

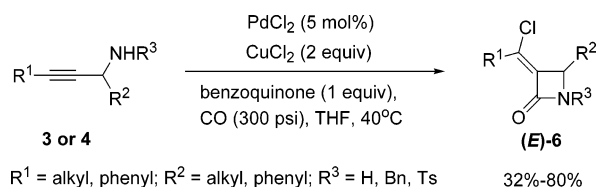
PdCl₂-Catalyzed Efficient Transformation of Propargylic Amines to (*E*)- α -Chloroalkylidene- β -lactams

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The PdCl₂-catalyzed cyclocarbonylation reaction of propargylic amines with CuCl₂ 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 activity¹ 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 PdCl₂-catalyzed cyclocarbonylation of propargylic amines affording (E)- α -chloroalkylidene- β -lactams highly selectively.

Results and Discussion

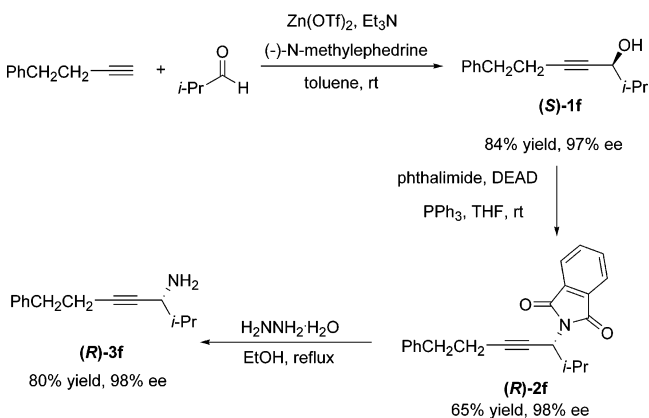
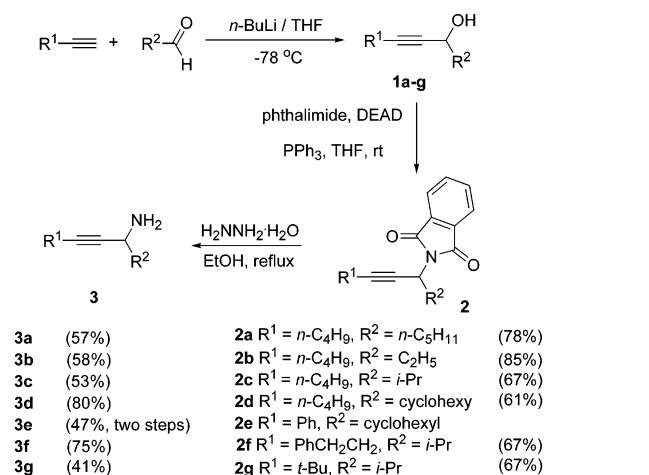
Synthesis of Starting Materials. A number of methods have been used for the synthesis of different propargylic amines. Propargylic amines **3a–g** were prepared through the application of the Mitsunobu reaction (Scheme 1).¹⁴ The optically active propargylic amine (*R*)-**3f** was prepared according to 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.

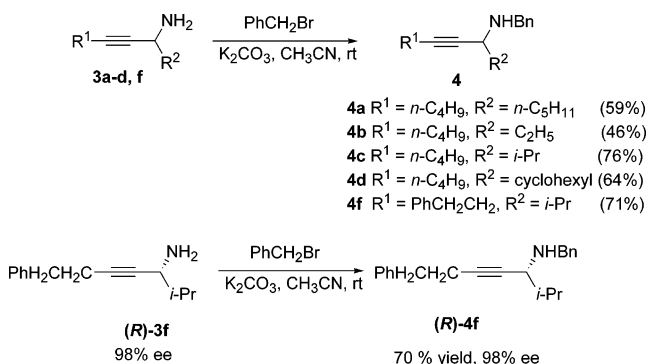
Propargylic amine **4l** was prepared via the reaction of the corresponding 1-alkynyllithium with the imine (Scheme 4).

Synthesis of (E)- α -Alkylidene- β -lactams via PdCl₂-Catalyzed Cyclocarbonylation of Propargylic Amines. Recently, we have observed that α -chloroal-

SCHEME 1



SCHEME 2



kylidene- β -lactones can be prepared from PdCl₂-catalyzed 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 PdCl₂ and 5 equiv of CuCl₂)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 PdCl₂ and 1.5 equiv of CuCl₂ (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

