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$PdCl_2$-Catalyzed Efficient Transformation of Propargylic Amines to (*E*)-α-Chloroalkylidene-*β*-lactams

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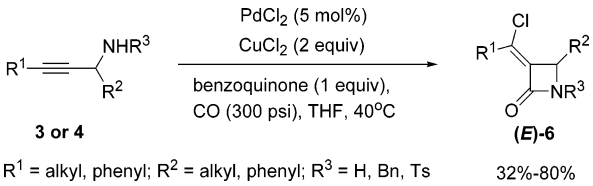

The $PdCl_2$-catalyzed cyclocarbonylation reaction of propargylic amines with $CuCl_2$ and benzoquinone afforded (*E*)-α-chloroalkylidene-*β*-lactams in moderate to good yields. The formation of the corresponding *Z*-isomers or five-membered products was not observed. The reaction of the readily available optically active propargylic amines provides a convenient synthesis of the corresponding (*E*)-α-chloroalkylidene-*β*-lactams with high ee values. The structure and the stereochemistry of the products were established by the X-ray single-crystal diffraction study of (*E*)-**6d** and (*E*)-**6e**, which indicates that the stereoselectivity in this reaction is different from what was observed with propargylic alcohols. A rationale for this reaction was proposed.

Introduction

Due to the biological activity[1] and their potentials as synthetic intermediates,[2] *β*-lactams (2-azetidinones) are one of the best known and intensely investigated heterocyclic ring systems. Since the introduction of penicillin into therapy, bacteria have developed an incredible and growing resistance to *β*-lactam antibiotics, essentially due to the hydrolytic ability of extremely active *β*-lactams, which can be overcome by using more stable *β*-lactam derivative.[3] Furthermore, the recent discoveries of some azetidin-2-ones displaying a broad range of enzyme−inhibitory activity justify a renewed interest in these compounds.[4] In this family, α-alkylidene-*β*-lactams are one of the most important skeletons which have attracted significant interest among synthetic and medicinal chemists over the years mainly because of their occurrence in some biologically active natural products and their potential as useful building blocks in organic synthesis.[5] Some of the most important methodologies for the preparation of α-alkylidene-*β*-lactams are summarized as follows: (1) the addition of chlorosulfonyl isocyanate with functionalized allenes;[6] (2) lactamization;[7] (3) elimination reaction of *β*-lactams forming the exocyclic C=C bonds;[8] (4) α-olefination reaction of *β*-lactams;[9] (5) Pd(0)-cata-

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lyzed cyclocarbonylative cyclization reaction of 2-bromo-2-alkenyl amides;[10] (6) Rh-catalyzed silylcarbonylation of propargylamines;[11] (7) [2+2] cycloaddition reactions of α-heteroatom substituted metallocarbenes with imines followed by hydrolysis;[12] and (8) radical stannylcarbonylation of propargylamines.[13] However, these known methods may, in some cases, suffer from lengthy procedures, harsh conditions, or low yields. Thus, new and efficient methodologies for α-alkylidene-*β*-lactams are still desirable. In this paper, we wish to report our recent results on the $PdCl_2$-catalyzed cyclocarbonylation of propargylic amines affording (*E*)-α-chloroalkylidene-*β*-lactams highly selectively.

Results and Discussion

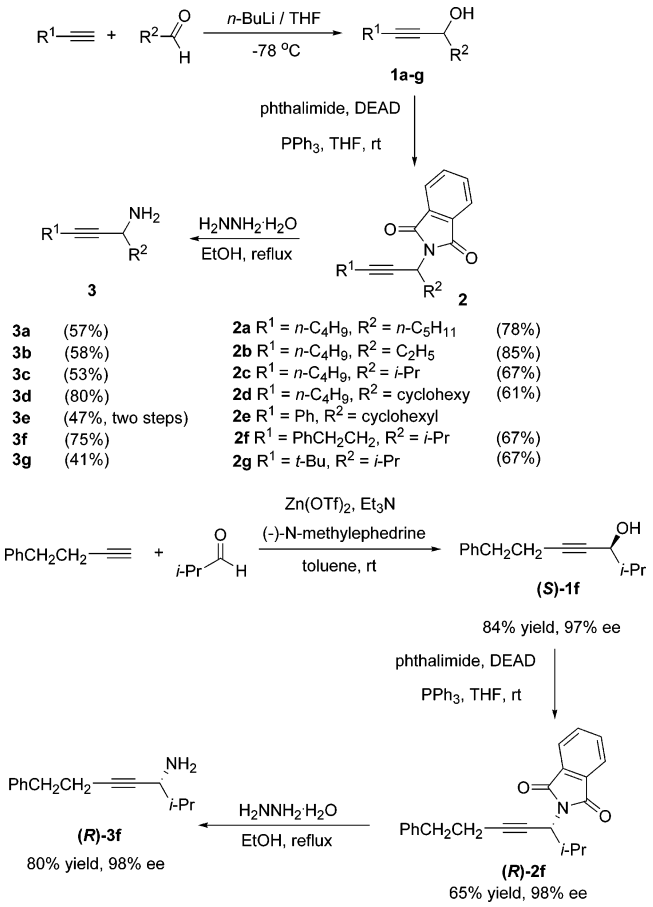
Synthesis of Starting Materials. A number of methods have been used for the synthesis of different propargylic amines. Propargylic amines **3a**−**g** were prepared through the application of the Mitsunobu reaction (Scheme 1).[14] The optically active propargylic amine (*R*)-**3f** was prepared according to the same procedure using optically active propargylic alcohol (*S*)-**1f**[1] as the starting point. Propargylic amines **4a**−**f** and (*R*)-**4f** were prepared via the *N*-benzylation of amines **3** (Scheme 2).[16]

