. General procedure for the synthesis of aminoenynes from corresponding esters

Enyne ester (0.19 mmol) was dissolved in 2 mL of toluene and cooled to −78 °C, a solution of DIBALH (0.19 mL, 0.19 mmol, 1.0 M in hexane) was added slowly, and then the mixture was stirred at −78 °C for 2 h. The reaction was quenched by water, the combined aqueous phases were extracted with Et_2O (3×5 mL). The combined organic layers were washed by brine, dried over Na_2SO_4, filtered, and concentrated to give the crude aldehydes. To a suspension of aldehyde and $MgSO_4$ (200 mg) in 2 mL dry toluene was added amine (0.19 mmol). The reaction mixture was stirred for 12 h at room temperature. The mixture was then filtered and concentrated in vacuo to afford the imine. The imine was dissolved in methanol (3 mL), sodium borohydride was added at 0 °C, and the reaction mixture was slowly warmed up to room temperature and stirred for 2 h. The reaction was quenched by water, extracted with ethyl acetate, the organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford yellow oil, which was purified by flash chromatography (EtOAc/MeOH=10:1, R_f=0.2) to obtain the *trans*-aminoenynes.

4.2.1.1. Compound ***1a****.* (*E*)-*N*-Phenethyldec-4-en-6-yn-1-amine, 37% yield. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.98 (t, *J*=7.2 Hz, 3H), 1.50–1.59 (m, 4H), 2.09 (t, *J*=6.8 Hz, 2H), 2.26 (dt, *J*=2.0, 7.2 Hz, 2H), 2.62 (t, *J*=7.2 Hz, 2H), 2.78–2.82 (m, 2H), 2.85–2.89 (m, 2H), 5.44

(dt, J=16, 2.0 Hz, 1H), 6.02 (dt, J=15.6, 7.2 Hz, 1H), 7.18–7.31 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 21.3, 22.2, 29.1, 30.7, 36.3, 49.1, 51.0, 79.1, 88.8, 110.3, 126.1, 128.4, 128.6, 140.0, 142.4. IR (film): ν 3025, 2960, 1453, 1126, 954 cm^{-1}. HRMS (MALDI) for $C_{18}H_{26}N$ (M+1), 256.20598 (calcd), found 256.20473.

4.2.1.2. Compound ***1j***. (*E*)-3-Methyl-*N*-phenethyldec-4-en-6-yn-1-amine. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.97–1.01 (m, 6H), 1.46–1.50 (m, 2H), 1.52–1.56 (m, 2H), 2.16–2.21 (m, 1H), 2.26 (dt, J=2.0, 7.2 Hz, 2H), 2.59 (dt, J=2.8, 7.6 Hz, 2H), 2.78–2.81 (m, 2H), 2.85–2.89 (m, 2H), 5.36–5.42 (m, 1H), 5.90 (dd, J=8.0, 16.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 13.5, 20.2, 21.3, 22.2, 35.3, 36.2, 36.6, 47.6, 51.0, 79.1, 88.8, 108.6, 126.0, 128.4, 128.6, 139.9, 148.0. IR (film): ν 2960, 1453, 1124, 957, 747 cm^{-1}. HRMS (MALDI) for $C_{19}H_{28}N$ (M+1), 270.22163 (calcd), found 270.22135.

4.2.2. General procedure for the base-catalyzed intramolecular hydroamination of conjugated enynes

Enyne **1** was dissolved in dry THF (0.4 M solution), was added with *n*-butyllithium (20 mol %, 1.6 M in hexane) at −78 °C and stirred at this temperature for 1 h. The reaction was quenched by methanol and purified by flash chromatography to obtain product **2** as light yellow oil.

4.2.2.1. Compound ***2a***. 2-(Hexa-1,2-dienyl)-1-phenethylpyrrolidine. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.87–0.97 (m, 3H), 1.37–1.42 (m, 2H), 1.62–1.89 (m, 3H), 1.92–2.02 (m, 3H), 2.23–2.30 (m, 1H), 2.33–2.41 (m, 1H), 2.79–2.86 (m, 3H), 3.05–3.15 (m, 1H), 3.17–3.22 (m, 1H), 4.98–5.04 (m, 1H), 5.09–5.19 (m, 1H), 7.17–7.29 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 22.0, 22.2 (minor), 22.3 (major), 30.8 (minor), 31.0 (major), 31.5 (major), 31.8 (minor), 35.2 (major), 35.3 (minor), 53.2, 55.6 (major), 55.8 (minor), 65.2 (minor), 65.3 (major), 91.2, 93.1, 125.8, 128.2, 128.5 (major), 128.6 (minor), 140.6, 204.3 (minor), 204.6 (major). IR (film): ν 2960, 2360, 2341, 1454, 955, 748, 669 cm^{-1}. HRMS (MALDI) for $C_{18}H_{26}N$ (M+1), 256.20598 (calcd), found 256.20486.

