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Article

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Double Addition of Alkynyllithium Reagents to Amides/ Lactams: A Direct and Flexible Synthesis of 3-Amino-1,4-diynes Bearing an Aza-Quaternary Carbon Center

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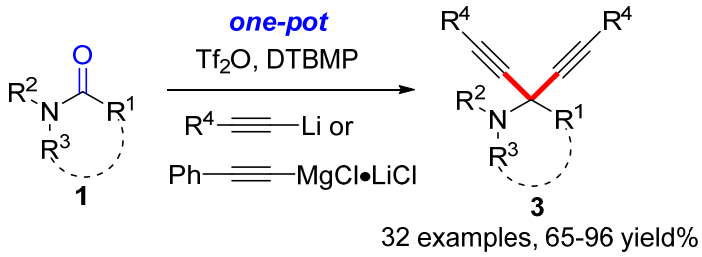


ABSTRACT: An efficient and mild protocol for the direct and flexible synthesis of 3-amino-1,4-diynes bearing an aza-quaternary carbon from tertiary amides and lactams has been established. The one-pot method consists of in situ activation of amides with trifluoromethanesulfonic anhydride follows by double addition of alkynyllithium reagents at a concentrated of 0.5 mol·L^{-1} in dichloromethane. This constitutes an extension of the method of direct reductive bisalkylation of amides that allows both employing alkynyllithium reagents as the first-addition nucleophiles, and incorporating an alkynyl group as the first-introduced group.

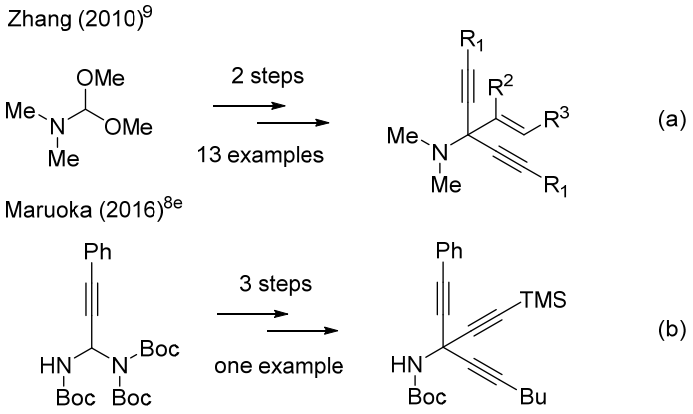
INTRODUCTION

Aza-quaternary carbon centres (α-tertiary amines)[1] and propargylic amines[2] are key structural motifs found in many natural products and medicinal agents. Although a number of methods have been developed for the preparation of propargylic amines,[2] the entrance to those containing an aza-quaternary centre is limited.[3-5] On the other hand, the rich chemistry of alkyne[6] rends 3-substituted 1,4-diynes versatile building blocks for the synthesis of 1,4-diene-containing natural products,[7a] heterocyclic libraries,[7b] medicinal agents,[7c] and materials.[7d] In recent years, several approaches to 3-amino-1,4-diynes (amino skipped diynes) have appeared.[8] However, the synthesis of 3-amino-1,4-diyne motif bearing an aza-quaternary carbon is rare, with only one fully elaborated method (Scheme 1, a),[9] and one isolated example described in a report of Maruoka (Scheme 1, b).[8e] Thus, it is highly desirable to develop flexible approaches to this class of building blocks from cheap and easily available feedstocks.

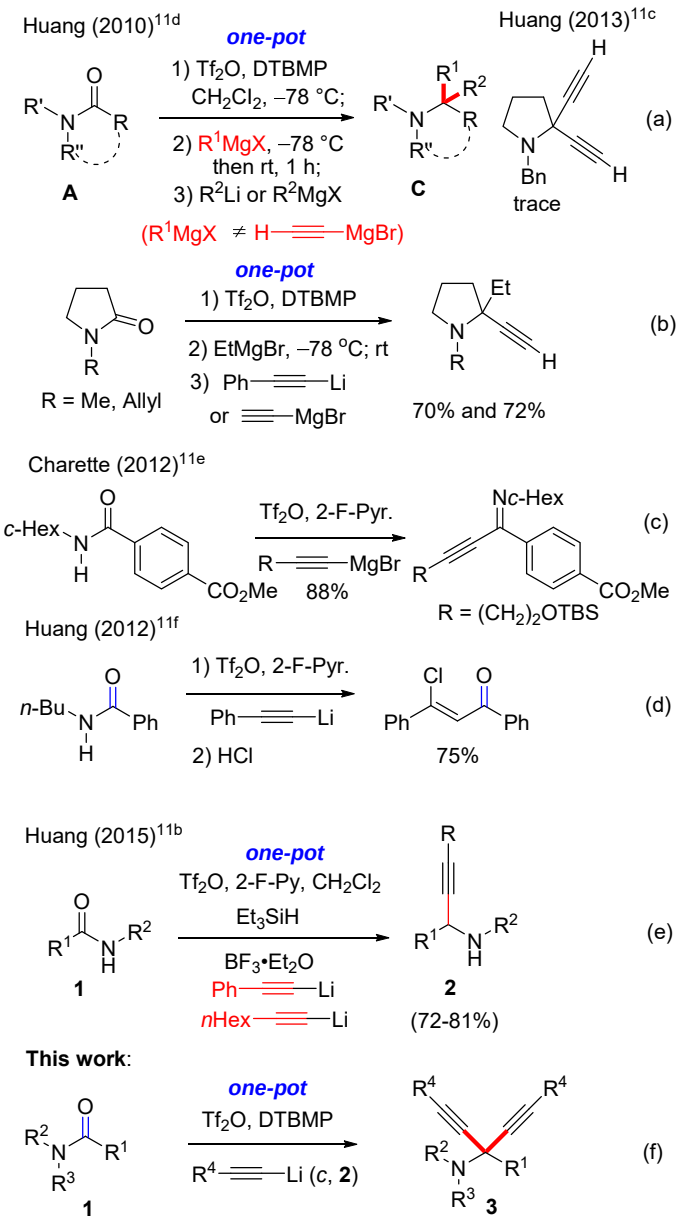
Amides are ubiquitous in nature and are products of numerous synthetic methods. Thus, the transformation of amides is essential for many total syntheses of natural products and medicinal agents. However, due to their high stability, only multistep-methods are available. In recent years, the direct transformation of amides has attracted considerable attention.[10-13] In this context, we reported in 2010 a method for the direct reductive di- and bis-alkylation of amides,[11d] which involves the in situ activation of an amide with trifluoromethanesulfonic anhydride (Tf_2O) followed by

double addition of a Grignard reagent or by successive addition of a Grignard reagent and a different organometallic reagent (RMgX or RLi)(Scheme 2, a,b). Featuring both the cleavage of C=O double bonds and formation of two C-C bonds in one pot, and the use of common organometallic reagents as nucleophiles, the method is quite efficient and versatile that has found synthetic applications.[13]

Scheme 1. Reported Methods for the Synthesis of 3-Amino-1,4-diynes Bearing Aza-quaternary Carbons (a and b)



Scheme 2. Reported Methods: Direct Reductive Di- or Bis-Alkylation of Tertiary Amides (a,b) and Reductive Mono-Alkylation of Secondary Amides (c-e) involving the Use of Alkynide as A Nucleophile; Highlight of This Work (f)



However, the method has two shortcomings. First, in performing the reductive bisalkylation, only Grignard reagents can be used as the first-addition nucleophiles, use of organolithium reagents led to complex products. Second, attempted double addition with ethynyl Grignard reagent was unsuccessful.[11c] Although, RC≡CMgBr and PhC≡CLi have been used by Charette[11e] and by our group[11c,f] as effective nucleophiles for the addition to activated secondary amides (Scheme 2, b-e), however,

only mono-addition leading to imines (or to ketones after hydrolysis) were possible. The double addition of RC≡CMgBr and PhC≡CLi to either tertiary or secondary amides are previously unknown.

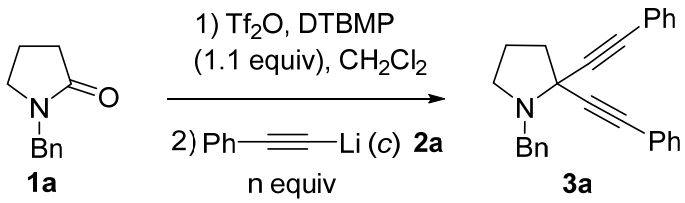
Herein we disclose that alkynyl lithium reagents could be used as the first-addition nucleophiles for the reductive dialkynylation of tertiary amides which opens an efficient access to 3-amino-1,4-diynes bearing aza-quaternary centre (Scheme 2, f). Moreover, a concentration effect was observed, which not only resulted in a significant improvement of yield for the reductive dialkynylation using alkynyllithium reagents, but also allowed using phenylethynyl Grignard reagents as nucleophiles for the same purpose.

RESULTS AND DISCUSSION

In view of developing a general method for the direct reductive dialkynylation of amides and lactams, we selected *N*-benzyl-γ-lactam (**1a**) as a model compound and (phenylethynyl)lithium as a nucleophile. At the outset of our investigation, we called for the conditions that we established previously[11d] with minor modification. In the event, in the presence of 2,6-di-*tert*-butyl-4-methylpyridine[10f] (DTBMP, 1.1 equiv), lactam **1a** was treated with trifluoromethanesulfonic anhydride (Tf_2O) at −78 °C, and the in situ generated activated species of lactam was captured by (phenylethynyl)lithium (3.0 equiv) at −78 °C, and the mixture was stirred at rt for 1 h. In this manner, the desired 3-amino-1,4-diyne (**3a**) was obtained in 65% yield (Table

1, entry 1). After many trials in order to optimize the conditions, we observed that reaction concentration has a significant impact on yield of the reaction. By increasing concentration from 0.1 mol·L^{-1} to 0.5 mol·L^{-1}, yield was increased from 65% to 95% (Table 1, entry 2). Further increase of concentration to 0.75 mol·L^{-1} resulted in a drop of yield (87%, entry 3). On the other hand, decreasing the equivalents of RLi to 2.5 resulted in a lower yield (91%, entry 4).

Table 1. Reaction Optimization-I: Concentration and Equivalents of Lithium Alkynides



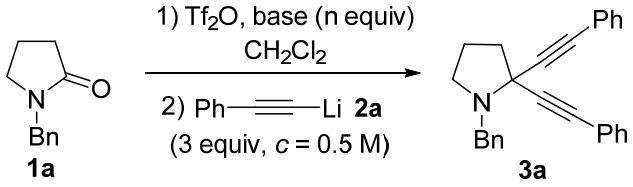
Entry	n	*c* (mol/L)	Yield (%)[a]
1	3.0	0.1	65
2	3.0	0.5	95
3	3.0	0.75	87
4	2.5	0.5	91

[a] Isolated yields.