Propargylic amine **4h** was prepared through the application of the known amination of propargylic mesylates (Scheme 3).[17] The optically active propargylic amines (*R*)-**4b**, (*S*)-**4b**, (*R*)-**4h**, and (*S*)-**4h** were prepared accordingly starting from the optically active propargylic alcohols (*S*)-**1b,** (*R*)-**1b,** (*S*)-**1h**, and (*R*)-**1h**, respectively.

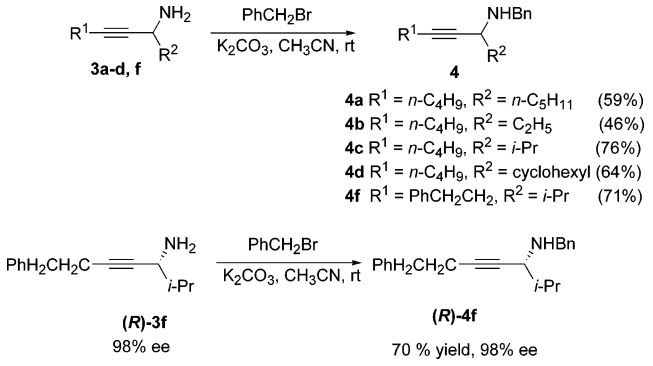
Propargylic amine ***4l*** was prepared via the reaction of the corresponding 1-alkynyllithium with the imine (Scheme 4).

Synthesis of (*E*)-α-Alkylidene-*β*-lactams via $PdCl_2$-Catalyzed Cyclocarbonylation of Propargylic Amines. Recently, we have observed that α-chloroalkylidene-*β*-lactones can be prepared from $PdCl_2$-catalyed cyclocarbonylation of 2-alkynols.[18] In our first try, the reaction of propargylic amine **3a** failed to afford the carbonylative cyclization reaction under the same reaction conditions (10 mol % of $PdCl_2$ and 5 equiv of $CuCl_2$)[18] (entry 1, Table 1). To our delight, when 2 equiv of benzoquinone were added to the reaction mixture, 31% of product (*E*)-**6a** was isolated under the action of 5 mol % of $PdCl_2$ and 1.5 equiv of $CuCl_2$ (entry 2, Table 1). Further studies showed that 1 equiv of benzoquinone is enough for the reaction and the reaction time is a key factor. When the reaction time was 8 h, the yield of product was improved to 52% (entry 4, Table 1). With a