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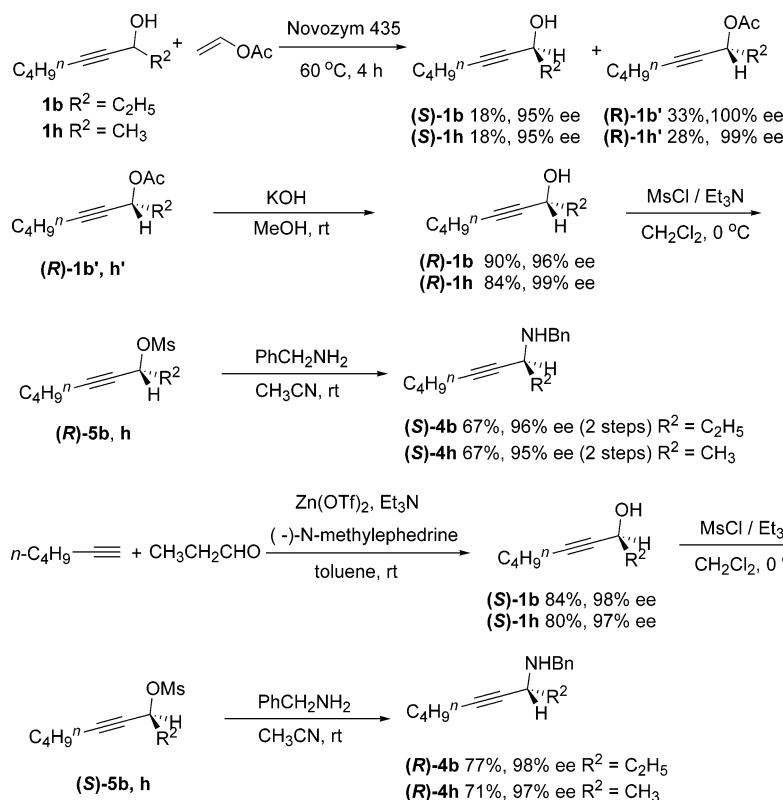
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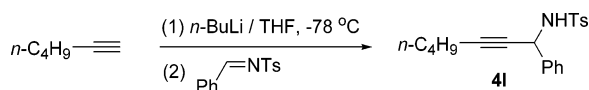
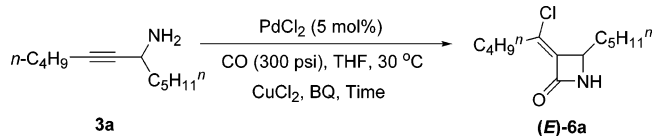
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SCHEME 3



SCHEME 4

TABLE 1. PdCl₂-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 H₂O 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 CuCl₂.

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 CuCl₂ afforded (*E*)-**6a** in similar yield. However, it should be noted that no (*E*)-**6a** was found in the absence of CuCl₂ (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 CuCl₂ when we added H₂O, 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 PdCl₂, 2 equiv of CuCl₂, 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

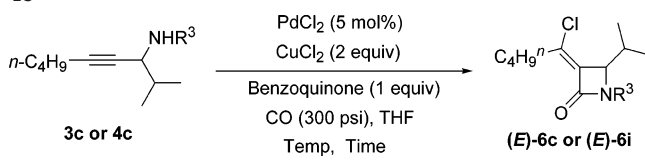
(19) Crystal data for compound (*E*)-**6d**: C₁₄H₂₂NOCl, MW = 255.78, monoclinic, space group C2/c, Mo Kα, final *R* indices [*I* > 2σ(*I*)], *R*₁ = 0.0764, *wR*₂ = 0.2031, *a* = 28.868(13) Å, *b* = 7.868(3) Å, *c* = 6.302(3) Å, α = 90°, β = 90°, γ = 90°, *V* = 1431.5(11) Å³, *T* = 293(2) K, *Z* = 4, reflections collected/unique 7200/2513 (*R*_{int} = 0.0941), no observation [*I* > 2σ(*I*)] 2080, parameters 151, CCDC 247772. Crystal data for compound (*E*)-**6e**: C₁₆H₁₈NOCl, MW = 275.76, monoclinic, space group C2/c, Mo Kα, final *R* indices [*I* > 2σ(*I*)], *R*₁ = 0.0512, *wR*₂ = 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) Å³, *T* = 293(2) K, *Z* = 2, reflections collected/unique 4341/3136 (*R*_{int} = 0.0620), no observation [*I* > 2σ(*I*)] 1625, parameters 245, CCDC 247771.