4.2.2.2. Compound ***2j***. 2-(Hexa-1,2-dienyl)-3-methyl-1-phenethylpyrrolidine. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.86–0.94 (m, 3H), 1.01 (t, J=6.4 Hz, 3H), 1.36–1.46 (m, 3H), 1.92–2.00 (m, 3H), 2.04–2.14 (m, 1H), 2.27–2.37 (m, 3H), 2.74–2.85 (m, 2H), 3.07–3.18 (m, 1H), 3.22–3.29 (m, 1H), 4.93–4.96 (m, 1H), 5.12–5.16 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 13.86 (minor), 13.88 (major), 18.3 (major), 18.4 (minor), 22.6, 31.0 (major), 31.1 (minor), 31.3 (minor), 31.4 (major), 35.16 (minor), 35.25 (major), 39.7 (major), 39.8 (minor), 52.48 (minor), 52.51 (major), 56.4 (minor), 56.6 (major), 73.9 (minor), 74.1 (major), 91.3, 92.7 (minor), 92.8 (major), 126.11 (minor), 126.14 (major), 128.5, 128.8 (minor), 128.9 (major), 141.0, 205.7 (major), 206.0 (minor). IR (film): ν 3027, 2955, 2871, 2790, 1961, 1496, 1121, 698 cm^{-1}. HRMS (MALDI) for $C_{19}H_{28}N$ (M+1), 270.22163 (calcd), found 270.22078.

4.2.3. Hydrogenation of pyrrolidine ***2j***

Pyrrolidine **2j** (131 mg, 0.49 mmol) was dissolved in methanol (5 mL), Pd/C (10%) was added and stirred under H_2 (1 atm) at room temperature overnight. The reaction mixture was filtered through Celite and the solvent was evaporated to yield the crude product, which was purified by flash chromatography (EtOAc/PE=1:1, R_f=0.3) to obtain **3j** (84 mg, 63%).

4.2.3.1. Compound ***3j***. 2-Hexyl-3-methyl-1-phenethylpyrrolidine. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.88 (t, J=7.2 Hz, 3H), 0.99 (d, J=6.8 Hz, 3H), 1.26–1.42 (m, 10H), 1.53–1.59 (m, 1H), 1.83–1.94 (m, 2H), 1.97–2.06 (m, 2H), 2.29 (ddd, J=5.6, 7.6, 17.2 Hz, 1H), 2.36 (ddd, J=5.6, 7.0, 11.6 Hz, 1H), 2.74–2.84 (m, 2H), 2.99 (ddd, J=6.4, 7.0, 9.2 Hz, 1H), 3.19 (dt, J=2.8, 9.6 Hz, 1H), 7.17–7.22 (m, 3H), 7.25–7.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 14.4, 20.9, 22.9, 26.0, 30.1, 31.7, 32.1, 33.2, 35.5, 37.8, 52.7, 57.1, 72.8, 126.2, 128.6, 128.9, 141.0. IR (film): ν 3027, 2952, 2926, 2855, 1454, 1118, 746, 697 cm^{-1}. HRMS (EI) for $C_{19}H_{32}N$ (M+1), 274.2530 (calcd), found 274.2538.

4.2.4. Synthesis of 1-methyl-2-(non-8-ynyl)pyrrolidine ***11***

Potassium hydride (570 mg, 5 mmol, 5.0 equiv, 30% in mineral oil) was washed with dry ether three times under argon. Then, 1,3-diaminepropane (10 mL) was added at room temperature and gently heated the flask until the mixture began to foam, then stirred for 1 h. The allene **2d** (215 mg, 1 mmol) was added slowly to the mixture at 0 °C, the resulting slurry was stirred at room temperature for 30 min, then quenched reaction with NH_4Cl solution at 0 °C under argon. The reaction mixture was extracted with EtOAc (3×10 mL), dried over Na_2SO_4, filtered, evaporated, and purified by flash chromatography (EtOAc/MeOH/Et_3N=5:5:0.1, R_f=0.2) to give alkyne **7** (174 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.17–1.44 (m, 11H), 1.47–1.56 (m, 2H), 1.63–1.70 (m, 2H), 1.72–1.78 (m, 1H), 1.87–1.96 (m, 2H), 2.05–2.14 (m, 1H), 2.18 (dt, J=2.8, 7.2 Hz, 2H), 2.30 (s, 3H), 3.05 (dt, J=2.0, 9.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 21.7, 26.5, 28.4, 28.6, 29.0, 29.8, 30.7, 33.6, 40.3, 57.2, 66.3, 68.0, 84.6. IR (film): ν 2929, 2856, 1121, 987 cm^{-1}. HRMS (EI) for $C_{14}H_{26}N$ (M+1), 208.2060 (calcd), found 208.2056.

4.2.5. Synthesis of compounds ***14*** *and* ***15***

To a mixture of alkyne (**11**) (1.8 mmol), $Pd(PPh_3)_4$ (30 mg, 0.026 mmol, 1.5 mol %), and CuI (8.4 mg, 0.045 mmol, 2.5 mol %) in Et_3N/THF (4/1, 5 mL) was added iodobenzene (**12**) or 1-iodo-2-methoxybenzene (**13**) (5.0 equiv) at room temperature. After the mixture was stirred overnight, the reaction was quenched with NH_4Cl solution and then extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated, and crude product was purified by flash chromatography (EtOAc/MeOH=10:1 with 1% Et_3N, R_f=0.2) to obtain product **14** or **15**.