SCHEME 1



SCHEME 2



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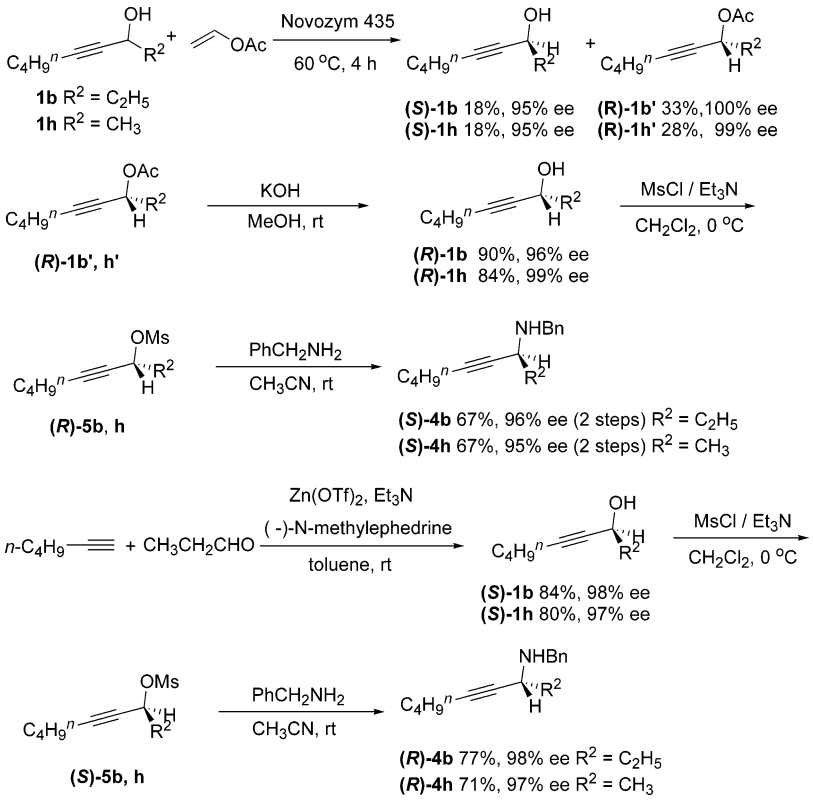
SCHEME 3



SCHEME 4

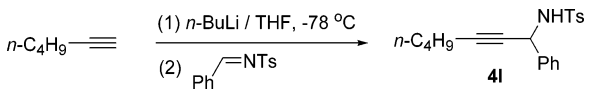
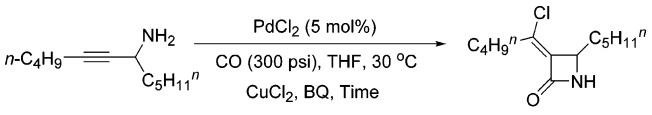


TABLE 1. $PdCl_2$-Catalyzed Cyclocarbonylation of Propargylic Amine 3a



entry	$CuCl_2$ (equiv)	benzoquinone (equiv)	time (h)	isolated yield (%)
1	5	-	2	trace
2	1.5	2	4	31
3	1.5	1	4	31
4	1.5	1	8	52
5	1.5	1	12	23
6	2	1	8	51
7	0	2	8	*a*
8[b]	2	1	8	*a*
9[c]	0	2	8	*a*
10[d]	0	2	8	*a*
11[e]	0	1	8	*a*

[a] No (*E*)-**6a** was detected. [b] 3 equiv of H_2O was added. [c] 2 equiv of HCl (12 M) was added. [d] 2 equiv of AcOH was added. [e] 2 equiv of LiCl was added instead of $CuCl_2$.

longer reaction time, the yield decreased probably due to the instability of *E*-**6a** (entries 5 and 6, Table 1). The reaction with 1 equiv of $CuCl_2$ afforded (*E*)-**6a** in similar yield. However, it should be noted that no (*E*)-**6a** was found in the absence of $CuCl_2$ (entry 7, Table 1). Although it was reported that an acid is required for the oxidation of a Pd(0) species by benzoquinone,[23] no (*E*)-**6a** was detected in the presence or absence of $CuCl_2$ when we added H_2O, HCl, AcOH, or LiCl (entries 8−11, Table 1), indicating that the addition of extra H^+ is not good for this transformation, since H^+ was generated in this reaction.

Further studies showed that in some cases the reaction temperature was another key factor. The yield of (*E*)-**6c** at 40 °C was much higher than that at 30 °C (entries 1 and 2, Table 2). Both the reaction temperature and time were key factors for the reaction of *N*-benzyl propargylic amines **4c**. From entries 3−5 of Table 2, it can be seen that the best reaction conditions are 5 mol % of $PdCl_2$, 2 equiv of $CuCl_2$, 1 equiv of benzoquinone, and CO (300 psi) in THF at 40 °C for 12 h. Under these reaction conditions, (*E*)-**6i** was isolated in 80% yield (entry 5, Table 2).