Next, effect of base additive was examined. Noteworthy is that even in the absence of base, the desired product was still obtained in 71% yield (Table 2, entry 1). Although 2-Cl-pyridine or 2-F-pyridine (entries 2 and 3) has little effect on the yield, introduction of DTBMP as a base additive substantially increased the yield to 95% (entries 4 and 5). Moreover, use of 1.1 equiv of DTBMP is enough to ensure a

high-yielding transformation. It is worth mentioning that during the chromatographic separation of the product, the expensive base additive DTBMP could be readily and concomitantly recovered and reused.

Table 2. Reaction Optimization-II: Base Additive



Entry	Base	n	Yield/ (%)[a]
1	none	0	71
2	2-Cl-Pyr.	1.1	71
3	2-F-Pyr.	1.1	77
4	DTBMP [b]	1.1	95
5	DTBMP	2.0	95

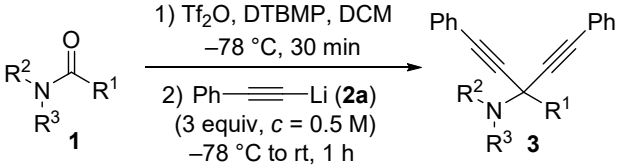
[a] Isolated yields. [b] DTBMP could be recovered during chromatographic isolation of products.

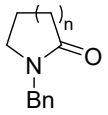
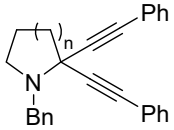
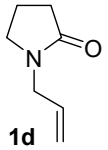
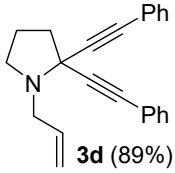
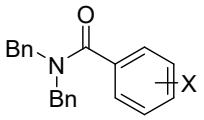
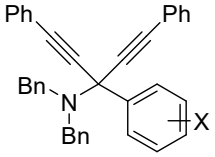
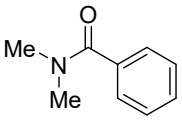
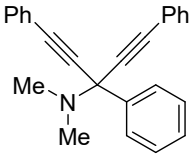
With the optimized reaction conditions in hand, reaction scope was investigated and the results are listed in Tables 3 and 4. As can be seen from Table 3, the one-pot reductive dialkynylation reaction can be extended to *N*-benzyl-δ-lactam (**1b**), *N*-benzyl-ε-lactam (**1c**), as well as *N*-allyl-γ-lactam (**1d**) (Table 3, entries 2-4), and the dialkynylation products **3b-3d** were obtained in 90%, 83%, and 89% yield, respectively. Besides lactams, benzamide (**1e,1j**) (Table 3, entry 5a,10), aromatic amides bearing either an electron-donating group (Me, OMe, **1f**, **1g**) (Table 3, entries 6 and 7) or an electron-withdrawing group (F) at *para*-position of the phenyl ring (**1h**) (Table 3, entry 8) turned out to be viable substrates, and the corresponding

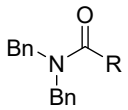
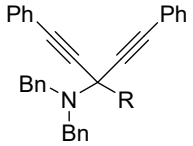
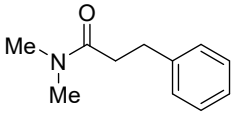
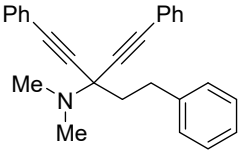
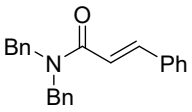
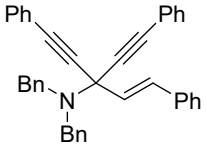
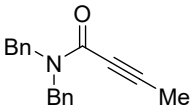
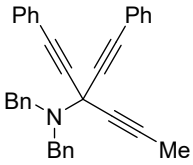
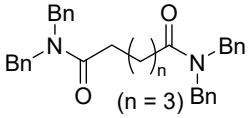
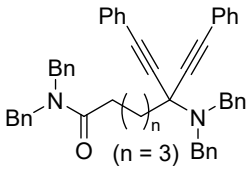
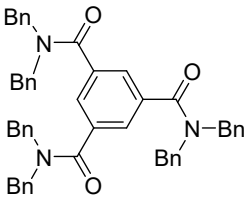
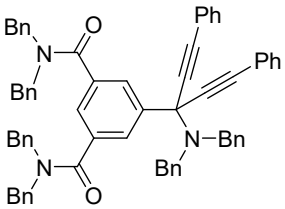
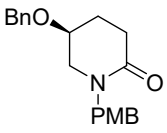
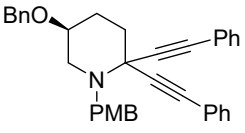
4-amino-1,4-diynes **3e-3h** were obtained in good to excellent yields. The reaction of *N*,*N*-dibenzyl-*o*-methylbenzamide (**1i**) produced the corresponding product **3i** in a moderate yield of 76% reflecting the steric effect (Table 3, entry 9). Aliphatic amides **1k, 1l**, and **1m** reacted smoothly to yield the desired **3k, 3l**, and **3m** in 91%, 70% and 90% yield, respectively (Table 3, entries 11-13a). The observed moderate yield from **1l** as compare to that from the long-chain amide **1k** may be attributed to the volatility of **3l**.

In view of synthesizing functionalized 3-amino-1,4-diynes, we proceeded to examine the chemoselective reductive dialkynylation of functionalized amides.

Table 3. Scope of Amides



Entry	Substrate	Product (Yield)[a]
		
1	**1a** (n = 1)	**3a** (n = 1, 95%)
2	**1b** (n = 2)	**3b** (n = 2, 90%)
3	**1c** (n = 3)	**3c** (n = 3, 83%)
4	 **1d**	 **3d** (89%)
		
5a	**1e** (X = H)	**3e** (X = H, 84%)
5b	1.00 g, 3.32 mmol	(81%)
6	**1f** (X = *p*-Me)	**3f** (X = *p*-Me, 82%)
7	**1g** (X = *p*-MeO)	**3g** (X = *p*-MeO, 81%)
8	**1h** (X = *p*-F)	**3h** (X = *p*-F, 81%)
9	**1i** (X = *o*-Me)	**3i** (X = *o*-Me, 76%)
10	 **1j**	 **3j** (95%)

Entry	Substrate	Product (Yield)[a]
11	 **1k** (R = *n*-$C_{11}H_{23}$)	 **3k** (R = *n*-$C_{11}H_{23}$, 91%)
12	**1l** (R = Me)	**3l** (R = Me, 70%)
13a	 **1m**	 **3m** (90%)
13b	1.00 g, 5.64 mmol	(85%)
14	 **1n**	 **3n** (73%)
15	 **1o**	 **3o** (82%)
16	 **1p**	 **3p** (65%)
17	 **1q**	 **3q** (67%; 66%[b])
18	 **1r**	 **3r** (91%)

[a] Isolated yields.

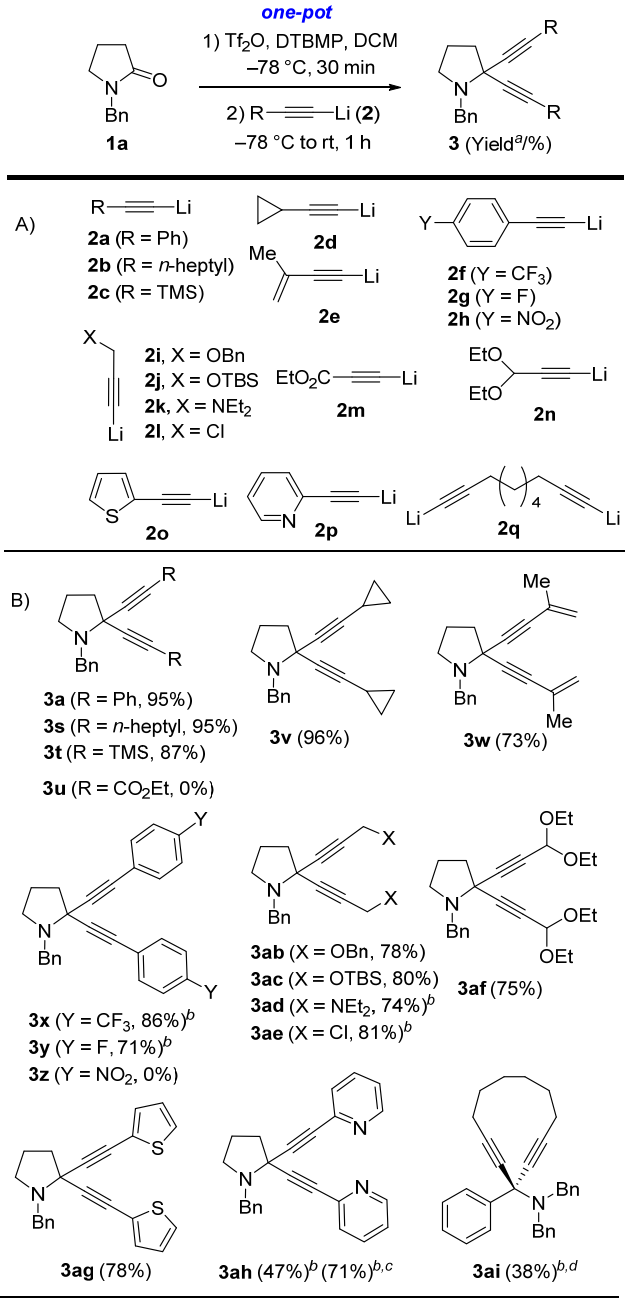
[b] Tf_2O (3.3 equiv), DTBMP (3.3 equiv), alkynyllithium (9.0 equiv).

Significantly, α,β-unsaturated amides **1n** and **1o** reacted chemoselectively at the carbonyl group to give highly unsaturated products **3n** and **3o** in 73% and 82% yield, respectively (Table 3, entries 14 and 15). It is worth noting that, subjecting of diamide **1p** and triamide **1q** to the standard conditions employing 3.0 equiv of alkynide, **3p** and **3q**, resulted from the reaction at only one carbonyl group, were obtained in 65% and 67% yield, respectively (Table 3, entries 16 and 17). In the case of triamide **1q**, even with the use of triple amount of reagents (Tf_2O/DTBMP, 3.3 equiv; alkynide, 9.0 equiv), still the dialkynylation product **3q** was obtained in 66% yield. Employing the enantio-enriched lactam (*S*)-**1r**, derived from Huang's building block,[13b] as a chiral substrate, the enantiomeric piperidine (*S*)-**3r** was isolated in excellent yield (Table 3, entry 18).