4.2.5.1. Compound ***14***. 1-Methyl-2-(9-phenylnon-8-ynyl)pyrrolidine, 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.26–1.35 (m, 8H), 1.42–1.48 (m, 2H), 1.50–1.64 (m, 2H), 1.69–1.77 (m, 2H), 1.81–1.87 (m, 1H), 1.94–2.03 (m, 2H), 2.18–2.22 (m, 1H), 2.27 (dd, J=9.2, 18.4 Hz, 1H), 2.38–2.41 (m, 4H), 3.25 (dt, J=2.8, 10.4 Hz, 1H), 7.26–7.28 (m, 3H), 7.38–7.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 21.6, 26.7, 28.7, 28.8, 29.1, 29.7, 30.4, 32.6, 39.8, 56.6, 66.8, 80.6, 90.4, 124.0, 127.4, 128.1, 131.5. IR (film): ν 2930, 2854, 2775, 1490, 1457, 1240 cm^{-1}. HRMS (EI) for $C_{20}H_{30}N$ (M+1), 284.2373 (calcd), found 284.2363.

4.2.5.2. Compound ***15***. 2-(9-(2-Methoxyphenyl)non-8-ynyl)-1-methyl-pyrrolidine, 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.23–1.34 (m, 7H), 1.43–1.50 (m, 3H), 1.59–1.81 (m, 5H), 1.89–1.96 (m, 1H), 1.99–2.04 (m, 1H), 2.15 (dd, J=9.2, 18.0 Hz, 1H), 2.33 (s, 3H), 2.46 (t, J=7.2 Hz, 2H), 3.11 (dt, J=2.0, 9.6 Hz, 1H), 3.87 (s, 3H), 6.84–6.89 (m, 2H), 7.21–7.25 (m, 1H), 7.36–7.38 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 21.7, 26.6, 28.75, 28.80, 29.1, 29.8, 30.6, 33.4, 40.2, 55.7, 57.1, 66.5, 76.6, 94.6, 110.5, 113.1, 120.3, 128.8, 133.6, 159.7. IR (film): ν 2928, 2855, 2773, 1457, 1260, 1025 cm^{-1}. HRMS (EI) for $C_{21}H_{30}N$ (M−1), 312.2322 (calcd), found 312.2324.

4.2.6. Synthesis of irniine ***16*** *and irnidine* ***17***

To a mixture of **14** or **15** in MeOH was added 10% Pd/C and stirred at room temperature under H_2 (1 atm) overnight. The reaction mixture was filtered and purified by flash chromatography (EtOAc/MeOH=10:1 with 1% Et_3N, R_f=0.2) to give natural product **16** or **17**.

4.2.6.1. Compound ***16***. Irniine,[33] 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.17–1.30 (m, 13H), 1.38–1.45 (m, 1H), 1.57–1.79 (m, 5H), 1.88–1.98 (m, 2H), 2.12 (ddd, J=9.2, 8.4, 9.2 Hz, 1H), 2.30 (s, 3H), 2.60 (t, J=8.4 Hz, 2H), 3.07 (ddd, J=2.0, 7.6, 7.2 Hz, 1H), 7.15–7.18 (m, 3H), 7.25–7.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 26.7, 29.3, 29.48, 29.51, 29.6, 30.0, 30.8, 31.5, 33.8, 36.0, 40.4, 57.3, 66.5, 125.5, 128.2, 128.4, 142.9. IR (film): ν 2925, 2853, 2774, 1454, 745, 697 cm^{-1}.

4.2.6.2. Compound ***17***. Irnidine,[37] 57% yield. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.19–1.31 (m, 13H), 1.42–1.51 (m, 1H), 1.53–1.60 (m, 2H), 1.65–1.73 (m, 2H), 1.76–1.82 (m, 1H), 1.90–1.96 (m, 1H), 2.02–2.06 (m, 1H), 2.17 (dd, J=9.2, 15.6 Hz, 1H), 2.34 (s, 3H), 2.59 (t, J=8.0 Hz, 2H), 3.13 (ddd, J=2.4, 10.0, 9.6 Hz, 1H), 3.81 (s, 3H), 6.83 (d, J=8.0 Hz, 1H), 6.87 (ddd, J=1.2, 9.6, 9.6 Hz, 1H), 7.12 (dd, J=1.6, 7.6 Hz, 1H), 7.16 (ddd, J=1.6, 8.0, 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 26.7, 29.49, 29.54, 29.57, 29.61, 29.8, 30.0, 30.1, 30.6, 33.4, 40.2, 55.2, 57.1, 66.6, 110.2, 120.2, 126.7, 129.7, 131.3, 157.4. IR (film): ν 2924, 2853, 2771, 1493, 1240, 1032, 749 cm^{-1}.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.045.

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