The stereochemistry of (*E*)-**6** was established by the single-crystal X-ray diffraction study of (*E*)-**6d** and (*E*)-**6e**.[18] The formation of the *Z*-isomers and the five-membered lactams was not observed through the ^1H

(19) Crystal data for compound (*E*)-**6d**: $C_{14}H_{22}NOCl$, MW = 255.78, monoclinic, space group *C*2/*c*, Mo Kα, final *R* indices [$I > 2\sigma(I)$], R1 = 0.0764, *w*R2 = 0.2031, a = 28.868(13) Å, b = 7.868(3) Å, c = 6.302(3) Å, α = 90°, β = 90°, γ = 90°, V = 1431.5(11) Å^3, T = 293(2) K, Z = 4, reflections collected/unique 7200/2513 (R_{int} = 0.0941), no observation [$I > 2\sigma(I)$] 2080, parameters 151. CCDC 247772. Crystal data for compound (*E*)-**6e**: $C_{16}H_{18}NOCl$, MW = 275.76, monoclinic, space group *C*2/*c*, Mo Kα, final *R* indices [$I > 2\sigma(I)$], R1 = 0.0512, *w*R2 = 0.0928, a = 8.6640(16) Å, b = 9.2920(17) Å, c = 9.9179(19) Å, α = 104.905(3)°, β = 103.761(3)°, γ = 101.298(3)°, V = 720.8(2) Å^3, T = 293(2) K, Z = 2, reflections collected/unique 4341/3136 (R_{int} = 0.0620), no observation [$I > 2\sigma(I)$] 1625, parameters 245. CCDC 247771.

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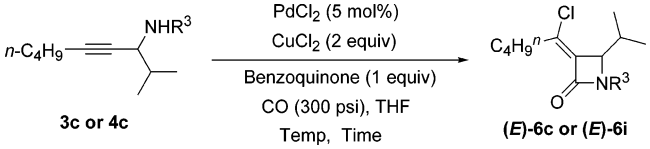
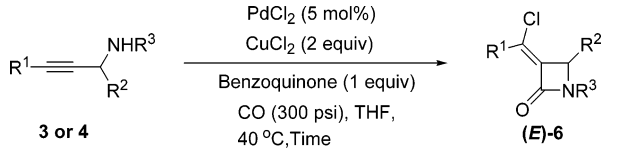
TABLE 2. $PdCl_2$-Catalyzed Cyclocarbonylation of Propargylic Amine 3c and *N*-Benzyl Propargylic Amine 4c



entry	R^3	temp (°C)	time (h)	product	isolated yield (%)
1	H (**3c**)	30	8	(*E*)-**6c**	32
2	H (**3c**)	40	8	(*E*)-**6c**	53
3	Bn (**4c**)	30	8	(*E*)-**6i**	15
4	Bn (**4c**)	40	8	(*E*)-**6i**	31
5	Bn (**4c**)	40	12	(*E*)-**6i**	80

TABLE 3. $PdCl_2$-Catalyzed Cyclocarbonylation Reaction of Various Propargylic Amines in the Presence of $CuCl_2$ and Benzoquinone



entry	R^1	R^2	R^3	time (h)	product	isolated yield (%)
1	n-C_4H_9	n-C_5H_{11}	H (**3a**)	8	(*E*)-**6a**	52
2	n-C_4H_9	C_2H_5	H (**3b**)	8	(*E*)-**6b**	48
3	n-C_4H_9	*i*-Pr	H (**3c**)	8	(*E*)-**6c**	53
4	n-C_4H_9	cyclohexyl	H (**3d**)	8	(*E*)-**6d**	50
5	Ph	cyclohexyl	H (**3e**)	10.5	(*E*)-**6e**	32
6	$PhCH_2CH_2$	*i*-Pr	H (**3f**)	8	(*E*)-**6f**	42
7	n-C_4H_9	n-C_5H_{11}	Bn (**4a**)	12	(*E*)-**6g**	61
8	n-C_4H_9	C_2H_5	Bn (**4b**)	12	(*E*)-**6h**	78
9	n-C_4H_9	*i*-Pr	Bn (**4c**)	12	(*E*)-**6i**	80
10	n-C_4H_9	cyclohexyl	Bn (**4d**)	12	(*E*)-**6j**	63
11	$PhCH_2CH_2$	*i*-Pr	Bn (**4f**)	12	(*E*)-**6k**	70
12	n-C_4H_9	Me	Bn (**4h**)	8	(*E*)-**6*l***	61
13	n-C_4H_9	Ph	Ts (**4l**)	12	(*E*)-**6m**	36
14	^{t}Bu	*i*-Pr	H (**3g**)	8		NR

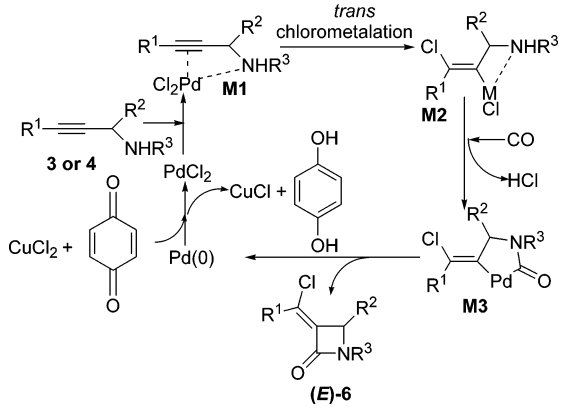
NMR and TLC analysis of the crude reaction mixtures. It is quite interesting to note that the stereochemistry is opposite to what was observed with propargylic alcohols.[18]