Next, we turned our attention to the scope of alkynyllithium reagents (Table 4). In addition to aromatic alkynyl lithium **2a**, aliphatic alkynyl lithium reagents such as **2b** and **2d** also reacted in excellent yields (95% and 96%). A good yield (87%) of **3t** was obtained from the reaction of lithium trimethylsilylethynide **2d**. (Cyclopropylethynyl)lithium (**2d**) served as an excellent nucleophile whereas the reaction of 3-Me-but-3-en-1-yn-1-yllithium (**2e**) afforded **3w** in a moderate yield (71%). Significantly, the addition of phenylethynyl lithium bearing a CF_3 substituent at the aromatic ring (**2f**) furnished the corresponding product **3x** in high yield, and the reaction of (*p*-fluorophenyl)ethynyl lithium (**2g**) proceeded smoothly to afford **3y** in

71% yield. It is worth mentioning that the synthesis of molecules incorporating a CF_3 or a F is a very important objective for the development of pharmaceuticals, agrochemicals, and functional materials.[14] However, attempted addition of (*p*-nitrophenyl)ethynyl lithium **2h** met with failure. Nevertheless, alkynyl lithium reagents bearing sensitive groups such as benzyloxymethyl (**2i**), [(*tert*-butyldimethylsilyl)oxy)methyl] (**2j**), (*N*,*N*-diethylamino)methyl (**2k**), and even

Table 4. Scope of Lithium Alkynides



[a] Isolated yields. [b] Yield based the recovered starting material.

[b] The solution of activated amide was added to alkynyl lithium solution.

[c] Yield based the recovered starting material.

[d] *c* (amide) = 0.09 mol·L^{-1}, *c* (alkynyl lithium) = 0.05 mol·L^{-1}.

chloromethyl (**2l**) are also effective nucleophiles to produce the corresponding 3-amino-1,4-diynes **3ab** – **3ae** in 78%, 80%, 74%, and 81% yield, respectively.

Although attempted addition of lithium reagent **2m** generated in situ from ethyl

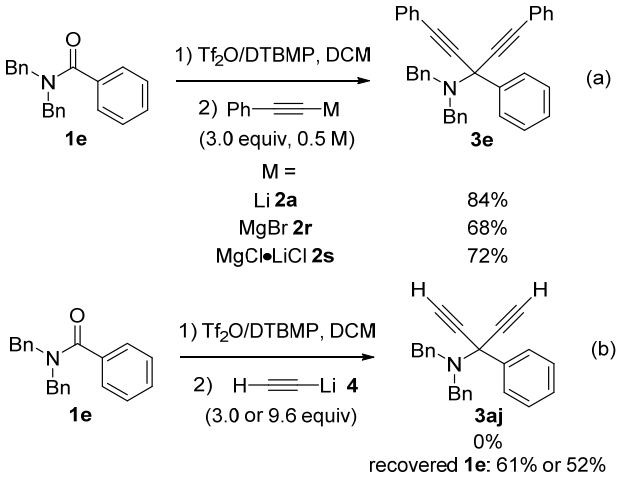
propiolate failed to the desired product **3u**, the reaction of alkynide derived from propiolaldehyde acetal (**2n**) proceeded smoothly to yield **3af** in 75% yield. In view of the widespread use of heterocycles in medicinal agents[15] and functional materials,[16] incorporation of heterocycles on the nucleophilic partner was envisioned. Interestingly, the reaction of (thiophen-2-ylethynyl)lithium (**2o**) produced **3ag** in a good yield (78%), and alkynyl lithium (**2p**) bearing a pyridinyl group could also serve as a nucleophile to produce the desired product **3ah** at a moderate yield (47%, 71% brsm). Finally, the reaction of the dilithium reagent **2q**, generated in situ from deca-1,9-diyne, afforded macrocyclic diyne **3ai** in 38% yield. Considering the fact that the formation of the second C-C bond involves the intramolecular addition of a *sp*-hybrid alkynide, linked via a C_6-chain to the first-added alkynyl group, to the same electrophilic carbon center, this annulation reaction is significant.

As a further demonstration of synthetic utility of the reaction, gram-scale synthesis was examined. The gram-scale reactions of **1e** with **2a** (Table 3, entry 5b) and **1m** with **2a** (Table 3, entry 13b) proceeded smoothly to give **3e** and **3m** in 81% and 85% yield, respectively.

Noteworthy is that although we failed to undertake the diethynylation of amides with ethynyl Grignard reagent (Scheme 2, a), under the current optimized reductive dialkynylation conditions developed for alkynyllithium reagents, the reactions of phenylethynyl Grignard reagents **2r** and **2s**[17] proceeded smoothly to yield **3e** albeit in

moderate yields (68% and 72%) (Scheme 3, a). Encouraged by these results, the reductive diethynylation of amide **1e** with ethynyllithium was further attempted, however, only some starting amide was recovered even with a large excess of ethynyllithium (Scheme 3, b).

Scheme 3. Employment of Phenylethynyl Grignard Reagents (a) and Ethynyllithium (b) for the Reductive Dialkynylation of Amides



In conclusion, we have developed a protocol for the one-pot transformation of C=O double bond of common amides/lactams into two C-C bonds with alkynyllithium reagents. Furthermore, in contrast with the failure with ethynyl Grignard reagent, under the optimized conditions, we were able to perform the reductive *gem*-alkynylation with phenylethynyl Grignard reagents **2r** and **2s**. This not only paved a direct and versatile entry to 3-amino-1,4-diynes bearing an aza-quaternary carbon, but also expanded the methodology of the direct reductive bisalkylation of amides on two aspects: the successful use of a type of organolithium reagents (alkynyllithium reagents) as the first-addition nucleophiles, and thus allowed the

introduction of unsaturated groups (alkynyl groups) as the first-incorporated nucleophiles. Further efforts to extend this methodology are underway and the results will be reported in due course.

EXPERIMENTAL SECTION

General: ^{1}H NMR and ^{13}C NMR spectra were recorded on a spectrometer at 400, 500, 600 MHz and 100, 125, 150 MHz, respectively. Chemical shifts (δ) of ^{1}H NMR and ^{13}C NMR respectively referenced to an internal standard (Me_4Si, 0 ppm for ^{1}H NMR and $CDCl_3$, 77.0 ppm for ^{13}C NMR). Melting points were determined on a Yanaco MP-500 micro melting point apparatus and were uncorrected. Optical rotations were measured with an Anton Paar MCP 500 polarimeter. Infrared spectra were measured with a Nicolet Avatar 330 FT-IR spectrometer using film KBr pellet techniques. HRMS spectra were recorded using a Bruker microFlex MALDI TOF MS/MS high-resolution mass spectrometer equipped with Fourier transform ion cyclotron resonance-Mass Spectrometry (FTICR-MS). Silica gel (300-400 mesh) was used for flash column chromatography (FC). Trifluoromethanesulfonic anhydride (Tf_2O) was distilled over phosphorous pentoxide. Dry dichloromethane were distilled over calcium hydride under argon. THF was distilled over sodium benzophenone ketyl under argon. All reactions were carried out under an argon atmosphere. Alkynes (**2a-2q**), *n*-BuLi, *i*PrMgCl·LiCl and other commercial reagents were used as received. The freshly prepared alkynyllithium reagents **2a-2q** and phenylethynyl Grignard

reagents **2r**, **2s** were titrated before use with salicylaldehyde phenylhydrazone according to the literature procedure.[18]

Synthesis of amides 1a-1r.

The known amides **1a-1c**[19a], **1d**[19b], **1e-1g**[19c], **1h**[19d], **1i**[19c], **1j**[19e], **1k**[19f], **1l**[19c], **1m**[19g] and **1n**[19h] were synthesized from acyl chlorides and amines by known procedure[19i], and spectral data of the known amides match those reported.[19]

The new amides **1o**, **1r**, and known amide **1p**, **1q** were synthesized according to the following specific procedure.

*N,N-Dibenzylbut-2-ynamide (**1o**)*

According to a literature procedure,[19j] to a cooled (0 °C) solution of 2-butynoic acid (252 mg, 3 mmol, 1.0 equiv) in DCM (7.5 mL, 0.4 M) were added dicyclohexylcarbodiimide (619 mg, 3 mmol, 1.0 equiv) and dibenzylamine (577 μL, 3 mmol, 1.0 equiv). The reaction was allowed to warm up to room temperature and stirred for 12 hours at room temperature. The solution was filtered through a short pad of silica gel, and washed with DCM. After being concentrated under reduced pressure, the resulting oil was purified by flash chromatography on silica gel eluting with EtOAc/hexane (1/5) to give amide **1o** (719 mg, yield: 91%) as a light yellow oil. IR (film): 3030, 2921, 2853, 2246, 2213, 1700, 1628, 1495, 1450, 1423, 1363, 1238, 1074, 976, 733, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.39-7.34 (m, 2H), 7.34-7.26 (m, 4H), 7.24 (d, J = 6.9 Hz, 2H), 7.19 (d, J = 6.9 Hz, 2H), 4.67 (s, 2H),

4.49 (s, 2H), 2.00 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 155.1, 136.3, 136.2, 128.8 (2C), 128.7 (2C), 128.4 (2C), 127.9, 127.7 (2C), 127.6, 89.8, 73.4, 51.3, 46.1, 4.1 ppm; HRMS (ESI) m/z calcd for $[C_{18}H_{18}NO]^+$ ($M+H^+$): 264.1383; found: 264.1386.