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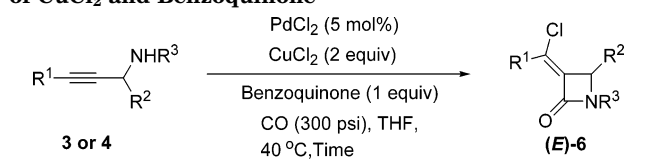
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TABLE 2. PdCl₂-Catalyzed Cyclocarbonylation of Propargylic Amine **3c** and *N*-Benzyl Propargylic Amine **4c**


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

TABLE 3. PdCl₂-Catalyzed Cyclocarbonylation Reaction of Various Propargylic Amines in the Presence of CuCl₂ and Benzoquinone


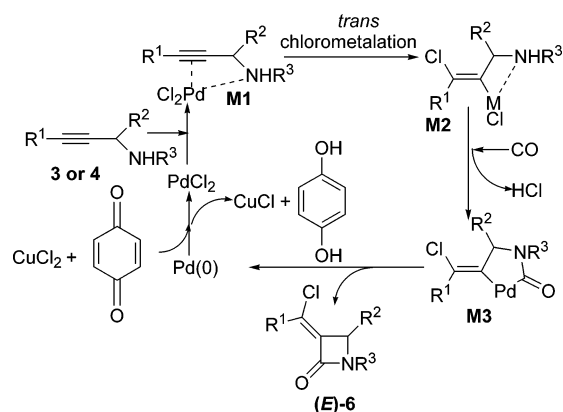
| entry | R ¹ | R ² | R ³ | time (h) | product | isolated yield (%) |
|-------|---|--|------------------|----------|-------------------------|--------------------|
| 1 | <i>n</i> -C ₄ H ₉ | <i>n</i> -C ₅ H ₁₁ | H (3a) | 8 | (<i>E</i>)- 6a | 52 |
| 2 | <i>n</i> -C ₄ H ₉ | C ₂ H ₅ | H (3b) | 8 | (<i>E</i>)- 6b | 48 |
| 3 | <i>n</i> -C ₄ H ₉ | <i>i</i> -Pr | H (3c) | 8 | (<i>E</i>)- 6c | 53 |
| 4 | <i>n</i> -C ₄ H ₉ | cyclohexyl | H (3d) | 8 | (<i>E</i>)- 6d | 50 |
| 5 | Ph | cyclohexyl | H (3e) | 10.5 | (<i>E</i>)- 6e | 32 |
| 6 | PhCH ₂ CH ₂ | <i>i</i> -Pr | H (3f) | 8 | (<i>E</i>)- 6f | 42 |
| 7 | <i>n</i> -C ₄ H ₉ | <i>n</i> -C ₅ H ₁₁ | Bn (4a) | 12 | (<i>E</i>)- 6g | 61 |
| 8 | <i>n</i> -C ₄ H ₉ | C ₂ H ₅ | Bn (4b) | 12 | (<i>E</i>)- 6h | 78 |
| 9 | <i>n</i> -C ₄ H ₉ | <i>i</i> -Pr | Bn (4c) | 12 | (<i>E</i>)- 6i | 80 |
| 10 | <i>n</i> -C ₄ H ₉ | cyclohexyl | Bn (4d) | 12 | (<i>E</i>)- 6j | 63 |
| 11 | PhCH ₂ CH ₂ | <i>i</i> -Pr | Bn (4f) | 12 | (<i>E</i>)- 6k | 70 |
| 12 | <i>n</i> -C ₄ H ₉ | Me | Bn (4h) | 8 | (<i>E</i>)- 6l | 61 |
| 13 | <i>n</i> -C ₄ H ₉ | Ph | Ts (4l) | 12 | (<i>E</i>)- 6m | 36 |
| 14 | ^t Bu | <i>i</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 PdCl₂-catalyzed cyclocarbonylation of various propargylic amines in the presence of CuCl₂ and benzoquinone. The typical results were summarized in Table 3, which led to the following conclusions: (1) the reaction is very general, R¹, R² can be alkyl, aryl group and R³ can be hydrogen (entries 1–6, Table 3), benzyl (entries 7–12, Table 3), and *p*-toluenesulfonyl group (entry 13, Table 3); (2) when R¹ was a bulky group such as ^tBu, 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 PdCl₂-catalyzed cyclocarbonylation of propargylic amines is depicted in Scheme 5.

SCHEME 5

glyc amines is depicted in Scheme 5. The coordination of the triple bond in **3** or **4** with PdCl₂ 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 CuCl₂ and benzoquinone to generate PdCl₂. Benzoquinone and CuCl₂ are both essential for a high-yielding reaction: CuCl₂ 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 CuCl₂ (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

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

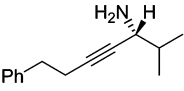
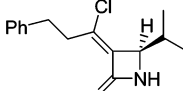
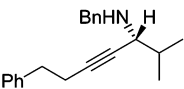
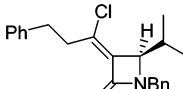
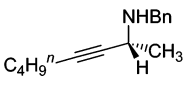
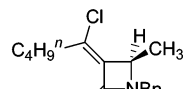
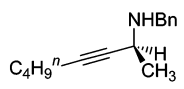
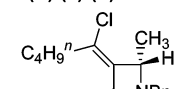
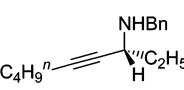
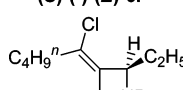
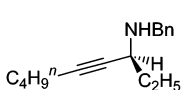
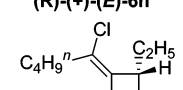
Synthesis of Starting Materials. Compounds **1a–h** were prepared via the reaction of the corresponding 1-alkynyllithium with aldehydes as reported.²⁰ Propargylic amines **3a–g** were prepared by the application of the Mitsunobu reaction.¹⁴

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 PPh₃ (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 N₂ 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

(24) Albéniz, A. C.; Espinet, P.; Martín-Ruiz, B. *Chem. Eur. J.* **2001**, 2481.