Then we investigated the $PdCl_2$-catalyzed cyclocarbonylation of various propargylic amines in the presence of $CuCl_2$ and benzoquinone. The typical results were summarized in Table 3, which led to the following conclusions: (1) the reaction is very general, R^1, R^2 can be alkyl, aryl group and R^3 can be hydrogen (entries 1−6, Table 3), benzyl (entries 7−12, Table 3), and *p*-toluenesulfonyl group (entry 13, Table 3); (2) when R^1 was a bulky group such as ^{t}Bu, the reaction did not proceed (entry 14, Table 3); and (3) the yields of products ranged from 32% to 80%.

Next we examined the cyclocarbonylation reaction of optically active propargylic amines under the standard reaction conditions. Some typical results are listed in Table 4. As can be seen from Table 4, both *R* and *S* substrates can smoothly afford the corresponding products. Racemization of the chiral centers in (*R*)- or (*S*)-**3** or -**4** was not obvious.

Mechanistic Considerations. A plausible mechanism for $PdCl_2$-catalyzed cyclocarbonylation of propargylic amines is depicted in Scheme 5. The coordination of the triple bond in **3** or **4** with $PdCl_2$ gave complex **M1**, which was followed by *trans*-chlorometalation to give **M2**. The subsequent coordination and insertion of CO afforded intermediate **M3**. Reductive elimination of **M3** would afford (*E*)-**6** and Pd(0), which would be oxidized with $CuCl_2$ and benzoquinone to generate $PdCl_2$. Benzoquinone and $CuCl_2$ are both essential for a high-yielding reaction: $CuCl_2$ may provide the source of Cl^- as well as serve as an oxidant since no *E*-**6a** was formed when LiCl was used instead of $CuCl_2$ (entry 11, Table 1). Benzoquinone is not only helpful for oxidation,[22,23] but also plays a key role in reductive elimination of **M3**.[24] Compared to the stereochemistry of the similar reaction with propargylic alcohols,[18] the *trans*-chlorometalation of the C−C triple bond may be due to the relatively stronger coordination ability of the amine functionality, which led to the attack of Cl^- from the outside of the coordination sphere of palladium.[25]

SCHEME 5



In summary, we have developed a mild and efficient methodology for the synthesis of (*E*)-α-chloroalkylidene-*β*-lactams in moderate to good yields. Highly optically active (*E*)-α-chloroalkylidene-*β*-lactams can be easily formed from the readily available optically active propargylic amines without obvious racemization. *trans*-Chlorometalation of the carbon−carbon triple bond was observed in the reaction. Further studies in this area are being pursued in our laboratory.

Experimental Section

Synthesis of Starting Materials. Compounds **1a**−**h** were prepared via the reaction of the corresponding 1-alkynyllithium with aldehydes as reported.[20] Propargylic amines **3a**−**g** were prepared by the application of the Mitsunobu reaction.[14]

Synthesis of *N*-(Dodec-5-yn-7-yl)amine (3a). Typical Procedure I. To a solution of **1a** (8.19 g, 45 mmol), phthalimide (7.296 g, 49.6 mmol), and PPh_3 (12.982 g, 49.5 mmol) in 300 mL of dry THF was added 25 mL (40% in toluene, 9.57 g/55 mmol) of diethyl azodicarboxylate. The resulting yellow solution was stirred under a N_2 atmosphere at room temperature for 29 h. The solvent was removed in vacuo to afford a semisolid, which was extracted with 1:1 ether−petroleum ether. The resulting precipitate was dissolved with several portions of 1:1 ether−petroleum ether. After concentration of