*N^1,N^1,N^6,N^6-Tetrabenzyladipamide (**1p**)*

Oxalyl chloride (1.27 mL, 15.0 mmol, 3.0 equiv) and a catalytic amount of DMF (0.15 mL) were added to a stirred solution of adipic acid (731 mg, 5.0 mmol, 1.0 equiv) in CH_2Cl_2 (20.0 mL, 0.25 M) at 0 °C. The mixture was stirred at room temperature for 4 h, then the reaction mixture was concentrated under reduced pressure to give a crude acyl chloride. The crude acyl chloride was dissolved in anhydrous CH_2Cl_2 (10 mL), and the solution was added dropwise to a round-bottom flask containing dibenzylamine (2.88 mL, 15.0 mmol, 3.0 equiv), Et_3N (2.08 mL, 15.0 mmol, 3.0 equiv), DMAP (122 mg, 1.0 mmol, 0.2 equiv) and CH_2Cl_2 (10 mL) at 0 °C. The reaction was slowly warmed to room temperature and stirred for 4 h. The reaction mixture was washed with 1N HCl (2 × 15 mL), and the aqueous phases were extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/hexane (1/2) to give amide **1p** (1.64 g, yield: 65%) as a white solid. Mp: 121-123 ºC; IR (film): 3029, 2922, 1645, 1605, 1495, 1452, 1422, 1362, 1301, 1215, 1141, 1080, 1029, 953,

733, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.24 (m, 12H), 7.20 (d, *J* = 6.8 Hz, 4H), 7.12 (d, *J* = 7.3Hz, 4H), 4.59 (s, 4H), 4.42 (s, 4H), 2.52-2.32 (m, 4H), 1.78-1.72 (m, 4H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 173.3 (2C), 137.5 (2C), 136.6 (2C), 128.96 (4C), 128.60 (4C), 128.3 (4C), 127.6 (2C), 127.4 (2C), 126.4 (4C), 49.9 (2C), 48.2 (2C), 33.0 (2C), 25.1 (2C) ppm; HRMS (ESI) *m/z* calcd for $[C_{34}H_{36}N_2O_2Na]^+$ ($M+Na^+$): 527.2669; found: 527.2677.

*N^1,N^1,N^3,N^3,N^5,N^5-Hexabenzylbenzene-1,3,5-tricarboxamide (**1q**)*

Oxalyl chloride (3.81 mL, 45.0 mmol, 4.5 equiv) and a catalytic amount of DMF (0.46 mL) were added to a stirred solution of 1,3,5-benzenetricarboxylic acid (2.1 g, 10 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL, 0.25 M) at 0 °C. The mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure to give a crude acyl chloride as a solid. The crude acyl chloride was added to a round-bottom flask containing dibenzylamine (8.65 mL, 45.0 mmol, 4.5 equiv), Et_3N (6.24 mL, 45.0 mmol, 4.5 equiv), DMAP (367 mg, 3.0 mmol, 0.3 equiv) and CH_2Cl_2 (80 mL) at 0 °C. The reaction was slowly warmed to room temperature and stirred for 4 h. The reaction mixture was diluted with CH_2Cl_2 (300 mL), and washed with 1N HCl (2 × 30 mL) and H_2O (3 × 80 mL). The organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/hexane (1/2) to give amide **1q** (4.64 g, yield: 62%) as a white foam solid. Mp: 58-60 ºC; IR (film):

3062, 3030, 2924, 1640, 1495, 1452, 1431, 1412, 1364, 1306, 1236, 1171, 1079, 1029, 949, 900, 734, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (s, 3H), 7.34 (br s, 9H), 7.25 (br s, 9H), 7.19 (d, *J* = 5.7 Hz, 6H), 7.00 (d, *J* = 5.5 Hz, 6H), 4.63 (s, 6H), 4.16 (s, 6H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 170.3 (3C), 137.1 (3C), 136.4 (3C), 135.7 (3C), 128.95 (6C), 128.81 (6C), 128.4 (6C), 127.78 (3C), 127.74 (3C), 126.8 (6C), 126.2 (3C), 51.4 (3C), 47.2 (3C) ppm; HRMS (ESI) *m/z* calcd for $[C_{51}H_{45}N_3O_3Na]^+$ ($M+Na^+$): 770.3359; found: 770.3366.

*(S)-5-(Benzyloxy)-1-(4-methoxybenzyl)piperidin-2-one (**1r**)*

To a solution of the known (3*S*)-benzyloxyglutarimide **5**[20] (1.02 g, 3.0 mmol, 1.0 equiv) in THF (15 mL, 0.2 M) at –30 °C was added $NaBH_4$ (227 mg, 18.0 mmol, 6.0 equiv) in one portion. The resulting suspension was stirred at –30 °C for 15 min before quenching with a saturated aqueous solution of $NaHCO_3$ (8 mL). After completion of the addition, the mixture was stirred for 1 h and then filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in anhydrous CH_2Cl_2 (30 mL) under nitrogen. To the resulting solution were added triethylsilane (4.79 mL, 30.0 mmol, 10.0 equiv) and boron trifluoride etherate (1.14 mL, 9.0 mmol, 3.0 equiv) dropwise at –78 °C. After being stirred at –78 °C for 6 h, the reaction mixture was allowed to warm to room temperature. and

stirred overnight. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/hexane (2/1) to give the corresponding lactam **1r** (693 mg, yield: 71%) as a light yellow oil. $[\alpha]_D^{25}$ +20.6 (*c* 1.0, $CHCl_3$); IR (film): 3030, 2931, 2836, 1640, 1585, 1512, 1494, 1455, 1417, 1359, 1303, 1246, 1176, 1089, 1030, 817, 738, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.22 (m, 5H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.56 (d, *J* = 14.7 Hz, 1H), 4.51-4.43 (m, 2H), 4.40 (d, *J* = 11.8 Hz, 1H), 3.77 (s, 3H), 3.32-3.24 (m, 2H), 2.79-2.53 (m, 1H), 2.41 (dt, *J* = 17.6, 5.9 Hz, 1H), 2.07-1.89 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.3, 159.0, 138.0, 129.4 (2C), 129.0, 128.4 (2C), 127.7, 127.4 (2C), 114.0 (2C), 70.6, 70.3, 55.3, 50.5, 49.3, 28.3, 25.9 ppm; HRMS (ESI) *m/z* calcd for $[C_{20}H_{23}NO_3Na]^+$ (M+ Na^+): 348.1570; found: 348.1569.

General Procedure for the Synthesis of 3-Amino-1,4-diynes 3a-3ai.

To a cooled (–78 ºC) solution of amide **1** (0.5 mmol, 1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (0.55 mmol, 1.1 equiv) in CH_2Cl_2 (3.0 mL, 0.17 M) was added dropwise trifluoromethanesulfonic anhydride (Tf_2O) (93 μL, 0.55 mmol, 1.1 equiv) via a syringe at –78 °C under Ar atmosphere. After being stirred for 30 min, a freshly prepared solution of alkynyllithium **2** (3.0 equiv) in THF (0.5 M) was added,

and the resulting mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 (4.0 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to give the corresponding tertiary amine **3**.

Lithium alkynides **2** solution were prepared from alkynes and *n*-BuLi solution according to the literature procedure. [21a]

Lithium acetylide **4** was prepared from acetylene and *n*-BuLi according to the literature procedure. [21b]

Phenylethynylmagnesium bromide **2r** was prepared from phenylacetylene and EtMgBr according to the literature procedure.[21c]

Phenylethynyl Grignard reagent **2s** was prepared from phenylacetylene and *i*PrMgCl·LiCl according to the literature procedure.[17]

*1-Benzyl-2,2-bis(phenylethynyl)pyrrolidine (**3a**)*[22]

Following general procedure, the reductive dialkynylation of lactam **1a** (88 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3a** (195 mg, yield: 95%) as a light yellow solid. Mp: 90.3-92.5 ºC; IR (film): 3060, 3030, 2957, 2823, 2221, 1600, 1573, 1498, 1454, 1443, 1364, 1305, 1268, 1190, 1166, 1115, 1071, 1028, 977, 921, 755, 690 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$): δ 7.57-7.46 (m, 4H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.36-7.29 (m, 7H), 7.28-7.21 (m, 2H), 3.95 (s, 2H), 2.75 (t, *J* = 7.3 Hz, 2H), 2.51 (t, *J* = 7.7 Hz, 2H), 2.00-1.89 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.7, 132.0 (4C), 129.1 (2C), 128.3 (8C), 126.9 (2C), 123.0, 87.9 (2C), 83.8 (2C), 58.3, 55.5, 49.9, 41.5, 21.1 ppm; HRMS (ESI) m/z calcd for $[C_{27}H_{24}N]^+$ ($M+H^+$): 362.1903; found: 362.1903.

*1-Benzyl-2,2-bis(phenylethynyl)piperidine (**3b**)*[22]

Following general procedure, the reductive dialkynylation of lactam **1b** (95 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3b** (169 mg, yield: 90%) as a light yellow solid. Mp: 81.3-83.6 ºC; IR (film): 3060, 3029, 2936, 2856, 2805, 2222, 1598, 1489, 1443, 1363, 1345, 1328, 1279, 1261, 1149, 1127, 1096, 1069, 1027, 980, 912, 755, 738, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55-7.46 (m, 4H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.37-7.27 (m, 8H), 7.23 (t, *J* = 7.3 Hz, 1H), 3.97 (s, 2H), 2.53 (t, *J* = 5.4 Hz, 2H), 2.27 (t, *J* = 5.8 Hz, 2H), 1.78-1.69 (m, 2H), 1.55-1.49 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 140.0, 131.9 (4C), 129.1 (2C), 128.3 (6C), 128.2 (2C), 126.8, 123.0 (2C), 88.4 (2C), 84.5 (2C), 58.3, 55.8, 47.3, 40.2, 25.5, 21.2 ppm; HRMS (ESI) m/z calcd for $[C_{28}H_{25}NK]^+$ ($M+K^+$): 414.1619; found: 414.1619.

*1-Benzyl-2,2-bis(phenylethynyl)azepane (**3c**)*[22]

Following general procedure, the reductive dialkynylation of lactam **1c** (102 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane

= 1/20), tertiary amine **3c** (162 mg, yield: 83%) as a light yellow solid. Mp: 85.0-86.9 ºC; IR (film): 3060, 3030, 2928, 2850, 2221, 1598, 1573, 1490, 1452, 1442, 1365, 1350, 1292, 1266, 1145, 1129, 1070, 1040, 1028, 992, 948, 755, 734, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53-7.44 (m, 6H), 7.34-7.23 (m, 9 H), 4.08 (s, 2H), 2.74-2.59 (m, 2H), 2.45-2.32 (m, 2H), 2.01-1.86 (m, 2H), 1.59-1.50 (m, 2H), 1.48-1.37 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 141.2, 132.0 (4C), 129.1 (2C), 128.3 (4C), 128.2 (2C), 128.1 (2C), 126.8, 123.2 (2C), 90.7 (2C), 82.1 (2C), 58.7, 58.2, 53.5, 47.0, 44.0, 30.5, 22.6 ppm; HRMS (ESI) *m/z* calcd for $[C_{29}H_{28}N]^+$ ($M+H^+$): 390.2216; found: 390.2216.