(25) Ma, S.; Lu, X. *J. Org. Chem.* **1991**, 56, 5120 and the references therein.

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

| $ \begin{array}{ccc} \text{R}^1-\text{C}\equiv\text{C}-\text{C}(\text{R}^2)\text{NHR}^3 & \xrightarrow[\text{CO (300 psi), THF, 40 }^\circ\text{C, Time}]{\text{PdCl}_2 \text{ (5 mol\%)} \\ \text{CuCl}_2 \text{ (2 equiv)} \\ \text{Benzoquinone (1 equiv)}} & \text{R}^1-\text{C}(\text{Cl})=\text{C}(\text{R}^2)-\text{C}(\text{O})\text{NHR}^3 \\ \text{(R)- or (S)-3 or 4} & & \text{(R)- or (S)-(E)-6} \end{array} $ | | | | | |
|--|---|----------|---|--------------------|-----------------|
| 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 \times 30 mL of Et₂O. The combined extracts were dried with Na₂SO₄, 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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75.4 MHz, CDCl₃) 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 C₁₂H₂₃N 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 K₂CO₃ (570 mg, 4.13 mmol) was added PhCH₂Br

(711 mg, 4.16 mmol) in 10 mL of dry CH₃CN. The reaction was stirred in N₂ 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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75.4 MHz, CDCl₃) 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*⁺ – C₅H₁₁, 94.72), 91 (100); IR (neat) 3368, 2221, 1604 cm⁻¹; HRMS (MALDI/DHB) calcd for C₁₉H₃₀N (*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 Et₃N (12.4 mL, 8.928 g, 88.4 mmol) in 90 mL of dry CH₂Cl₂. 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 CH₂Cl₂ was added dropwise. After being stirred at 0 °C for 4 h the reaction was extracted with 3 \times 15 mL of CH₂Cl₂. The combined extracts were washed with saturated aqueous NaHCO₃ and NaCl solution, dried over Na₂SO₄, and evaporated to afford 408 mg of **5** (yellow oil). The reaction of the above obtained **5** and BnNH₂ (0.44 mL, 430 mg, 4.0 mmol) in 4 mL of dry CH₃CN was stirred at room

temperature for 24 h. Then the solution was extracted with 3×15 mL of Et₂O. The combined extracts were washed with saturated NaCl and dried over Na₂SO₄. 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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75.4 MHz, CDCl₃) 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⁺ – CH₃, 36.99), 91 (100); IR (neat) 2932, 2228, 1603 cm^{–1}; HRMS calcd for C₁₅H₂₁N (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 NH₄Cl was added to the reaction mixture to stop the reaction. The mixture was extracted with Et₂O, washed by saturated NaCl solution, and dried over Na₂SO₄. 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**. ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75.4 MHz, CDCl₃) 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.

PdCl₂-Catalyzed Cyclocarbonylation Reaction of Various Propargylic Amines in the Presence of CuCl₂ 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 CuCl₂ (188 mg, 1.39 mmol) in 10 mL of dry THF was stirred for 5 min at room temperature followed by the addition of PdCl₂ (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 CH₂Cl₂. 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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75.4 MHz, CDCl₃) 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(³⁷Cl), 1.57), 244 (M⁺ + 1(³⁵Cl), 5.06), 41 (100); IR (neat) 3235, 1748, 1713 cm^{–1}; HRMS calcd for C₁₃H₂₂NO (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 CuCl₂ (165 mg, 1.22 mmol) in 8 mL of dry THF was stirred for 5 min at room temperature followed by the addition of PdCl₂ (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 CH₂Cl₂. 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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75.4 MHz, CDCl₃) 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⁺(³⁷Cl), 1.24), 305 (M⁺(³⁵Cl), 4.07), 264 (M⁺ – C₃H₇(³⁷Cl), 35.84), 262 (M⁺ – C₃H₇(³⁵Cl), 100); IR (neat) 1748, 1713 cm^{–1}; HRMS (MALDI/DHB) calcd for C₁₈H₂₅³⁵ClNO (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), PdCl₂ (7 mg, 0.04 mmol), CuCl₂ (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); $[\alpha]_D^{20}$ +65.7 (c = 1.45, CHCl₃).

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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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