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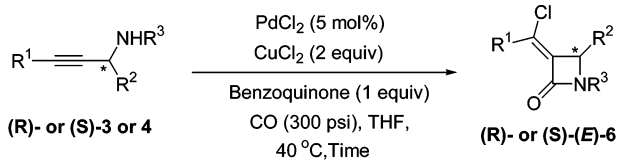
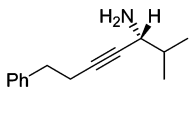
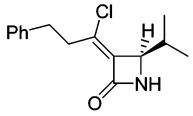
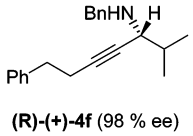
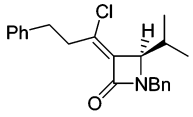
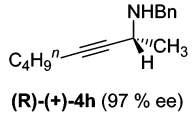
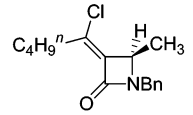
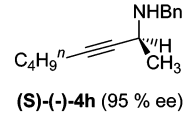
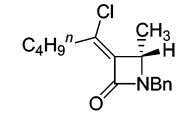
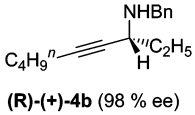
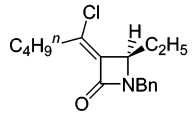
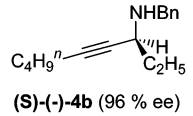
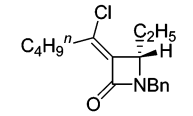
TABLE 4. The Synthesis of Optically Active (*E*)-α-Chloroalkylidene-*β*-lactams



(R)- or (S)-3 or 4 → **(R)- or (S)-(*E*)-6**

Entry	(R)- or (S)- 3 or 4	Time (h)	(R)- or (S)-(*E*)-6	Yield of (*E*)-6 (%)	Ee of (*E*)-6 (%)
1	 **(R)-(-)-3f** (98 % ee)	8	 **(R)-(+)-(*E*)-6f**	55	97
2	 **(R)-(+)-4f** (98 % ee)	16	 **(R)-(+)-(*E*)-6k**	50	98
3	 **(R)-(+)-4h** (97 % ee)	12	 **(R)-(+)-(*E*)-6l**	55	94
4	 **(S)-(-)-4h** (95 % ee)	12	 **(S)-(-)-(*E*)-6l**	53	93
5	 **(R)-(+)-4b** (98 % ee)	12	 **(R)-(+)-(*E*)-6h**	49	98
6	 **(S)-(-)-4b** (96 % ee)	12	 **(S)-(-)-(*E*)-6h**	57	91

the filtrate, the residue was purified via flash chromatography on silica gel with petroleum ether/ether (20:1) to yield 10.962 g (78%) of **2a**.

A solution of the above **2a** (10.781 g, 34.7 mmol) and 10 mL of hydrazine hydrate in 180 mL of absolute EtOH was heated to reflux for 5.5 h resulting in the formation of a white precipitate. The reaction mixture was cooled to room temperature followed by the addition of 40 mL of concentrated HCl. After being stirred for 1 h, the precipitate was removed by filtration and the filtrate was concentrated to a solid residue, which was diluted with ether. The mixture was brought to pH >10 by the addition of aqueous NaOH. The solution was extracted with 7 × 30 mL of Et_2O. The combined extracts were dried with Na_2SO_4, filtered, concentrated, and purified via flash chromatography on silica gel (eluent: petroleum ether: ethyl acetate 15:1) to afford 3.568 g (57%) of **3a**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60−3.45 (m, 1 H), 2.18 (dt, J = 2.0 and 6.8 Hz, 2 H), 1.62−1.20 (m, 14 H), 0.91 (t, J = 7.1 Hz, 3 H), 0.90 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 83.7, 82.3, 43.6, 38.5, 31.4, 30.9, 25.7, 22.5, 21.8, 18.2, 13.9, 13.5; MS (EI) *m/z* (%) 182 (M^+ + 1, 19.60), 110 (100); IR (neat) 2931, 2228, 1593 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{23}N$ 181.1831, found 181.1821.

Synthesis of *N*-(Dodec-5-yn-7-yl)-*N*-benzylamine (4a). Typical Procedure II. To a solution of **3a** (710 mg, 3.92 mmol) and K_2CO_3 (570 mg, 4.13 mmol) was added $PhCH_2Br$ (711 mg, 4.16 mmol) in 10 mL of dry CH_3CN. The reaction was stirred in N_2 atmosphere at room temperature for 20 h. The precipitate was removed by filtration and the residue was purified via flash chromatography on silica gel (eluent: petroleum ether:ethyl acetate 20:1) to afford 629 mg (59%) of **4a**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.20 (m, 5 H), 4.01 (d, J = 12.6 Hz, 1 H), 3.79 (d, J = 12.6 Hz, 1 H), 3.34 (dt, J = 1.9 and 5.6 Hz, 1 H), 2.24 (dt, J = 1.5 and 6.8 Hz, 2 H), 1.75−1.13 (m, 13 H), 0.93 (t, J = 7.4 Hz, 3 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 140.3, 128.3, 128.3, 126.8, 83.9, 81.4, 51.4, 49.6, 36.3, 31.6, 31.1, 25.7, 22.6, 21.9, 18.4, 14.0, 13.6; MS (EI) *m/z* (%) 272 (M^+ + 1, 4.33), 271 (M^+, 1.93), 200 ($M^+ - C_5H_{11}$, 94.72), 91 (100); IR (neat) 3368, 2221, 1604 cm^{-1}; HRMS (MALDI/DHB) calcd for $C_{19}H_{30}N$ (M^+ + 1) 272.2373, found 272.2378.