*1-Allyl-2,2-bis(phenylethynyl)pyrrolidine (**3d**)*

Following general procedure, the reductive dialkynylation of lactam **1d** (63 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3d** (139 mg, yield: 89%) as a light yellow oil. IR (film): 3079, 3032, 2958, 2920, 2812, 2220, 1643, 1598, 1573, 1498, 1443, 1418, 1348, 1305, 1273, 1253, 1192, 1167, 1115, 1070, 1028, 994, 917, 755, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55-7.42 (m, 4H), 7.37-7.26 (m, 6H), 6.13-5.93 (m, 1H), 5.28 (d, J = 17.1 Hz, 1H), 5.13 (d, J = 10.1 Hz, 1H), 3.46 (d, J = 6.5 Hz, 2H), 2.85 (t, J = 7.2 Hz, 2H), 2.49 (t, J = 7.8 Hz, 2H), 2.07-1.86 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 136.3 (2C), 131.9 (4C), 128.3 (2C), 128.2 (4C), 122.8, 117.1, 87.4 (2C), 83.9 (2C), 57.9, 54.3, 50.0, 41.5, 20.9 ppm; HRMS (ESI) *m/z* calcd for $[C_{23}H_{21}NNa]^+$ ($M+H^+$): 334.1566; found: 334.1574.

*N,N-Dibenzyl-1,3,5-triphenylpenta-1,4-diyn-3-amine (**3e**)*

Following general procedure, the reductive dialkynylation of amide **1e** (151 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3e** (205 mg, yield: 84%) as a light yellow solid. Mp: 119.7-121.9 ºC; IR (film): 3061, 3028, 2921, 2849, 2222, 1664, 1598, 1490, 1449, 1372, 1262, 1134, 1090, 1069, 1028, 982, 800, 755, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 7.8 Hz, 2H), 7.42-7.22 (m, 17H), 7.12 (t, J = 7.3 Hz, 4H), 7.06 (t, J = 7.3 Hz, 2H), 3.95 (s, 4H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 142.3, 140.4 (2C), 131.9 (4C), 128.8 (4C), 128.4 (2C), 128.3 (2C), 128.22, 128.2 (4C), 128.0 (2C), 127.7 (4C), 126.3 (2C), 122.7 (2C), 88.1 (2C), 86.7 (2C), 62.9, 55.5 (2C) ppm; HRMS (ESI) m/z calcd for $[C_{37}H_{30}N]^+$ ($M+H^+$): 488.2373; found: 488.2376.

*N,N-Dibenzyl-1,5-diphenyl-3-(p-tolyl)penta-1,4-diyn-3-amine (**3f**)*

Following general procedure, the reductive dialkynylation of amide **1f** (158 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3f** (206 mg, yield: 82%) as a light yellow solid. Mp: 125.8-127.9 ºC; IR (film): 3060, 3028, 2922, 2847, 2223, 1599, 1506, 1490, 1453, 1443, 1263, 1068, 1028, 983, 951, 805, 756, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 7.9 Hz, 2H), 7.37-7.31 (m, 4H), 7.31-7.23 (m, 10H), 7.18 (d, J = 7.9 Hz, 2H), 7.11 (t, J = 7.4 Hz, 4H), 7.05 (t, J = 7.4 Hz, 2H), 3.94 (s, 4H), 2.34 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 140.2 (2C), 139.4, 138.0, 131.9 (4C), 129.0 (2C), 128.9 (4C), 128.4 (2C), 128.2 (4C), 127.9 (2C), 127.7 (4C), 126.3 (2C), 122.9 (2C),

88.3 (2C), 86.5 (2C), 62.6, 55.5 (2C), 21.2 ppm; HRMS (ESI) *m*/*z* calcd for $[C_{38}H_{31}NNa]^+$ ($M+Na^+$): 524.2349; found: 524.2348.

*N,N-Dibenzyl-3-(4-methoxyphenyl)-1,5-diphenylpenta-1,4-diyn-3-amine (**3g**)*

Following general procedure, the reductive dialkynylation of amide **1g** (166 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3g** (210 mg, yield: 81%) as a light yellow oil. IR (film): 3061, 3030, 2949, 2837, 2223, 1599, 1507, 1490, 1454, 1442, 1251, 1170, 1069, 1029, 833, 805, 755, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 4H), 7.31-7.27 (m, 6H), 7.24 (d, *J* = 7.7 Hz, 4H), 7.14-7.10 (m, 4H), 7.08-7.04 (m, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 3.94 (s, 4H), 3.81 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 159.4, 140.5 (2C), 134.4, 131.9 (4C), 129.2 (2C), 128.8 (4C), 128.3 (2C), 128.1 (4C), 127.7 (4C), 126.2 (2C), 122.8 (2C), 113.5 (2C), 88.2 (2C), 86.4 (2C), 62.3, 55.4 (2C), 55.3 ppm; HRMS (ESI) m/z calcd for $[C_{38}H_{31}NNaO]^+$ ($M+Na^+$): 540.2298; found: 540.2294.

*N,N-Dibenzyl-3-(4-fluorophenyl)-1,5-diphenylpenta-1,4-diyn-3-amine (**3h**)*

Following general procedure, the reductive dialkynylation of amide **1h** (160 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3h** (205 mg, yield: 81%) as a light yellow solid. Mp: 152.5-154.9 ºC; IR (film): 3062, 3029, 2923, 2844, 2222, 1602, 1507, 1504, 1491, 1454, 1443, 1264, 1225, 1156, 1064, 1028, 983, 951, 838, 817, 756, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 8.03 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.39-7.33 (m, 4H),

7.32-7.26 (m, 6H), 7.23 (d, J = 7.4 Hz, 4H), 7.12 (t, J = 7.3 Hz, 4H), 7.07 (t, J = 7.1 Hz, 2H), 7.03 (t, J = 8.6 Hz, 2H), 3.95 (s, 4H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 162.6 (d, J_{FC} = 247.4 Hz), 140.3 (2C), 138.07 (d, J_{FC}= 2.8 Hz), 132.0 (4C), 129.87 (d, J_{FC} = 8.2 Hz, 2C), 128.9 (4C), 128.6 (2C), 128.3 (4C), 127.9 (4C), 126.5 (2C), 122.6 (2C), 115.0 (d, J_{FC} = 21.9 Hz, 2C), 87.9 (2C), 87.0 (2C), 62.4, 55.6 (2C) ppm; HRMS (ESI) *m/z* calcd for $[C_{37}H_{28}FNNa]^+$ ($M+H^+$): 528.2098; found: 528.2098.

*N,N-Dibenzyl-1,5-diphenyl-3-(o-tolyl)penta-1,4-diyn-3-amine (**3i**)*

Following general procedure, the reductive dialkynylation of amide **1i** (158 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3i** (191 mg, yield: 76%) as a light yellow solid; Mp: 131.4-133.7 ºC; IR (film): 3061, 3028, 2961, 2920, 2849, 2220, 1659, 1598, 1490, 1454, 1443, 1383, 1261, 1081, 1027, 801, 755, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 7.3 Hz, 1H), 7.48-7.42 (m, 4H), 7.34-7.30 (m, 6H), 7.23-7.15 (m, 2H), 7.12-7.00 (m, 11H), 3.96 (s, 4H), 2.87 (s, 3H) pm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 140.0, 138.3, 137.8, 132.6, 131.9 (4C), 129.4 (4C), 129.1, 128.5 (2C), 128.4, 128.3 (4C), 127.7 (4C), 126.3 (2C), 125.4 (2C), 122.9 (2C), 87.7 (2C), 87.0 (2C), 63.8, 56.1 (2C), 21.6 ppm; HRMS (ESI) m/z calcd for $[C_{38}H_{31}NNa]+$ ($M+Na^+$): 524.2349; found: 524.2346.

*N,N-Dimethyl-1,3,5-triphenylpenta-1,4-diyn-3-amine (**3j**)*

Following general procedure, the reductive dialkynylation of amide **1j** (75 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane

= 1/20), tertiary amine **3j** (159 mg, yield: 95%) as a light yellow oil. IR (film): 3059, 2950, 2860, 2822, 2779, 1597, 1489, 1470, 1443, 1267, 1216, 1173, 1060, 1007, 995, 966, 755, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.7 Hz, 2H), 7.58-7.44 (m, 4H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.35-7.18 (m, 7H), 2.42 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 141.3, 131.9 (4C), 128.5 (2C), 128.29 (4C), 128.27 (2C), 128.2, 127.7 (2C), 122.8 (2C), 86.8 (2C), 86.3 (2C), 63.0, 40.5 (2C) ppm; HRMS (ESI) m/z calcd for $[C_{25}H_{22}N]^+$ ($M+H^+$): 336.1747; found: 336.1750.

*N,N-Dibenzyl-1-phenyl-3-(phenylethynyl)tetradec-1-yn-3-amine (**3k**)*

Following general procedure, the reductive dialkynylation of amide **1k** (190 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3k** (257 mg, yield: 91%) as a light yellow oil. IR (film): 3062, 3029, 2925, 2853, 2220, 1560, 1490, 1454, 1443, 1371, 1312, 1263, 1069, 1028, 958, 755, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45-7.33 (m, 8H), 7.32-7.25 (m, 6H), 7.19 (t, *J* = 7.3 Hz, 4H), 7.12 (t, *J* = 7.3 Hz, 2H), 4.04 (s, 4H), 2.02-1.91 (m, 2H), 1.84-1.69 (m, 2H), 1.31-1.19 (m, 16H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 140.90 (2C), 131.88 (4C), 128.82 (4C), 128.20 (6C), 127.88 (4C), 126.45 (2C), 123.04 (2C), 116.23, 89.13 (2C), 84.32 (2C), 60.26, 55.79 (2C), 41.78, 31.97, 30.20, 29.63, 29.50, 29.47, 29.39, 25.25, 22.73, 14.15 ppm; HRMS (ESI) m/z calcd for $[C_{37}H_{30}N]^+$ ($M+H^+$): 488.2373; found: 488.2376.

*N,N-Dibenzyl-3-methyl-1,5-diphenylpenta-1,4-diyn-3-amine (**3l**)*

Following general procedure, the reductive dialkynylation of amide **1l** (120 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3l** (149 mg, yield: 70%) as a light yellow solid. Mp: 94.1-96.5 ºC; IR (film): 3061, 3028, 2922, 2842, 2221, 1598, 1490, 1453, 1443, 1370, 1279, 1167, 1118, 1070, 1027, 755, 691 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.41 (m, 4H), 7.38 (d, *J* = 7.5 Hz, 4H), 7.33-7.27 (m, 6H), 7.21 (t, *J* = 7.4 Hz, 4H), 7.13 (t, *J* = 7.2 Hz, 2H), 4.04 (s, 4H), 1.76 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 141.05 (2C), 131.92 (4C), 128.67 (4C), 128.31 (2C), 128.26 (4C), 127.99 (4C), 126.54 (2C), 122.89 (2C), 89.79 (2C), 83.35 (2C), 55.89 (2C), 55.67, 30.98 ppm; HRMS (ESI) m/z calcd for $[C_{32}H_{27}NNa]^+$ ($M+Na^+$): 448.2030; found: 448.2036.

*N,N-Dimethyl-3-phenethyl-1,5-diphenylpenta-1,4-diyn-3-amine (**3m**)*

Following general procedure, the reductive dialkynylation of amide **1m** (89 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3m** (80 mg, yield: 90%) as a light yellow solid. IR (film): 3025, 2955, 2860, 1598, 1489, 1469, 1453, 1443, 1306, 1217, 1157, 1091, 1070, 1040, 755, 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.48 (m, 4H), 7.35-7.26 (m, 10H), 7.22-7.18 (m, 1H), 3.15-3.03 (m, 2H), 2.54 (s, 6H), 2.38-2.28 (m, 2H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 142.0, 132.0 (4C), 128.6 (4C), 128.5 (2C), 128.4 (4C), 126.1, 122.9 (2C), 87.3 (2C), 84.8 (2C), 59.2, 42.7, 40.5 (2C), 31.7 ppm; HRMS (ESI) m/z calcd for $[C_{27}H_{26}N]^+$ ($M+H^+$): 364.2060; found: 364.2067.

*(E)-N,N-Dibenzyl-1,5-diphenyl-3-(phenylethynyl)pent-1-en-4-yn-3-amine (**3n**)*

Following general procedure, the reductive dialkynylation of amide **1n** (164 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3n** (187 mg, yield: 73%) as a light yellow oil. IR (film): 3060, 3028, 2963, 2924, 2849, 2220, 1599, 1491, 1453, 1443, 1213, 1377, 1360, 1261, 1098, 1070, 1027, 800, 755, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.7 Hz, 2H), 7.55-7.51 (m, 2H), 7.42 (d, *J* = 7.4 Hz, 4H), 7.38- 7.32 (m, 5H), 7.28-7.21 (m, 8H), 7.20-7.12 (m, 4H), 6.75 (d, *J* = 10.2 Hz, 1H), 5.09 (d, *J* = 10.2 Hz, 1H), 3.80 (d, *J* = 14.0 Hz, 2H), 3.67 (d, *J* = 14.0 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 145.9 (2C), 141.2, 139.5, 131.85 (2C), 131.78 (2C), 128.8 (4C), 128.58 (2C), 128.56, 128.39 (2C), 128.26 (4C), 128.10 (2C), 127.98 (2C), 127.3 (2C), 126.8 (2C), 122.8, 122.4, 108.9, 93.8, 87.8, 87.2, 84.6, 63.2, 54.0 (2C) ppm; HRMS (ESI) m/z calcd for $[C_{39}H_{31}NNa]^+$ ($M+Na^+$): 536.2349; found: 536.2349.

*N,N-Dibenzyl-1-phenyl-3-(phenylethynyl)hexa-1,4-diyn-3-amine (**3o**)*

Following general procedure, the reductive dialkynylation of amide **1o** (132 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3o** (184 mg, yield: 82%) as a yellow oil. IR (film): 3083, 3061, 3028, 2919, 2850, 2230, 1707, 1676, 1599, 1490, 1454, 1443, 1375, 1261, 1188, 1137, 1091, 1061, 1028, 966, 755, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.39-7.34 (m, 8H), 7.31-7.26 (m, 6H), 7.17 (t, *J* = 7.3 Hz, 4H), 7.10 (t, *J* = 7.1 Hz, 2H), 4.10 (s, 4H), 1.84 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 140.1 (2C), 132.0 (2C), 129.0

(2C), 128.5 (2C), 128.1 (4C), 127.8 (4C), 126.5 (2C), 122.3 (2C), 86.5 (2C), 83.2 (2C), 80.6, 76.4, 55.4 (2C), 51.8, 3.87 ppm; HRMS (ESI) m/z calcd for $[C_{34}H_{28}N]^+$ ($M+H^+$): 450.2216; found: 450.2228.

*N,N-Dibenzyl-6-(dibenzylamino)-8-phenyl-6-(phenylethynyl)oct-7-ynamide (**3p**)*

Following general procedure, the reductive dialkynylation of amide **1p** (121 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3p** (225 mg, yield: 65%) as a yellow oil. IR (film): 3061, 3028, 2925, 2848, 2225, 1648, 1599, 1491, 1452, 1452, 1442, 1421, 1362, 1206, 1099, 1976, 1028, 953, 756, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44-7.24 (m, 20H), 7.21-7.03 (m, 10H), 4.56 (s, 2H), 4.36 (s, 2H), 4.02 (s, 4H), 2.32 (t, J = 7.7 Hz, 2H), 1.99-1.91 (m, 2H), 1.85-1.73 (m, 2H), 1.66-1.59 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): 173.5, 140.8 (2C), 137.6, 136.7, 131.9 (4C), 129.0 (2C), 128.8 (4C), 128.6 (2C), 128.3 (4C), 128.2 (4C), 127.9 (4C), 127.6, 127.3, 126.5 (2C), 126.45 (2C), 122.8 (2C); 88.8 (2C), 84.4 (2C), 60.2, 55.8 (2C), 49.9, 48.0, 41.5, 33.2, 25.3, 25.2 ppm; HRMS (ESI) *m/z* calcd for $[C_{50}H_{46}N_2NaO]^+$ ($M+Na^+$): 713.3502; found: 713.3494.

*N^1,N^1,N^3,N^3-Tetrabenzyl-5-(3-(dibenzylamino)-1,5-diphenylpenta-1,4-diyn-3-yl)isopht halamide (**3q**)*

Following general procedure except using three times of the following reagents [Tf_2O (3.3 equiv), DTBMP (3.3 equiv) and alkynyllithium (9.0 equiv)], the reductive

dialkynylation of lactam **1q** (374.0 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3q** (313 mg, yield: 66%) as a yellow oil. IR (film): 3062, 3029, 2924, 2850, 2222, 1640, 1601, 1494, 1452, 1416, 1364, 1264, 1233, 1189, 1078, 1029, 950, 898, 803, 756, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 1.5 Hz, 2H), 7.58 (t, J = 1.5 Hz, 1H), 7.39-7.25 (m, 19H), 7.21-7.10 (m, 11H), 7.08-6.93 (m, 10H), 4.67 (s, 4H), 4.24 (s, 4H), 3.86 (s, 4H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): 171.0 (2C), 143.4, 139.7 (2C), 136.7 (2C), 136.5 (2C), 136.0 (2C), 131.9 (4C), 128.8 (brs, 8C), 128.7 (4C), 128.6 (2C), 128.3 (brs, 4C), 128.2 (4C), 127.8 (brs, 4C), 127.7 (4C), 127.6 (2C), 127.0 (brs, 4C), 126.5 (2C), 125.3 (2C), 122.2, 87.5 (2C), 86.9 (2C), 60.4, 55.4 (2C), 51.7 (2C), 47.0 (2C) ppm; HRMS (ESI) *m*/*z* calcd for $[C_{67}H_{55}N_3NaO_2]^+$ ($M+Na^+$): 956.4186; found: 956.4188.

*(S)-5-Benzyloxy)-1-(4-methoxybenzyl)-2,2-bis(phenylethynyl)piperidine (**3r**)*

Following general procedure, the reductive dialkynylation of lactam **1r** (163 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/10), tertiary amine **3r** (233 mg, yield: 91%) as a yellow solid. Mp: 111.3-113.9 ºC; $[\alpha]_D^{25}$ –22.0 (*c* 1.0, $CHCl_3$); IR (film): 3061, 3031, 2931, 2833, 2220, 1611, 1598, 1585, 1511, 1489, 1453, 1443, 1364, 1301, 1249, 1172, 1152, 1090, 1035, 982, 908, 829, 756, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55-7.42 (m, 4H), 7.38-7.28 (m, 9H), 7.27-7.20 (m, 4H), 6.87 (d, J = 8.33 Hz, 2H), 4.43 (s, 2H), 4.31 (d, J = 12.9 Hz,

1H), 3.81 (s, 3H), 3.56 (d, *J* = 12.9 Hz, 1H), 3.50-3.39 (m, 1H), 2.86 (dd, *J* = 11.4, 3.2 Hz, 1H), 2.56-2.37 (m, 2H), 2.29-2.12 (m, 1H), 2.11-1.96 (m, 1H), 1.93-1.73 (m, 1H) ppm; $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): 158.8, 138.7, 132.1 (2C), 132.0 (2C), 131.5, 130.3 (2C), 128.5 (2C), 128.5 (2C), 128.4 (4C), 127.8 (2C), 127.6, 122.9 (2C), 113.8 (2C), 89.3, 86.2, 86.1, 83.6, 73.7, 70.5, 57.4, 55.4, 55.2, 50.7, 37.7, 27.5 ppm; HRMS (ESI) *m*/*z* calcd for $[C_{36}H_{34}NO_2]^+$ $(M+H^+)$: 512.2590; found: 512.2597.

*1-Benzyl-2,2-di(non-1-yn-1-yl)pyrrolidine (**3s**)*

Following general procedure, the reductive dialkynylation of lactam **1a** (88 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3s** (193 mg, yield: 95%) as a light yellow oil. IR (film): 3027, 2956, 2928, 2856, 2221, 1602, 1495, 1454, 1378, 1259, 1218, 1164, 1130, 1097, 1072, 1028, 803, 738, 699 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.2 Hz, 2H), 7.30 (dd, *J* = 7.4, 7.2 Hz, 2H), 7.23 (*t*, J = 7.4 Hz, 1H), 3.75 (s, 2H), 2.58 (t, *J* = 7.2 Hz, 2H), 2.36-2.13 (m, 6H), 1.91-1.74 (m, 2H), 1.59 (m, 4H), 1.48-1.37 (m, 5H), 1.32-1.23 (m, 11H), 0.88 (t, *J* = 7.1 Hz, 6H) ppm; $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 139.9, 129.0 (2C), 128.1 (2C), 126.7, 83.6 (2C), 79.0 (2C), 57.5, 55.2, 49.5, 41.4, 31.8 (2C), 28.87 (2C), 28.85 (2C), 28.8 (2C), 22.7 (2C), 20.8, 18.8 (2C), 14.1 (2C) ppm; HRMS (ESI) *m*/*z* calcd for $[C_{29}H_{43}NNa]^+$ $(M+H^+)$: 428.3288; found: 428.3287.