***N*-(Oct-3-yn-2-yl)-*N*-benzylamine (4h).** To a solution of **1h** (5.565 g, 44.2 mmol) was added Et_3N (12.4 mL, 8.928 g, 88.4 mmol) in 90 mL of dry CH_2Cl_2. After the reaction mixture was cooled to 0 °C, a solution of MsCl (5.13 mL, 7.594 g, 66.3 mmol) in 15 mL of CH_2Cl_2 was added dropwise. After being stirred at 0 °C for 4 h the reaction was extracted with 3 × 15 mL of CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$ and NaCl solution, dried over Na_2SO_4, and evaporated to afford 408 mg of **5** (yellow oil). The reaction of the above obtained **5** and $BnNH_2$ (0.44 mL, 430 mg, 4.0 mmol) in 4 mL of dry CH_3CN was stirred at room

temperature for 24 h. Then the solution was extracted with 3 × 15 mL of Et_2O. The combined extracts were washed with saturated NaCl and dried over Na_2SO_4. After evaporation, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether:ethyl acetate 10:1) to afford 260 mg (61%, two steps) of **4h**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.00 (m, 5 H), 3.99 (d, J = 12.6 Hz, 1 H), 3.79 (d, J = 12.6 Hz, 1 H), 3.60−3.40 (m, 1 H), 2.22 (dt, J = 1.7 and 7.1 Hz, 2 H), 1.80−1.25 (m, 5 H), 1.34 (d, J = 6.9 Hz, 3 H), 0.93 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 140.1, 128.4, 128.3, 126.9, 83.2, 82.2, 51.4, 44.6, 31.0, 22.7, 21.9, 18.3, 13.6; MS (EI) *m/z* (%) 215 (M^+, 0.69), 200 ($M^+ - CH_3$, 36.99), 91 (100); IR (neat) 2932, 2228, 1603 cm^{-1}; HRMS calcd for $C_{15}H_{21}N$ (M^+) 215.1674, found 215.1689.

***N*-(1-Phenyl-2-heptynyl)-*p*-toluenesulfonamide (4l).**[21] In a flame-dried argon-flushed flask, a solution of 1-hexyne (818 mg, 10 mmol) in 15 mL of dried THF was cooled to −78 °C. Then *n*-BuLi (6.25 mL, 1.6 M in hexane, 10 mmol) was added dropwise to the solution via a syringe. After the mixture was stirred at −78 °C for 30 min, a solution of *N*-(*p*-toluenesulfonyl)benzaldimine (2.593 g, 10 mmol) in 10 mL of dried THF was added. The reaction mixture was stirred at −78 °C and warmed to room temperature overnight. Then saturated aqueous NH_4Cl was added to the reaction mixture to stop the reaction. The mixture was extracted with Et_2O, washed by saturated NaCl solution, and dried over Na_2SO_4. After evaporation, the residue was purified via flash chromatography on silica gel with petroleum ether/ethyl acetate (5:1) to yield 2.968 g (87%) of **4l**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, J = 1.8 and 6.9 Hz, 2 H), 7.52−7.42 (m, 2 H), 7.38−7.25 (m, 5 H), 5.29 (dt, J = 2.0 and 9.0 Hz,1 H), 4.99 (d, J = 8.4 Hz, 1 H), 2.43 (s, 3 H), 2.01−1.89 (m, 2 H), 1.38−1.18 (m, 4 H), 0.92−0.79 (m, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 143.2, 138.1, 137.5, 129.3, 128.5, 128.1, 127.4, 127.2, 87.4, 76.5, 49.4, 30.3, 21.8, 21.5, 18.2, 13.5.

$PdCl_2$-Catalyzed Cyclocarbonylation Reaction of Various Propargylic Amines in the Presence of $CuCl_2$ and Benzoquinone. Synthesis of (*E*)-6a. Typical Procedure III. In a flame-dried nitrogen-flushed flask, a solution of **3a** (165 mg, 0.91 mmol) and anhydrous $CuCl_2$ (188 mg, 1.39 mmol) in 10 mL of dry THF was stirred for 5 min at room temperature followed by the addition of $PdCl_2$ (8 mg, 0.045 mmol) and benzoquinone (98 mg, 0.91 mmol). Then the flask was transferred to a Parr pressure reactor. The Parr reactor was charged with 300 psi of CO gas. After the mixture was stirred for 8 h at 40 °C, the gas was ventilated, and the residue was diluted with CH_2Cl_2. Filtration through a short column of silica gel, evaporation, and flash chromatography on silica gel (eluent: petroleum ether:ethyl acetate 15:1) afforded 116 mg (52%) of (*E*)-**6a**.