*1-Benzyl-2,2-bis((trimethylsilyl)ethynyl)pyrrolidine (**3t**)*

Following general procedure, the reductive dialkynylation of lactam **1t** (88 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane

= 1/20), tertiary amine **3t** (154 mg, yield: 87%) as a light yellow solid. Mp: 81.8-84.8 ºC; IR (film): 3029, 2960, 2900, 2822, 2160, 1604, 1495, 1454, 1408, 1364, 1250, 1208, 1169, 1140, 1114, 1027, 978, 926, 881, 843, 760, 700, 646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (t, J = 7.5 Hz, 2H), 7.35 (dd, J = 7.5, 7.1 Hz, 2H), 7.28 (t, J = 7.1 Hz, 1H), 3.77 (s, 2H), 2.64 (t, J = 7.2 Hz, 2H), 2.34 (t, J = 7.7 Hz, 2H), 1.90-1.80 (m, 2H), 0.24 (s, 18H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.7, 129.2 (2C), 128.2 (2C), 103.8 (2C), 87.8 (2C), 58.4, 55.3, 49.6, 41.3, 20.9, 0.16 (6C) ppm; HRMS (ESI) m/z calcd for $[C_{21}H_{32}NSi_2]^+$ ($M+H^+$): 354.2068; found: 354.2068.

*1-Benzyl-2,2-bis(cyclopropylethynyl)pyrrolidine (**3v**)*

Following general procedure, the reductive dialkynylation of lactam **1a** (88 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3v** (167 mg, yield: 96%) as a light yellow oil. IR (film): 3089, 3062, 3011, 2956, 2864, 2808, 2239, 1603, 1495, 1454, 1427, 1360, 1252, 1186,1172, 1104, 1073, 1052, 1028, 928, 864, 812, 738, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 7.1 Hz, 2H), 7.33 (dd, J = 7.3, 7.2 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 3.73 (s, 2H), 2.59 (t, J = 7.2 Hz, 2H), 2.24 (t, J = 8.0 Hz, 2H), 1.85-1.74 (m, 2H), 1.35-1.27 (m, 2H), 0.84-0.76 (m, 4H), 0.75-0.69 (m, 4H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 139.9, 129.1 (2C), 128.2 (2C), 126.8, 86.7 (2C), 74.1 (2C), 57.4, 55.2, 49.6, 41.5, 20.8, 8.5 (4C), -0.37 (2C) ppm; HRMS (ESI) m/z calcd for $[C_{21}H_{24}N]^+$ ($M+H^+$): 290.1903; found: 290.1903.

*1-Benzyl-2,2-bis(3-methylbut-3-en-1-yn-1-yl)pyrrolidine (**3w**)*

Following general procedure, the reductive dialkynylation of lactam **1a** (88 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3w** (106 mg, yield: 73%) as a light yellow oil. IR (film): 2957, 2918, 2849, 2221, 1613, 1453, 1384, 1307, 1199, 1139, 1125, 1093, 1028, 897, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 7.7 Hz, 2H), 7.31 (dd, J = 7.7, 7.0 Hz, 2H), 7.23 (t, J = 7.0 Hz, 1H), 5.35-5.31 (m, 2H), 5.26-5.22 (m, 2H), 3.78 (s, 2H), 2.64 (t, J = 7.3 Hz, 2H), 2.35 (t, J = 7.7 Hz, 2H), 1.92 (s, 6H), 1.89-1.80 (m, 2H) ppm; $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 139.6, 129.0 (2C), 128.2 (2C), 126.9, 126.5 (2C), 122.1 (2C), 86.8 (2C), 84.7 (2C), 58.0, 55.3, 49.7, 41.2, 23.7 (2C), 20.9 ppm; HRMS (ESI) *m/z* calcd for $[C_{21}H_{24}N]^+$ ($M+H^+$): 290.1903; found: 290.1907.

*1-Benzyl-2,2-bis((4-(trifluoromethyl)phenyl)ethynyl)pyrrolidine (**3x**)*

Following general procedure except that the solution of activated amide was added to alkynyllithium solution, the reductive dialkynylation of lactam **1a** (88 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3x** (214 mg, yield: 86%) as a light yellow solid. Mp: 69.3-71.9 ºC; IR (film): 2925, 2854, 2223, 1615, 1456, 1406, 1378, 1323, 1261, 1169, 1132, 1105, 1067, 1017, 842 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (s, 8H), 7.42 (d, J = 7.5 Hz, 2H), 7.33 (dd, J = 7.5, 7.2 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 3.94 (s, 2H), 2.78 (t, J = 7.2 Hz, 2H), 2.54 (t, J = 7.7 Hz, 2H), 1.98-1.88 (m, 2H) ppm; $^{13}C\{^{1}H\}$ NMR (150

MHz, $CDCl_3$): δ 139.2, 132.2 (4C), 130.2 (q, J_{FC} = 32.5 Hz, 2C), 129.0 (2C), 128.3 (2C), 127.1 (2C), 126.5, 125.2 (q, J_{FC} = 3.8 Hz, 4C), 123.9 (q, J_{FC} = 271.6 Hz, 2C), 89.9 (2C), 82.7 (2C), 58.1, 55.5, 50.0, 41.4, 21.1 ppm; HRMS (ESI) *m*/*z* calcd for $[C_{29}H_{22}F_6N]^+$ ($M+H^+$): 498.1651; found: 498.1655.

*1-Benzyl-2,2-bis((4-fluorophenyl)ethynyl)pyrrolidine (**3y**)*

Following general procedure except that the activated solution of amide was added to alkynyllithium solution, the reductive dialkynylation of lactam **1a** (88 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3y** (141 mg, yield: 71%) as a light yellow solid. Mp: 70.8-73.3 ºC; IR (film): 3029, 2924, 2853, 2824, 2224, 1601, 1507, 1454, 1364, 1306, 1231, 1156, 1115, 1093, 1015, 835, 742, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50-7.44 (m, 4H), 7.42 (d, *J* = 7.4 Hz, 2H), 7.32 (dd, *J* = 7.4, 7.3 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 3.92 (s, 2H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.49 (t, *J* = 7.7 Hz, 2H), 1.98-1.88 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 162.6 (d, J_{FC} = 248.9 Hz, 2C), 139.5, 133.8 (d, J_{FC} = 8.2 Hz, 2C), 129.0 (2C), 128.2 (2C), 126.9, 118.9 (d, J_{FC} = 3.5 Hz, 2C), 115.5 (d, J_{FC}= 22.1 Hz, 2C), 87.5 (2C), 82.7 (2C), 58.2, 55.4, 49.9, 41.4, 21.1 ppm; HRMS (ESI) *m*/*z* calcd for $[C_{27}H_{21}F_2NNa]^+$ ($M+Na^+$): 420.1534; found: 420.1534.

*1-Benzyl-2,2-bis(3-(benzyloxy)prop-1-yn-1-yl)pyrrolidine (**3ab**)*

Following general procedure, the reductive dialkynylation of lactam **1a** (88 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane

= 1/10), tertiary amine **3ab** (175 mg, yield: 78%) as a light yellow oil. IR (film): 3029, 2949, 2851, 2223, 1603, 1495, 1454, 1354, 1249, 1215, 1173, 1074, 1028, 913, 738, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.26 (m, 15H), 4.70 (s, 4H), 4.33 (s, 4H), 3.90 (s, 2H), 2.73 (t, J = 7.2 Hz, 2H), 2.44 (t, J = 7.7 Hz, 2H), 1.99-1.86 (m, 2H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 139.5, 137.5 (2C), 128.9 (2C), 128.5 (4C), 128.3 (2C), 128.2 (4C), 127.9 (2C), 127.0, 85.0 (2C), 79.5 (2C), 71.5 (2C), 57.47 (2C), 57.46 (2C), 55.2, 49.7, 41.3, 21.0 ppm; HRMS (ESI) m/z calcd for $[C_{31}H_{32}NO_2]^+$ ($M+H^+$): 450.2428; found: 450.2430.

*1-Benzyl-2,2-bis(3-((tert-butyldimethylsilyl)oxy)prop-1-yn-1-yl)pyrrolidine (**3ac**)*

Following general procedure, the reductive dialkynylation of lactam **1a** (88 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3ac** (199 mg, yield: 80%) as a light yellow oil. IR: 3029, 2955, 2929, 2885, 2857, 2710, 2210, 1602, 1495, 1472, 1463, 1389, 1364, 1300, 1254, 1218, 1163, 1126, 1090, 1006, 837, 815, 778, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, J = 7.9 Hz, 2H), 7.30 (dd, J = 8.0, 7.2 Hz, 2H), 7.23 (t, J = 7.2 Hz, 1H), 4.38 (s, 4H), 3.77 (s, 2H), 2.60 (t, J = 7.2 Hz, 2H), 2.30 (t, J = 7.7 Hz, 2H), 1.91-1.74 (m, 2H), 0.92 (s, 18H), 0.15 (s, 12H) ppm; $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 139.6, 128.9 (2C), 128.1 (2C), 126.8, 83.0 (2C), 82.2 (2C), 57.3, 55.1, 51.8 (2C), 49.5, 40.8, 25.8 (6C), 20.8, 18.3, -5.0 (4C) ppm; HRMS (ESI) m/z calcd for $[C_{29}H_{47}NO_2Si_2Na]^+$ ($M+Na^+$): 520.3038; found: 520.3055.

*3,3'-(1-Benzylpyrrolidine-2,2-diyl)bis(N,N-diethylprop-2-yn-1-amine) (**3ad**)*

Following general procedure except that the activated solution of amide was added to alkynyllithium solution, the reductive dialkynylation of lactam **1a** (88 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/5), tertiary amine **3ad** (141 mg, yield: 74%) as a light yellow oil. IR (film): 3027, 2970, 2934, 2875, 2817, 2224, 1495, 1454, 1384, 1374, 1321, 1248, 1209, 1156, 1122, 1091, 1071, 752, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 1H), 3.79 (s, 2H), 3.53 (s, 4H), 2.65-2.54 (m, 10H), 2.31 (t, J = 7.8 Hz, 2H), 1.88-1.78 (m, 2H), 1.11 (t, J = 7.3 Hz, 12H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.7, 128.9 (2C), 128.2 (2C), 126.8, 83.7 (2C), 77.6 (2C), 57.5, 55.3, 49.5, 47.3 (2C), 41.5, 40.7 (2C), 20.8, 12.7 (4C) ppm; HRMS (ESI) m/z calcd for $[C_{25}H_{38}N_3]^+$ ($M+H^+$): 380.3060; found: 380.3065.