(*E*)-α-(1-Chloropentylidene)-β-(*n*-pentyl)-β-lactam ((*E*)-6a): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (br s, 1 H), 4.17 (dd, J = 3.2 and 8.3 Hz, 1 H), 2.85−2.65 (m, 2 H), 2.05−1.90 (m, 1 H), 1.68−1.51 (m, 3 H), 1.50−1.18 (m, 8 H), 0.93 (t, J = 7.4 Hz, 3 H), 0.90 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 162.8, 137.7, 136.4, 57.6, 34.5, 31.8, 31.5, 29.1, 24.7, 22.4, 21.5, 13.9, 13.7; MS (EI) *m/z* (%) 246 ($M^+ + 1(^{37}Cl)$, 1.57), 244 ($M^+ + 1(^{35}Cl)$, 5.06), 41 (100); IR (neat) 3235, 1748, 1713 cm^{-1}; HRMS calcd for $C_{13}H_{22}NO$ ($M^+ - Cl$) 208.1701, found 208.1715.

Synthesis of ((*E*)-6i). Typical Procedure IV. In a flame-dried nitrogen-flushed flask, a solution of **4c** (142 mg, 0.58 mmol) and anhydrous $CuCl_2$ (165 mg, 1.22 mmol) in 8 mL of dry THF was stirred for 5 min at room temperature followed by the addition of $PdCl_2$ (6 mg, 0.034 mmol) and benzoquinone (68 mg, 0.63 mmol). Then the flask was transferred to a Parr pressure reactor. The Parr reactor was charged with 300 psi of CO gas. After the mixture was stirred for 12 h at 40 °C, the gas was ventilated, and the residue was diluted with CH_2Cl_2. Filtration through a short column of silica gel, evaporation, and flash chromatography on silica gel (eluent: petroleum ether:ethyl 20:1) afforded 143 mg (80%) of (*E*)-**6i**.

(*E*)-α-(1-Chloropentylidene)-β-(isopropyl)-*N*-benzyl-β-lactam ((*E*)-6i): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.21 (m, 5 H), 4.86 (d, J = 15 Hz, 1 H), 4.09 (d, J = 15 Hz, 1 H), 4.00 (d, J = 2.1 Hz, 1 H), 2.99−2.83 (m, 1 H), 2.80−2.65 (m, 1 H), 2.32−2.15 (m, 1 H), 1.70−1.53 (m, 2 H), 1.45−1.31 (m, 2 H), 1.01−0.88 (m, 9 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 162.7, 135.7, 135.5, 135.4, 128.7, 128.2, 127.7, 65.2, 45.6, 34.9, 29.2, 28.0, 21.5, 19.3, 16.6, 13.7; MS (EI) *m/z* (%) 307 ($M^+(^{37}Cl)$, 1.24), 305 ($M^+(^{35}Cl)$, 4.07), 264 ($M^+ - C_3H_7(^{37}Cl)$, 35.84), 262 ($M^+ - C_3H_7(^{35}Cl)$, 100); IR (neat) 1748, 1713 cm^{-1}; HRMS (MALDI/DHB) calcd for $C_{18}H_{25}{}^{35}ClNO$ ($M^+ + 1$) 306.1619, found 306.1640.

(*R*)-(+)-(*E*)-α-(1-Chloro-3-phenylpropylidene)-β-(isopropyl)-β-lactam ((*R*)-(+)-(*E*)-6f): The reaction of (*R*)-(-)-**3f** (154 mg, 0.77 mmol, 98% ee), $PdCl_2$ (7 mg, 0.04 mmol), $CuCl_2$ (217 mg, 1.6 mmol), and benzoquinone (87 mg, 0.8 mmol) afforded 111 mg (55% yield) of (*R*)-(+)-(*E*)-**6f** with 97% ee as determined by HPLC analysis (Chiralcel OJ, *n*-hexane:*i*-PrOH 90:10, 230 nm), t_r = 7.8 (minor), 9.9 (major); $[\alpha]^{20}_D$ +65.7 (c = 1.45, $CHCl_3$).

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Supporting Information Available: Typical experimental procedure and analytical data for all products not listed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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