*1-Benzyl-2,2-bis(3-chloroprop-1-yn-1-yl)pyrrolidine (**3ae**)*

Following general procedure except that the activated solution of amide was added to alkynyllithium solution, the reductive dialkynylation of lactam **1a** (88 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3ae** (149 mg, yield: 81%) as a light yellow solid. Mp: 36.3-39.3 ºC; IR (film): 3028, 2985, 2953, 2880, 2826, 2224, 1603, 1495, 1454, 1430, 1365, 1300, 1262, 1222, 1176, 1130, 1090, 1071, 1028, 914, 741, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (t, J = 7.1 Hz, 2H), 7.35 (t, J = 7.1 Hz, 2H), 7.28 (t, J = 7.1 Hz, 1H),

4.23 (s, 4H), 3.80 (s, 2H), 2.68 (t, J = 7.2 Hz, 2H), 2.36 (t, J = 7.7 Hz, 2H), 1.94-183 (m, 2H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 139.2, 129.0 (2C), 128.2 (2C), 127.0, 84.5 (2C), 78.7 (2C), 57.2, 55.1, 49.7, 40.9, 30.4 (2C), 20.9 ppm; HRMS (ESI) m/z calcd for $[C_{17}H_{18}Cl_2N]^+$ ($M+H^+$):306.0811; found: 306.0811.

*1-Benzyl-2,2-bis(3,3-diethoxyprop-1-yn-1-yl)pyrrolidine (**3af**)*

Following general procedure, the reductive dialkynylation of lactam **1a** (88 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/10), tertiary amine **3af** (155 mg, yield: 75%) as a yellow oil. IR (film): 2976, 2927, 2884, 2221, 1598, 1506, 1454, 1355, 1328, 1219, 1156, 1114, 1093, 1052, 1012, 834, 738, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 7.4 Hz, 4H), 7.30 (dd, J = 7.4 Hz, 7.0 Hz, 2H), 7.24 (t, J = 7.0 Hz, 1H), 5.33 (s, 2H), 3.82-3.70 (m, 4H), 3.78 (s, 2H), 3.67-3.53 (m, 4H), 2.62 (t, J = 7.4 Hz, 2H), 2.36 (t, J = 7.61 Hz, 2H), 1.91-1.77 (m, 2H), 1.24 (t, J = 1.22 Hz, 12H) ppm; $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 139.3, 128.9 (2C), 128.2 (2C), 126.9, 91.4 (2C), 83.2 (2C), 79.2 (2C), 60.9 (2C), 60.86 (2C), 57.1, 55.1, 49.6, 40.9, 20.9, 15.1 (4C) ppm; HRMS (ESI) m/z calcd for $[C_{25}H_{35}NNaO_4]^+$ ($M+Na^+$): 436.2458; found: 436.2456.

*1-Benzyl-2,2-bis(thiophen-2-ylethynyl)pyrrolidine (**3ag**)*

Following general procedure, the reductive dialkynylation of lactam **1a** (88 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3ag** (146 mg, yield: 78%) as a light yellow solid. Mp: 100.5-101.9 ºC; IR (film): 2919, 2850, 2218, 1654, 1636, 1457, 1424, 1384, 1138,

1125, 1092, 1028, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 7.3 Hz, 2H), 7.31 (dd, J = 8.0, 7.3 Hz, 2H), 7.28-7.16 (m, 5H), 6.97 (t, J = 4.0 Hz, 2H), 3.90 (s, 2H), 2.73 (t, J = 7.2 Hz, 2H), 2.49 (t, J = 7.9 Hz, 2H), 2.02-1.82 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 139.4, 132.4 (2C), 129.1 (2C), 128.3 (2C), 127.2 (2C), 127.02, 126.96 (2C), 122.8 (2C), 91.3 (2C), 77.2 (2C), 58.6, 55.5, 49.9, 41.3, 21.1 ppm; HRMS (ESI) *m*/*z* calcd for $[C_{23}H_{20}NS_2]^+$ ($M+H^+$): 374.1032; found: 374.1038.

*2,2'-((1-Benzylpyrrolidine-2,2-diyl)bis(ethyne-2,1-diyl))dipyridine (**3ah**)*

Following general procedure except that the activated solution of amide was added to alkynyl lithium solution, the reductive dialkynylation of lactam **1a** (88 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/5), tertiary amine **3ah** (85 mg, yield: 47%) as a light yellow solid and recovered starting material **1a** (29.9 mg). Mp: 98.7-101.4 ºC; IR (film): 3058, 2957, 2824, 2222, 1581, 1562, 1463, 1427, 1306, 1274, 1150, 1124, 988, 778, 739, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.58 (d, J = 4.4 Hz, 2H), 7.64 (t, J = 7.7 Hz, 2H), 7.52-7.38 (m, 4H), 7.30 (t, J = 7.3 Hz, 2H), 7.26-7.18 (m, 3H), 4.02 (s, 2H), 2.78 (t, J = 7.2 Hz, 2H), 2.59 (t, J = 7.8 Hz, 2H), 2.02-1.91 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.9 (2C), 143.0, 139.4, 136.1 (2C), 128.9 (2C), 128.2 (2C), 127.6 (2C), 126.9 (2C), 122.9 (2C), 87.3 (2C), 83.4 (2C), 58.0, 55.3, 49.8, 41.2, 21.1 ppm; HRMS (ESI) *m*/*z* calcd for $[C_{25}H_{22}N_3]^+$ ($M+H^+$): 364.1808; found: 364.1811.

*N,N-Dibenzyl-1-phenylcycloundeca-2,10-diyn-1-amine (**3ai**)*

To a cooled (–78 ºC) solution of amide **1e** (151 mg, 0.5 mmol, 1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (113 mg, 0.55 mmol, 1.1 equiv) in CH_2Cl_2 (6.0 mL, 0.09 M), trifluoromethanesulfonic anhydride (Tf_2O) (93 μL, 0.55 mmol, 1.1 equiv) was added dropwise via a syringe at –78 °C under Ar atmosphere, and the reaction was stirred for 30 min. The above mixture was added to the freshly prepared alkynyldilithium (1.5 equiv) THF solution (0.05 M) at –78 °C, then the resulting mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with a saturated aqueous Na_2CO_3 (4.0 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluenting with EtOAc/hexane (1/40) to give the corresponding tertiary amine **3ai** (79 mg, yield: 38%) as a light yellow oil. IR (film): 3027, 2923, 2851, 2221, 1655, 1648, 1603, 1492, 1449, 1384, 1199, 1138, 1125, 1092, 1028, 958, 758, 743, 697 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.88 (d, J = 7.6 Hz, 2H), 7.33 (dd, J = 7.6, 7.2 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 7.19 (d, J = 7.3 Hz, 4H), 7.11 (dd, J = 7.3, 7.1 Hz, 4H), 7.05 (t, J = 7.1 Hz, 2H), 3.76 (s, 4H), 2.21-2.13 (m, 4H), 1.72-1.58 (m, 8H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 142.1, 141.1 (2C), 128.7 (4C), 128.2 (2C), 127.9, 127.8 (2C), 127.6 (4C), 126.1 (2C), 92.7 (2C), 83.5 (2C), 55.6 (2C), 50.9, 27.7 (2C), 27.4 (2C), 19.2 (2C) ppm; HRMS (ESI) *m*/*z* calcd for $[C_{31}H_{32}N]^+$ ($M+H^+$): 418.2529; found: 418.2540.

Gram-scale synthesis

*N,N-Dibenzyl-1,3,5-triphenylpenta-1,4-diyn-3-amine (**3e**)*

To a cooled (–78 ºC) solution of amide **1e** (1.00 g, 3.32 mmol, 1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (750 mg, 3.65 mmol, 1.1 equiv) in CH_2Cl_2 (19.5 mL, 0.17 M) was added dropwise trifluoromethanesulfonic anhydride (Tf_2O) (614 μL, 3.65 mmol, 1.1 equiv) via a syringe at –78 °C under Ar atmosphere. After being stirred for 30 min, a freshly prepared solution of (phenylethynyl)lithium **2a** (3.0 equiv) in THF (0.5 M) was added, and the resulting mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 (27.0 mL), and extracted with CH_2Cl_2 (3 × 33 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane = 1/20) to give the corresponding tertiary amine **3e** (1.30 g, yield: 81%) as a light yellow solid. The spectral data are identical with those described above for **3e.**

*N,N-Dimethyl-3-phenethyl-1,5-diphenylpenta-1,4-diyn-3-amine (**3m**)*

To a cooled (–78 ºC) solution of amide **1m** (1.00g, 5.64 mmol, 1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (1.27 g, 6.21 mmol, 1.1 equiv) in CH_2Cl_2 (33.2 mL, 0.17 M) was added dropwise trifluoromethanesulfonic anhydride (Tf_2O) (1.04 mL, 6.21 mmol, 1.1 equiv) via a syringe at –78 °C under Ar atmosphere. After being

stirred for 30 min, a freshly prepared solution of (phenylethynyl)lithium **2a** (3.0 equiv) in THF (0.5 M) was added, and the resulting mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 (45.0 mL), and extracted with CH_2Cl_2 (3 × 56 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane = 1/10) to give the corresponding tertiary amine **3m** (1.74 g, yield: 85%) as a light yellow solid. The spectral data are identical with those described above for **3m.**

Employment of Phenylethynyl Grignard Reagents (a) and Ethynyllithium (b) for the Reductive Dialkynylation of Amide 1e.

(a) Phenylethynyl Grignard Reagents

Following general procedure, the reductive dialkynylation of amide **1e** (151 mg, 0.5 mmol) with phenylethynylmagnesium bromide **2r** (3.0 equiv) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3e** (166 mg, yield: 68%) as a light yellow solid. The spectral data are identical with those described above.

Following general procedure, the reductive dialkynylation of amide **1e** (151 mg, 0.5 mmol) with phenylethynyl Grignard reagent **2s** (3.0 equiv) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), tertiary amine **3e** (176

mg, yield: 72%) as a light yellow solid. The spectral data are identical with those described above.

(b) Ethynyllithium

Following the general procedure except that the solution of activated amide was added to an ethynyllithium solution, the reductive diethynylation of amide **1e** (151 mg, 0.5 mmol) with ethynyllithium **4** (3.0 equiv or 9.6 equiv) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/5), only the recovered amide **1e** (92 mg, 61% yield or 78 mg, 52% yield).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of new compounds and known starting compounds (PDF).

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Notes

The authors declare no conflict of interest.

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